Hepatic Stellate Cells: Protean, Multifunctional, and Enigmatic Cells of the Liver

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Abstract

The hepatic stellate cell has surprised and engaged physiologists, pathologists, and hepatologists for over 130 years, yet clear evidence of its role in hepatic injury and fibrosis only emerged following the refinement of methods for its isolation and characterization. The paradigm in liver injury of activation of quiescent vitamin A-rich stellate cells into proliferative, contractile, and fibrogenic myofibroblasts has launched an era of astonishing progress in understanding the mechanistic basis of hepatic fibrosis progression and regression. But this simple paradigm has now yielded to a remarkably broad appreciation of the cell's functions not only in liver injury, but also in hepatic development, regeneration, xenobiotic responses, intermediary metabolism, and immunoregulation. Among the most exciting prospects is that stellate cells are essential for hepatic progenitor cell amplification and differentiation. Equally intriguing is the remarkable plasticity of stellate cells, not only in their variable intermediate filament phenotype, but also in their functions. Stellate cells can be viewed as the nexus in a complex sinusoidal milieu that requires tightly regulated autocrine and paracrine cross-talk, rapid responses to evolving extracellular matrix content, and exquisite responsiveness to the metabolic needs imposed by liver growth and repair. Moreover, roles vital to systemic homeostasis include their storage and mobilization of retinoids, their emerging capacity for antigen presentation and induction of tolerance, as well as their emerging relationship to bone marrow-derived cells. As interest in this cell type intensifies, more surprises and mysteries are sure to unfold that will ultimately benefit our understanding of liver physiology and the diagnosis and treatment of liver disease.

I. Introduction

The hepatic stellate cell, first described by Kupffer in the 19th century, has emerged in the past 25 years as a remarkably versatile mesenchymal cell that is vital to hepatocellular function and the liver's response to injury. Indeed, the paradigm of stellate cell activation into contractile myofibroblasts as the major pathway in hepatic fibrogenesis associated with liver injury has dominated the focus of studies on this fascinating cell type. Beyond this well-known role, however, a broad range of newly discovered activities, some of which are entirely unexpected, have ignited mounting interest and led to a greater understanding of the complexity of cellular homeostasis in liver. Progress in this area has accelerated as a result of greatly refined methods of cellular isolation, sophisticated genetic models of disease, and improved tools of analysis, including flow cytometry, quantitative real-time PCR, confocal imaging, and molecular markers of cellular origin and phenotype. As a result, the number of related publications has grown dramatically (Fig. 1).

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Countless studies have explored the importance of hepatic stellate cells in liver fibrosis and repair, but a more comprehensive review article about this cell type, apart from its role in fibrosis, has been lacking for at least a decade. Thus this review will primarily highlight the tremendous breadth of new knowledge about the features of the stellate cell and its functions and responses in all aspects of liver function, rather than emphasizing only its role in fibrosis, for which several recent reviews are recommended (35,165,167,213,263,313,363).

A. Historical Perspective

Kupffer's initial description of stellate cells was made in 1876, using a gold chloride method that identifies vitamin A-containing droplets (678). Referring to these cells as "sternzellen" ("star cells" in German) (24,677), their identity was later confirmed by Rothe (1882) (677). Kupffer's initial observations failed to distinguish stellate cells from resident hepatic macrophages (now referred to as "Kupffer cells"), however, leading to some confusion about whether sternzellen were phagocytic, a property normally associated only with macrophages. Ironically, more recent studies have confirmed that indeed stellate cells can phagocytose apoptotic bodies (85), although the India Ink method used by Kupffer to document phagocytosis almost surely identified macrophages, not stellate cells.

A range of staining techniques were subsequently used to characterize stellate cells, including a Golgi silver method used by Zimmerman to identify "hepatic pericytes," a fat-staining method used by Ito to define "fat-storing cells" (266), and a silver impregnation technique used by Suzuki to describe "interstitial cells." More recently, Bronfenmajer, Schaffner, and Popper (75) proposed the name "lipocytes" to reflect their role in fat (vitamin A) uptake and pointed out the resemblance of these cells to fibroblasts. Finally, Nakane (433) and Wake (678) firmly established the stellate cell as a discrete cell type capable of storing vitamin A. Wake (676–678), using Kupffer's original gold chloride method to provide the definitive descriptions of stellate cells in situ, thereby established that "perisinusoidal cells" were the same as those described initially by Kupffer almost 100 years earlier.

An important functional role of stellate cells in liver repair emerged from the seminal descriptions by Kent (295) and others (409,459,718) revealing the close proximity of this cell type to collagen fibers in injured liver. Their work also suggested that stellate cells were precursors to the "fibroblasts" often described in liver injury. The consistent morphological association between hepatic stellate cells and extracellular matrix (398) provoked interest in the early 1980s in developing methods to isolate stellate cells from rat (172,321), mouse (103), and human liver (171,699) (see sect. ɪᴠA).

B. Nomenclature

With the explosive growth in studies of hepatic stellate cells, confusion arose because of its many different names, prompting investigators in the field to agree in 1996 to a standardized name, *hepatic stellate cell*, to refer to the resting form of this cell type found in normal liver, a term now widely adopted (448a), instead of a litany of synonyms, including *perisinusoidal cell, Ito cell, lipocyte, parasinusoidal cell*, and *fat-storing cell*.

II. Ultrastructure and Morphological Features

Hepatic stellate cells are located in the subendothelial space, between the basolateral surface of hepatocytes and the anti-luminal side of sinusoidal endothelial cells. They comprise approximately one-third of the nonparenchymal cell population and ~15% of the total number of resident cells in normal liver (200,271). Some studies describe a slight pericentral predominance in normal human liver (75), while in porcine liver they are more prominent in

periportal zones (682); the functional significance of these divergent patterns between species, if any, is unclear.

A. Ultrastructure

Stellate cells in normal liver have spindle-shaped cell bodies with oval or elongated nuclei (see Fig. 2). Their perikaryons lie in recesses between neighboring parenchymal cells. Ultrastructurally, their have moderately developed rough endoplasmic reticulum (rER), juxtanuclear small Golgi complex (142), and prominent dendritic cytoplasmic processes (Fig. 3) (674). The subendothelial processes wrap around sinusoids between endothelial cells and hepatocytes. On each of these processes, there are numerous thorny microprojections (spines) (679). The function of these projections had been obscure until a recent, elegant study has demonstrated that these protrusions serve a vital role as the cell's leading edge in "sensing" chemotactic signals, and then transmitting them to the cell's mechanical apparatus to generate a contractile force (414).

A single stellate cell usually surrounds more than two nearby sinusoids (679). On the other side of the cell (i.e., the anti-luminal surface), multiple processes extend across the space of Disse to make contact with hepatocytes (679,680). This intimate contact between stellate cells and their neighboring cell types may facilitate intercellular transport of soluble mediators and cytokines. In addition, stellate cells are directly adjacent to nerve endings (56,658), which is consistent with reports identifying neurotrophin receptors (95), and with functional studies confirming neurohumoral responsiveness of stellate cells (336,455,550).

B. Retinoid Storage

The most characteristic feature of stellate cells in normal liver is their cytoplasmic storage of vitamin (retinoid) droplets (678). In unfixed tissue or cultured cells, the retinoid droplets exhibit a striking, rapidly fading blue-green autofluorescence when excited with the light of ~328 nm (Fig. 4) (174,499). The number of droplets varies with the species and the abundance of vitamin A stores of the organism (499,587). The vitamin A droplets in stellate cells display a heterogeneous pattern, with the volume of droplets differing depending on the intralobular position of the cells (192). Vitamin A fluorescence is more concentrated in periportal regions than pericentral regions (682,739). Two types of vitamin A droplets have been described (675): type I droplets are membrane bound and of variable size, but usually smaller than 2 μm in diameter. They are likely derived from "multivesicular bodies," which are considered a type of lysosome (194,708). Type II droplets are not membrane bound and are larger (up to 8 μm). The relationship between types I and II droplets and their functional differences are unclear. According to Wake (675), type II fat droplets form by fusion of several type I droplets. Yamamoto and Ogawa (708), however, believed type II droplets to be the precursor of type I droplets.

A well-known feature of artic animals, particularly polar bears, seals, and Arctic foxes, is their high concentration of hepatic vitamin A (586), such that early explorers who ate uncooked polar bear liver suffered from a syndrome of hypervitaminosis A, which is characterized by severe liver injury (449). However, there are no distinct features of these arctic mammals identified to date that distinguish their vitamin A storage pathways from those of humans, and thus the reason why these animals are protected from hepatic toxicity due to vitamin A is unclear. Moreover, the requirement for vitamin A-storing cells appears to be a vital evolutionary trait, since stellate cells can be identified even in relatively primitive vertebrates including halibut (722) and the lamprey (681).

During liver injury, the fine structure of stellate cells changes considerably. They lose their characteristic droplets and become "activated" (see sect. VI). The rER becomes enlarged,

accompanied with a well-developed Golgi apparatus, suggesting active protein synthesis (174,421) (Fig. 4). Bundles of numerous microfilaments appear beneath the cell membrane (142). The activated stellate cells then evolve into myofibroblast-like cells (see sect. vi) with newly formed collagen fibrils surrounding them.

III. Origin and Cytoskeletal Phenotype of Stellate Cells

A. Embryologic Origin(s)

The embryologic origin of stellate cells has been elusive. Currently, the bulk of evidence supports their originating from either endoderm (300,624,666) or the septum transversum (553) as it forms from cardiac mesenchyme during invagination of the hepatic bud (135,728, 733). In support of a septum transversum origin, stellate cells express the mesoderm transcriptional factor Foxf1, which is typically localized to the septum transversum mesenchyme during liver development (280). In support of an endoderm origin, on the other hand, it has been suggested that stellate cells and hepatoblasts share a common origin based on the transient coexpression of cytokeratins in both cell types (300,666).

Stellate cells appear in the second half of the third month of gestation in human development (193). At birth in rats, stellate cells have still not reached their final size, which requires an additional 5 weeks (680). A more recent study has characterized a population of vitamin A-storing cells from day 13 fetal rat liver having a surface phenotype of intercellular adhesion molecule 1 (ICAM-1)$^+$, vascular cell adhesion molecule 1 (VCAM-1)$^+$, and β_3-integrin$^+$ (331). The cells are able to proliferate in serum-free hormonally defined medium and express hepatocyte growth factor (HGF), stromal-derived growth factor-1, and Hlx homeodomain transcription factor, implicating them in regulating hepatic development. Further characterization of these cells is likely to lead to efforts to assess their contribution to hepatocellular growth and progenitor cell expansion.

In humans, a population of cells has been characterized in midgestation of embryonic liver development using specific antibodies that are CD34$^+$ cytokeratin (CK)7/8$^+$ and also express CD13, CD59, nerve growth factor receptor (NGFR), desmin, and α-smooth muscle actin (α-SMA), leading the authors to conclude that they represent embryonic precursors of adult stellate cells derived from endoderm (193,624). These cells were larger with more cytoplasm than CD34$^+$CK7/8$^-$ cells and had cytoplasmic projections, also characteristic of stellate cells.

Confusion has increased in the past decade because a neural crest origin has also been suggested based on stellate cells' expression of several neural crest markers, including glial fibrillary acidic protein (GFAP), nestin, neurotrophins and their receptors, N-CAM, synaptophysin, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), Rho-N, N-cadherin (192), as well as cellular prion protein (249). However, fate mapping studies of neural crest-derived cells in developing mouse liver have recently failed to localize to hepatic stellate cells during late gestation (94,193), undermining the possibility of a neural origin.

A separate issue is whether stellate cells and sinusoidal endothelial cells derive from a common precursor cell, a likely possibility given their shared mesenchymal phenotype, close proximity in situ, and joint expression of several angiogenic effectors, for example, receptors for vascular endothelial cell growth factor (VEGF) (10). However, no studies have specifically addressed this issue, either in models of development, liver injury, or regeneration following partial hepatectomy, despite the fact that endothelial cells are vital to liver development (403).

The source of activated stellate cells and myofibroblasts in liver injury has provoked extensive study and debate (590), especially the notion that bone marrow contributes a substantial fraction of these cells. This issue is discussed in detail in section iii*B*; however, at least one study

indicates that bone marrow may also contribute to quiescent stellate cells as well (26), possibly from circulating "fibrocytes" that home to the liver (314). Mice administered a bone marrow transplant containing cells expressing green fluorescent protein (GFP) but without liver injury had evidence of GFP expression in their livers (26). Although the turnover of stellate cells in normal liver is unknown, it seems unlikely that substantial repopulation from bone marrow occurs in the absence of liver injury or a specific stimulus to bone marrow cell recruitment. Moreover, recent studies examining bone marrow contributions to hepatocyte repopulation have emphasized the important contribution of cell fusion to the apparent amplification of bone marrow-derived cells (216,651).

B. Heterogeneity and Plasticity of Hepatic Stellate Cells

As implied in the preceding paragraphs, the development of antibodies to a range of cytoskeletal and cell surface markers has facilitated the extensive characterization of the stellate cell's phenotype. What has emerged from these analyses is an appreciation of their tremendous heterogeneity and plasticity in adult liver, depending on their lobular location, the species examined, and whether the tissue is normal or injured.

In 1984, Yokoi (718) detected desmin in stellate cells, an intermediate filament typical of contractile cells. This finding suggested a similarity between stellate cells and myogenic cells. Since then, desmin has been widely used as a "gold standard" for identifying stellate cells in rodent liver, although in humans its expression is unreliable (171,571). A more recent study suggests that a significant fraction of stellate cells may lack vitamin A (31,517), indicating a heterogeneous phenotype in these cells, as detailed below. Desmin-negative cells are concentrated in the pericentral zone, where they may represent up to 50% of the total stellate cell pool whereas periportal stellate cells are typically desmin positive (31).

α-SMA is one of the six actin isoforms expressed in mammalian tissues. Its presence is typical for vascular smooth muscle cells (179,606) and myofibroblasts, or contractile fibroblasts, where it is localized within microfilament bundles (572,589). Induction of α-SMA is the single most reliable marker of stellate cell activation (see sect. v), because it is absent from other resident liver cells in either normal or injured liver except the smooth muscle cells surrounding large vessels. Interestingly, while its expression connotes a contractile phenotype, its genetic deletion leads to enhanced fibrosis in a rodent model of renal injury (632).

These early observations of stellate cell plasticity rapidly led to the conclusion that rather than a single cell type with an identical retinoid and cytoskeletal phenotype, stellate cells contain variable amounts of vitamin A and differing combinations of intracellular filaments, depending on their lobular location, the species studied, whether the liver was normal or injured, and the nature of the liver injury (i.e., biliary vs. parenchymal). Moreover, as described in section vıA, there is a continuum of changes in gene expression during stellate cell activation, such that the quiescent cell first becomes activated, then continues to evolve into a myofibroblast-like cell. However, activated stellate cells are distinct from myofibroblasts in their vitamin content, contractile activity, and relative responsiveness to cytokines, particularly transforming growth factor (TGF)-β. Even when stellate cells reach replicative senescence, the pattern of gene expression continues to evolve, with acquisition of a more inflammatory and less fibrogenic phenotype (574).

The plasticity of stellate cell phenotype was underscored by findings from a double transgenic mouse in which a GFP was driven by the collagen I promoter, while a red fluorescent protein (RFP) was controlled by the α-SMA promoter (166,367). In this study there were mixed populations of activated cells, some of which expressed GFP or RFP alone, others of which expressed both. Specific patterns of gene expression were seen in cells expressing α-SMA, with higher levels of ICAM-1, MMP-13, reelin, TIMP1, and synaptophysin mRNAs. Along

this theme, another study demonstrated that stellate cell activation in liver fibrosis is also associated with a switch from E- to N-cadherin expression (353), raising the interesting prospect that stellate cells undergo epithelial to mesenchymal transition (601). In addition, in cholestatic liver injury, portal fibroblasts may be a more important source of activated myofibroblasts than stellate cells around proliferating bile ducts (41). Collectively, these findings reinforce earlier histochemical data highlighting the heterogeneity of stellate cells with respect to both classical markers of stellate cell activation and even raise the possibility of transdifferentiation from epithelium.

C. Extrahepatic Stellate Cells

Following the detailed characterization of hepatic stellate cells, it became clear that similar cells existed in other organs. In particular, pancreatic stellate cells are nearly identical to hepatic stellate cells, and both are presumed to share a common origin (77,466). Pancreatic stellate cells display the same heterogeneous cytoskeletal phenotype as hepatic stellate cells. The similarity is further reinforced by a direct transcriptome analysis of the two cell types, revealing that while isolated human hepatic and pancreatic stellate cells differ considerably compared with skin fibroblasts, there were only 29 mRNAs that were different between the two types of stellate cells. Most of the divergent genes were mRNAs regulating extracellular matrix expression and turnover, cell adhesion, or cell-cell communication, in addition to three transcription factor genes (77). Furthermore, it is likely that these minor differences between hepatic and pancreatic stellate cells could have arisen primarily as a result of different culture conditions rather than fundamental differences between the two cell types. Similarities between hepatic and pancreatic stellate cells also extend to pathways of fibrogenesis, including similar roles of cytokines (13) and alcohol metabolites (14), especially acetaldehyde (see Ref. 466 for review).

Still, there are fundamental differences in the micro-environments of hepatic and pancreatic stellate cells that could condition these cells to respond differently to normal homeostatic controls and to injury. For example, liver receives a dual blood supply that includes predominantly venous blood, such that hepatic stellate cells are less prone to ischemia when arterial blood flow is compromised. On the other hand, pancreatic injury, unlike hepatic injury, is associated with disruption of zymogen granules containing proteases, exposing resident cells to proteolysis. It is tempting to speculate that either or both of these differences may contribute to the enhanced regenerative capacity of liver compared with pancreas. Another difference is that desmoplasia is a far more common component of pancreatic cancer than hepatocellular carcinoma, with evidence that pancreatic cancer cells release potent fibrogenic mediators (30).

While less thoroughly characterized, vitamin A-storing cells are present in a variety of other tissues including lung, kidney, and intestine (243,431,678); lipid droplets in these sites increase in rats with hypervitaminosis A (431). In addition, cell types resembling activated stellate cells are also demonstrable in injured kidney (361) and lung (294), where pathways of fibrogenesis are thought to be quite similar. One key difference between kidney and liver fibrogenic cells, however, is the apparently larger contribution of epithelial to mesenchymal cell transition in renal fibrosis than in liver (281,601).

IV. Models and Methods of Characterizing Stellate Cells

A. Cell Isolation Methods

The development of techniques for isolating and cultivating hepatic stellate cells represented a major advance in exploring the cell's roles in normal and injured liver. Studies 25–30 years ago characterized the growth of mesenchymal cells derived from liver tissue, which in

retrospect may have been derived from stellate cells (182,672). Cell studies of this type described a "fibroblast-like" phenotype with potential for extracellular matrix production. With the realization that such cells were likely derived from stellate cells, Knook et al. (321), then our laboratory (172,174), utilized in situ digestion followed by density gradient centrifugation to isolate stellate cells based on their buoyancy attributable to intracellular vitamin A. Initially these methods required vitamin A supplementation to increase yields, until it was recognized that vitamin A content increased in normal rats with age. By using larger, older rats (>350 g), yields of 40–100 million cells per normal animal (95–99% purity) were obtained routinely, which were increased further in animals with liver injury (unpublished observation). Several different gradient materials can be utilized, including metrizamide (321), arabinogalactan (172), or Nycodenz (241). Considerations for the choice of material include precision, reproducibility, cost, and ease of preparation. Gradient separation has also been used to successfully isolate stellate cells from normal human liver suitable for primary culture, although purity is less than for rodent cells (171).

Density gradient separation remains the most widely used approach for stellate cell isolation, but favors the isolation of cells that are relatively vitamin A-rich and therefore less "activated." Indeed, in animals with liver injury, large numbers of stellate cells are recovered from higher density (i.e., lower level) gradient layers; such vitamin A-poor cells are typically more activated in terms of cytoskeletal markers and extracellular matrix gene expression. The difficulty with these vitamin A-poor isolates is their heterogeneity, since they may contain significant numbers of sinusoidal endothelial cells and Kupffer cells (172). Studies of such isolates therefore may be confounded because of paracrine stimulation of stellate cells by soluble mediators from other nonparenchymal cells, an issue discussed in section v*H* describing gene array profiling of stellate cells.

Two cell isolation approaches that avoid density gradients are fluorescent cell sorting and explant culture. Cell sorting, based on endogenous vitamin A fluorescence, has been reported in one study (406). Lower yields and dependence on costly technology greatly limit its applicability, although it remains valuable for obtaining ultrapurified stellate cells. Outgrowth of activated stellate cells from human liver biopsy material has gained favor (60,691) and is reminiscent of earlier studies (182,672), albeit now utilizing more refined cell markers. The limitations of this approach are the potential heterogeneity of the culture and the inability to track early events in cellular activation, since the method relies on outgrowth of activated cells on plastic in tissue culture. Still, careful characterization of the cells by immunostaining for cytoskeletal markers and extracellular matrix products does allow for the generation of meaningful data.

While methods for stellate cell isolation were initially developed in rats and then adapted to humans, the development of transgenic and knockout mouse models has more recently required the isolation of murine stellate cells. The methods required are fundamentally the same but require a larger number of animals to achieve an adequate yield. A growing number of such models have utilized either standard isolation or in situ analysis with cell specific markers to characterize the cells (239,280,510,608,645).

B. Cell Lines

To overcome the need for primary cell isolation entirely, stellate cell clones/lines have been developed which recapitulate some features of the in vivo activated phenotype; their use has increased dramatically in recent years (219). Such stable, immortal cell lines offer the advantage of a ready supply of cells, homogeneity, and the potential for many investigators to work in the same carefully defined system. Cell lines currently in use have been generated by either spontaneous immortalization in long-term culture, stable expression of simian virus 40 (SV40) T antigen, or ectopic expression of telomerase. Cell lines each differ somewhat in their

state of activation, transfectability, and mRNA expression profiles (see sect. vH), but in general have accelerated progress in elucidating stellate cell biology and hepatic fibrosis. However, it is prudent to always validate findings derived from cell lines to the in vivo state using either primary stellate cells or in situ methods to confirm that gene or protein expression identified in cell lines is physiologically relevant. A large number of lines have been reported, but only those most extensively studied are described below.

Several rodent stellate cell lines have been characterized. Greenwel, Rojkind, and co-workers (208) reported stellate cell clones derived from normal or CCl_4-treated rat liver, which have variable levels of collagen gene expression and responsiveness to interleukin-6. Subsequently, our laboratory characterized a rat stellate cell line generated by stable expression of the SV40 T antigen (671). This line, termed "HSC-T6," is particularly valuable for studies of retinoid metabolism based on their similar retinoid phenotype as primary cells (671). Similarly, the "PAV-1" line displays features of retinoid metabolism akin to that of primary cells (563, 564). A recent addition is the rat line "PQ" generated by single cell cloning, which has key features of primary stellate cells (474), although there is not evidence yet that the line is truly immortalized.

Several human stellate cell lines have also been generated. The L190 line is derived from a human hepatic mesenchymal cell tumor (428). The cells accumulate vitamin A, express a large number of matrix components, morphologically resemble stellate cells, and express smooth muscle actin; monoclonal antibodies raised to these cells recognized tenascin, an extracellular matrix glycoprotein known to be secreted by stellate cells (428). Another cell line, "GRX," is derived from fibrotic tissue of a mouse with schistosomal liver disease (69). Like L190 cells, its morphology, vitamin A production, and matrix production are similar to stellate cells, although neither L190 nor GRX has been distinguished from vascular smooth muscle cells with certainty. In part this reflects the lack of a stellate cell-specific marker (see sect. mB). Nonetheless, such cell lines may be useful tools to explore the biology of stellate cells, although correlation with cells both in primary cells and in vivo will be essential. Schnabl et al. (574) described a cell line immortalized by ectopic expression of the human telomerase gene, thereby preventing cellular senescence that typically accompanies telomere shortening (574); this line has been extensively characterized by cDNA microarray (574,575). Similarly, we generated two human stellate cell lines, LX-1 and LX-2 using SV40 T antigen for LX-1 cells, and spontaneous immortalization in low serum for LX-2 cells, and have extensively validated their similarities to human culture activated stellate cells (704). A particular advantage of LX-2 cells is their relative transfectability, which facilitates introduction of ectopic genes by transient transient at a higher efficiency than in most cell lines. The line has also been used in a number of subsequent studies examining responses to cytokines, hypoxia, and other stimuli (34,85–87,89,[228],[483],596,629,636,730). Other human cell lines include one created by telomerase expression in the L190 cells (597) and another derived from explant culture (691).

A recent report describes a cryopreservation technique for freezing primary stellate cells using dimethyl sulfoxide (442). If reproducible in other laboratories, the technique will also accelerate progress by enabling the sharing of cells between investigators, especially those without the means to isolate their own primary cells.

C. Effects of Matrix and Culture Conditions

Progressive cellular activation, as defined by loss of vitamin A, proliferation, and increased extracellular matrix production, occurs when stellate cells are plated in primary culture on standard tissue culture plastic (see Fig. 3) (29,173,195). This "spontaneous activation" can be exploited to study cellular events similar to those occurring in liver injury and can be further accelerated by incubation in conditioned medium from hepatic macrophages (168,404,405). Early primary culture is important for studying signaling events in stellate cell activation, but

is limited by the heavy dependence on repeated cell isolations and by prep-to-prep variability. The problem can be overcome somewhat by passaging cells with trypsin and replating to increase yields; however, this leads to progressive deviation from the quiescent phenotype.

In addition to using uncoated plastic as a culture substratum, stellate cells grow well on a variety of extracellular matrices which can up- or downregulate their activation (579). For example, when grown on a type I collagen matrix, stellate cells are more fibrogenic in response to TGF-β than on type IV collagen (114). Even more striking is the preservation of a quiescent phenotype when stellate cells are maintained on a laminin-rich gel that mimics the effects of a basement membrane (173,181,463). This quiescent phenotype can also be maintained if cells are prevented from adhering by growth in suspension on a nonadherent surface (176).

While the effect of a gel on preserving stellate cell quiescence was reproducible, we and other investigators were unable to define a specific matrix constituent that conferred quiescence. However, a fascinating explanation for the effects of a gel substratum has been offered by recent studies implicating matrix stiffness as the key determinant of stellate cell activation in these systems (694). Thus the deformability of the substrate, in addition to, or instead of, its chemical composition may regulate stellate cell responsiveness. While the receptors that mediate these responses are not firmly identified, integrins are strong candidates based on their important role in mediating cell-substratum interactions in stellate cells and other mesenchymal cell types. The emergence of matrix stiffness as regulator of stellate cell biology resonates with recent clinical studies utilizing a device that measures stiffness to determine the physical state of liver and in particular its matrix content (160). Continued efforts to refine both chemical and physical determinants of stellate cell function are critical to optimize methods for developing artificial liver devices, where the physical properties of the substratum and cell-cell interactions may be vital to preserving differentiated hepatic function (215). In particular, use of three-dimensional culture systems may be particularly relevant to such efforts by recapitulating a more physiological microenvironment (227,585,631).

D. Other Models: Liver Slices, In Vivo Methods

Liver slices were developed decades ago in an attempt to preserve the native milieu of resident liver cells, but were abandoned when methods for primary cell isolation were developed. With continued refinements, however, liver slices again offer some unique advantages (664,668) and have more recently been used to test drug targeting methods (410,411), antifibrotic therapies (224), and cell fate during injury and repair following exposure to hepatotoxins (221). The slice technology can be complemented with either real-time PCR for stellate cell-specific genes (665) or laser-capture microdissection to enrich for stellate cells recovered from within the slice.

In vivo methods for stellate cell analysis were developed as a result of refined culture methods and improved antibodies suitable for in situ immunohistochemistry. Maher et al. (371) pioneered the use of stellate cell isolation from injured rodents to characterize their gene expression as a reflection of their in vivo behavior, an approach which has now been adapted to a variety of models and species. Concordance between levels of gene and protein expression in these isolated cells and tissue is extremely high, further validating the method. At the same time, countless studies have used tissue immunohistochemistry to identify stellate cells in liver, but the most prominent proteins analyzed to date include α-SMA, desmin, and GFAP (see Ref. 192 for review).

Identifying promoters that selectively drive transgene expression in stellate cells of mice has been a difficult challenge. Recent studies, however, have convincingly used components of either collagen $\alpha(1)I$, collagen $\alpha2(I)$, or α-SMA promoters to direct transgene expression in activated stellate cells (311,312,367). More challenging has been the identification of

transgenic promoters to ectopically express genes in quiescent stellate cells. For this purpose, a recent study described use of a 2.2-kb promoter of the GFAP gene (700), which corresponds to separate findings using the same promoter fragment to drive reporter gene expression in cultured stellate cells (407). The development of these important tools should provide significant new opportunities for genetic mouse models in which gene expression is selectively augmented or knocked out in hepatic stellate cells but unaffected in other resident liver cell types.

V. Functions of Hepatic Stellate Cells in Normal Liver

A. Role in Liver Development and Regeneration

Stellate cells can be found within the progenitor cell niche in normal and regenerating liver, which is situated near the Canals of Hering (549,716,717) (see sect. ɪɪɪ). The functional importance of these stellate cells is supported by evidence that mouse fetal liver-derived Thy1$^+$ cells, which express classical features of hepatic stellate cells (α-SMA, desmin, and vimentin), promote maturation of hepatic progenitors through cell-cell contact in culture (26). Progenitor cell expansion can also be driven by vagal stimulation (96), but it is unclear if this pathway requires participation by stellate cells. Regardless, this finding suggests that the denervated (i.e., transplanted) liver may lack a vital pathway controlling hepatic regeneration after injury. Adding to the intrigue of these cells, quiescent stellate cells also express epimorphin, a mesenchymal morphogenic protein, which is increased after partial hepatectomy, coincident with a decline in stellate cell expression of α-SMA (723). Similarly, another stellate cell-derived morphogen, pleiotrophin, is also secreted by stellate cells and may contribute to hepatocyte regeneration (20).

Stellate cells may also be vital to the development of intrahepatic bile ducts during development (352). This observation complements evidence of paracrine interactions between bile duct epithelium and either stellate cells or portal fibroblasts both in culture (330) and in vivo (307). It also complements findings of synemin (an intermediate filament typically associated with stellate cells) expression in both stellate cells and the epithelial component of the ductular reaction to various liver diseases and cholangiocarcinoma (569). Similarly, in a rat study of hepatic responses to a carcinogen, a subset of nestin positive cells (i.e., stellate cells) coexpressed hepatocyte and epithelial markers (323). Finally, the recent characterization of a fetal hepatic stellate cell isolate from rat (331) could accelerate efforts to explore the stellate cell's role in bile duct and progenitor expansion in culture and in vivo models.

In addition to their emerging role in hepatic development, there is growing evidence that stellate cells are also vital to the hepatic regenerative response in adult liver, but further investigation is urgently needed. An important study has identified neurotrophin signaling as a paracrine pathway in stellate cells that contributes to hepatocellular growth following injury, in part through stimulation of HGF secretion by stellate cells (481). In a similar approach, mice heterozygous for the Foxf1 forkhead transcription factor (Foxf1 +/−) display defective stellate cell activation after CCl$_4$ administration, as assessed by α-SMA expression (280). At the same time, these animals have increased liver cell injury and apoptosis, but reduced fibrosis and diminished expression of Notch-2 and IP-10, compared with wild-type controls. Most intriguingly, the animals have defective epithelial regeneration, although it is difficult to tease out the potential mechanisms based on these data alone. In particular, it is unclear if products of activated stellate cells are required to attenuate hepatocyte injury, enhance hepatocellular regeneration, or both. The role of stellate cells in hepatic regeneration would be ideally addressed if methods are developed to determine the impact of ablating or inactivating these cells on regeneration of normal liver following partial hepatectomy. A genetic model of cell-specific deletion has been quite informative in understanding the role of hepatic macrophages (133,164) in liver injury and repair, for example.

A number of potential hepatocyte mitogens are secreted by stellate cells, including HGF (368,568), epidermal growth factor (29,416,427), epimorphin (723), and pleiotrophin (20). As yet, however, their relative contribution and modes of regulation during hepatic regeneration have not been clarified.

Even more interesting, a subset of hepatic stellate cells express CD133, which is a stem cell marker (326), suggesting that stellate cells might have pleuripotent potential in developing or adult liver. This very intriguing finding merits further exploration, as two recent studies have identified CD133 as a marker of stemlike cells in several tissues (532,726), including colon cancer (451,526).

B. Retinoid Metabolism

In normal liver, stellate cells play a key role in the storage and transport of retinoids (vitamin A compounds). Under physiological conditions, ~50–80% of total retinoid of the body is stored in the liver (62), of which 80–90% is stored in stellate cells (240,241). Most vitamin A is stored in cytoplasmic droplets in the form of retinyl esters, predominantly retinyl palmitate (240, 241). The composition of these droplets is affected by dietary intake. They contain not only retinoids, but also significant amounts of triglycerides, phospholipids, cholesterol, and free fatty acids (425,706).

Dietary retinol in the intestinal epithelium is esterified with long-chain fatty acids and packaged into chylomicrons for transport to the systemic circulation through mesenteric lymphatics. In the liver, these retinol-containing chylomicrons are taken up by hepatocytes and then transferred to stellate cells for storage; a small amount remains within hepatocytes. Within hepatocytes, retinyl esters are hydrolyzed to free retinol before being transferred to stellate cells (63). This process is mediated by retinol-binding protein (RBP) (61). In addition, stellate cells also take up RBP-bound retinoids directly from circulating blood (8). Direct release of RBP-bound retinol from stellate cells into plasma may also occur (62). The storage and transport of retinoids are influenced by the vitamin A status of the animal. In vitamin A-deficient conditions, dietary retinoids transported to the liver are rapidly bound to RBP in hepatocytes and exported to the circulation without transfer to stellate cells (40,63).

Several retinoid-related proteins have been identified in stellate cells, including cellular retinol-binding protein (CRBP), retinol palmitate hydrolase, cellular retinoic acid-binding protein (CRABP), bile salt-dependent and -independent retinol ester hydrolase, and acyl coenzyme A:retinal acyltransferase (59,175). Whether stellate cells produce RBP is still in question, because of contradictory reports on the presence of RBP mRNA in stellate cells between different studies (64,175).

1. Effects of retinoids on stellate cells—The biological role of retinoids in regulating stellate cell activation remains a puzzle. Although loss of retinoid is a prominent feature accompanying stellate cell activation both in vivo (421) and in culture (175), it is unknown whether this process is a prerequisite for activation to occur. The reports about effects of retinoids on stellate cells and fibrogenesis are contradictory (115,116,199,236,[423],[460],[461], 563,582,583,588). In culture, both retinol and retinoic acid suppress stellate cell proliferation, and retinoic acid (RA) is 1,000 times more potent than retinol (116). In contrast, 9-*cis*-RA and 9,13-di-*cis*-RA, two metabolites of RA, promote fibrosis by upregulating plasminogen activator, which in turn induces the production and activation of TGF-β (460,461). This process is mediated by RA receptor (RAR)-α. However, in another study using a rat model of fibrosis induced by bile duct ligation, the increase in TGF-β production was attributed to diminished RA signaling in stellate cells (457). More recently, divergent effects of all-*trans*-RA and 9-*cis*-RA on stellate cells have been observed (234). There are also different effects between natural and synthetic retinoids (236).

Since almost all the vitamin A in liver is stored in stellate cells, studies examining retinoid content in whole liver predominantly reflect the features of retinoids in stellate cells. Accordingly, loss of total retinoid but increased RA in liver during injury may have implications for stellate cell function (440). These observations differ from changes observed in vitamin-A deficient animals, in whom expression of lecithin:acyl transferase (LRAT), the enzyme responsible for esterifying retinol, is downregulated rapidly along with a retinoic acid responsive cytochrome *P*-450, Cyp26 (551).

C. Immunoregulation

The emergence of stellate cells as significant mediators of hepatic immunoregulation has been among the most surprising discoveries about the cell type (369) (see Fig. 5). Stellate cells can amplify the inflammatory response by inducing infiltration of mono- and polymorphonuclear leukocytes. Activated stellate cells produce chemokines that include monocyte chemotactic peptide (MCP)-1 (393), CCL21 (66), RANTES, and CCR5 (580). They express toll-like receptors (TLRs) (472), indicating a capacity to interact with bacterial lipopolysaccharide (LPS), which in turn stimulates stellate cells (76). Stellate cells also can function as professional antigen presenting cells (660,670,700) that can stimulate lymphocyte proliferation or apoptosis (322). In addition to mononuclear cell chemoattractants, stellate cells produce neutrophil chemoattractants, which could contribute to the neutrophil accumulation characteristic of alcoholic liver disease (372), as well as complement protein C4 (153), which contributes to the liver's inflammatory response.

Stellate cells both regulate leukocyte behavior and are affected by specific lymphocyte populations. For example, CD8 cells harbor more fibrogenic activity towards stellate cells than CD4 cells (559), which may explain in part the increased hepatic fibrosis seen in patients with hepatitis C virus (HCV)/human immunodeficiency virus (HIV) coinfection, where CD4/CD8 ratios are reduced, compared with patients mono-infected with HCV alone.

The role of pattern recognition receptors in stellate cells is also being uncovered. Activated human stellate cells express TLR4 and the other two molecules (CD14 and MD2) which together form the LPS receptor complex (472). Low concentrations of LPS induce activation of NFκB and JNK in activated human stellate cells, leading to expression of chemokines and adhesion molecules. Mouse stellate cells express TLR4 and TLR2 and respond to a range of pathogen-associated molecular patterns (PAMPs) including LPS, lipoteichoic acid, and *N*-acetyl muramyl peptide with secretion of interleukin (IL)-6, TGF-β, and MCP-1 (76,471). These in vitro results suggest that bacterial wall products produce an inflammatory phenotype in stellate cells, but notably do not induce matrix deposition, since fibronectin and collagen transcripts were not increased. Signaling to stellate cells via TLR4 may function to enhance an adaptive immune response against bacterial pathogens. It is also possible that ligation of TLR4 is just the initial step of a series of signals that are required for differentiation of stellate cells into a fully fibrogenic phenotype. This may occur by recruitment of Th2-type Kupffer cells or other immune cells, which provide additional signals such as IL-13. In addition, TLR4 signaling leads to downregulation of a TGF-β pseudoreceptor, BAMBI (584), which thereby amplifies fibrogenic activity of stellate cells.

Although TLRs and members of the caterpillar family were identified as recognizing molecular patterns in pathogens, there is no theoretical constraint limiting recognition of "self" molecular patterns that are usually hidden inside cells. In fact, there is increasing evidence that self molecules may activate some of these receptors. The best evidence is presentation of apoptotic mammalian DNA, which is relatively CpG rich and can activate TLR9 (669). This pathway is important in auto-activation of B cells and may have a role in the activation of stellate cells by apoptotic cells (83). A further example is the activation of immune cells by uric acid, which is dependent on the presence of NALP3 and the adaptor molecule ASC (399). It will be important

to identify the molecules from apoptotic bodies that provoke stellate cells, as none have been identified; pattern recognition receptors may play an important role in this process. Of equal importance, the identification of apoptotic fragments from damaged hepatocytes as fibrogenic stimuli is an important conceptual advance, which has led to new approaches to hepatoprotective therapies using caspase inhibitors in patients with chronic liver disease (663).

The interactions between the immune system and stellate cells are not unidirectional; instead, there is significant evidence that stellate cells also modulate the hepatic immune response. This is best demonstrated by their expression of the costimulatory molecule B7-H1 (PDL-1 or programmed death ligand-1) on activated but not resting stellate cells (725). B7-H1 binds to PD1, which is an immunoglobulin superfamily member related to CD28 and CTLA-4, but which lacks the membrane proximal cystine that allows these molecules to homodimerize (206). PD1 is expressed on a range of immune cells including CD4$^+$ T cells, and at very low levels PD1 activation is sufficient to inhibit the earliest stages of T-cell activation. PD1 also inhibits expression of the cell survival gene bcl-xl and limits activation of Akt. The final effect of PD1 may be very context dependent, and influenced by the stage of T-cell differentiation and the degree of stimulation via the T-cell receptor. Stellate cells induced apoptosis of T cells activated in an alloassay, but did not inhibit proliferation or cytokine production. This suggests that activated stellate cells have a mechanism for inhibiting T cell-mediated cytotoxicity and conversely can induce T-cell apoptosis. An immunotolerizing role is also suggested by experimental models in mice in which transplanted stellate cells protect islet allografts from rejection (102), as well as enhancing engraftment of transplanted hepatocytes (49).

D. Secretion of Lipoproteins, Growth Factors, and Cytokines

1. Apolipoproteins and lipids—Stellate cells secrete apolipoprotein E (162,512), a feature characteristic of smooth muscle cells (375). In one study they also expressed apo A-I and apo A-IV (512), whereas in another, the mRNAs for apo A-I and A-IV were not detected by PCR (162). The functional importance of apolipoprotein production in stellate cells is not clearly defined.

Another family of lipids, prostaglandins, is also secreted by stellate cells. Prostaglandins play important roles in hepatic metabolism and inflammation, as well as neural-mediated vasoregulation. In early primary culture, rat stellate cells rapidly release prostaglandin (PG) $F_{2\alpha}$ and D_2 when incubated with the neurotransmitter norepinephrine or ATP (25). This finding has special in vivo relevance because of the close proximity of stellate cells to nerve endings in normal liver (see sect. ᴜ). Highly activated rat stellate cells also produce PGI_2 and PGE_2 in response to ethanol, which appears to be dependent on production of acetaldehyde (159). The production of leukotriene C_4 and B_4 has also been reported (48). To date, the roles of prostaglandins in stellate cell activity are not fully clarified.

2. Production of growth factors and cytokines—Stellate cells are an important source of cytokines in the liver (see Table 1). Signal transduction through binding of these cytokines to their membrane receptors comprises the main pattern of cell-cell interactions in both normal and injured liver. A consistent theme throughout studies of stellate cell signaling is the importance of autocrine signaling. For virtually all growth factors, stellate cells not only secrete cytokines but also respond to them, emphasizing the importance of tightly regulated local control of cytokine action within the pericellular milieu.

Stellate cells secrete TGF-α and epidermal growth factor (EGF), two potent epithelial growth factors that play important roles in hepatocyte proliferation during liver regeneration (29, 416,427). TGF-α and EGF also stimulate mitosis in stellate cells (416,699), creating an autocrine loop for cellular activation. HGF is a more potent hepatocyte mitogen produced by

stellate cells (368,568). Production of HGF by stellate cells diminishes during acute liver injury (368). Stem cell factor (SCF) has also been identified in stellate cells in rats undergoing liver regeneration induced by partial hepatectomy combined with 2-acetoaminofluorene (177). In addition, insulin-like growth factor (IGF) I and II are secreted by stellate cells (487,737).

Platelet-derived growth factor (PDGF), a dimer of two subunits referred to as A- and B-chain, is the most potent stellate cell mitogen described thus far (488,491–493). PDGF A-chain mRNA has been detected in activated human stellate cells (387). During liver injury, stellate cells display increased PDGF production as well as the upregulation of PDGF receptors (496,702). An interesting model emphasizing the activity of PDGF in liver is one in which a mouse with transgenic expression of PDGF-C not only stimulates fibrosis, but also leads to the development of hepatocellular carcinoma (HCC) (113). This is one of only very few models resembling human liver disease in which fibrosis precedes cancer, similar to most cases of HCC, which arise in cirrhotic livers.

Acidic fibroblast growth factor (aFGF) is another mitogenic cytokine that has been identified in stellate cells in situ in late hepatic development and during hepatic regeneration (397). Stellate cells also display an autocrine loop for basic FGF (bFGF), which is mitogenic towards culture-activated rodent and human stellate cells (397,493,547,548,699).

Stellate cells produce macrophage colony-stimulating factor (M-CSF) (488) and MCP-1 (112,395), which regulate macrophage accumulation and growth (see sect. vC). MCP-1 production is stimulated by thrombin, IL-1α, interferon-γ, and tissue necrosis factor (TNF)-α (391,395). It is blocked by H-7, an inhibitor of protein kinase C (PKC) (395), suggesting the involvement of PKC in the signaling pathway leading to MCP production. M-CSF synthesis is stimulated by PDGF and bFGF (488). The secretion by stellate cells of these macrophage growth factors may play a role in amplifying the inflammatory and fibrogenic response during liver injury.

The neutrophil inflammatory response in injured liver is also amplified by stellate cells through the production of platelet activating factor (PAF). PAF promotes chemotaxis of neutrophils and stimulates their activation (489). Its production is increased by thrombin, LPS, and calcium ionophores (489). PAF and its receptors are induced on stellate cells during experimental fibrosis (712).

Generation of an increasing number of chemokines has been ascribed to stellate cells. These include cytokine-induced neutrophil chemoattractant (CINC), a rat form of human IL-8 (372), RANTES (580), C-X-C chemokine ligand 1 (81), and macrophage inflammatory protein-2 (81,612) among others (385) (see Fig. 5). Upregulation of at least one chemokine, eotaxin, may portend a more aggressive course of hepatitis and fibrosis in patients with chronic HCV (627).

Stellate cells may participate in amplifying the acute phase response by secreting IL-6 (208, 646). LPS, IL-1β, and TNF-α are potent stimuli of IL-6 production (646). On the other hand, IL-10 is an anti-inflammatory cytokine produced by stellate cells.

Upregulation of IL-10 occurs in early stellate cell activation (645,685) and has prominent antifibrogenic activity by downregulating collagen I expression while upregulating interstitial collagenase. IL-10 knockout mice develop severe hepatic fibrosis following CCl_4 administration (364,365,644).

Stellate cells also express several adhesion molecules, including ICAM-1 (237), VCAM-1 (318), and neural cell adhesion molecule (NCAM) (317,435,436). The expression of ICAM-1 is increased following stellate cell activation and may play a role in lymphocyte adherence to

activated stellate cells (237). In situ studies have demonstrated an upregulation of both ICAM-1 and VCAM-1 following CCl$_4$-induced liver injury(318). The peaks of the immunoreactivity of these two molecules coincided with maximal cell infiltration; moreover, the inflammatory cytokine TNF-α increases the transcripts of both CAMs (318). It is likely that ICAM and VCAM are involved in modulating the recruitment of inflammatory cells during liver injury. Stellate cells expressing NCAM have been found in close proximity to nerve endings in the liver (317). The function of this adhesion molecule in stellate cells is not known.

TGF-β is one of the most important cytokines expressed following liver injury. Stellate cells secrete latent TGF-β1 in response to injury, which, after its activation, exerts potent fibrogenic effects in both autocrine and paracrine patterns, with autocrine being most important (58, 209,213,359,504). TGF-β1 is increased in experimental and human hepatic fibrosis (97,213). Upregulation of TGF-β1 in activated stellate cells occurs through multiple mechanisms. Factors including Sp1 (272) and KLF6 (306) transactivate the TGF-β1 promoter, which has multiple GC boxes, the promoter element responsive to these transcription factors. There are also multiple mechanisms mediating the activation of latent TGF-β1, including cell surface activation following binding to cell-surface mannose-6-phosphate/IGF-II receptor (117) or binding to a number of proteins secreted by stellate cells (209), such as α_2-macroglobulin (9), decorin, and biglycan (417). Recent studies suggest the important role of local plasminogen activator (PA)/plasmin in activating latent TGF-β1(255,460,461). This mechanism is regulated by metabolites of RA. The signaling of TGF-β1 in rat stellate cells involves the activation of Ras, Raf-1, MEK, and mitogen-activated protein (MAP) kinase (522). The roles of Smads have been extensively explored in recent years in stellate cells (71,239,256,257,[282],[325],[349],[357],[359], [362],[458],[467],[595],[596],656,698,732,734) (see sect. vE).

Activated stellate cells also produce activin, a structurally related member of the TGF-β family (482). A natural inhibitor of activin is follistatin, whose expression decreases during stellate cell activation, leading to more unopposed activin activity (482).

Connective tissue growth factor (CTGF) (also known as CCN2) is a growth factor modulator protein that promotes fibrogenesis in skin, lung, and kidney (73,134,185,217,[248],267,470, 507,599). CTGF is strongly expressed during hepatic fibrosis, and stellate cells appear to be one source of this cytokine in the liver (475,477); however, hepatocytes may be even more important (214). While earlier studies had suggested CTGF is regulated by TGF-β in stellate cells, a more recent report indicates that its expression in stellate cells is TGF-β and Smad 2/3 independent, in contrast to hepatocytes where CTGF regulation is TGF-β dependent (214). These findings are particularly interesting in emphasizing that the regulation of the same cytokine may be completely divergent between two resident liver cell populations, pointing to the potential of cell- and pathway-specific inhibition of a factor that is widely expressed (214).

Endothelin-1 (ET-1) was originally identified as a potent vasoconstrictor produced mainly by endothelial cells (711). Stellate cells are a major source as well as a target of this cytokine during liver injury (286,289,376,377,495,535,539,545). ET-1 has a prominent contractile effect on stellate cells and myofibroblasts, which may contribute to portal hypertension in the cirrhotic liver (309,393,534). In addition, ET-1 promotes the proliferation of early-cultured stellate cells, whereas it inhibits fully activated ones (i.e., cultured for more than 1 wk) (544). These responses are mediated through ET-1 receptors (see sect. vE). Interestingly, stellate cells also produce nitric oxide (NO), a physiological antagonist to ET-1 (540). NO production is attributable to the activity of the inducible form of NO synthase in stellate cells (540) and is highly responsive to proinflammatory cytokines or endotoxemia (36,238,483,641,643). NO may play a role in the maintenance of microcirculation during liver injury.

Stellate cells also secrete cystatin C (212), a serum protein filtered by the kidney and used as a sensitive marker of glomerular filtration rate (621). Interestingly, the blood levels of cystatin C predict risk of death from a myocardial infarction or cardiovascular deaths, for unclear reasons (600).

E. Biology of Membrane and Nuclear Receptors

1. Biology of membrane receptors—Cytokines regulate stellate cell biology by specific and high-affinity binding to their membrane receptors. So far, several cytokine receptors have been identified in either quiescent or activated stellate cells (see Table 1). In addition, other receptors such as integrin, whose ligands are not cytokines, are also important in regulating stellate cell behavior. The generation of a monoclonal antibody to membrane proteins or synthetic carriers that mimic the receptor-binding domains of key cytokines may facilitate the development of stellate cell-specific targeting in vivo for diagnostic and therapeutic applications (45,139).

PDGF receptor was the first membrane receptor identified in stellate cells. It is composed of α- or β-subunits as either homodimers or heterodimers. In rat stellate cells, the β-subunit is the predominant isoform (233,486,493,496), whereas in human stellate cells, both α- and β-subunits are detectable (699). Activated PDGF receptor recruits the signaling molecule Ras, followed by activation of ERK/MAP kinase pathway (91,163). In addition, phosphoinositol 3-kinase (PI 3-kinase) and STAT-1 also contribute to PDGF signaling in stellate cells (291, 390). There is also evidence that PDGF signaling requires NADPH oxidase (2). The presence of PDGF receptors has been exploited by developing targeting reagents intended to direct therapies directly to stellate cells (3,46).

TGF-β receptors have been extensively characterized in stellate cells (71,213,259,693). All three forms of TGF-β receptors, types I, II, and III (betaglycan), are expressed. TGF-β1 binding and responsiveness are greatly enhanced during activation in vivo and in vitro (176) and induced by corticosteroids (697). A complex signaling pathway downstream of TGF-β receptors has been uncovered in stellate cells involving classical TGF-β intracellular effectors, the Smad proteins, in particular Smads 1, 2, and 3 (71,259,693,698) and the inhibitor of differentiation (Id) protein (698). Interestingly, Smad signaling evolves with stellate cell activation (128,130,357) and plays different roles during progressive cellular activation (656). Recent findings suggest that altered Smad signaling may underlie the stellate cell's response to matrix stiffness (694). An endogenous antagonist to Smad-2/3-mediated stellate cell activation is Smad7 (129,324). Antagonism of TGF-β signaling is an important and promising approach to antifibrotic therapy, either through administration of *N*-acetyl cysteine (325), Smad7 (129), soluble TGF-β receptors (197,657), interferon-γ (695), bone morphogenic protein-7 (729), or a variety of other means (359).

CTGF receptors expressed by stellate cells include $av\beta_3$-integrin (185) and the low-density lipoprotein receptor-related protein (LRP), which is a heparin-dependent adhesion receptor (CTGF) (186). The effects of ET-1 are mediated through two G protein-coupled receptors. Receptor types A and B have been identified in both quiescent and activated stellate cells (245,289,535,537). The relative prevalence of ET_A and ET_B receptors changes with stellate cell activation (495). The ET_B receptor is the predominant mediator of stellate cell contraction (535) and can be antagonized by a Rho-ROCK inhibitor (290). In addition, the proliferative effect of ET-1 in quiescent stellate cells is mediated through the ET_A receptor (495), whereas its growth inhibitory effect in activated stellate cells is mediated through the ET_B receptor (377).

In view of their contractile activity and potential role in vasoregulation, it is not surprising that stellate cells express a large number of other receptors, cytoskeletal proteins, and intracellular

mediators that either enhance or antagonize cellular contraction (see Ref. 534 for review). Mediators of contraction include ROCK (290), Rho GTP binding proteins (285,715), a sodium-calcium exchanger that is induced during cellular activation (432), and eicosanoids (287). Relaxants include NO (342), C-type and atrial natriuretic peptides (205,637), which regulate calcium signaling following interaction with its receptor, as well as carbon monoxide generated by stellate cell-derived heme oxygenase (350,623).

Induction of receptors for VEGF has been identified during stellate cell activation both in vivo and in culture (10,12,109,400). VEGF receptor upregulation is associated with enhanced mitogenesis in response to VEGF, which is further synergized by bFGF. Because VEGF plays a critical role in angiogenesis, this finding suggests that stellate cells may be involved in typical "angiogenic" responses, broadening their potential roles in both wound healing and tumor formation (343).

Stellate cells also express the receptor for thrombin, a serine protease derived from prothrombin (388), which may stimulate migration of active cells (202). The binding of thrombin to its receptor leads to cellular proliferation and increased production of MCP-1. In addition, other proteinase receptors are expressed on stellate cells, indicating the presence of complex regulation of their multiple functions (38,78,154–156,180,494).

In addition to receptors for cytokines, other membrane receptors have also been characterized in stellate cells. Integrins are a special type of membrane receptor that transduce signals from extracellular matrix to cells (232,418). They are heterodimeric transmembrane proteins composed of α- and β-subunits whose ligands are matrix molecules rather than cytokines. Several integrins, disintegrins, related molecules, and their downstream effectors have been identified in stellate cells, including $\alpha1\beta1$, $\alpha2\beta1$, $\alpha6\beta4$, $\alpha8\beta1$, $\alpha v\beta1$, and $\alpha v\beta3$, and integrin-linked kinase (92,140,178,185,[220],[269],[302],[339],[347],[392],[408],[447],[494],[508],[509],[593],694,735,736,738). In particular, integrin ligands contain an arginine (Arg)-glycine (Gly)-aspartate (Asp) tripeptide sequence. The common presence of Arg-Gly-Asp (RGD) within many integrin ligands has raised the possibility of using competitive RGD antagonists to block integrin-mediated pathways in fibrogenesis (268). Another matrix binding molecule, CD44, the hyaluronic acid receptor, has been identified on activated stellate cells (301), which promotes cellular migration.

An unusual family of tyrosine kinase receptors called "discoidin domain receptors" (DDR) has been uncovered, whose ligands are fibrillar collagens rather than growth factors (334). The intriguing identification of DDR mRNA in activated stellate cells (251,382,456,463,704) raises the possibility that this receptor may mediate interactions between stellate cells and the surrounding interstitial matrix, particularly as it accumulates in progressive liver injury.

Stellate cells express cannabinoid receptors, molecules that evolved as a component of an endogenous cannabinoid signaling pathway (123,274,332,727). Endogenous cannabinoids can provoke stellate cell death via necrosis involving mitochondrial reactive oxygen species (603–605). Initial studies of the role of cannabinoids in hepatic fibrosis had yielded apparently paradoxical findings, which have largely been reconciled now that the divergent effects on liver fibrosis of the two cannabinoid G protein-coupled receptors (CB1 and CB2) have been clarified. Studies in human stellate cells demonstrate that activation of CB2 is anti-fibrogenic (279), and stimulation of cultured stellate cells with an endogenous cannabinoid, anandamide, provokes stellate cell death, albeit through a CB2 ligand-independent pathway (605). In experimental models of liver injury, CB1 receptor is induced primarily in hepatic stellate cells as they activate into myofibroblasts during liver injury (279,638). Antagonism of this receptor in an acute model of injury due to CCl_4 or in isolated cells led to decreased expression of TGF-β, the most potent fibrogenic cytokine; this reduces cellular proliferation and increases

myofibroblast apoptosis, both of which would effectively reduce fibrosis. In addition, stellate cells from CB1 receptor −/− mice display reduced phosphorylation of ERK and Akt, which explains the cells' decreased cellular growth and survival, respectively (638).

Studies of weight regulation and appetite have uncovered complex signaling pathways both in the brain and in the periphery, especially the liver. In particular, adipokines, or hormones produced by adipose (among other sources), are emerging as major mediators of hepatic metabolism, injury, and fibrosis (106,127,386). Stellate cells express leptin (501) and its receptors (253,254,468,565), which mediate a range of biologic activities, including fibrogenesis (88,105,566), in part by enhancing TGF-β (636), cell survival (505), inflammation (5,252) and by repressing metalloproteinase expression (88). Leptin's natural counterregulator, adiponectin, is also expressed by stellate cells (701) and is antifibrotic (106,127,282,386).

Hepatic stellate cells express P2Y receptors, which link extracellular ATP to inositol trisphosphate-mediated cytosolic calcium signaling (132,328). Stellate cells only express the type I inositol trisphosphate receptor, which shifts into the nucleus upon cellular activation (328), suggesting a novel pathway for regulation of fibrogenesis. Other nucleotide receptors have also been identified on stellate cells (634).

Adenosine receptors are expressed by stellate cells, and they provide at least two signals, the stimulation of fibrosis and the provision of a "stop signal" as stellate cells reach sites of injury following migration (228). Antagonism of adenosine signaling by caffeine through its phosphodiesterase antagonism could explain the protective effect of coffee drinking on liver injury and the development of hepatic fibrosis in large epidemiologic surveys (99,315,556, 557).

Activity of the hedgehog (Hh) signal pathway has been identified in stellate cells (602). The presence of this pathway is quite interesting, since it was initially described in the development of *Drosophila* as a segment polarity gene required for embryonic patterning and is often reactivated in tumors (345,630). Hh signaling contributes to stellate cell activation (602), but an even more exciting issue is whether this pathway also contributes to the potential pleuripotency of stellate cells, as suggested by their expression of CD133 (326) (see sect. vA).

Chemokine receptors are a family G protein-coupled receptor mediating a range of cellular activities including leukocyte chemotaxis, angiogenesis, myofibroblast proliferation and migration, neoplasia, and the response to viral antigens (101,296,385). They are particularly attractive therapeutic targets because their structure makes them inherently "targetable" (196). Chemokine receptors identified thus far on stellate cells include CCCR5, whose ligand, RANTES, is induced by NFκB signaling, and stimulates stellate cell migration and proliferation (580) (see Fig. 5). The cells also express CXCR3, which can activate Ras, Akt, and PI 3-kinase, also leading to migration and proliferation (67). As with virtually all cytokine pathways in stellate cells, components of autocrine signaling are present, although in the case of MCP-1, its conventional receptor, CCR2, does not mediate MCP-1's effects, suggesting the presence of an as-yet-unidentified receptor (394).

As noted in section v, stellate cells are assuming an increasingly central role in inflammatory signaling. In addition to chemokine receptors, they express CD40 (581), which provides an important functional bridge to immune cells, which express CD40 ligand. CD40L engagement by stellate cells stimulates production of MCP-1 and IL-8, which are both proinflammatory signals.

Angiotensin receptors have assumed vital importance in stellate cell biology based both on their key role in cellular activation and on mounting evidence that their antagonism represents a very promising antifibrotic strategy (37). Activated human and rodent stellate cells express

all components of the renin-angiotensin system including angiotensin II and its cognate receptor (38,688,690). Moreover, infusion of angiotensin II induces stellate cell activation and inflammation in rats (36). The effects of angiotensin are mediated through NADPH oxidase, a multiprotein complex that generates reactive oxygen species (39,120). Within this complex, only rac1 has been identified as a functionally active component (120), as underscored by a transgenic mouse model in which over-expression of rac1 in stellate cells amplified injury and fibrosis (104). Most importantly, antagonism of angiotensin signaling, either by angiotensin converting enzyme inhibitors, or by receptor antagonists, is antifibrotic in animal models (278,515,689), and in a retrospective human study of patients following liver transplantation (527). As a result of this promising animal and retrospective human data, a controlled prospective trial of angiotensin II type I receptor antagonist, irbesartan, is underway in France (http://clinicaltrials.gov/ct/show/NCT00265642?order=2).

Although not a cytokine, ferritin, an iron binding protein, also binds specifically to high-affinity cellular receptors on stellate cells (516). Activation-dependent binding of ferritin is followed by internalization and is dependent on the H subunit (516). While these findings are intriguing, it is uncertain whether ferritin binding is functionally related to stellate cell activation.

A number of other membrane receptor systems have been identified on stellate cells, including those for hydroxytamine (351), somatostatin (611), catecholamines (455,560), endogenous opioids (137), serotonin (554), and oxidized LDL (CD36) (576). Stellate cells also express receptors for advanced glycation end products (RAGE) (150), a member of the immunoglobulin superfamily. Consistent with their neural phenotype, stellate cells express neurotrophin receptors (95). Interestingly, serotonin receptors, in particular SSR2, SSR3, and SSR5 (611), are induced during stellate cell activation (473,554). These receptors downregulate cellular activation (337,524), suggesting that octreotide and other somatostatin analogs merit exploration as antifibrotic agents.

2. Biology of nuclear receptors—A dramatic increase in knowledge about intracellular nuclear receptors has greatly benefited our understanding of stellate cell biology. These receptors are members of the nuclear hormone receptor superfamily (659). In the presence of their cognate ligands, they translocate to the nucleus and act as transcription factors. Not only has information emerged about retinoid receptors in stellate cells, but also about the entire nuclear receptor family, in particular peroxisome proliferators activated receptors (PPARs), as well as the farnesoid X receptor (FXR).

Retinoid receptors have been extensively explored in stellate cells given their important role in retinoid metabolism. However, no clear, coherent model for retinoid receptors in this cell type has emerged, and some of the data are contradictory. Stellate cells express retinoic acid receptors (RAR) α, β, and γ (175,692) as well as retinoid X receptors (RXR) α and β, but not γ (659).

In culture, RXR-α is the dominant receptor (659), but stellate cells express all six major isoforms (RAR-α, -β, -γ and RXR-α, -β, -γ)(671) and modulate a number of target genes, including cellular retinol binding protein (CRBP) (671) and collagen I (684). Natural and synthetic retinoids elicit a range of activities (236): synthetic RXR agonists and 9-*cis*-RA downregulate stellate cell proliferation and synthesis of collagen I and fibronectin. In contrast, all-*trans*-RA and RAR agonists both reduce collagen I, collagen III, and fibronectin but have no effect on stellate cell proliferation. Finally, RAR-specific antagonists provoke stellate cell mitogenesis. In cultured stellate cells, an increase in 9,13-di-*cis*-RA transactivates RAR-α and stimulates plasminogen activation and TGF-β-dependent procollagen synthesis (461). These findings are paralleled in vivo in an experimental model of porcine serum-induced fibrosis, in which 9,13-di-*cis*-RA increases despite a decrease in total retinoid content (461), suggesting

that this relatively minor RAR-*α* ligand may have a pivotal role in retinoid-mediated fibrogenesis.

In contrast to a lack of clarity about retinoid receptors in stellate cells, exciting advances have been made in understanding PPARs, a family of transcription factors also belonging to the nuclear receptor superfamily (145). For example, PPAR-*γ* is predominantly expressed in adipose tissue where it regulates lipid metabolism and adipocyte differentiation. Yet, PPAR-*γ* is also expressed in human stellate cells, and its activity is reduced during activation in culture (183). PPAR-*γ* functions as a heterodimer with RXR, the 9-*cis*-RA receptor (183). The PPAR-*γ* ligands 15-deoxy-prostaglandin J_2 (15d-PGJ$_2$) and ciglitizone decrease PDGF-induced proliferation of activated stellate cells and inhibit *α*-SMA expression during stellate cell activation (389). This suggests that reduced transcriptional activity of PPAR-*γ* augments stellate cell activation and modulates mitogen-induced proliferation in activated cells. Furthermore, prostaglandins produced by stellate cells through the upregulation of COX-2 expression may exert autocrine effects through PPAR-*γ*, which are blocked by COX-2 antagonism (497).

Increasing evidence that PPAR-*γ* ligands are antifibrotic towards cultured stellate cells (422, 732) and in animals (184,292,648) has led to promising clinical trial results for the treatment of fatty liver and fibrosis associated with the metabolic syndrome (44,441,503). Ongoing trials are further exploring the efficacy of PPAR-*γ* ligands not only in NASH, but also in other types of chronic liver disease, including HCV. At least one mechanism of PPAR-*γ*'s antifibrotic activity involves suppression of the proximal alpha1(I) collagen promoter via inhibition of p300-facilitated binding of the transcription factor NF-1 (714).

Other PPARs, although less extensively studied than PPAR-*γ*, are also active in stellate cells (146). In particular, PPAR-*β* stimulates stellate cell proliferation (235). While increasing attention is directed to PPAR-*δ* in general (341), no reports have described its expression yet in stellate cells.

Pregnane-X-receptor has been identified in stellate cells and PXR ligands inhibition cellular activation in culture (229). In vivo, pregnenolone-16*α*-carbonitrile, a PXR ligand, inhibits fibrogenesis through both PXR-dependent and -independent pathways (384).

Stellate cells also express the vitamin D receptor (190), suggesting a potential role of these cells in vitamin D homeostasis and responsiveness. In support of this prospect, 1,25-dihydroxyvitamin D_3 is mitogenic in cultured stellate cells (356).

Estrogens, in particular, 17*β*-estradiol (358) and estradiol (598,703,713), are antifibrotic in liver, which may contribute to the decreased risk of fibrosis progression in females compared with males (57,124,686). Indeed, in cultured stellate cells, estradiol inhibits activation through an antioxidant effect, whereas this activity is antagonized by progesterone (265); estradiol's effect may be mediated by estrogen receptor (ER)-*β*, since stellate cells express ER-*β* but not ER-*α* (598).

Glucocorticoid receptor is also expressed by stellate cells (511), but its contribution to stellate cell behavior has not been explored.

The FXR is a major regulator of bile flow by stimulating expression of several key genes involved in cellular bile acid export (107,531), and its therapeutic activation may become a major advance in the management of cholestasis (616). Surprisingly, however, FXR is also expressed by stellate cells, where it has an antifibrotic activity through upregulation of its target molecule SHP (155,156). FXR ligands suitable for human administration have been developed,

and clinical trials for cholestatic liver diseases are anticipated, with antifibrotic trials likely to follow.

Liver X receptor, a nuclear receptor that is a nutritional sensor of cholesterol metabolism and major regulator of lipid metabolism, lipid metabolism, glucose homeostasis, and inflammation (42), has also been identified in stellate cells (655), further implicating this cell type as a participant in lipid homeostasis.

F. Adipogenic Features

The extensive characterization of signaling pathways for leptin, adiponectin, and PPAR-γ in stellate cells has highlighted remarkable parallels between this cell type and adipocytes. This relationship has been emphasized in studies by Tsukamoto and co-workers (594,653,655), underscoring that the transcriptional program required for adipocyte differentiation is nearly identical to that required for maintaining stellate cells in their quiescent, vitamin A-storing phenotype. In particular, forced expression of either PPAR-γ or sterol regulatory element binding protein 1c (SREBP-1c), two key regulators of adipogenesis, or incubation of stellate cells with an "adipogenic" mix of soluble factors, drive the cells towards a quiescent phenotype (594,653). In contrast, two anti-adipogenic signals, TNF-α and Wnt, promote activation (655). Stellate cells also express a number of other adipogenic transcription factors, including CCAAT/enhancer-binding protein (C/EBP)α, C/EBPβ, C/EBPδ, PPAR-γ, liver X receptor-α, SREBP-1c, and adipocyte-specific genes (594), as well as adipokines including leptin and adiponectin (127,386).

G. Detoxifying and Antioxidant Enzymes, pH Regulation, and Generation of Oxidant Stress

Several enzymes involved in both intermediary metabolism and detoxification of ethanol and xenobiotics have been identified in stellate cells. Stellate cells contain alcohol (93) and acetaldehyde (710) dehydrogenase, although it is unlikely that the cell type plays a significant role in ethanol detoxification based on its relatively low numbers compared with hepatocytes. However, the cells may be responsive not only to lipid peroxides and hydrogen peroxide generated during ethanol metabolism (98,207,443,445,446), but also to acetaldehyde adducts, which stimulate the secretion of chemokines (299).

Stellate cells express several *P*-450 enzymes, specifically CYP2C11, 3A2, 2D1, Cyp2S1 (383), and CYP3A (480). Interestingly, activity of these enzymes decreases during culture-induced activation (707), possibly rendering stellate cells more sensitive to either xenobiotics or oxidant stress.

The α-, μ-, and π-isoforms of glutathione *S*-transferase have been identified in stellate cells, both by enzymatic assay as well as Northern and Western blots (344); these enzymes are important for detoxification of xenobiotics and the response to oxidant stress, a finding with implications for both normal liver function as well as the response to injury (122). Activated stellate cells also express stellate cell activation associated protein (STAP), an endogenous peroxidase catabolizing hydrogen peroxide and lipid hydroperoxides (288). Stellate cells contain glutathione synthase (373), as well as the mRNA for the glutathione peroxidase I, the selenium-dependent isoform (335), which is induced during stellate cell activation in vivo. Glutathione levels may in fact discriminate between oxidative stress and activation due to TGF-β1 (119). On the other hand, manipulation of glutathione stores in stellate cells has no effect on cellular activation (373). Interestingly, whereas culture-induced stellate cell activation leads to accumulation of glutathione, activation in vivo does not (374), highlighting one of the rare examples where culture-induced activation pathways are divergent from those associated with stellate cell activation in vivo. Finally, addition of *N*-acetyl-L-cysteine (NAC) to stellate cells,

which restores cellular glutathione levels, leads to stellate cell cycle arrest and induction of p21 (302).

Stellate cells also have tightly regulated systems for monitoring cellular pH (125), which are closely linked to cellular activation. Specifically, the Na^+/H^+ exchanger is the main intracellular (pH_i) regulator in rat stellate cells, and stellate cell activation is associated with an increase in pH_i and in PDGF-stimulated activity of the Na^+/H^+ exchanger (125,626). Inhibition of this transporter by amiloride (125) has led to studies in animal models demonstrating an antifibrotic effect of antagonizing this transporter (47).

There is mounting evidence for a key role of NADPH oxidase (NOX) in mediating several pathways critical to stellate cell activation, including responses to angiotensinogen II and PDGF, apoptosis of cellular debris, and generation of oxidant stress (120). Specifically, stellate cells express key components ($p22^{phox}$, $gp91^{phox}$, $p47^{phox}$, and $p67^{phox}$) of a nonphagocytic form of NADPH oxidase that produces superoxide (2). This enzyme is induced during stellate cell activation and generates superoxide upon engagement of ANG II with its receptors (39). ANG II signaling leads to phosphorylation of the p47 subunit of NOX, increased superoxide production, and stellate cell activation, responses which are blunted in p47 −/− mice (39). These animals have reduced fibrosis after liver injury due to bile duct ligation, attesting to the biological relevance of this pathway. Interestingly, phagocytic activity of stellate cells towards apoptotic bodies is also linked to NOX induction, with increased oxidative stress; this response is inhibited by the NOX inhibitor diphenylene iodonium (DPI) (730). Finally, NOX also mediates downstream effects of PDGF receptor signaling, and DPI blocks proliferative effects of PDGF (2).

H. Transcriptome and Proteome Analyses

The development of array technologies to characterize patterns of gene (i.e., mRNA) expression from the entire transcriptome has provided a valuable tool for uncovering new information about cellular and molecular biology of liver (23). In general, microarrays can be used clinically to define features of disease, forecast prognosis, and predict response to therapies. While in the clinical setting arrays have been primarily applied to the management of cancer, the technology is proving equally valuable in defining cellular and tissue responses in nonmalignant diseases, including fibrosis and tissue repair. In particular, cDNA microarrays have been used to interrogate stellate cells in the hope of uncovering new insights into the cell's complex biology. This approach offers several benefits for the study of stellate cells: *1*) to uncover novel genes not previously ascribed to these cells; *2*) to define pathways or clusters of gene expression that underlie phenotypic transitions of stellate cells, in particular stellate cell activation associated with hepatic fibrogenesis; *3*) to validate stellate cell culture models by demonstrating similar patterns of gene expression as cells in vivo; and *4*) to reveal potential targets of antifibrotic therapies.

By applying these criteria, the mountain of information typically provided by a microarray experiment can be placed in some rational context (573). While the technology continues to evolve, current methods utilize platforms (i.e., silicon chips) that contain the entire transcriptome, although they do not routinely distinguish alternative mRNA splice forms of genes (111), which is an increasingly important mechanism of genetic diversity (187,614). For each potentially new transcript, it is also essential to validate the reported expression or change using a more direct method, typically quantitative realtime PCR or related methods including Northern or Western hybridization. With continued standardization of microarray methods and publication requirements that obligate investigators to make their raw data available publicly (131,136,247), array results can be used by all investigators to either validate findings or define new research questions, thereby accelerating progress considerably.

Studies utilizing gene array methodologies have begun to apply each of these four benefits to stellate cell analysis, using either human or rodent cells or immortalized cell lines. For example, an unanticipated role of Wnt signaling was uncovered by a comparison of quiescent rat primary (early culture) stellate cells from normal liver, to cells activated by growth in culture for 8–14 days (273). Not only was Wnt signaling induction validated directly, but the array methodology also confirmed the induction of Wnt target genes, which were complemented by evidence of Wnt induction in vivo. Similarly, in an analysis of activated stellate cells from mouse using serial analysis of gene expression (SAGE), a technique conceptually similar to subtractive hybridization (667), a novel intracellular mediator of bone morphogenic protein, gremlin, was identified (65). Novel genes have also been uncovered in a recent cDNA microarray study of activated rat stellate cells, including the chemokines CCL6, CXCL14; proteases MMP-10 and MMP-23; neural markers neutrotrimin, neurexin-1, and synaptotagmin-9; fat metabolism enzyme LRAT; cell surface receptors adenosine receptor 2a, GRP 91; and cytoskeletal proteins anillin, plexin, and C1 (121). A similar approach was employed in a study analyzing gene expression patterns in human stellate cells isolated from human fibrotic liver, compared with normal primary stellate cells (561). In another report comparing stellate cells from normal rat liver, cirrhotic liver, and normal cells activated by growth on plastic, there were distinct differences between normal cells and those activated by plastic, but fewer differences between stellate cells from normal versus cirrhotic liver (275).

Recently, gene expression patterns from stellate cells isolated from normal rat liver were compared with rats with fibrosis from either CCl_4 or bile duct ligation, or to normal cells activated by growth on plastic (121). Expression profiles in stellate cells between the two fibrotic models were remarkably similar but differed substantially from ultrapurified (i.e., using flow cytometry) culture-activated stellate cells. However, when stellate cells were isolated using standard gradient methods alone, which typically contain ~5% of other nonparenchymal cells (especially Kupffer cells), the gene expression pattern much more closely resembled activated stellate cells from fibrotic liver. This might suggest that the most widely used stellate cell isolation methods with gradient centrifugation alone are most relevant to understanding the biology of stellate cells in vivo. Studies have also been conducted to identify genes associated with activation of mouse stellate cells, revealing additional transcripts that regulate a range of cellular functions, several of which were not anticipated (360).

In a microarray study of human stellate cells after extended culture, cells became senescent and switched from a primarily fibrogenic to an inflammatory phenotype, with decreased proliferation gene expression and increased apoptosis (575). Those inflammatory genes included IL-8, cyclooxygenase 2, superoxide dismutase, and ICAM-1, among others (575). There were also cytoskeletal rearrangements and reduced expression of fibrogenic mRNAs. However, findings were not validated directly to demonstrate that the phenotypes described in culture had a counterpart in vivo.

Array methodology has also been used to define pathways and target genes affected by a specific stimulus. For example, a study in the human LX-2 stellate cell line identified genes associated with the response to hypoxia, revealing transcripts associated with kinase activation, cellular respiration, membrane transport, transcriptional regulation, and protease activities, among others (596).

Array has also been used extensively to validate that the gene expression patterns of immortalized stellate cell line resemble those of primary cells. Such studies have analyzed a human line expressing ectopic telomerase (574), as well as human stellate cells immortalized with either the SV40 T antigen or low-serum conditions (704).

In addition to analyses of isolated stellate cells, a number of studies have characterized gene array patterns from whole liver to assess evolution of mRNA expression during disease, primarily HCV. In part, these studies are performed to identify gene clusters that may reveal novel pathways of disease or predict clinical outcomes. While this approach cannot directly ascribe gene expression to stellate cells, in many cases their contribution to the pool of expressed mRNAs can be inferred, but must be validated using in situ methods or analysis of isolated cells. Nonetheless, at least six studies in humans (22,53,338,591,592,610) and one in rats (506) have explored this question, with interesting results. For example, one study of HCV-infected livers (591) identified mRNAs for the fibrosis-associated protein extracellular matrix metalloproteinase inducer (EMMPRIN) (CD147) and discoidin domain receptor-1 (CD167), which had not previously been identified in liver, prompting the need to explore these transcripts in isolated stellate cells. Another study indicated that genes involved in matrix turnover and immune response may be critically associated with the transition from mild to moderate fibrosis (22), highlighting the key role of stellate cell behavior in this transition. Similarly, an analysis of human livers with HCV uncovered an abundance of transcripts associated with inflammation and matrix turnover in early fibrosis, whereas in advanced fibrosis genes associated with cellular proliferation predominated (338). Yet another study in whole liver of patients with HCV reported a predominance of transcription factors that are regulated by interferon (53). Finally, in a study of patients who had serial liver biopsies following liver transplantation for HCV (610), discrete gene expression patterns emerged that predicted fibrosis progression, including transcripts clearly associated with activated stellate cells/myofibroblasts, for example, collagen XII, a calcium channel, and two myosin polypeptides and a myosin binding protein. This study is particularly important because gene expression patterns were compared in samples from the same patients during disease progression, beginning with a normal donor organ at the time of transplant.

Proteomics technology remains a rapidly evolving approach to probe cell and tissue function, including liver, and offers the advantages of identifying different posttranslational modifications, including phosphorylation and glycosylation, as well as uncovering new proteins or protein isoforms (23,484,613). A number of studies have used proteomics to characterize proteomic patterns in whole liver of rodents (161,705) and either human liver (415,498), or serum (231), but only one study to date has specifically characterized the proteome of quiescent and activated stellate cells. Bach Khristensen and colleagues (27) described over 300 stellate cell proteins, including a novel globin molecule, STAP or cytoglobin, which has been characterized in detail in follow-up studies (19,434). In addition, they identified 26 other proteins regulated similarly in culture and in vivo, including upregulation of calcyclin, calgizzarin, and galectin-1 as well as downregulation of liver carboxylesterase 10 and serine protease inhibitor 3 (27). These results demonstrate the promise of using proteomics to uncover information complementary to that obtained by cDNA microarray.

Among proteomics studies of whole liver reported to date, the vast majority of proteins identified are derived from hepatocytes, as their total protein content vastly exceeds proteins derived from stellate or other nonparenchymal cells. Nonetheless, some stellate cell-related proteins may emerge from this approach.

In addition to genomics and proteomics, a whole range of other "omics" technologies are being developed (333,426). The term *omics* refers to the analysis of different classes of molecules, processes, or functions and structures as systems (297). Currently, these include glycomics, kinomics, metabolonomics nutrigenomics, toxicogenomics, and ecotoxicoproteomics; it would seem inevitable that these technologies will be applied to stellate cell biology. To date, however, only glycomics has been studied in relation to hepatic fibrosis to uncover patterns of protein glycosylation in serum that correlate with the stage of disease (79).

VI. Stellate Cell Responses in Liver Injury and Repair

A. Stellate Cell Activation: Features, Regulation, and Reversibility

The clarification of stellate cell responses in hepatic injury and repair has been a significant turning point in understanding the basis of hepatic fibrosis. In particular, the identification of stellate cell activation as a key event in fibrogenesis has provided an important framework for conceptualizing the liver's response to injury. As noted in section ı, this review is not intended to focus primarily on mechanism of hepatic fibrosis, but rather on broader aspects of stellate cell behavior. The reader is referred to many recent reviews for more comprehensive updates on fibrosis pathogenesis (35,165,167,213,313,363).

Stellate cell "activation" refers to the conversion of a resting vitamin A-rich cell to one that is proliferating, fibrogenic, and contractile. While it is increasingly clear that other mesenchymal cell populations also contribute to extracellular matrix accumulation, stellate cell activation remains the most dominant pathway leading to hepatic fibrosis (see Fig. 6). Moreover, stellate cell activation represents a continuum, such that early changes in cellular phenotype may be distinct from those occurring with progressive injury and activation in terms of growth characteristics, response to soluble mediators, inflammatory signaling, and apoptotic potential (128,204,210,504,552,575). Finally, the paradigm of activation of resident mesechymal cells into fibrogenic myofibroblasts extends to many tissues beyond liver (243).

Activation consists of two major phases: initiation and perpetuation, followed by resolution of fibrosis if injury subsides (see Fig. 7).

Initiation (also called a "preinflammatory stage") refers to early changes in gene expression and phenotype that render the cells responsive to other cytokines and stimuli. Initiation results mostly from paracrine stimulation, primarily due to changes in surrounding extracellular matrix, as well as exposure to lipid peroxides and products of damaged hepatocytes.

Perpetuation results from the effects of these stimuli on maintaining the activated phenotype and generating fibrosis. Perpetuation involves autocrine as well as paracrine loops. It is comprised of several discrete responses including proliferation, contractility, fibrogenesis, matrix degradation, retinoid loss, and inflammatory cell infiltration.

Resolution of fibrosis refers to pathways that either drive the stellate cell to apoptosis, or contribute to their reversion to a more quiescent phenotype.

1. Initiation—The earliest changes observed during stellate activation result from paracrine stimulation by all neighboring cell types, including sinusoidal endothelium, Kupffer cells, hepatocytes, and platelets. As noted above, early injury to endothelial cells stimulates production of cellular fibronectin, which has an activating effect on stellate cells (270). Endothelial cells are also likely to participate in conversion of TGF-β from the latent to active, profibrogenic form. Platelets are another important source of paracrine stimuli, including PDGF, TGF-β, and EGF (28).

Kupffer cell infiltration and activation also contribute to stellate cell activation. Kupffer cells stimulate matrix synthesis, cell proliferation, and release of retinoids by stellate cells through the actions of cytokines (especially TGF-β) and reactive oxygen intermediates/lipid peroxides (55).

Hepatocytes are a potent source of fibrogenic lipid peroxides, although effects on stellate cell collagen synthesis and proliferation may be dose dependent (450). Hepatocyte apoptosis following injury also promotes stellate cell initiation through a process mediated by Fas (83,

84). This process may involve the TNF-related apoptosis-inducing ligand (TRAIL) (83,84). Whereas hepatocyte necrosis associated with lipid peroxidation is considered a classical inflammatory and fibrogenic stimulus, recent findings also implicate apoptosis, or programmed cell death, in the fibrogenic response. Apoptotic fragments released from hepatocytes are fibrogenic towards cultured stellate cells (85) and activate Kupffer cells (82) (see sect. v*C*). Also, Fas-mediated hepatocyte apoptosis is fibrogenic in vivo in experimental animals (84).

The cytochrome CYP2E1 plays an important role in the generation of reactive oxygen species that stimulate hepatic stellate cells (443). Cultured hepatic stellate cells grown in the presence of the HepG2 cell line expressing CYP2E1 (E47 cells) leads to increased production of collagen, an effect prevented in the presence of antioxidants or a CYP2E1 inhibitor (443). These data suggest that the CYP2E1-derived reactive oxygen species are responsible for the increased collagen production. In similar experiments using cocultured hepatic stellate and E47 cells, the addition of arachidonic acid plus ferric nitrilotriacetate (agents that potentiate oxidative stress) further induced collagen synthesis (444). These findings may help to explain the pathogenesis of liver injury in alcoholic liver disease since CYP2E1 is alcohol inducible.

2. Perpetuation—Perpetuation of stellate cell activation involves at least seven discrete changes in cell behavior: proliferation, chemotaxis, fibrogenesis, contractility, matrix degradation, retinoid loss, and WBC chemoattractant/cytokine release. The net effect of these changes is to increase accumulation of extracellular matrix. As an example, proliferation and chemotaxis lead to increased numbers of collagen-producing cells. Cytokine release by stellate cells can amplify the inflammatory and fibrogenic tissue responses, and matrix proteases may hasten the replacement of normal matrix with one typical of the wound "scar."

A) Proliferation: PDGF is the most potent stellate cell mitogen identified (68,486). Induction of PDGF receptors early in stellate cell activation increases responsiveness to this potent mitogen (702). Downstream pathways of PDGF signaling have been carefully characterized in stellate cells and include PI 3-kinase, among others (340,494). In addition to proliferation, PDGF stimulates Na^+/H^+ exchange, providing a potential site for therapeutic intervention by blocking ion transport (126). Other compounds with mitogenic activity in stellate cells and a potential role in fibrogenesis include vascular endothelial cell growth factor (720), thrombin and its receptor (388,391), EGF, TGF-α, keratinocyte growth factor (620), and bFGF (724). Signaling pathways for these and other mitogens have been greatly clarified in stellate cells, offering many potential sites for therapeutic intervention (see Ref. 494).

B) Chemotaxis: Stellate cells can migrate towards cytokine chemoattractants (369,385,494), explaining in part why stellate cells align within inflammatory septae in vivo. A number of chemoattractants have been identified, prominent among which are PDGF (250,310), MCP-1 (394), and CXCR3 (67). In contrast, adenosine (228) blunts chemotaxis and may immobilize cells once they reach the site of injury (see also sect. v*D*). The mechanical features of stellate cell chemotaxis have recently been explored, revealing that PDGF-stimulated chemotaxis is associated with cell spreading at the tip, movement of the cell body towards the stimulant, and retraction of trailing protrusions associated with transient myosin phosphorylation (414).

C) Fibrogenesis: Stellate cells generate fibrosis not only by increased cell numbers, but also by increasing matrix production per cell. The best-studied component of hepatic scar is collagen type I, the expression of which is regulated both transcriptionally and posttranscriptionally in hepatic stellate cells by a growing number of stimuli and pathways. A detailed review of collagen gene regulation in stellate cells is beyond the focus of this review, but several recent references are recommended (7,188,257,258,[260],[354],528,617–619,652).

The most potent stimulus for production of collagen I and other matrix constituents by stellate cells is TGF-*β*, which is derived from both paracrine and autocrine sources (see Refs. 71, 213,259 for reviews). Signals downstream of TGF-*β* include a family of bifunctional molecules known as Smads, upon which many extracellular and intracellular signals converge to fine-tune and enhance TGF-*β*'s effects during fibrogenesis (259) (see sect. vD). TGF-*β* also stimulates the production of other matrix components including cellular fibronectin and proteoglycans (198). In addition to a major role for Smad proteins, TGF-*β*1 stimulates collagen in stellate cells through a hydrogen peroxide- and C/EBP*β*-dependent mechanism (189). The response of Smads in stellate cells differs between acute and chronic injury to further favor matrix production (128,357,628).

As mentioned above, lipid peroxidation products are emerging as important stimuli to extracellular matrix production (625). Their effects may be amplified by loss of antioxidant capacity of stellate cells as they activate (see sect. vG) (696). These important insights have provided the rationale for the evaluation of antioxidants in the treatment of a variety of liver diseases.

Connective tissue growth factor (CTGF/CCN2) is also a potent fibrogenic signal towards stellate cells (185,475,476,507) and may be specifically upregulated by hyperglycemia and hyperinsulinemia (477). While stimulation of CTGF production has traditionally been considered TGF-*β* dependent (217), the possibility of TGF-*β*-independent regulation is increasingly likely (73).

D) Contractility: Contractility of stellate cells may be a major determinant of early and late increases in portal resistance during liver fibrosis. The collagenous bands typical of end-stage cirrhosis contain large numbers of activated stellate cells (534,536,537). These impede portal blood flow by constricting individual sinusoids and by contracting the cirrhotic liver. The acquisition of a contractile phenotype during stellate cell activation has been documented in culture and in vivo and is mediated in part by receptors that interact with the extracellular matrix and are driven by calcium signaling (413). As noted in section vD, endothelin-1 and nitric oxide are major counterregulators controlling stellate cell contractility, in addition to a growing list of additional mediators including angiotensinogen II, eicosanoids, atrial natriuretic peptide, somatostatin, and carbon monoxide, among others (see Refs. 525,534,536,537 for reviews). While most studies implicate calcium signaling in response to endothelin-1-induced contractility (490), a recent study contradicts that view by demonstrating calcium-independent contractile force in stellate cells (413).

As stellate cells activate, the expression of the cytoskeletal protein *α*-SMA is increased (514, 538), which confers increased contractile potential. More extensive descriptions of *α*-SMA and other contractile filaments are reviewed above and in several reports (192,448,525,546,661). While the conventional wisdom is that *α*-actin expression enhances tissue fibrosis, mice lacking this protein in myofibroblasts have increased renal fibrosis in experimental glomerulonephritis (633), suggesting that *α*-actin induction may be a counterregulatory response to enhanced fibrogenesis by myofibroblasts, including activated stellate cells.

E) Matrix Degradation: Fibrosis reflects a balance between matrix production and degradation. The degradation of extracellular matrix is a key event in hepatic fibrosis. Early disruption of the normal hepatic matrix by matrix-degrading proteases hastens its replacement by scar matrix, which has deleterious effects on cell function. Disruption of the normal liver matrix is also a requirement for tumor invasion and desmoplasia (15) and may be particularly relevant to pancreatic stellate cells (466). Degradation in these contexts is referred to as being "pathological." On the other hand, resorption of excess matrix in patients with chronic liver disease provides the opportunity to reverse hepatic dysfunction and portal hypertension.

An understanding of mechanisms involved in matrix remodeling has evolved significantly in the past several years. A critical element in matrix remodeling is a family of matrix-metalloproteinases (also known as matrixins). These are calcium-dependent enzymes that specifically degrade collagens and noncollagenous substrates (16,50,262). As a general rule, the matrix-metalloproteinases fall into five categories based upon their substrate specificity: *1*) interstitial collagenases (MMP-1, -8, -13), *2*) gelatinases (MMP-2,-9, and fibroblast activation protein), *3*) stromelysins (MMP-3, -7, -10, -11), *4*) membrane type (MMP-14, -15, -16, -17, -24, -25), and *5*) metalloelastase (MMP-12).

Stellate cells are the principal source of MMP-2 (18,420), MMP-9 (226), MMP-13 (the rodent equivalent of MMP-1) (567), and stromelysin (673). Activation of latent MMP-2 may require interaction with hepatocytes (639,640). Markedly increased expression of MMP-2 is characteristic of cirrhosis (51). MMP-9 may also be secreted by stellate cells (225,227).

A major determinant of progressive fibrosis is failure to degrade the increased interstitial or scar matrix. Matrix metalloproteinase-1 (MMP-1) is the main protease that can degrade type I collagen, the principal collagen in fibrotic liver. Sources of this enzyme are not as clearly established as for the type IV collagenases. Stellate cells express MMP-1 mRNA, but little enzyme can be detected (420).

Regulation of matrix metalloproteinase activity occurs at many levels, among which is their inactivation by binding to tissue inhibitors of metalloproteinases (TIMPs) (262). Stellate cells also produce functional TIMP-1 and TIMP-2 (17), and sustained production of these proteins during liver injury could inhibit the activity of interstitial collagenases, leading to reduced degradation of the accumulating matrix during liver injury. TIMP-1 also is anti-apoptotic towards stellate cells (429), and thus its sustained expression in liver injury will enlarge the population of activated stellate cells by preventing their clearance. In support of TIMP's role in vivo, transgenic overexpression of TIMP-1 in liver, or administration of TIMP neutralizing antibodies, both delay regression of liver fibrosis in experimental animals (721).

Stellate cells express uroplasminogen activator receptor (uPA-R) and its inhibitor (PAI-1), as well as other components of the plasmin system (152,154,255,320,348,731). These findings suggest that stellate cells contain most, if not all, of the molecules necessary to either activate or inhibit metalloproteinases.

Most recently, increased proteolytic activity ascribed to a disintegrin and metalloproteinase with thrombospondin type repeats (ADAMS)-13 has been reported in activated stellate cells (447). However, the native substrate(s) and biological role of this protease is not known.

F) Retinoid Loss (See Sect. II*A*): Activation of stellate cells is accompanied by the loss of the characteristic perinuclear retinoid (vitamin A) droplets. In culture, retinoid is stored as retinyl esters, whereas the form of retinoid released outside the cell during activation is retinol, suggesting that there is intracellular hydrolysis of esters prior to export (175). Whether retinoid loss is required for stellate cells to activate, and which retinoids might accelerate or prevent activation are not clarified.

3. Resolution—As attention has turned to the treatment of liver fibrosis, the issue of how stellate cell activation resolves has become quite critical (147,169,170,262). Two potential pathways account for reduction in activated stellate cells, either reversion to a quiescent phenotype or clearance through apoptosis. Although reversion can be accomplished in cultured stellate cells through transfer of activated cells to a basement membrane matrix (181,462), this has not been validated in vivo. To do so, genetic lineage tracing would be required to confirm

that cells once activated have resumed a quiescent phenotype; however, such studies have not yet been reported.

In contrast, a large amount of evidence supports the importance of stellate cell apoptosis during regression of liver fibrosis (262,264). In culture, stellate cells are sensitive to CD95-L and TRAIL-mediated apoptosis, and NK cells can induce apoptosis of stellate cells by a TRAIL-mediated mechanism (510) (see sect. vC). NGF derived from hepatocytes is also apoptotic towards stellate cells (454) and is antagonized by serotonin receptor signaling (554). Apoptosis requires an intact proteosomal degradation pathway, since its inhibition prevents stellate cell apoptosis (6). In a recent study (510), an antifibrotic effect of NK cells was indicated by the presence of increased fibrosis in mice depleted of NK cells by anti-asialo-GM1 antibody and by decreased fibrosis after NK cell activation by a TLR3 ligand poly I:C. The NK cell-induced stellate cell apoptosis was specific for activated stellate cells that expressed the NK cell activating receptor NKG2D. The activated NK cells deliver a lethal blow to stellate cells by inducing apoptosis with TRAIL. In this study, NK cell function was dependent on interferon-γ and provided an explanation for earlier experiments demonstrating an important antifibrotic role for interferon-γ (541). The antifibrotic role of NK cells was further supported by evidence of their direct adhesion to stellate cells in mouse livers, and by the development of greater fibrosis in mice genetically deficient in NK cells (412). Most recently, these findings have been reinforced by studies in humans with HCV (424). In addition to NK cells, activated Kupffer cells can also provoke stellate cell apoptosis by a unique caspase 9- and a receptor-interacting protein-dependent mechanism (158).

The antifibrotic role of NK cells is also consistent with the clinical data of increased liver fibrosis in the setting of therapeutic immunosuppression. The effect of single immunosuppressive agents on NK cell function is minimal, but the combination of cyclosporine and corticosteroids results in significant loss of NK cell cytotoxicity (246). In addition, cyclosporine renders some cells resistant to NK cell-mediated cytotoxicity. The effect of HIV infection on NK cell number and function is more complex. Some NK cell subsets coexpress CD4 and HIV coreceptors and are targets for infection with HIV. NK cells from HIV-infected patients have reduced cytolytic activity and decreased production of cytokines (149). The hypothesis that NK cells limit liver fibrosis by inducing stellate cell apoptosis predicts that NK cell function will be relatively impaired in individuals with rapid progression of fibrosis compared with those in whom liver fibrosis progresses slowly. It may also explain why fibrosis accelerates with aging (502), since NK cell function declines with age.

B. Transcriptional Regulation of Stellate Cell Behavior

Evolving concepts of transcriptional gene regulation have now been applied to stellate cell biology and fibrosis (see Fig. 8). Both genetic and epigenetic regulation are critical to stellate cell responses and are reviewed extensively in several recent articles (141,379,380,529,594, 654). In addition, evidence of posttranscriptional control has been described in stellate cells as well (355).

Stellate cell activation may result from either "activating" events, such as induction of transcription factor splice forms, as well as loss of repressive signaling. These complex cascades illustrate how transcriptional regulation in stellate cells is finely tuned and involves several interdependent layers of both transcriptional, translational, posttranslational, and epigenetic control. In addition, the identification of microRNAs has emerged as a major new pathway of gene regulation in many systems including cancer (662); however, this area has not yet been explored in stellate cells.

A growing number of transcription factors have been identified in stellate cells, yet these only represent a small number of the total number of factors contributing to transcriptional control

(see Table 2). Many target genes of these transcription factors in stellate cells have been reported, but those target genes most intensively evaluated have included type I collagen (α_1- and α_2-chains), TGF-β1 and TGF-β receptors, MMP-2, TIMPs 1 and 2, and α-SMA (141, 379,380,529,594,654).

The following four examples illustrate how stellate cell activation may be controlled by widely divergent regulatory pathways, including transcription factors that contribute to stellate cell activation directly and whose deletion attenuates fibrosis (e.g., Foxf1 and JunD), alternative splicing of a growth inhibitory transcription factor (e.g., KLF6), epigenetic regulation of a factor regulating stellate cell survival (e.g., NFκB), and regulation of a transcription factor whose expression maintains stellate cell quiescence (e.g., Lhx2).

1. Foxf1 and JunD—The requirement for "activating" transcription factors is the most direct transcriptional pathway to provoke stellate cell activation. As discussed in section $_vA$, Foxf1 expression contributes to the activation of stellate cells, and deletion of one Foxf1 allele reduces stellate cell activation and fibrosis (280). A remarkably similar story has emerged about JunD, which is a member of the AP-1 transcription factor complex (276). Studies initially performed in cultured stellate cells identified JunD as a transcriptional regulator of TIMP-1 (609), a molecule whose sustained expression in injured liver contributes to stellate cell survival and inhibition of matrix degradation. More recently, this finding has been complemented by evidence that JunD knockout mice are protected from CCl$_4$-induced hepatic fibrosis, associated with reduced numbers of activated stellate cells and diminished expression of hepatic TIMP-1 (608). Moreover, stellate cells isolated from these JunD −/− animals have reduced TIMP-1 expression, whereas the activation of JunD in wild-type cells requires ERK-dependent phosphorylation of a specific serine residue (Ser-100) (608).

2. KLF6—Several years ago we employed subtractive hybridization cloning to isolate cDNAs upregulated during early stellate cell activation in vivo (335). Among these was a novel zinc finger transcription factor, which was initially termed "Zf9" and is now called "Kruppel-like factor 6 (KLF6)" that is rapidly induced as an immediate-early gene during stellate cell activation in vivo and in culture is a member of a growing family of related zinc finger transcription factors that share identical C2H2 COOH-terminal DNA binding domains (54). Because KLF6 was induced during stellate cell activation, we assumed that it stimulated this process and identified a number of relevant transcriptional targets including TGF-β1 and its receptors (306), urokinase type plasminogen activator (70,615). Subsequently, we identified KLF6 as a growth inhibitory protein that functions as a tumor suppressor gene that inactivated a number of cancers including prostate (439), colon (521), and hepatocellular carcinoma (327). These findings were paradoxical to our initial studies in that they contradicted the presumption that KLF6 is growth promoting in stellate cells. The paradox may have been resolved with the discovery that KLF6 is alternatively spliced (437,438) and that growth-promoting short forms, rather than full-length isoforms, are overexpressed during stellate cell activation. This observation is currently being further evaluated with attempts to identify stimuli that drive alternative splicing of stellate cells during injury responses and cancer.

3. Epigenetic regulation of NFκB activity—Methylation of CpG islands in upstream regulatory regions typically leads to gene repression. Elegant studies by Mann and colleagues (140,380,452,453) have demonstrated induction during stellate cell activation of two key molecules contributing to methylation of CpG islands, the repressors CBF1 and MeCP2. These molecules critically regulate expression of IκB, the major NFκB repressor complex. When stellate cells are quiescent, CBF1 and MeCP2 are low, and thus transcription of the IκB gene is high. The net effect is strong inhibition of NFκB activity, leading to stellate cell apoptosis and decreased fibrogenesis. In contrast, when CBF1 and MeCP2 are high, IκB is repressed and NFκB activity is disinhibited or increased, which promotes stellate cell survival and therefore

increased fibrosis. This finding has been exploited by demonstrating that sulfasalazine, a commonly used anti-inflammatory drug indicated for treatment of inflammatory bowel disease, inhibits the kinase (IKK) that activates IκB. Based on the findings in isolated stellate cells, sulfasalazine and related compounds accelerate recovery from experimental fibrosis by clearance of activated stellate cells through apoptosis (223,453). Since these activated cells typically express high levels of TIMP-1, a metalloproteinase inhibitor, their clearance leads to increased net activity of matrix degrading proteases.

4. Lhx2—This LIM homeodomain protein had been explored primarily for its role in neural and hematopoietic differentiation (500) before its significance to stellate cell activation was uncovered. Initial analysis of the Lhx2 knockout mouse revealed that late fetal demise was due to loss of hematopoiesis in liver (500). Subsequently, Carlsson and colleagues (683) recognized that the liver phenotype was due to excessive accumulation of extracellular matrix (ECM) in these Lhx2 −/− livers. Indeed, stellate cells in these livers are highly activated and account for this ECM accumulation, and overexpression of Lhx2 in normal cultured stellate cells also leads to decreased activation and ECM gene expression. Thus Lhx2 appears to be a transcriptional factor that preserves stellate cell quiescence, raising the interesting concept that activation of stellate cells may be a "default" pathway requiring tonic inhibition by Lhx2 and possibly related factors. Recently, the same approaches have identified a similar role for the transcription factor FoxO1, since stellate cell activation and fibrosis are amplified in cells or mice with reduced FoxO1 activity (1).

C. Paracrine Interactions With Other Resident Liver Cells

Stellate cells exist in a multicellular milieu where cell-cell interactions underlie the tightly regulated homeostatic control required for normal liver function and the response to disease. Interactions between stellate cells and inflammatory cells have been extensively reviewed in section v*C*, but bidirectional regulatory pathways between stellate and other resident liver cells are equally important (370).

In normal liver, hepatocytes and stellate cells cooperate in retinoid metabolism where the compounds are first taken up by hepatocytes, then transferred to stellate cells for storage (see sect. ii*A*). In liver injury, hepatocytes are a potent source of fibrogenic lipid peroxides (366, 443,625) and Fas-mediated apoptotic fragments (84,85) as well as acute phase reactants (319) and plasminogen activators (731). α_2-Macroglobulin generated by hepatocytes may reduce fibrogenesis by sequestering TGF-β (577). Cytokine cross-talk is equally important and includes TGF-β (58,419), TGF-α (284), insulin-like growth factors and binding proteins (72, 211,607), HGF (108,305,469,709), VEGF (109), NGF (21,454), CTGF (507), IL-6 (32), thrombospondin (430), as well as other paracrine factors derived from hepatic tumor cells (34,148). Stellate cells may also support hepatocyte function ex vivo, which could advance the development of liver support devices (687). There is also evidence that HCV-infected hepatocytes may release fibrogenic factors towards stellate cells (578,647), which could explain how patients with normal serum transaminases infected with HCV can still develop hepatic fibrosis. Similarly, HCC cells expressing the HBV X protein stimulate stellate cells to produce the angiogenic molecule angiopoieitin-2 (562). Finally, in hemachromatosis, iron-laden hepatocytes are thought to contribute to hepatic stellate cell activation (518,519).

Stellate cell interactions with Kupffer cells were among the first paracrine interactions described among nonparenchymal cells in liver (55,164,168,316,370,404,405) and may be either pro- or antifibrotic. Kupffer cell infiltration typically precedes stellate cell activation in animal models of liver injury (242,277). Release of chemotactic mediators, for example MCP-1 or osteopontin (293), contributes to their infiltration. Kupffer cell-derived fibrogenic mediators include TGF-β (404,405) and lipid peroxides (642). In support of their role in activating stellate

cells, Kupffer cell inactivation by gadolinium chloride reduces stellate cell activation and fibrosis in animal models (530). In hemachromatosis, iron accumulation in Kupffer cells and macrophages is thought to induce stellate cell activation (346,485). Kupffer cells may also be stimulated by apoptotic fragments to release fibrogenic mediators (82). On the other hand, Kupffer cells may stimulate stellate cell apoptosis (158). Cross-talk between stellate and Kupffer cells following exposure to LPS may also impair liver regeneration (4).

Stellate and sinusoidal endothelial cells are likely to have a common embryologic precursor. This fact, combined with their close physical proximity, makes paracrine interactions quite likely and potentially important. Controlled, coordinated release of proteases may be a critical early event in hepatic regeneration (303,304), possibly to activate latent mitogens including HGF (396). Both cell types exhibit coordinated induction of VEGF receptors during liver injury (10). This interaction may be especially important during tumorigenesis (464). In addition, early changes in cellular fibronectin splice forms generated by sinusoidal endothelium activate hepatic stellate cells (270). Other pathways shared between these two cell types include TGF-β (58,118), IGF-I (117), leptin (253,254), plasminogen (348), endothelin, and nitric oxide (533,542,543,719).

Recent studies provide mounting evidence of close interactions between stellate cells and bile duct epithelium. Such a relationship might explain why activated stellate cells encircle proliferating bile ducts in cholestatic liver injury (308). In culture, secretions from bile duct epithelium induce α-SMA in perisinusoidal fibrogenic cells (330) due to stimulation by MCP-1. Most intriguing is the intimate relationship between stellate cells and bile duct cells during liver development and repair (see sect. III) raising the possibility that stellate cells are required for differentiation of bipotential epithelial cells into biliary epithelium or even the possibility of *trans*differentiation between the two cell types.

D. Behavior of Stellate Cells in Liver Disease

Involvement of stellate cells in the fibrotic response to liver injury has been recognized for several years (75,459) (see sect. I). Stellate cell activation from a quiescent to a highly fibrogenic cell in diseased liver is characterized morphologically by enlargement of rER, diminution of vitamin A droplets, ruffled nuclear membrane, appearance of contractile filaments, and proliferation (555,570). Cells with features of both quiescent and activated cells are often called "transitional cells." Studies in animals have defined the time course and localization of proliferating stellate cells in different models of injury (242,277,378,635). These and related studies consistently demonstrate active proliferation of stellate cells in regions of greatest injury, which is typically preceded by an influx of inflammatory cells and is associated with extracellular matrix accumulation.

The recognition of stellate cells' importance in normal and injured liver has led to a greater appreciation of their role in many human liver diseases (401). Alcoholic liver disease is the best-studied example, with numerous reports documenting features of activation in situ (230, 244,459). Activation of stellate cells, as assessed by expression of α-SMA, may occur in the presence of steatosis alone (520), suggesting that bland steatosis may be a precursor of hepatic fibrosis, even without apparent inflammation. Studies of viral hepatitis (201,218,222,261, 298) and massive hepatic necrosis (52,144) have confirmed morphological and immunohistological features of stellate cell activation. In hepatocellular carcinoma (143,649) and biliary malignancy (569), activated stellate cells contribute to the accumulation of tumor stroma. These findings are supported by animal studies suggesting that activated stellate cells contribute to hepatic metastases (464,465), and culture studies demonstrating paracrine activation of stellate cells by tumoral cells (148). In addition, a primary benign tumor of stellate cells, spongiotic pericytoma, has been described in rats treated with carcinogens (622), as well as a malignant tumor from which the L190 stellate cell-like cell line has been derived (428).

Stellate cells have been characterized in a number of other human diseases, including vascular disease (570), hematologic malignancy (570), biliary disease (570), mucopolysaccharidosis (523), acetaminophen overdose (402), and leishmaniasis (138) as well as in drug abusers (650). In addition, stellate cells have been readily identified in fibrosis and granuloma formation associated with schistosomiasis (33,74,100). In primary biliary cirrhosis (PBC), a slowly progressive cholestatic disease primarily in woman, large multivesicular stellate cells have been described (80), the significance of which is unclear. In PBC, these may be seen at the same time as portal fibroblasts (203), and both cell types are likely to generate fibrosis.

Stimulation of stellate cells by lipid peroxides may be important in many forms of liver fibrosis, but is particularly pertinent to diseases associated with iron overload. A role for lipid peroxides is suspected in these diseases (e.g., hemochromatosis), based on both in situ studies that show a correlation between the presence of aldehyde adducts and stellate cell collagen gene expression (43,283,478,479).

Because α-SMA is a sensitive marker of activated stellate cells in situ, it is increasingly used as an early indication of fibrogenic activity in human liver disease, even before extracellular matrix accumulates. For example, two studies have used α-actin staining to predict early development of liver fibrosis in patients following liver transplantation for HCV (191,558). Similar studies have been performed in patients with nonalcoholic fatty liver disease, which also has a variable rate of fibrosis (110,151). The value of using α-actin staining to quantify fibrogenesis is underscored by its inclusion as a primary end point in clinical trials of antifibrotics in HCV refractory to antiviral therapies (http://clinicaltrials.gov/ct/show/NCT00244751?order=9).

VII. Unanswered Questions and Future Directions

The unfolding mysteries of the hepatic stellate cell and the breadth of its protean features have far exceeded anyone's imagination when the cell was first isolated over 20 years ago. With that in mind, it is difficult to predict what additional surprises will emerge from ongoing study of this fascinating cell type. Nonetheless, some key issues are likely to challenge current and future investigators. In particular, the stellate cells' pleuripotency and roles in both liver development and regeneration merit intense evaluation and await the development of better genetic models to confirm these prospects. Continued elucidation of the stellate cell's immune functions is very important, in particular its contribution to the unusually high immunotolerance of liver, as well as its potential role in viral infection (including HIV), graft versus host disease, and fibrogenesis. More evidence of subtle and complex crosstalk between stellate cells and inflammatory cell subsets is sure to emerge. The myriad, intersecting pathways of hepatic stellate cell activation will continue to yield new paradigms relevant to tissue repair in other organs as well. We still await evidence that activated stellate cells can revert to a more quiescent state in vivo, which will require sophisticated genetic models but could provide further evidence of the cell's remarkable plasticity. The use of stellate cells to support hepatocellular differentiation in culture and hepatocyte engraftment in vivo are also promising new roles. Based on these findings, the potential use of stellate cells in liver assist devices merits further study and could create new prospects for patients with end-stage liver disease. One thing is certain, stellate cells will continue to fascinate, engage, and excite liver biologists, immunologists, and clinicians for the foreseeable future.

Acknowledgments

References

1. Adachi M, Osawa Y, Uchinami H, Kitamura T, Accili D, Brenner DA. The forkhead transcription factor FoxO1 regulates proliferation and transdifferentiation of hepatic stellate cells. Gastroenterology 2007;132:1434–1446. [PubMed: 17408630]

2. Adachi T, Togashi H, Suzuki A, Kasai S, Ito J, Sugahara K, Kawata S. NAD(P)H oxidase plays a crucial role in PDGF-induced proliferation of hepatic stellate cells. Hepatology 2005;41:1272–1281. [PubMed: 15915457]

3. Adrian JE, Poelstra K, Scherphof GL, Molema G, Meijer DK, Reker-Smit C, Morselt HW, Kamps JA. Interaction of targeted liposomes with primary cultured hepatic stellate cells: involvement of multiple receptor systems. J Hepatol 2006;44:560–567. [PubMed: 16368158]

4. Akita K, Okuno M, Enya M, Imai S, Moriwaki H, Kawada N, Suzuki Y, Kojima S. Impaired liver regeneration in mice by lipopolysaccharide via TNF-alpha/kallikrein-mediated activation of latent TGF-beta. Gastroenterology 2002;123:352–364. [PubMed: 12105863]

5. Aleffi S, Petrai I, Bertolani C, Parola M, Colombatto S, Novo E, Vizzutti F, Anania FA, Milani S, Rombouts K, Laffi G, Pinzani M, Marra F. Upregulation of proinflammatory and proangiogenic cytokines by leptin in human hepatic stellate cells. Hepatology 2005;42:1339–1348. [PubMed: 16317688]

6. Anan A, Baskin-Bey ES, Bronk SF, Werneburg NW, Shah VH, Gores GJ. Proteasome inhibition induces hepatic stellate cell apoptosis. Hepatology 2006;43:335–344. [PubMed: 16440346]

7. Anania FA, Womack L, Jiang M, Saxena NK. Aldehydes potentiate alpha(2)(I) collagen gene activity by JNK in hepatic stellate cells. Free Radical Biol Med 2001;30:846–857. [PubMed: 11295527]

8. Andersen KB, Nilsson A, Blomhoff HK, Oyen TB, Gabrielsen OS, Norum KR, Blomhoff R. Direct mobilization of retinol from hepatic perisinusoidal stellate cells to plasma. J Biol Chem 1992;267:1340–1344. [PubMed: 1730653]

9. Andus T, Ramadori G, Heinrich PC, Knittel T, Meyer zum Buschenfelde KH. Cultured Ito cells of rat liver express the alpha 2-macroglobulin gene. Eur J Biochem 1987;168:641–646. [PubMed: 2444437]

10. Ankoma-Sey V, Matli M, Chang KB, Lalazar A, Donner DB, Wong L, Warren RS, Friedman SL. Coordinated induction of VEGF receptors in mesenchymal cell types during rat hepatic wound healing. Oncogene 1998;17:115–121. [PubMed: 9671320]

12. Ankoma-Sey V, Wang Y, Dai Z. Hypoxic stimulation of vascular endothelial growth factor expression in activated rat hepatic stellate cells. Hepatology 2000;31:141–148. [PubMed: 10613739]

13. Apte MV, Haber PS, Darby SJ, Rodgers SC, McCaughan GW, Korsten MA, Pirola RC, Wilson JS. Pancreatic stellate cells are activated by proinflammatory cytokines: implications for pancreatic fibrogenesis. Gut 1999;44:534–541. [PubMed: 10075961]

14. Apte MV, Wilson JS. Stellate cell activation in alcoholic pancreatitis. Pancreas 2003;27:316–320. [PubMed: 14576494]

15. Arii S, Mise M, Harada T, Furutani M, Ishigami S, Niwano M, Mizumoto M, Fukumoto M, Imamura M. Overexpression of matrix metalloproteinase 9 gene in hepatocellular carcinoma with invasive potential. Hepatology 1996;24:316–322. [PubMed: 8690399]

16. Arthur MJ. Collagenases and liver fibrosis. J Hepatol 1995;22:43–48. [PubMed: 7665849]

17. Arthur MJ. Fibrogenesis. II. Metalloproteinases and their inhibitors in liver fibrosis. Am J Physiol Gastrointest Liver Physiol 2000;279:G245–G249. [PubMed: 10915630]

18. Arthur MJ, Stanley A, Iredale JP, Rafferty JA, Hembry RM, Friedman SL. Secretion of 72 kDa type IV collagenase/gelatinase by cultured human lipocytes. Analysis of gene expression, protein synthesis and proteinase activity. Biochem J 1992;287:701–707. [PubMed: 1445234]

19. Asahina K, Kawada N, Kristensen DB, Nakatani K, Seki S, Shiokawa M, Tateno C, Obara M, Yoshizato K. Characterization of human stellate cell activation-associated protein and its expression in human liver. Biochim Biophys Acta 2002;1577:471–475. [PubMed: 12359339]

20. Asahina K, Sato H, Yamasaki C, Kataoka M, Shiokawa M, Katayama S, Tateno C, Yoshizato K. Pleiotrophin/heparin-binding growth-associated molecule as a mitogen of rat hepatocytes and its role in regeneration and development of liver. Am J Pathol 2002;160:2191–2205. [PubMed: 12057922]

21. Asai K, Tamakawa S, Yamamoto M, Yoshie M, Tokusashi Y, Yaginuma Y, Kasai S, Ogawa K. Activated hepatic stellate cells overexpress p75NTR after partial hepatectomy and undergo apoptosis on nerve growth factor stimulation. Liver Int 2006;26:595–603. [PubMed: 16762005]

22. Asselah T, Bieche I, Laurendeau I, Paradis V, Vidaud D, Degott C, Martinot M, Bedossa P, Valla D, Vidaud M, Marcellin P. Liver gene expression signature of mild fibrosis in patients with chronic hepatitis C. Gastroenterology 2005;129:2064–2075. [PubMed: 16344072]

23. Asselah T, Bieche I, Paradis V, Bedossa P, Vidaud M, Marcellin P. Genetics, genomics, proteomics: implications for the diagnosis and the treatment of chronic hepatitis C. Semin Liver Dis 2007;27:13–27. [PubMed: 17295174]

24. Aterman K. The parasinusoidal cells of the liver: a historical account. Histochem J 1986;18:279–305. [PubMed: 2427483]

25. Athari A, Hanecke K, Jungermann K. Prostaglandin F2 alpha and D2 release from primary Ito cell cultures after stimulation with noradrenaline and ATP but not adenosine. Hepatology 1994;20:142–148. [PubMed: 8020883]

26. Baba S, Fujii H, Hirose T, Yasuchika K, Azuma H, Hoppo T, Naito M, Machimoto T, Ikai I. Commitment of bone marrow cells to hepatic stellate cells in mouse. J Hepatol 2004;40:255–260. [PubMed: 14739096]

27. Bach Kristensen D, Kawada N, Imamura K, Miyamoto Y, Tateno C, Seki S, Kuroki T, Yoshizato K. Proteome analysis of rat hepatic stellate cells. Hepatology 2000;32:268–277. [PubMed: 10915733]

28. Bachem MG, Melchior R, Gressner AM. The role of thrombocytes in liver fibrogenesis: effects of platelet lysate and thrombocyte-derived growth factors on the mitogenic activity and glycosaminoglycan synthesis of cultured rat liver fat storing cells. J Clin Chem Clin Biochem 1989;27:555–565. [PubMed: 2607320]

29. Bachem MG, Meyer D, Melchior R, Sell KM, Gressner AM. Activation of rat liver perisinusoidal lipocytes by transforming growth factors derived from myofibroblastlike cells. A potential mechanism of self perpetuation in liver fibrogenesis. J Clin Invest 1992;89:19–27. [PubMed: 1729271]

30. Bachem MG, Zhou Z, Zhou S, Siech M. Role of stellate cells in pancreatic fibrogenesis associated with acute and chronic pancreatitis. J Gastroenterol Hepatol 2006;21 3:S92–S96. [PubMed: 16958683]

31. Ballardini G, Groff P, Badiali dGL, Schuppan D, Bianchi FB. Ito cell heterogeneity: desmin-negative Ito cells in normal rat liver. Hepatology 1994;19:440–446. [PubMed: 7507464]

32. Bansal MB, Kovalovich K, Gupta R, Li W, Agarwal A, Radbill B, Alvarez CE, Safadi R, Fiel MI, Friedman SL, Taub RA. Interleukin-6 protects hepatocytes from CCl4-mediated necrosis and apoptosis in mice by reducing MMP-2 expression. J Hepatol 2005;42:548–556. [PubMed: 15763341]

33. Bartley PB, Ramm GA, Jones MK, Ruddell RG, Li Y, McManus DP. A contributory role for activated hepatic stellate cells in the dynamics of *Schistosoma japonicum* egg-induced fibrosis. Int J Parasitol 2006;36:993–1001. [PubMed: 16806222]

34. Basu A, Saito K, Meyer K, Ray RB, Friedman SL, Chang YH, Ray R. Stellate cell apoptosis by a soluble mediator from immortalized human hepatocytes. Apoptosis 2006;11:1391–1400. [PubMed: 16830231]

35. Bataller R, Brenner DA. Liver fibrosis. J Clin Invest 2005;115:209–218. [PubMed: 15690074]

36. Bataller R, Gabele E, Schoonhoven R, Morris T, Lehnert M, Yang L, Brenner DA, Rippe RA. Prolonged infusion of angiotensin II into normal rats induces stellate cell activation and proinflammatory events in liver. Am J Physiol Gastrointest Liver Physiol 2003;285:G642–G651. [PubMed: 12773299]

37. Bataller R, Sancho-Bru P, Gines P, Brenner DA. Liver fibrogenesis: a new role for the renin-angiotensin system. Antioxid Redox Signal 2005;7:1346–1355. [PubMed: 16115040]

38. Bataller R, Sancho-Bru P, Gines P, Lora JM, Al-Garawi A, Sole M, Colmenero J, Nicolas JM, Jimenez W, Weich N, Gutierrez-Ramos JC, Arroyo V, Rodes J. Activated human hepatic stellate cells express

the renin-angiotensin system and synthesize angiotensin II. Gastroenterology 2003;125:117–125. [PubMed: 12851877]

39. Bataller R, Schwabe RF, Choi YH, Yang L, Paik YH, Lindquist J, Qian T, Schoonhoven R, Hagedorn CH, Lemasters JJ, Brenner DA. NADPH oxidase signal transduces angiotensin II in hepatic stellate cells and is critical in hepatic fibrosis. J Clin Invest 2003;112:1383–1394. [PubMed: 14597764]

40. Batres RO, Olson JA. A marginal vitamin A status alters the distribution of vitamin A among parenchymal and stellate cells in rat liver. J Nutr 1987;117:874–879. [PubMed: 3585540]

41. Beaussier M, Wendum D, Schiffer E, Dumont S, Rey C, Lienhart A, Housset C. Prominent contribution of portal mesenchymal cells to liver fibrosis in ischemic and obstructive cholestatic injuries. Lab Invest 2007;87:292–303. [PubMed: 17260005]

42. Beaven SW, Tontonoz P. Nuclear receptors in lipid metabolism: targeting the heart of dyslipidemia. Annu Rev Med 2006;57:313–329. [PubMed: 16409152]

43. Bedossa P, Houglum K, Trautwein C, Holstege A, Chojkier M. Stimulation of collagen alpha 1(I) gene expression is associated with lipid peroxidation in hepatocellular injury: a link to tissue fibrosis? Hepatology 1994;19:1262–1271. [PubMed: 8175151]

44. Belfort R, Harrison SA, Brown K, Darland C, Finch J, Hardies J, Balas B, Gastaldelli A, Tio F, Pulcini J, Berria R, Ma JZ, Dwivedi S, Havranek R, Fincke C, DeFronzo R, Bannayan GA, Schenker S, Cusi K. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. N Engl J Med 2006;355:2297–2307. [PubMed: 17135584]

45. Beljaars L, Meijer DK, Poelstra K. Targeting hepatic stellate cells for cell-specific treatment of liver fibrosis. Front Biosci 2002;7:e214–e222. [PubMed: 11991830]

46. Beljaars L, Molema G, Schuppan D, Geerts A, De Bleser PJ, Weert B, Meijer DK, Poelstra K. Successful targeting to rat hepatic stellate cells using albumin modified with cyclic peptides that recognize the collagen type VI receptor. J Biol Chem 2000;275:12743–12751. [PubMed: 10777570]

47. Benedetti A, Di Sario A, Casini A, Ridolfi F, Bendia E, Pigini P, Tonnini C, D'Ambrosio L, Feliciangeli G, Macarri G, Svegliati-Baroni G. Inhibition of the NA(+)/H(+) exchanger reduces rat hepatic stellate cell activity and liver fibrosis: an in vitro and in vivo study. Gastroenterology 2001;120:545–556. [PubMed: 11159895]

48. Beno DW, Mullen J, Davis BH. Lipoxygenase inhibitors block PDGF-induced mitogenesis: a MAPK-independent mechanism that blocks fos and egr. Am J Physiol Cell Physiol 1995;268:C604–C610.

49. Benten D, Kumaran V, Joseph B, Schattenberg J, Popov Y, Schuppan D, Gupta S. Hepatocyte transplantation activates hepatic stellate cells with beneficial modulation of cell engraftment in the rat. Hepatology 2005;42:1072–1081. [PubMed: 16250034]

50. Benyon RC, Arthur MJ. Extracellular matrix degradation and the role of hepatic stellate cells. Semin Liver Dis 2001;21:373–384. [PubMed: 11586466]

51. Benyon RC, Iredale JP, Goddard S, Winwood PJ, Arthur MJ. Expression of tissue inhibitor of metalloproteinases 1 and 2 is increased in fibrotic human liver. Gastroenterology 1996;110:821–831. [PubMed: 8608892]

52. Bernard PH, Le Bail B, Carles J, Fawaz R, Balabaud C, Rosenbaum J, Bioulac-Sage P. Morphology of hepatic stellate cells in patients with fulminant or subfulminant hepatitis requiring liver transplantation. J Submicrosc Cytol Pathol 1996;28:5–12. [PubMed: 8929622]

53. Bieche I, Asselah T, Laurendeau I, Vidaud D, Degot C, Paradis V, Bedossa P, Valla DC, Marcellin P, Vidaud M. Molecular profiling of early stage liver fibrosis in patients with chronic hepatitis C virus infection. Virology 2005;332:130–144. [PubMed: 15661146]

54. Bieker JJ. Kruppel-like factors: three fingers in many pies. J Biol Chem 2001;276:34355–34358. [PubMed: 11443140]

55. Bilzer M, Roggel F, Gerbes AL. Role of Kupffer cells in host defense and liver disease. Liver Int 2006;26:1175–1186. [PubMed: 17105582]

56. Bioulac-Sage P, Lafon ME, Saric J, Balabaud C. Nerves and perisinusoidal cells in human liver. J Hepatol 1990;10:105–112. [PubMed: 2407769]

57. Bissell DM. Sex and hepatic fibrosis. Hepatology 1999;29:988–989. [PubMed: 10051508]

58. Bissell DM, Wang SS, Jarnagin WR, Roll FJ. Cell-specific expression of transforming growth factor-beta in rat liver. Evidence for autocrine regulation of hepatocyte proliferation. J Clin Invest 1995;96:447–455. [PubMed: 7615817]

59. Blaner WS, Hendriks HFJ, Brouwer A, de Leeuw AM, Knook DL, Goodman DS. Retinoids, retinoid binding proteins and retinyl palmitate hydrolase distributions in different types of rat liver cells. J Lipid Res 1985;26:1241–1251. [PubMed: 4067418]

60. Blazejewski S, Preaux AM, Mallat A, Brocheriou I, Mavier P, Dhumeaux D, Hartmann D, Schuppan D, Rosenbaum J. Human myofibroblastlike cells obtained by outgrowth are representative of the fibrogenic cells in the liver. Hepatology 1995;22:788–797. [PubMed: 7657284]

61. Blomhoff R, Berg T, Norum KR. Transfer of retinol from parenchymal to stellate cells in liver is mediated by retinol binding protein. Proc Natl Acad Sci USA 1988;85:3455–3458. [PubMed: 3368453]

62. Blomhoff R, Green MH, Berg T, Norum KR. Transport and storage of vitamin A. Science 1990;250:399–404. [PubMed: 2218545]

63. Blomhoff R, Helgerud P, Rasmussen M, Berg T, Norum KR. In vivo uptake of chylomicron [^{3}H] retinyl ester by rat liver: evidence for retinol transfer from parenchymal to nonparenchymal cells. Proc Natl Acad Sci USA 1982;79:7326–7330. [PubMed: 6961410]

64. Blomhoff R, Norum KR, Berg T. Hepatic uptake of [^{3}H]retinol bound to the serum retinol binding protein involves both parenchymal and perisinusoidal stellate cells. J Biol Chem 1985;260:13571–13575. [PubMed: 4055748]

65. Boers W, Aarrass S, Linthorst C, Pinzani M, Elferink RO, Bosma P. Transcriptional profiling reveals novel markers of liver fibrogenesis: gremlin and insulin-like growth factor-binding proteins. J Biol Chem 2006;281:16289–16295. [PubMed: 16606614]

66. Bonacchi A, Petrai I, Defranco RM, Lazzeri E, Annunziato F, Efsen E, Cosmi L, Romagnani P, Milani S, Failli P, Batignani G, Liotta F, Laffi G, Pinzani M, Gentilini P, Marra F. The chemokine CCL21 modulates lymphocyte recruitment and fibrosis in chronic hepatitis C. Gastroenterology 2003;125:1060–1076. [PubMed: 14517790]

67. Bonacchi A, Romagnani P, Romanelli RG, Efsen E, Annunziato F, Lasagni L, Francalanci M, Serio M, Laffi G, Pinzani M, Gentilini P, Marra F. Signal transduction by the chemokine receptor CXCR3: activation of Ras/ERK, Src, phosphatidylinositol 3-kinase/Akt controls cell migration and proliferation in human vascular pericytes. J Biol Chem 2001;276:9945–9954. [PubMed: 11136732]

68. Borkham-Kamphorst E, van Roeyen CR, Ostendorf T, Floege J, Gressner AM, Weiskirchen R. Pro-fibrogenic potential of PDGF-D in liver fibrosis. J Hepatol. In press.

69. Borojevic R, Monteiro AN, Vinhas SA, Domont GB, Mourao PA, Emonard H, Grimaldi GJ, Grimaud JA. Establishment of a continuous cell line from fibrotic schistosomal granulomas in mice livers. In Vitro Cell Dev Biol 1985;21:382–390. [PubMed: 4030623]

70. Botella LM, Sanchez-Elsner T, Sanz-Rodriguez F, Kojima S, Shimada J, Guerrero-Esteo M, Cooreman MP, Ratziu V, Langa C, Vary CP, Ramirez JR, Friedman S, Bernabeu C. Transcriptional activation of endoglin and transforming growth factor-beta signaling components by cooperative interaction between Sp1 and KLF6: their potential role in the response to vascular injury. Blood 2002;100:4001–4010. [PubMed: 12433697]

71. Breitkopf K, Godoy P, Ciuclan L, Singer MV, Dooley S. TGF-beta/Smad signaling in the injured liver. Z Gastroenterol 2006;44:57–66. [PubMed: 16397841]

72. Brenzel A, Gressner AM. Characterization of insulin-like growth factor (IGF)-I-receptor binding sites during in vitro transformation of rat hepatic stellate cells to myofibroblasts. Eur J Clin Chem Clin Biochem 1996;34:401–409. [PubMed: 8790975]

73. Brigstock DR. The CCN family: a new stimulus package. J Endocrinol 2003;178:169–175. [PubMed: 12904165]

74. Brito JM, Borojevic R. Liver granulomas in schistosomiasis: mast cell-dependent induction of SCF expression in hepatic stellate cells is mediated by TNF-α. J Leukoc Biol 1997;62:389–396. [PubMed: 9307079]

75. Bronfenmajer S, Schaffner F, Popper H. Fat-storing cells (lipocytes) in human liver. Arch Path 1966;82:447–453. [PubMed: 5923468]

76. Brun P, Castagliuolo I, Pinzani M, Palu G, Martines D. Exposure to bacterial cell wall products triggers an inflammatory phenotype in hepatic stellate cells. Am J Physiol Gastrointest Liver Physiol 2005;289:G571–G578. [PubMed: 15860640]

77. Buchholz M, Kestler HA, Holzmann K, Ellenrieder V, Schneiderhan W, Siech M, Adler G, Bachem MG, Gress TM. Transcriptome analysis of human hepatic and pancreatic stellate cells: organ-specific variations of a common transcriptional phenotype. J Mol Med. 2005

78. Caligiuri A, De Franco RM, Romanelli RG, Gentilini A, Meucci M, Failli P, Mazzetti L, Rombouts K, Geerts A, Vanasia M, Gentilini P, Marra F, Pinzani M. Antifibrogenic effects of canrenone, an antialdosteronic drug, on human hepatic stellate cells. Gastroenterology 2003;124:504–520. [PubMed: 12557155]

79. Callewaert N, Van Vlierberghe H, Van Hecke A, Laroy W, Delanghe J, Contreras R. Noninvasive diagnosis of liver cirrhosis using DNA sequencer-based total serum protein glycomics. Nat Med 2004;10:429–434. [PubMed: 15152612]

80. Cameron RG, Neuman MG, Blendis LM. Multivesicular stellate cells in primary biliary cirrhosis. Hepatology 1997;26:550–553. [PubMed: 9303481]

81. Canbay A, Feldstein A, Baskin-Bey E, Bronk SF, Gores GJ. The caspase inhibitor IDN-6556 attenuates hepatic injury and fibrosis in the bile duct ligated mouse. J Pharmacol Exp Ther 2004;308:1191–1196. [PubMed: 14617689]

82. Canbay A, Feldstein AE, Higuchi H, Werneburg N, Grambihler A, Bronk SF, Gores GJ. Kupffer cell engulfment of apoptotic bodies stimulates death ligand and cytokine expression. Hepatology 2003;38:1188–1198. [PubMed: 14578857]

83. Canbay A, Friedman S, Gores GJ. Apoptosis: the nexus of liver injury and fibrosis. Hepatology 2004;39:273–278. [PubMed: 14767974]

84. Canbay A, Higuchi H, Bronk SF, Taniai M, Sebo TJ, Gores GJ. Fas enhances fibrogenesis in the bile duct ligated mouse: a link between apoptosis and fibrosis. Gastroenterology 2002;123:1323–1330. [PubMed: 12360492]

85. Canbay A, Taimr P, Torok N, Higuchi H, Friedman S, Gores GJ. Apoptotic body engulfment by a human stellate cell line is profibrogenic. Lab Invest 2003;83:655–663. [PubMed: 12746475]

86. Cao Q, Mak KM, Lieber CS. DLPC and SAMe combined prevent leptin-stimulated TIMP-1 production in LX-2 human hepatic stellate cells by inhibiting HO-mediated signal transduction. Liver Int 2006;26:221–231. [PubMed: 16448461]

87. Cao Q, Mak KM, Lieber CS. DLPC and SAMe prevent alpha1(I) collagen mRNA up-regulation in human hepatic stellate cells, whether caused by leptin or menadione. Biochem Biophys Res Commun 2006;350:50–55. [PubMed: 16996477]

88. Cao Q, Mak KM, Lieber CS. Leptin enhances alpha1(I) collagen gene expression in LX-2 human hepatic stellate cells through JAK-mediated H(2)O(2)-dependent MAPK pathways. J Cell Biochem 2006;97:188–197. [PubMed: 16173077]

89. Cao Q, Mak KM, Lieber CS. Leptin represses matrix metalloproteinase-1 gene expression in LX2 human hepatic stellate cells. J Hepatol 2007;46:124–133. [PubMed: 17030072]

91. Carloni V, Defranco RM, Caligiuri A, Gentilini A, Sciammetta SC, Baldi E, Lottini B, Gentilini P, Pinzani M. Cell adhesion regulates platelet-derived growth factor-induced MAP kinase and PI-3 kinase activation in stellate cells. Hepatology 2002;36:582–591. [PubMed: 12198650]

92. Carloni V, Romanelli RG, Pinzani M, Laffi G, Gentilini P. Expression and function of integrin receptors for collagen and laminin in cultured human hepatic stellate cells. Gastroenterology 1996;110:1127–1136. [PubMed: 8613002]

93. Casini A, Pellegrini G, Ceni E, Salzano R, Parola M, Robino G, Milani S, Dianzani MU, Surrenti C. Human hepatic stellate cells express class I alcohol dehydrogenase and aldehyde dehydrogenase but not cytochrome P4502E1. J Hepatol 1998;28:40–45. [PubMed: 9537862]

94. Cassiman D, Barlow A, Vander Borght S, Libbrecht L, Pachnis V. Hepatic stellate cells do not derive from the neural crest. J Hepatol 2006;44:1098–1104. [PubMed: 16458991]

95. Cassiman D, Denef C, Desmet VJ, Roskams T. Human and rat hepatic stellate cells express neurotrophins and neurotrophin receptors. Hepatology 2001;33:148–158. [PubMed: 11124831]

96. Cassiman D, Libbrecht L, Sinelli N, Desmet V, Denef C, Roskams T. The vagal nerve stimulates activation of the hepatic progenitor cell compartment via muscarinic acetylcholine receptor type 3. Am J Pathol 2002;161:521–530. [PubMed: 12163377]

97. Castilla A, Prieto J, Fausto N. Transforming growth factors beta 1 and alpha in chronic liver disease. Effects of interferon alpha therapy. N Engl J Med 1991;324:933–940. [PubMed: 1900574]

98. Cederbaum AI. Cytochrome P450 2E1-dependent oxidant stress and upregulation of anti-oxidant defense in liver cells. J Gastroenterol Hepatol 2006;21 3:S22–S25. [PubMed: 16958665]

99. Chan ES, Montesinos MC, Fernandez P, Desai A, Delano DL, Yee H, Reiss AB, Pillinger MH, Chen JF, Schwarzschild MA, Friedman SL, Cronstein BN. Adenosine A(2A) receptors play a role in the pathogenesis of hepatic cirrhosis. Br J Pharmacol 2006;148:1144–1155. [PubMed: 16783407]

100. Chang D, Ramalho LN, Ramalho FS, Martinelli AL, Zucoloto S. Hepatic stellate cells in human *Schistosomiasis mansoni*: a comparative immunohistochemical study with liver cirrhosis. Acta Trop 2006;97:318–323. [PubMed: 16473318]

101. Charo IF, Ransohoff RM. The many roles of chemokines and chemokine receptors in inflammation. N Engl J Med 2006;354:610–621. [PubMed: 16467548]

102. Chen CH, Kuo LM, Chang Y, Wu W, Goldbach C, Ross MA, Stolz DB, Chen L, Fung JJ, Lu L, Qian S. In vivo immune modulatory activity of hepatic stellate cells in mice. Hepatology 2006;44:1171–1181. [PubMed: 17058227]

103. Chen W, Gendrault JL, Steffan AM, Jeandidier E, Kirn A. Isolation, culture and main characteristics of mouse fat-storing cells: interaction with viruses. Hepatology 1989;9:352–362. [PubMed: 2465986]

104. Choi SS, Sicklick JK, Ma Q, Yang L, Huang J, Qi Y, Chen W, Li YX, Goldschmidt-Clermont PJ, Diehl AM. Sustained activation of Rac1 in hepatic stellate cells promotes liver injury and fibrosis in mice. Hepatology 2006;44:1267–1277. [PubMed: 17058265]

105. Choudhury J, Mirshahi F, Murthy KS, Yager DR, Sanyal AJ. Physiologic concentrations of leptin increase collagen production by non-immortalized human hepatic stellate cells. Metabolism 2006;55:1317–1322. [PubMed: 16979401]

106. Chuang JH, Wang PW, Tai MH. An adipocentric view of liver fibrosis and cirrhosis. Chang Gung Med J 2004;27:855–868. [PubMed: 15754775]

107. Claudel T, Staels B, Kuipers F. The Farnesoid X receptor: a molecular link between bile acid and lipid and glucose metabolism. Arterioscler Thromb Vasc Biol 2005;25:2020–2030. [PubMed: 16037564]

108. Corpechot C, Barbu V, Wendum D, Chignard N, Housset C, Poupon R, Rosmorduc O. Hepatocyte growth factor and c-Met inhibition by hepatic cell hypoxia: a potential mechanism for liver regeneration failure in experimental cirrhosis. Am J Pathol 2002;160:613–620. [PubMed: 11839582]

109. Corpechot C, Barbu V, Wendum D, Kinnman N, Rey C, Poupon R, Housset C, Rosmorduc O. Hypoxia-induced VEGF and collagen I expressions are associated with angiogenesis and fibrogenesis in experimental cirrhosis. Hepatology 2002;35:1010–1021. [PubMed: 11981751]

110. Cortez-Pinto H, Baptista A, Camilo ME, de Moura MC. Hepatic stellate cell activation occurs in nonalcoholic steatohepatitis. Hepatogastroenterology 2001;48:87–90. [PubMed: 11269008]

111. Cuperlovic-Culf M, Belacel N, Culf AS, Ouellette RJ. Microarray analysis of alternative splicing. Omics 2006;10:344–357. [PubMed: 17069512]

112. Czaja MJ, Geerts A, Xu J, Schmiedeberg P, Ju Y. Monocyte chemoattractant protein 1 (MCP-1) expression occurs in toxic rat liver injury and human liver disease. J Leukoc Biol 1994;55:120–126. [PubMed: 8283136]

113. Czochra P, Klopcic B, Meyer E, Herkel J, Garcia-Lazaro JF, Thieringer F, Schirmacher P, Biesterfeld S, Galle PR, Lohse AW, Kanzler S. Liver fibrosis induced by hepatic overexpression of PDGF-B in transgenic mice. J Hepatol 2006;45:419–428. [PubMed: 16842882]

114. Davis BH. Transforming growth factor beta responsiveness is modulated by the extracellular collagen matrix during hepatic ito cell culture. J Cell Physiol 1988;136:547–553. [PubMed: 3170650]

115. Davis BH, Coll D, Beno DW. Retinoic acid suppresses the response to platelet-derived growth factor in human hepatic Ito-cell-like myofibroblasts: a post-receptor mechanism independent of raf/fos/jun/egr activation. Biochem J 1993;294:785–791. [PubMed: 8379934]

116. Davis BH, Kramer RT, Davidson NO. Retinoic acid modulates rat Ito cell proliferation, collagen, transforming growth factor beta production. J Clin Invest 1990;86:2062–2070. [PubMed: 2254460]

117. De Bleser PJ, Jannes P, van Buul-Offers SC, Hoogerbrugge CM, van Schravendijk CF, Niki T, Rogiers V, van den Brande JL, Wisse E, Geerts A. Insulin-like growth factor-II/mannose 6-

phosphate receptor is expressed on CCl4-exposed rat fat-storing cells and facilitates activation of latent transforming growth factor-beta in cocultures with sinusoidal endothelial cells. Hepatology 1995;21:1429–1437. [PubMed: 7737649]

118. De Bleser PJ, Niki T, Rogiers V, Geerts A. Transforming growth factor-beta gene expression in normal and fibrotic rat liver. J Hepatol 1997;26:886–893. [PubMed: 9126804]

119. De Bleser PJ, Xu G, Rombouts K, Rogiers V, Geerts A. Glutathione levels discriminate between oxidative stress and transforming growth factor-beta signaling in activated rat hepatic stellate cells. J Biol Chem 1999;274:33881–33887. [PubMed: 10567349]

120. De Minicis S, Brenner DA. NOX in liver fibrosis. Arch Biochem Biophys. In press.

121. De Minicis S, Seki E, Uchinami H, Brenner DA, Schwabe RF. Gene expression profiles during hepatic stellate cell activation in culture and in vivo (Abstract). Hepatology 2006;44:265A.

122. DeLeve LD. Glutathione defense in non-parenchymal cells. Semin Liver Dis 1998;18:403–413. [PubMed: 9875557]

123. Demuth DG, Molleman A. Cannabinoid signalling. Life Sci 2006;78:549–563. [PubMed: 16109430]

124. Di Martino V, Lebray P, Myers RP, Pannier E, Paradis V, Charlotte F, Moussalli J, Thabut D, Buffet C, Poynard T. Progression of liver fibrosis in women infected with hepatitis C: long-term benefit of estrogen exposure. Hepatology 2004;40:1426–1433. [PubMed: 15565616]

125. Di Sario A, Baroni GS, Bendia E, D'Ambrosio L, Ridolfi F, Marileo JR, Jezequel AM, Benedetti A. Characterization of ion transport mechanisms regulating intracellular pH in hepatic stel-late cells. Am J Physiol Gastrointest Liver Physiol 1997;273:G39–G48.

126. Di Sario A, Bendia E, Taffetani S, Marzioni M, Candelaresi C, Pigini P, Schindler U, Kleemann HW, Trozzi L, Macarri G, Benedetti A. Selective Na^+/H^+ exchange inhibition by cariporide reduces liver fibrosis in the rat. Hepatology 2003;37:256–266. [PubMed: 12540775]

127. Ding X, Saxena NK, Lin S, Xu A, Srinivasan S, Anania FA. The roles of leptin and adiponectin: a novel paradigm in adipocytokine regulation of liver fibrosis and stellate cell biology. Am J Pathol 2005;166:1655–1669. [PubMed: 15920151]

128. Dooley S, Delvoux B, Lahme B, Mangasser-Stephan K, Gressner AM. Modulation of transforming growth factor beta response and signaling during transdifferentiation of rat hepatic stellate cells to myofibroblasts. Hepatology 2000;31:1094–1106. [PubMed: 10796885]

129. Dooley S, Hamzavi J, Breitkopf K, Wiercinska E, Said HM, Lorenzen J, Ten Dijke P, Gressner AM. Smad7 prevents activation of hepatic stellate cells and liver fibrosis in rats. Gastroenterology 2003;125:178–191. [PubMed: 12851882]

130. Dooley S, Streckert M, Delvoux B, Gressner AM. Expression of Smads during in vitro transdifferentiation of hepatic stellate cells to myofibroblasts. Biochem Biophys Res Commun 2001;283:554–562. [PubMed: 11341760]

131. Draghici S, Khatri P, Eklund AC, Szallasi Z. Reliability and reproducibility issues in DNA microarray measurements. Trends Genet 2006;22:101–109. [PubMed: 16380191]

132. Dranoff JA, Ogawa M, Kruglov EA, Gaca MD, Sevigny J, Robson SC, Wells RG. Expression of P2Y nucleotide receptors and ectonucleotidases in quiescent and activated rat hepatic stellate cells. Am J Physiol Gastrointest Liver Physiol 2004;287:G417–G424. [PubMed: 14764443]

133. Duffield JS, Forbes SJ, Constandinou CM, Clay S, Partolina M, Vuthoori S, Wu S, Lang R, Iredale JP. Selective depletion of macrophages reveals distinct, opposing roles during liver injury and repair. J Clin Invest 2005;115:56–65. [PubMed: 15630444]

134. Duncan MR, Frazier KS, Abramson S, Williams S, Klapper H, Huang X, Grotendorst GR. Connective tissue growth factor mediates transforming growth factor beta-induced collagen synthesis: down-regulation by cAMP. FASEB J 1999;13:1774–1786. [PubMed: 10506580]

135. Duncan SA. Mechanisms controlling early development of the liver. Mech Dev 2003;120:19–33. [PubMed: 12490293]

136. Dupuy A, Simon RM. Critical review of published microarray studies for cancer outcome and guidelines on statistical analysis and reporting. J Natl Cancer Inst 2007;99:147–157. [PubMed: 17227998]

137. Ebrahimkhani MR, Kiani S, Oakley F, Kendall T, Shariftabrizi A, Tavangar SM, Moezi L, Payabvash S, Karoon A, Hoseininik H, Mann DA, Moore KP, Mani AR, Dehpour AR. Naltrexone,

an opioid receptor antagonist, attenuates liver fibrosis in bile duct ligated rats. Gut 2006;55:1606–1616. [PubMed: 16543289]

138. El Hag IA, Hashim FA, el Toum IA, Homeida M, el Kalifa M, el Hassan AM. Liver morphology and function in visceral leishmaniasis (Kala-azar). J Clin Pathol 1994;47:547–551. [PubMed: 8063939]

139. Elrick LJ, Leel V, Blaylock MG, Duncan L, Drever MR, Strachan G, Charlton KA, Koruth M, Porter AJ, Wright MC. Generation of a monoclonal human single chain antibody fragment to hepatic stellate cells—a potential mechanism for targeting liver anti-fibrotic therapeutics. J Hepatol 2005;42:888–896. [PubMed: 15885360]

140. Elsharkawy AM, Oakley F, Mann DA. The role and regulation of hepatic stellate cell apoptosis in reversal of liver fibrosis. Apoptosis 2005;10:927–939. [PubMed: 16151628]

141. Eng FJ, Friedman SL. Transcriptional regulation in hepatic stellate cells. Semin Liver Dis 2001;21:385–395. [PubMed: 11586467]

142. Enzan, H.; Hayashi, Y.; Miyazaki, E.; Naruse, K.; Tao, R.; Kuroda, N.; Nakayama, H.; Kiyoku, H.; Hiroi, M.; Saibara, T. Morphological aspects of hepatic fibrosis and Ito cells (hepatic stellate cells), with special reference to their myofibroblastic transformation. In: Tanikawa, K.; Ueno, T., editors. Liver Diseases and Hepatic Sinusoidal Cells. Tokyo: Springer-Verlag; 1999. p. 219-231.

143. Enzan H, Himeno H, Iwamura S, Onishi S, Saibara T, Yamamoto Y, Hara H. Alpha-smooth muscle actin-positive perisinusoidal stromal cells in human hepatocellular carcinoma. Hepatology 1994;19:895–903. [PubMed: 8138263]

144. Enzan H, Himeno H, Iwamura S, Saibara T, Onishi S, Yamamoto Y, Miyazaki E, Hara H. Sequential changes in human Ito cells and their relation to postnecrotic liver fibrosis in massive and submassive hepatic necrosis. Virchows Archiv 1995;426:95–101. [PubMed: 7704328]

145. Evans RM, Barish GD, Wang YX. PPARs and the complex journey to obesity. Nat Med 2004;10:355–361. [PubMed: 15057233]

146. Everett L, Galli A, Crabb D. The role of hepatic peroxisome proliferator-activated receptors (PPARs) in health and disease. Liver 2000;20:191–199. [PubMed: 10902968]

147. Fallowfield JA, Iredale JP. Reversal of liver fibrosis and cirrhosis—an emerging reality. Scott Med J 2004;49:3–6. [PubMed: 15012043]

148. Faouzi S, Lepreux S, Bedin C, Dubuisson L, Balabaud C, Bioulac-Sage P, Desmouliere A, Rosenbaum J. Activation of cultured rat hepatic stellate cells by tumoral hepatocytes. Lab Invest 1999;79:485–493. [PubMed: 10212001]

149. Fauci AS, Mavilio D, Kottilil S. NK cells in HIV infection: paradigm for protection or targets for ambush. Nat Rev Immunol 2005;5:835–843. [PubMed: 16239902]

150. Fehrenbach H, Weiskirchen R, Kasper M, Gressner AM. Upregulated expression of the receptor for advanced glycation end products in cultured rat hepatic stellate cells during transdifferentiation to myofibroblasts. Hepatology 2001;34:943–952. [PubMed: 11679965]

151. Feldstein AE, Papouchado BG, Angulo P, Sanderson S, Adams L, Gores GJ. Hepatic stellate cells and fibrosis progression in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2005;3:384–389. [PubMed: 15822044]

152. Fibbi G, Pucci M, Grappone C, Pellegrini G, Salzano R, Casini A, Milani S, Del Rosso M. Functions of the fibrinolytic system in human Ito cells and its control by basic fibroblast and platelet-derived growth factor. Hepatology 1999;29:868–878. [PubMed: 10051491]

153. Fimmel CJ, Brown KE, O'Neill R, Kladney RD. Complement C4 protein expression by rat hepatic stellate cells. J Immunol 1996;157:2601–2609. [PubMed: 8805663]

154. Fiorucci S, Antonelli E, Distrutti E, Severino B, Fiorentina R, Baldoni M, Caliendo G, Santagada V, Morelli A, Cirino G. PAR1 antagonism protects against experimental liver fibrosis. Role of proteinase receptors in stellate cell activation. Hepatology 2004;39:365–375. [PubMed: 14767989]

155. Fiorucci S, Antonelli E, Rizzo G, Renga B, Mencarelli A, Riccardi L, Orlandi S, Pellicciari R, Morelli A. The nuclear receptor SHP mediates inhibition of hepatic stellate cells by FXR and protects against liver fibrosis. Gastroenterology 2004;127:1497–1512. [PubMed: 15521018]

156. Fiorucci S, Rizzo G, Antonelli E, Renga B, Mencarelli A, Riccardi L, Orlandi S, Pruzanski M, Morelli A, Pellicciari R. A farnesoid X receptor-small heterodimer partner regulatory cascade modulates tissue metalloproteinase inhibitor-1 and matrix metalloprotease expression in hepatic

stellate cells and promotes resolution of liver fibrosis. J Pharmacol Exp Ther 2005;314:584–595. [PubMed: 15860571]

158. Fischer R, Cariers A, Reinehr R, Haussinger D. Caspase 9-dependent killing of hepatic stellate cells by activated Kupffer cells. Gastroenterology 2002;123:845–861. [PubMed: 12198711]

159. Flisiak R, Baraona E, Li J, Lieber CS. Effects of ethanol on prostanoid production by liver fat-storing cells. Hepatology 1993;18:153–159. [PubMed: 8325606]

160. Foucher J, Chanteloup E, Vergniol J, Castera L, Le Bail B, Adhoute X, Bertet J, Couzigou P, de Ledinghen V. Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. Gut 2006;55:403–408. [PubMed: 16020491]

161. Fountoulakis M, Suter L. Proteomic analysis of the rat liver. J Chromatogr B Analyt Technol Biomed Life Sci 2002;782:197–218.

162. Friedman G, Liu LM, Friedman SL, Boyles JK. Apolipoprotein E is secreted by cultured lipocytes of the rat liver. J Lipid Res 1991;32:107–114. [PubMed: 2010682]

163. Friedman SL. Cytokines and fibrogenesis. Semin Liver Dis 1999;19:129–140. [PubMed: 10422196]

164. Friedman SL. Mac the knife? Macrophages–the double-edged sword of hepatic fibrosis. J Clin Invest 2005;115:29–32. [PubMed: 15630440]

165. Friedman SL. Molecular regulation of hepatic fibrosis, an integrated cellular response to tissue injury. J Biol Chem 2000;275:2247–2250. [PubMed: 10644669]

166. Friedman SL. Stellate cells: a moving target in hepatic fibrogenesis. Hepatology 2004;40:1041–1043. [PubMed: 15486918]

167. Friedman SL. Transcriptional regulation of stellate cell activation. J Gastroenterol Hepatol 2006;21 3:S79–S83. [PubMed: 16958680]

168. Friedman SL, Arthur MJ. Activation of cultured rat hepatic lipocytes by Kupffer cell conditioned medium. Direct enhancement of matrix synthesis and stimulation of cell proliferation via induction of platelet-derived growth factor receptors. J Clin Invest 1989;84:1780–1785. [PubMed: 2556445]

169. Friedman SL, Arthur MJ. Reversing hepatic fibrosis. Science Medicine 2002;8:194–205.

170. Friedman SL, Bansal MB. Reversal of hepatic fibrosis: fact or fantasy? Hepatology 2006;43:S82–S88. [PubMed: 16447275]

171. Friedman SL, Rockey DC, McGuire RF, Maher JJ, Boyles JK, Yamasaki G. Isolated hepatic lipocytes and Kupffer cells from normal human liver: morphological and functional characteristics in primary culture. Hepatology 1992;15:234–243. [PubMed: 1735526]

172. Friedman SL, Roll FJ. Isolation and culture of hepatic lipocytes, Kupffer cells, sinusoidal endothelial cells by density gradient centrifugation with Stractan. Anal Biochem 1987;161:207–218. [PubMed: 3578783]

173. Friedman SL, Roll FJ, Boyles J, Arenson DM, Bissell DM. Maintenance of differentiated phenotype of cultured rat hepatic lipocytes by basement membrane matrix. J Biol Chem 1989;264:10756–10762. [PubMed: 2732246]

174. Friedman SL, Roll FJ, Boyles J, Bissell DM. Hepatic lipocytes: the principal collagen-producing cells of normal rat liver. Proc Natl Acad Sci USA 1985;82:8681–8685. [PubMed: 3909149]

175. Friedman SL, Wei S, Blaner WS. Retinol release by activated rat hepatic lipocytes: regulation by Kupffer cell-conditioned medium and PDGF. Am J Physiol Gastrointest Liver Physiol 1993;264:G947–G952.

176. Friedman SL, Yamasaki G, Wong L. Modulation of transforming growth factor beta receptors of rat lipocytes during the hepatic wound healing response. Enhanced binding and reduced gene expression accompany cellular activation in culture and in vivo. J Biol Chem 1994;269:10551–10558. [PubMed: 8144642]

177. Fujio K, Evarts RP, Hu Z, Marsden ER, Thorgeirsson SS. Expression of stem cell factor and its receptor, c-kit, during liver regeneration from putative stem cells in adult rat. Lab Invest 1994;70:511–516. [PubMed: 7513770]

178. Fujita T, Maesawa C, Oikawa K, Nitta H, Wakabayashi G, Masuda T. Interferon-gamma down-regulates expression of tumor necrosis factor-alpha converting enzyme/a disintegrin and metalloproteinase 17 in activated hepatic stellate cells of rats. Int J Mol Med 2006;17:605–616. [PubMed: 16525716]

179. Gabbiani G, Schmid E, Winter S, Chaponnier C, de Ckhastonay C, Vandekerckhove J, Weber K, Franke WW. Vascular smooth muscle cells differ from other smooth muscle cells: predominance of vimentin filaments and a specific alpha-type actin. Proc Natl Acad Sci USA 1981;78:298–302. [PubMed: 7017714]

180. Gaca MD, Zhou X, Benyon RC. Regulation of hepatic stellate cell proliferation and collagen synthesis by proteinase-activated receptors. J Hepatol 2002;36:362–369. [PubMed: 11867180]

181. Gaca MD, Zhou X, Issa R, Kiriella K, Iredale JP, Benyon RC. Basement membrane-like matrix inhibits proliferation and collagen synthesis by activated rat hepatic stellate cells: evidence for matrix-dependent deactivation of stellate cells. Matrix Biol 2003;22:229–239. [PubMed: 12853033]

182. Galambos JT, Hollingsworth MA, Falek A, Warren WD, McCain JR. The rate of synthesis of glycosaminoglycans and collagen by fibroblasts cultured from adult human liver biopsies. J Clin Invest 1977;60:107–114. [PubMed: 874075]

183. Galli A, Crabb D, Price D, Ceni E, Salzano R, Surrenti C, Casini A. Peroxisome proliferator-activated receptor gamma transcriptional regulation is involved in platelet-derived growth factor-induced proliferation of human hepatic stellate cells. Hepatology 2000;31:101–108. [PubMed: 10613734]

184. Galli A, Crabb DW, Ceni E, Salzano R, Mello T, Svegliati-Baroni G, Ridolfi F, Trozzi L, Surrenti C, Casini A. Antidiabetic thiazolidinediones inhibit collagen synthesis and hepatic stellate cell activation in vivo and in vitro. Gastroenterology 2002;122:1924–1940. [PubMed: 12055599]

185. Gao R, Brigstock DR. Connective tissue growth factor (CCN2) induces adhesion of rat activated hepatic stellate cells by binding of its C-terminal domain to integrin alpha(v)beta(3) and heparan sulfate proteoglycan. J Biol Chem 2004;279:8848–8855. [PubMed: 14684735]

186. Gao R, Brigstock DR. Low density lipoprotein receptor-related protein (LRP) is a heparin-dependent adhesion receptor for connective tissue growth factor (CTGF) in rat activated hepatic stellate cells. Hepatol Res 2003;27:214–220. [PubMed: 14585398]

187. Garcia-Blanco MA. Alternative splicing: therapeutic target and tool. Prog Mol Subcell Biol 2006;44:47–64. [PubMed: 17076264]

188. Garcia-Ruiz I, de la Torre P, Diaz T, Esteban E, Fernandez I, Munoz-Yague T, Solis-Herruzo JA. Sp1 and Sp3 transcription factors mediate malondialdehyde-induced collagen alpha 1(I) gene expression in cultured hepatic stellate cells. J Biol Chem 2002;277:30551–30558. [PubMed: 12055194]

189. Garcia-Trevijano ER, Iraburu MJ, Fontana L, Dominguez-Rosales JA, Auster A, Covarrubias-Pinedo A, Rojkind M. Transforming growth factor beta1 induces the expression of alpha1(I) procollagen mRNA by a hydrogen peroxide-C/EBPbeta-dependent mechanism in rat hepatic stellate cells. Hepatology 1999;29:960–970. [PubMed: 10051504]

190. Gascon-Barre M, Demers C, Mirshahi A, Neron S, Zalzal S, Nanci A. The normal liver harbors the vitamin D nuclear receptor in nonparenchymal and biliary epithelial cells. Hepatology 2003;37:1034–1042. [PubMed: 12717384]

191. Gawrieh S, Papouchado BG, Burgart LJ, Kobayashi S, Charlton MR, Gores GJ. Early hepatic stellate cell activation predicts severe hepatitis C recurrence after liver transplantation. Liver Transpl 2005;11:1207–1213. [PubMed: 16184568]

192. Geerts A. History, heterogeneity, developmental biology, functions of quiescent hepatic stellate cells. Semin Liver Dis 2001;21:311–335. [PubMed: 11586463]

193. Geerts A. On the origin of stellate cells: mesodermal, endodermal or neuro-ectodermal? J Hepatol 2004;40:331–334. [PubMed: 14739107]

194. Geerts A, Bouwens L, Wisse E. Ultrastructure and function of hepatic fat-storing and pit cells. J Electr Micr Tech 1990;14:247–256.

195. Geerts A, Vrijsen R, Rauterberg J, Burt A, Schellinck P, Wisse E. In vitro differentiation of fat-storing cells parallels marked increase of collagen synthesis and secretion. J Hepatol 1989;9:59–68. [PubMed: 2504809]

196. Gelfand EV, Cannon CP. Rimonabant: a selective blocker of the cannabinoid CB1 receptors for the management of obesity, smoking cessation and cardiometabolic risk factors. Expert Opin Invest Drugs 2006;15:307–315.

197. George J, Roulot D, Koteliansky VE, Bissell DM. In vivo inhibition of rat stellate cell activation by soluble transforming growth factor beta type II receptor: a potential new therapy for hepatic fibrosis. Proc Natl Acad Sci USA 1999;96:12719–12724. [PubMed: 10535989]

198. George J, Wang SS, Sevcsik AM, Sanicola M, Cate RL, Koteliansky VE, Bissell DM. Transforming growth factor-beta initiates wound repair in rat liver through induction of the EIIIA-fibronectin splice isoform. Am J Pathol 2000;156:115–124. [PubMed: 10623659]

199. Geubel AP, De Galocsy C, Alves N, Rahier J, Dive C. Liver damage caused by therapeutic vitamin A administration: estimate of dose-related toxicity in 41 cases. Gastroenterology 1991;100:1701–1709. [PubMed: 2019375]

200. Giampieri MP, Jezequel AM, Orlandi F. The lipocytes in normal human liver. Digestion 1981;22:165–169. [PubMed: 7308589]

201. Giannelli G, Antonaci S. Immunological and molecular aspects of liver fibrosis in chronic hepatitis C virus infection. Histol Histopathol 2005;20:939–944. [PubMed: 15944944]

202. Gillibert-Duplantier J, Neaud V, Blanc JF, Bioulac-Sage P, Rosenbaum J. Thrombin inhibits migration of human hepatic myofibroblasts. Am J Physiol Gastrointest Liver Physiol 2007;293:G128–G136. [PubMed: 17379757]

203. Goddard CJ, Smith A, Hoyland JA, Baird P, McMahon RF, Freemont AJ, Shomaf M, Haboubi NY, Warnes TW. Localisation and semiquantitative assessment of hepatic procollagen mRNA in primary biliary cirrhosis. Gut 1998;43:433–440. [PubMed: 9863492]

204. Gong W, Pecci A, Roth S, Lahme B, Beato M, Gressner AM. Transformation-dependent susceptibility of rat hepatic stellate cells to apoptosis induced by soluble Fas ligand. Hepatology 1998;28:492–502. [PubMed: 9696016]

205. Gorbig MN, Gines P, Bataller R, Nicolas JM, Garcia-Ramallo E, Tobias E, Titos E, Rey MJ, Claria J, Arroyo V, Rodes J. Atrial natriuretic peptide antagonizes endothelin-induced calcium increase and cell contraction in cultured human hepatic stellate cells. Hepatology 1999;30:501–509. [PubMed: 10421660]

206. Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu Rev Immunol 2005;23:515–548. [PubMed: 15771580]

207. Greenwel P, Dominguez-Rosales JA, Mavi G, Rivas-Estilla AM, Rojkind M. Hydrogen peroxide: a link between acetaldehyde-elicited alpha1(I) collagen gene up-regulation and oxidative stress in mouse hepatic stellate cells. Hepatology 2000;31:109–116. [PubMed: 10613735]

208. Greenwel P, Rubin J, Schwartz M, Hertzberg EL, Rojkind M. Liver fat-storing cell clones obtained from a CCl4-cirrhotic rat are heterogeneous with regard to proliferation, expression of extracellular matrix components, interleukin-6, connexin 43. Lab Invest 1993;69:210–216. [PubMed: 8394478]

209. Gressner AM. Cytokines and cellular crosstalk involved in the activation of fat-storing cells. J Hepatol 1995;22:28–36. [PubMed: 7665846]

210. Gressner AM. Transdifferentiation of hepatic stellate cells (Ito cells) to myofibroblasts: a key event in hepatic fibrogenesis. Kidney Int Suppl 1996;54:S39–S45. [PubMed: 8731193]

211. Gressner AM, Lahme B, Brenzel A. Molecular dissection of the mitogenic effect of hepatocytes on cultured hepatic stellate cells. Hepatology 1995;22:1507–1518. [PubMed: 7590670]

212. Gressner AM, Lahme B, Meurer SK, Gressner O, Weiskirchen R. Variable expression of cystatin C in cultured trans-differentiating rat hepatic stellate cells. World J Gastroenterol 2006;12:731–738. [PubMed: 16521186]

213. Gressner AM, Weiskirchen R, Breitkopf K, Dooley S. Roles of TGF-beta in hepatic fibrosis. Front Biosci 2002;7:D793–807. [PubMed: 11897555]

214. Gressner O, Lahme B, Gressner AM, Demirci I, Weiskirchen W. Differential effects of TGF-β on connective tissue growth factor expression in hepatic stellate cells and hepatocytes. J Hepatol 2007;47:699–710. [PubMed: 17629588]

215. Griffith LG, Swartz MA. Capturing complex 3D tissue physiology in vitro. Nat Rev Mol Cell Biol 2006;7:211–224. [PubMed: 16496023]

216. Grompe M. The origin of hepatocytes. Gastroenterology 2005;128:2158–2160. [PubMed: 15940647]

217. Grotendorst GR. Connective tissue growth factor: a mediator of TGF-beta action on fibroblasts. Cytokine Growth Factor Rev 1997;8:171–179. [PubMed: 9462483]

218. Guido M, Rugge M, Leandro G, Fiel IM, Thung SN. Hepatic stellate cell immunodetection and cirrhotic evolution of viral hepatitis in liver allografts. Hepatology 1997;26:310–314. [PubMed: 9252139]

219. Gutierrez-Ruiz MC, Gomez-Quiroz LE. Liver fibrosis: searching for cell model answers. Liver Int 2007;27:434–439. [PubMed: 17403182]

220. Gutierrez-Ruiz MC, Robles-Diaz G, Kershenobich D. Emerging concepts in inflammation and fibrosis. Arch Med Res 2002;33:595–599. [PubMed: 12505109]

221. Guyot C, Combe C, Balabaud C, Bioulac-Sage P, Desmouliere A. Fibrogenic cell fate during fibrotic tissue remodelling observed in rat and human cultured liver slices. J Hepatol 2007;46:142–150. [PubMed: 17069927]

222. Guyot C, Lepreux S, Combe C, Doudnikoff E, Bioulac-Sage P, Balabaud C, Desmouliere A. Hepatic fibrosis and cirrhosis: the (myo)fibroblastic cell subpopulations involved. Int J Biochem Cell Biol 2006;38:135–151. [PubMed: 16257564]

223. Habens F, Srinivasan N, Oakley F, Mann DA, Ganesan A, Packham G. Novel sulfasalazine analogues with enhanced NF-kB inhibitory and apoptosis promoting activity. Apoptosis 2005;10:481–491. [PubMed: 15909110]

224. Hagens WI, Olinga P, Meijer DK, Groothuis GM, Beljaars L, Poelstra K. Gliotoxin non-selectively induces apoptosis in fibrotic and normal livers. Liver Int 2006;26:232–239. [PubMed: 16448462]

225. Han YP. Matrix metalloproteinases, the pros and cons, in liver fibrosis. J Gastroenterol Hepatol 2006;21 3:S88–S91. [PubMed: 16958682]

226. Han YP, Yan C, Zhou L, Qin L, Tsukamoto H. A matrix metalloproteinase-9 activation cascade by hepatic stellate cells in transdifferentiation in the three-dimensional extracellular matrix. J Biol Chem 2007;282:12928–12939. [PubMed: 17322299]

227. Han YP, Zhou L, Wang J, Xiong S, Garner WL, French SW, Tsukamoto H. Essential role of matrix metalloproteinases in interleukin-1-induced myofibroblastic activation of hepatic stellate cell in collagen. J Biol Chem 2004;279:4820–4828. [PubMed: 14617627]

228. Hashmi AZ, Hakim W, Kruglov EA, Watanabe A, Watkins W, Dranoff JA, Mehal WZ. Adenosine inhibits cytosolic calcium signals and chemotaxis in hepatic stellate cells. Am J Physiol Gastrointest Liver Physiol 2007;292:G395–G401. [PubMed: 17053161]

229. Haughton EL, Tucker SJ, Marek CJ, Durward E, Leel V, Bascal Z, Monaghan T, Koruth M, Collie-Duguid E, Mann DA, Trim JE, Wright MC. Pregnane x receptor activators inhibit human hepatic stellate cell transdifferentiation in vitro. Gastroenterology 2006;131:194–209. [PubMed: 16831602]

230. Hautekeete ML, Dodeman I, Azais-Braesco V, Van den Berg K, Seynaeve C, Geerts A. Hepatic stellate cells and liver retinoid content in alcoholic liver disease in humans. Alcohol Clin Exp Res 1998;22:494–500. [PubMed: 9581658]

231. He QY, Lau GK, Zhou Y, Yuen ST, Lin MC, Kung HF, Chiu JF. Serum biomarkers of hepatitis B virus infected liver inflammation: a proteomic study. Proteomics 2003;3:666–674. [PubMed: 12748946]

232. Hehlgans S, Haase M, Cordes N. Signalling via integrins: implications for cell survival and anticancer strategies. Biochim Biophys Acta 2007;1775:163–180. [PubMed: 17084981]

233. Heldin P, Pertoft H, Nordlinder H, Heldin CH, Laurent TC. Differential expression of platelet-derived growth factor alpha- and beta-receptors on fat-storing cells and endothelial cells of rat liver. Exp Cell Res 1991;193:364–369. [PubMed: 1848517]

234. Hellemans K, Grinko I, Rombouts K, Schuppan D, Geerts A. All-*trans* and 9-*cis* retinoic acid alter rat hepatic stellate cell phenotype differentially. Gut 1999;45:134–142. [PubMed: 10369717]

235. Hellemans K, Michalik L, Dittie A, Knorr A, Rombouts K, De Jong J, Heirman C, Quartier E, Schuit F, Wahli W, Geerts A. Peroxisome proliferator-activated receptor-beta signaling contributes to enhanced proliferation of hepatic stellate cells. Gastroenterology 2003;124:184–201. [PubMed: 12512042]

236. Hellemans K, Verbuyst P, Quartier E, Schuit F, Rombouts K, Chandraratna RA, Schuppan D, Geerts A. Differential modulation of rat hepatic stellate phenotype by natural and synthetic retinoids. Hepatology 2004;39:97–108. [PubMed: 14752828]

237. Hellerbrand Wang SC, Tsukamoto H, Brenner DA, Rippe RA. Expression of intracellular adhesion molecule 1 by activated hepatic stellate cells. Hepatology 1996;24:670–676. [PubMed: 8781341]

238. Helyar L, Bundschuh DS, Laskin JD, Laskin DL. Induction of hepatic Ito cell nitric oxide production after acute endotoxemia. Hepatology 1994;20:1509–1515. [PubMed: 7527004]

239. Henderson NC, Mackinnon AC, Farnworth SL, Poirier F, Russo FP, Iredale JP, Haslett C, Simpson KJ, Sethi T. Galectin-3 regulates myofibroblast activation and hepatic fibrosis. Proc Natl Acad Sci USA 2006;103:5060–5065. [PubMed: 16549783]

240. Hendriks HF, Blaner WS, Wennekers HM, Piantedosi R, Brouwer A, de Leeuw AM, Goodman DS, Knook DL. Distributions of retinoids, retinoid-binding proteins and related parameters in different types of liver cells isolated from young and old rats. Eur J Biochem 1988;171:237–244. [PubMed: 2828051]

241. Hendriks HF, Verhoofstad WA, Brouwer A, de Leeuw AM, Knook DL. Perisinusoidal fat-storing cells are the main vitamin A storage sites in rat liver. Exp Cell Res 1985;160:138–149. [PubMed: 4043241]

242. Hines JE, Johnson SJ, Burt AD. In vivo responses of macrophages and perisinusoidal cells to cholestatic liver injury. Am J Pathol 1993;142:511–518. [PubMed: 8434646]

243. Hinz B, Phan SH, Thannickal VJ, Galli A, Bochaton-Piallat ML, Gabbiani G. The myofibroblast. One function multiple origins. Am J Pathol 2007;170:1807–1816. [PubMed: 17525249]

244. Horn T, Junge J, Christoffersen P. Early alcoholic liver injury. Activation of lipocytes in acinar zone 3 and correlation to degree of collagen formation in the Disse space. J Hepatol 1986;3:333–340. [PubMed: 3559143]

245. Housset C, Rockey DC, Bissell DM. Endothelin receptors in rat liver: lipocytes as a contractile target for endothelin 1. Proc Natl Acad Sci USA 1993;90:9266–9270. [PubMed: 8415690]

246. Hudnall SD. Cyclosporin A renders target cells resistant to immune cytolysis. Eur J Immunol 1991;21:221–226. [PubMed: 1846819]

247. Husser CS, Buchhalter JR, Raffo OS, Shabo A, Brown SH, Lee KE, Elkin PL. Standardization of microarray and pharmacogenomics data. Methods Mol Biol 2006;316:111–157. [PubMed: 16671403]

248. Igarashi A, Nashiro K, Kikuchi K, Sato S, Ihn H, Fujimoto M, Grotendorst GR, Takehara K. Connective tissue growth factor gene expression in tissue sections from localized scleroderma, keloid, other fibrotic skin disorders. J Invest Dermatol 1996;106:729–733. [PubMed: 8618012]

249. Ikeda K, Kawada N, Wang YQ, Kadoya H, Nakatani K, Sato M, Kaneda K. Expression of cellular prion protein in activated hepatic stellate cells. Am J Pathol 1998;153:1695–1700. [PubMed: 9846959]

250. Ikeda K, Wakahara T, Wang YQ, Kadoya H, Kawada N, Kaneda K. In vitro migratory potential of rat quiescent hepatic stellate cells and its augmentation by cell activation. Hepatology 1999;29:1760–1767. [PubMed: 10347119]

251. Ikeda K, Wang LH, Torres R, Zhao H, Olaso E, Eng FJ, Labrador P, Klein R, Lovett D, Yancopoulos GD, Friedman SL, Lin HC. Discoidin domain receptor 2 interacts with Src and Shc following its activation by type I collagen. J Biol Chem 2002;277:19206–19212. [PubMed: 11884411]

252. Ikejima K, Honda H, Yoshikawa M, Hirose M, Kitamura T, Takei Y, Sato N. Leptin augments inflammatory and profibrogenic responses in the murine liver induced by hepatotoxic chemicals. Hepatology 2001;34:288–297. [PubMed: 11481614]

253. Ikejima K, Lang T, Zhang YJ, Yamashina S, Honda H, Yoshikawa M, Hirose M, Enomoto N, Kitamura T, Takei Y, Sato N. Expression of leptin receptors in hepatic sinusoidal cells. Comp Hepatol 2004;3 1:S12. [PubMed: 14960164]

254. Ikejima K, Takei Y, Honda H, Hirose M, Yoshikawa M, Zhang YJ, Lang T, Fukuda T, Yamashina S, Kitamura T, Sato N. Leptin receptor-mediated signaling regulates hepatic fibrogenesis and remodeling of extracellular matrix in the rat. Gastroenterology 2002;122:1399–1410. [PubMed: 11984526]

255. Imai S, Okuno M, Moriwaki H, Muto Y, Murakami K, Shudo K, Suzuki Y, Kojima S. 9,13-Di-*cis*-retinoic acid induces the production of tPA and activation of latent TGF-beta via RAR alpha in a human liver stellate cell line, LI90. FEBS Lett 1997;411:102–106. [PubMed: 9247151]

256. Inagaki Y, Kushida M, Higashi K, Itoh J, Higashiyama R, Hong YY, Kawada N, Namikawa K, Kiyama H, Bou-Gharios G, Watanabe T, Okazaki I, Ikeda K. Cell type-specific intervention of transforming growth factor beta/Smad signaling suppresses collagen gene expression and hepatic fibrosis in mice. Gastroenterology 2005;129:259–268. [PubMed: 16012952]

257. Inagaki Y, Mamura M, Kanamaru Y, Greenwel P, Nemoto T, Takehara K, Ten Dijke P, Nakao A. Constitutive phosphorylation and nuclear localization of Smad3 are correlated with increased collagen gene transcription in activated hepatic stellate cells. J Cell Physiol 2001;187:117–123. [PubMed: 11241356]

258. Inagaki Y, Nemoto T, Kushida M, Sheng Y, Higashi K, Ikeda K, Kawada N, Shirasaki F, Takehara K, Sugiyama K, Fujii M, Yamauchi H, Nakao A, De Crombrugghe B, Watanabe T, Okazaki I. Interferon alfa down-regulates collagen gene transcription and suppresses experimental hepatic fibrosis in mice. Hepatology 2003;38:890–899. [PubMed: 14512876]

259. Inagaki Y, Okazaki I. Emerging insights into transforming growth factor beta smad signal in hepatic fibrogenesis. Gut 2007;56:284–292. [PubMed: 17303605]

260. Inagaki Y, Truter S, Greenwel P, Rojkind M, Unoura M, Kobayashi K, Ramirez F. Regulation of the alpha 2(I) collagen gene transcription in fat-storing cells derived from a cirrhotic liver. Hepatology 1995;22:573–579. [PubMed: 7635427]

261. Inuzuka S, Ueno T, Torimura T, Sata M, Abe H, Tanikawa K. Immunohistochemistry of the hepatic extracellular matrix in acute viral hepatitis. Hepatology 1990;12:249–256. [PubMed: 2202635]

262. Iredale JP. Hepatic stellate cell behavior during resolution of liver injury. Semin Liver Dis 2001;21:427–436. [PubMed: 11586470]

263. Iredale JP. Models of liver fibrosis: exploring the dynamic nature of inflammation and repair in a solid organ. J Clin Invest 2007;117:539–548. [PubMed: 17332881]

264. Issa R, Williams E, Trim N, Kendall T, Arthur MJ, Reichen J, Benyon RC, Iredale JP. Apoptosis of hepatic stellate cells: involvement in resolution of biliary fibrosis and regulation by soluble growth factors. Gut 2001;48:548–557. [PubMed: 11247901]

265. Itagaki T, Shimizu I, Cheng X, Yuan Y, Oshio A, Tamaki K, Fukuno H, Honda H, Okamura Y, Ito S. Opposing effects of oestradiol and progesterone on intracellular pathways and activation processes in the oxidative stress induced activation of cultured rat hepatic stellate cells. Gut 2005;54:1782–1789. [PubMed: 16284289]

266. Ito T. Cytological studies on stellate cells of Kupffer and fat storing cells in the capillary wall of human liver. Acta Anat Nippon 1951;26:2.

267. Ito Y, Aten J, Bende RJ, Oemar BS, Rabelink TJ, Weening JJ, Goldschmeding R. Expression of connective tissue growth factor in human renal fibrosis. Kidney Int 1998;53:853–861. [PubMed: 9551391]

268. Iwamoto H, Sakai H, Kotoh K, Nakamuta M, Nawata H. Soluble Arg-Gly-Asp peptides reduce collagen accumulation in cultured rat hepatic stellate cells. Dig Dis Sci 1999;44:1038–1045. [PubMed: 10235616]

269. Iwamoto H, Sakai H, Nawata H. Inhibition of integrin signaling with Arg-Gly-Asp motifs in rat hepatic stellate cells. J Hepatol 1998;29:752–759. [PubMed: 9833913]

270. Jarnagin WR, Rockey DC, Koteliansky VE, Wang SS, Bissell DM. Expression of variant fibronectins in wound healing: cellular source and biological activity of the EIIIA segment in rat hepatic fibrogenesis. J Cell Biol 1994;127:2037–2048. [PubMed: 7806580]

271. Jezequel AM, Novelli G, Venturini C, Orlandi F. Quantitative analysis of the perisinusoidal cells in human liver; the lipocytes. Front Gastrointestinal Res 1984;8:85–90.

272. Ji C, Casinghino S, McCarthy TL, Centrella M. Multiple and essential Sp1 binding sites in the promoter for transforming growth factor-beta type I receptor. J Biol Chem 1997;272:21260–21267. [PubMed: 9261136]

273. Jiang F, Parsons CJ, Stefanovic B. Gene expression profile of quiescent and activated rat hepatic stellate cells implicates Wnt signaling pathway in activation. J Hepatol 2006;45:401–409. [PubMed: 16780995]

274. Jimenez W. Endocannabinoids and liver disease. Hepatology 2005;41:983–985. [PubMed: 15841444]

275. Jiroutova A, Slavkovsky R, Cermakova M, Majdiakova L, Hanovcova I, Bolehovska R, Hajzlerova M, Radilova H, Ruszova E, Kanta J. Expression of mRNAs related to connective tissue metabolism in rat hepatic stellate cells and myofibroblasts. Exp Toxicol Pathol 2007;58:263–273. [PubMed: 17056239]

276. Jochum W, Passegue E, Wagner EF. AP-1 in mouse development and tumorigenesis. Oncogene 2001;20:2401–2412. [PubMed: 11402336]

277. Johnson SJ, Hines JE, Burt AD. Macrophage and perisinusoidal cell kinetics in acute liver injury. J Pathol 1992;166:351–358. [PubMed: 1517890]

278. Jonsson JR, Clouston AD, Ando Y, Kelemen LI, Horn MJ, Adamson MD, Purdie DM, Powell EE. Angiotensin-converting enzyme inhibition attenuates the progression of rat hepatic fibrosis. Gastroenterology 2001;121:148–155. [PubMed: 11438504]

279. Julien B, Grenard P, Teixeira-Clerc F, Van Nhieu JT, Li L, Karsak M, Zimmer A, Mallat A, Lotersztajn S. Antifibrogenic role of the cannabinoid receptor CB2 in the liver. Gastroenterology 2005;128:742–755. [PubMed: 15765409]

280. Kalinichenko VV, Bhattacharyya D, Zhou Y, Gusarova GA, Kim W, Shin B, Costa RH. Foxf1 +/− mice exhibit defective stellate cell activation and abnormal liver regeneration following CCl4 injury. Hepatology 2003;37:107–117. [PubMed: 12500195]

281. Kalluri R, Neilson EG. Epithelial-mesenchymal transition and its implications for fibrosis. J Clin Invest 2003;112:1776–1784. [PubMed: 14679171]

282. Kamada Y, Tamura S, Kiso S, Matsumoto H, Saji Y, Yoshida Y, Fukui K, Maeda N, Nishizawa H, Nagaretani H, Okamoto Y, Kihara S, Miyagawa J, Shinomura Y, Funahashi T, Matsuzawa Y. Enhanced carbon tetrachloride-induced liver fibrosis in mice lacking adiponectin. Gastroenterology 2003;125:1796–1807. [PubMed: 14724832]

283. Kamimura S, Gaal K, Britton RS, Bacon BR, Triadafilopoulos G, Tsukamoto H. Increased 4-hydroxynonenal levels in experimental alcoholic liver disease: association of lipid peroxidation with liver fibrogenesis. Hepatology 1992;16:448–453. [PubMed: 1639354]

284. Kato J, Sato Y, Inui N, Nakano Y, Takimoto R, Takada K, Kobune M, Kuroiwa G, Miyake S, Kohgo Y, Niitsu Y. Ethanol induces transforming growth factor-alpha expression in hepatocytes, leading to stimulation of collagen synthesis by hepatic stellate cells. Alcohol Clin Exp Res 2003;27:58S–63S. [PubMed: 12960509]

285. Kato M, Iwamoto H, Higashi N, Sugimoto R, Uchimura K, Tada S, Sakai H, Nakamuta M, Nawata H. Role of Rho small GTP binding protein in the regulation of actin cytoskeleton in hepatic stellate cells. J Hepatol 1999;31:91–99. [PubMed: 10424288]

286. Kawada N, Harada K, Ikeda K, Kaneda K. Morphological study of endothelin-1-induced contraction of cultured hepatic stellate cells on hydrated collagen gels. Cell Tissue Res 1996;286:477–486. [PubMed: 8929350]

287. Kawada N, Klein H, Decker K. Eicosanoid-mediated contractility of hepatic stellate cells. Biochem J 1992;285:367–371. [PubMed: 1379043]

288. Kawada N, Kristensen DB, Asahina K, Nakatani K, Minamiyama Y, Seki S, Yoshizato K. Characterization of a stellate cell activation-associated protein (STAP) with peroxidase activity found in rat hepatic stellate cells. J Biol Chem 2001;276:25318–25323. [PubMed: 11320098]

289. Kawada N, Kuroki T, Kobayashi K, Inoue M, Kaneda K, Decker K. Action of endothelins on hepatic stellate cells. J Gastroenterol 1995;30:731–738. [PubMed: 8963390]

290. Kawada N, Seki S, Kuroki T, Kaneda K. ROCK inhibitor Y-27632 attenuates stellate cell contraction and portal pressure increase induced by endothelin-1. Biochem Biophys Res Commun 1999;266:296–300. [PubMed: 10600496]

291. Kawada N, Uoya M, Seki S, Kuroki T, Kobayashi K. Regulation by cAMP of STAT1 activation in hepatic stellate cells. Biochem Biophys Res Commun 1997;233:464–469. [PubMed: 9144559]

292. Kawaguchi K, Sakaida I, Tsuchiya M, Omori K, Takami T, Okita K. Pioglitazone prevents hepatic steatosis, fibrosis, enzyme-altered lesions in rat liver cirrhosis induced by a choline-deficient L-amino acid-defined diet. Biochem Biophys Res Commun 2004;315:187–195. [PubMed: 15013444]

293. Kawashima R, Mochida S, Matsui A, YouLuTu ZY, Ishikawa K, Toshima K, Yamanobe F, Inao M, Ikeda H, Ohno A, Nagoshi S, Uede T, Fujiwara K. Expression of osteopontin in Kupffer cells and hepatic macrophages and stellate cells in rat liver after carbon tetrachloride intoxication: a

possible factor for macrophage migration into hepatic necrotic areas. Biochem Biophys Res Commun 1999;256:527–531. [PubMed: 10080931]

294. Keane MP, Strieter RM, Lynch JP 3rd, Belperio JA. Inflammation and angiogenesis in fibrotic lung disease. Semin Respir Crit Care Med 2006;27:589–599. [PubMed: 17195136]

295. Kent G, Gay S, Inouye T, Bahu R, Minick OT, Popper H. Vitamin A containing lipocytes and formation of type III collagen in liver injury. Proc Natl Acad Sci USA 1976;73:3719–3722. [PubMed: 1068482]

296. Kershenobich Stalnikowitz D, Weissbrod AB. Liver fibrosis and inflammation. A review. Ann Hepatol 2003;2:159–163. [PubMed: 15115954]

297. Keusch GT. What do -omics mean for the science and policy of the nutritional sciences? Am J Clin Nutr 2006;83:520S–522S. [PubMed: 16470024]

298. Khan MA, Poulos JE, Brunt EM, Li L, Solomon H, Britton RS, Bacon BR, Di Bisceglie AM. Hepatic alpha-smooth muscle actin expression in hepatitis C patients before and after interferon therapy. Hepatogastroenterology 2001;48:212–215. [PubMed: 11268968]

299. Kharbanda KK, Todero SL, Shubert KA, Sorrell MF, Tuma DJ. Malondialdehyde-acetaldehyde-protein adducts increase secretion of chemokines by rat hepatic stellate cells. Alcohol 2001;25:123–128. [PubMed: 11747982]

300. Kiassov AP, Van Eyken P, van Pelt JF, Depla E, Fevery J, Desmet VJ, Yap SH. Desmin expressing nonhematopoietic liver cells during rat liver development: an immunohistochemical and morphometric study. Differentiation 1995;59:253–258. [PubMed: 8575647]

301. Kikuchi S, Griffin CT, Wang SS, Bissell DM. Role of CD44 in epithelial wound repair: migration of rat hepatic stellate cells utilizes hyaluronic acid and CD44v6. J Biol Chem 2005;280:15398–15404. [PubMed: 15691832]

302. Kim KY, Rhim T, Choi I, Kim SS. *N*-acetylcysteine induces cell cycle arrest in hepatic stellate cells through its reducing activity. J Biol Chem 2001;276:40591–40598. [PubMed: 11509553]

303. Kim TH, Mars WM, Stolz DB, Michalopoulos GK. Expression and activation of pro-MMP-2 and pro-MMP-9 during rat liver regeneration. Hepatology 2000;31:75–82. [PubMed: 10613731]

304. Kim TH, Mars WM, Stolz DB, Petersen BE, Michalopoulos GK. Extracellular matrix remodeling at the early stages of liver regeneration in the rat. Hepatology 1997;26:896–904. [PubMed: 9328311]

305. Kim WH, Matsumoto K, Bessho K, Nakamura T. Growth inhibition and apoptosis in liver myofibroblasts promoted by hepatocyte growth factor leads to resolution from liver cirrhosis. Am J Pathol 2005;166:1017–1028. [PubMed: 15793283]

306. Kim Y, Ratziu V, Choi SG, Lalazar A, Theiss G, Dang Q, Kim SJ, Friedman SL. Transcriptional activation of transforming growth factor beta1 and its receptors by the Kruppel-like factor Zf9/core promoter-binding protein and Sp1. Potential mechanisms for autocrine fibrogenesis in response to injury. J Biol Chem 1998;273:33750–33758. [PubMed: 9837963]

307. Kinnman N, Francoz C, Barbu V, Wendum D, Rey C, Hultcrantz R, Poupon R, Housset C. The myofibroblastic conversion of peribiliary fibrogenic cells distinct from hepatic stellate cells is stimulated by platelet-derived growth factor during liver fibrogenesis. Lab Invest 2003;83:163–173. [PubMed: 12594232]

308. Kinnman N, Goria O, Wendum D, Gendron MC, Rey C, Poupon R, Housset C. Hepatic stellate cell proliferation is an early platelet-derived growth factor-mediated cellular event in rat cholestatic liver injury. Lab Invest 2001;81:1709–1716. [PubMed: 11742041]

309. Kinnman N, Housset C. Peribiliary myofibroblasts in biliary type liver fibrosis. Front Biosci 2002;7:D496–503. [PubMed: 11815289]

310. Kinnman N, Hultcrantz R, Barbu V, Rey C, Wendum D, Poupon R, Housset C. PDGF-mediated chemoattraction of hepatic stellate cells by bile duct segments in cholestatic liver injury. Lab Invest 2000;80:697–707. [PubMed: 10830780]

311. Kinoshita K, Iimuro Y, Otogawa K, Saika S, Inagaki Y, Nakajima Y, Kawada N, Fujimoto J, Friedman SL, Ikeda K. Adeno-virus-mediated expression of BMP-7 suppresses the development of liver fibrosis in rats. Gut 2007;56:706–714. [PubMed: 17127702]

312. Kinoshita K, Iimuro Y, Fujimoto J, Inagaki Y, Namikawa K, Kiyama H, Nakajima Y, Otogawa K, Kawada N, Friedman SL, Ikeda K. Targeted and regulable expression of transgenes in hepatic

stellate cells and myofibroblasts in culture and in vivo using an adenoviral Cre-LoxP system to antagonise hepatic fibrosis. Gut 2007;56:396–404. [PubMed: 16956920]

313. Kisseleva T, Brenner DA. Hepatic stellate cells and the reversal of fibrosis. J Gastroenterol Hepatol 2006;21 3:S84–S87. [PubMed: 16958681]

314. Kisseleva T, Uchinami H, Feirt N, Quintana-Bustamante O, Segovia JC, Schwabe RF, Brenner DA. Bone marrow-derived fibrocytes participate in pathogenesis of liver fibrosis. J Hepatol 2006;45:429–438. [PubMed: 16846660]

315. Klatsky AL, Morton C, Udaltsova N, Friedman GD. Coffee, cirrhosis, transaminase enzymes. Arch Intern Med 2006;166:1190–1195. [PubMed: 16772246]

316. Kmiec Z. Cooperation of liver cells in health and disease. Adv Anat Embryol Cell Biol 2001;161:1–151.

317. Knittel T, Aurisch S, Neubauer K, Eichhorst S, Ramadori G. Cell-type-specific expression of neural cell adhesion molecule (N-CAM) in Ito cells of rat liver. Up-regulation during in vitro activation and in hepatic tissue repair. Am J Pathol 1996;149:449–462. [PubMed: 8701984]

318. Knittel T, Dinter C, Kobold D, Neubauer K, Mehde M, Eichhorst S, Ramadori G. Expression and regulation of cell adhesion molecules by hepatic stellate cells (HSC) of rat liver: involvement of HSC in recruitment of inflammatory cells during hepatic tissue repair. Am J Pathol 1999;154:153–167. [PubMed: 9916930]

319. Knittel T, Fellmer P, Neubauer K, Kawakami M, Grundmann A, Ramadori G. The complement-activating protease P100 is expressed by hepatocytes and is induced by IL-6 in vitro and during the acute phase reaction in vivo. Lab Invest 1997;77:221–230. [PubMed: 9314946]

320. Knittel T, Fellmer P, Ramadori G. Gene expression and regulation of plasminogen activator inhibitor type I in hepatic stellate cells of rat liver. Gastroenterology 1996;111:745–754. [PubMed: 8780581]

321. Knook DL, Seffelaar AM, de Leeuw AM. Fat-storing cells of the rat liver. Their isolation and purification. Exp Cell Res 1982;139:468–471. [PubMed: 7084333]

322. Kobayashi S, Seki S, Kawada N, Morikawa H, Nakatani K, Uyama N, Ikeda K, Nakajima Y, Arakawa T, Kaneda K. Apoptosis of T cells in the hepatic fibrotic tissue of the rat: a possible inducing role of hepatic myofibroblast-like cells. Cell Tissue Res 2003;311:353–364. [PubMed: 12658443]

323. Koenig S, Probst I, Becker H, Krause P. Zonal hierarchy of differentiation markers and nestin expression during oval cell mediated rat liver regeneration. Histochem Cell Biol. 2006

324. Kopp J, Preis E, Said H, Hafemann B, Wickert L, Gressner AM, Pallua N, Dooley S. Abrogation of transforming growth factor-beta signaling by SMAD7 inhibits collagen gel contraction of human dermal fibroblasts. J Biol Chem 2005;280:21570–21576. [PubMed: 15788410]

325. Kopp J, Seyhan H, Muller B, Lanczak J, Pausch E, Gressner AM, Dooley S, Horch RE. *N*-acetyl-L-cysteine abrogates fibrogenic properties of fibroblasts isolated from Dupuytren's disease by blunting TGF-beta signalling. J Cell Mol Med 2006;10:157–165. [PubMed: 16563228]

326. Kordes C, Sawitza I, Muller-Marbach A, Ale-Agha N, Keitel V, Klonowski-Stumpe H, Haussinger D. CD133(+) hepatic stellate cells are progenitor cells. Biochem Biophys Res Commun 2007;352:410–417. [PubMed: 17118341]

327. Kremer-Tal S, Reeves HL, Narla G, Thung SN, Schwartz M, Difeo A, Katz A, Bruix J, Bioulac-Sage P, Martignetti JA, Friedman SL. Frequent inactivation of the tumor suppressor Kruppel-like factor 6 (KLF6) in hepatocellular carcinoma. Hepatology 2004;40:1047–1052. [PubMed: 15486921]

328. Kruglov E, Correa P, Arora G, Yu J, Nathanson MH, Dranoff JA. Molecular basis for calcium signaling in hepatic stellate cells. Am J Physiol Gastrointest Liver Physiol 2007;292:G975–G982. [PubMed: 17204544]

330. Kruglov EA, Nathanson RA, Nguyen T, Dranoff JA. Secretion of MCP-1/CCL2 by bile duct epithelia induces myofibroblastic transdifferentiation of portal fibroblasts. Am J Physiol Gastrointest Liver Physiol Gastrointest Liver Physiol 2006;290:G765–771.

331. Kubota H, Yao H, Reid LM. Identification and characterization of vitamin-A storing cells in fetal liver: implication of functional importance of hepatic stellate cells in development and hematopoiesis. Stem Cells 2007;25:2339–2349. [PubMed: 17585172]

332. Kunos G. The discovery of endogenous cannabinoids. Brain Res Bull 1999;50:359–360. [PubMed: 10643435]

333. Kussmann M, Raymond F, Affolter M. OMICS-driven biomarker discovery in nutrition and health. J Biotechnol 2006;124:758–787. [PubMed: 16600411]

334. Labrador JP, Azcoitia V, Tuckermann J, Lin C, Olaso E, Manes S, Bruckner K, Goergen JL, Lemke G, Yancopoulos G, Angel P, Martinez C, Klein R. The collagen receptor DDR2 regulates proliferation and its elimination leads to dwarfism. EMBO Rep 2001;2:446–452. [PubMed: 11375938]

335. Lalazar A, Wong L, Yamasaki G, Friedman SL. Early genes induced in hepatic stellate cells during wound healing. Gene 1997;195:235–243. [PubMed: 9305769]

336. Laleman W, Van Landeghem L, Severi T, Vander Elst I, Zeegers M, Bisschops R, Van Pelt J, Roskams T, Cassiman D, Fevery J, Nevens F. Both Ca^{2+}-dependent and -independent pathways are involved in rat hepatic stellate cell contraction and intrahepatic hyperresponsiveness to methoxamine. Am J Physiol Gastrointest Liver Physiol 2007;292:G556–G564. [PubMed: 17008556]

337. Lang A, Sakhnini E, Fidder HH, Maor Y, Bar-Meir S, Chowers Y. Somatostatin inhibits pro-inflammatory cytokine secretion from rat hepatic stellate cells. Liver Int 2005;25:808–816. [PubMed: 15998432]

338. Lau DT, Luxon BA, Xiao SY, Beard MR, Lemon SM. Intrahepatic gene expression profiles and alpha-smooth muscle actin patterns in hepatitis C virus induced fibrosis. Hepatology 2005;42:273–281. [PubMed: 15986378]

339. Le Pabic H, L'Helgoualc'h A, Coutant A, Wewer UM, Baffet G, Clement B, Theret N. Involvement of the serine/threonine p70(S6) kinase in TGF-beta1-induced ADAM12 expression in cultured human hepatic stellate cells. J Hepatol 2005;43:1038–1044. [PubMed: 16139919]

340. Lechuga CG, Hernandez-Nazara ZH, Hernandez E, Bustamante M, Desierto G, Cotty A, Dharker N, Choe M, Rojkind M. PI3K is involved in PDGF-β receptor upregulation post-PDGF-BB treatment in mouse HSC. Am J Physiol Gastrointest Liver Physiol 2006;291:G1051–G1061. [PubMed: 16990448]

341. Lee CH, Olson P, Hevener A, Mehl I, Chong LW, Olefsky JM, Gonzalez FJ, Ham J, Kang H, Peters JM, Evans RM. PPARdelta regulates glucose metabolism and insulin sensitivity. Proc Natl Acad Sci USA 2006;103:3444–3449. [PubMed: 16492734]

342. Lee JS, Kang Decker N, Chatterjee S, Yao J, Friedman S, Shah V. Mechanisms of nitric oxide interplay with Rho GTPase family members in modulation of actin membrane dynamics in pericytes and fibroblasts. Am J Pathol 2005;166:1861–1870. [PubMed: 15920170]

343. Lee JS, Semela D, Iredale J, Shah VH. Sinusoidal remodeling and angiogenesis: a new function for the liver-specific pericyte? Hepatology 2007;45:817–825. [PubMed: 17326208]

344. Lee SJ, Friedman SL, Whalen R, Boyer TD. Cellular sources of glutathione *S*-transferase P in primary cultured rat hepatocytes: localization by in situ hybridization. Biochem J 1994;299:79–83. [PubMed: 8166662]

345. Lees C, Howie S, Sartor RB, Satsangi J. The hedgehog signalling pathway in the gastrointestinal tract: implications for development, homeostasis, disease. Gastroenterology 2005;129:1696–1710. [PubMed: 16285967]

346. Leicester KL, Olynyk JK, Brunt EM, Britton RS, Bacon BR. CD14-positive hepatic monocytes/macrophages increase in hereditary hemochromatosis. Liver Int 2004;24:446–451. [PubMed: 15482341]

347. Levine D, Rockey DC, Milner TA, Breuss JM, Fallon JT, Schnapp LM. Expression of the integrin alpha8beta1 during pulmonary and hepatic fibrosis. Am J Pathol 2000;156:1927–1935. [PubMed: 10854216]

348. Leyland H, Gentry J, Arthur MJ, Benyon RC. The plasminogen-activating system in hepatic stellate cells. Hepatology 1996;24:1172–1178. [PubMed: 8903394]

349. Li G, Xie Q, Shi Y, Li D, Zhang M, Jiang S, Zhou H, Lu H, Jin Y. Inhibition of connective tissue growth factor by siRNA prevents liver fibrosis in rats. J Gene Med. 2006

350. Li L, Julien B, Grenard P, Teixeira-Clerc F, Mallat A, Lotersztajn S. Molecular mechanisms regulating the antifibrogenic protein heme-oxygenase-1 in human hepatic myofibroblasts. J Hepatol 2004;41:407–413. [PubMed: 15336443]

351. Li T, Weng SG, Leng XS, Peng JR, Wei YH, Mou DC, Wang WX. Effects of 5-hydroxytamine and its antagonists on hepatic stellate cells. Hepatobiliary Pancreat Dis Int 2006;5:96–100. [PubMed: 16481292]

352. Libbrecht L, Cassiman D, Desmet V, Roskams T. The correlation between portal myofibroblasts and development of intrahepatic bile ducts and arterial branches in human liver. Liver 2002;22:252–258. [PubMed: 12100576]

353. Lim YS, Lee HC, Lee HS. Switch of cadherin expression from E- to N-type during the activation of rat hepatic stellate cells. Histochem Cell Biol 2007;127:149–160. [PubMed: 16955247]

354. Lindquist J, Stefanovic B, Brenner D. Regulation of collagen alpha1(I) expression in hepatic stellate cells. J Gastroenterol 2000;35 12:80–83. [PubMed: 10779224]

355. Lindquist JN, Parsons CJ, Stefanovic B, Brenner DA. Regulation of alpha1(I) collagen messenger RNA decay by interactions with alphaCP at the 3′-untranslated region. J Biol Chem 2004;279:23822–23829. [PubMed: 14973140]

356. Lissoos TW, Beno DW, Davis BH. 1,25-Dihydroxyvitamin D$_3$ activates Raf kinase and Raf perinuclear translocation via a protein kinase C-dependent pathway. J Biol Chem 1993;268:25132–25138. [PubMed: 8227076]

357. Liu C, Gaca MD, Swenson ES, Vellucci VF, Reiss M, Wells RG. Smads 2 and 3 are differentially activated by transforming growth factor-beta (TGF-beta) in quiescent and activated hepatic stellate cells. Constitutive nuclear localization of Smads in activated cells is TGF-beta-independent. J Biol Chem 2003;278:11721–11728. [PubMed: 12547835]

358. Liu QH, Li DG, Huang X, Zong CH, Xu QF, Lu HM. Suppressive effects of 17beta-estradiol on hepatic fibrosis in CCl4-induced rat model. World J Gastroenterol 2004;10:1315–1320. [PubMed: 15112349]

359. Liu X, Hu H, Yin JQ. Therapeutic strategies against TGF-beta signaling pathway in hepatic fibrosis. Liver Int 2006;26:8–22. [PubMed: 16420505]

360. Liu XJ, Yang L, Luo FM, Wu HB, Qiang Q. Association of differentially expressed genes with activation of mouse hepatic stellate cells by high-density cDNA microarray. World J Gastroenterol 2004;10:1600–1607. [PubMed: 15162533]

361. Liu Y. Renal fibrosis: new insights into the pathogenesis and therapeutics. Kidney Int 2006;69:213–217. [PubMed: 16408108]

362. Liu Y, Wang LF, Zou HF, Song XY, Xu HF, Lin P, Zheng HH, Yu XG. Expression and location of Smad2, 4 mRNAs during and after liver fibrogenesis of rats. World J Gastroenterol 2006;12:1577–1582. [PubMed: 16570350]

363. Lotersztajn S, Julien B, Teixeira-Clerc F, Grenard P, Mallat A. Hepatic fibrosis: molecular mechanisms and drug targets. Annu Rev Pharmacol Toxicol 2005;45:605–628. [PubMed: 15471534]

364. Louis H, Le Moine O, Peny MO, Quertinmont E, Fokan D, Goldman M, Deviere J. Production and role of interleukin-10 in concanavalin A-induced hepatitis in mice. Hepatology 1997;25:1382–1389. [PubMed: 9185757]

365. Louis H, Van Laethem JL, Wu W, Quertinmont E, Degraef C, Van den Berg K, Demols A, Goldman M, Le Moine O, Geerts A, Deviere J. Interleukin-10 controls neutrophilic infiltration, hepatocyte proliferation, liver fibrosis induced by carbon tetrachloride in mice. Hepatology 1998;28:1607–1615. [PubMed: 9828225]

366. MacDonald GA, Bridle KR, Ward PJ, Walker NI, Houglum K, George DK, Smith JL, Powell LW, Crawford DH, Ramm GA. Lipid peroxidation in hepatic steatosis in humans is associated with hepatic fibrosis and occurs predominantly in acinar zone 3. J Gastroenterol Hepatol 2001;16:599–606. [PubMed: 11422610]

367. Magness ST, Bataller R, Yang L, Brenner DA. A dual reporter gene transgenic mouse demonstrates heterogeneity in hepatic fibrogenic cell populations. Hepatology 2004;40:1151–1159. [PubMed: 15389867]

368. Maher JJ. Cell-specific expression of hepatocyte growth factor in liver. Upregulation in sinusoidal endothelial cells after carbon tetrachloride. J Clin Invest 1993;91:2244–2252. [PubMed: 7683700]

369. Maher JJ. Interactions between hepatic stellate cells and the immune system. Semin Liver Dis 2001;21:417–426. [PubMed: 11586469]

370. Maher JJ, Friedman SL. Parenchymal and nonparenchymal cell interactions in the liver. Semin Liver Dis 1993;13:13–20. [PubMed: 8446905]

371. Maher JJ, Friedman SL, Roll FJ, Bissell DM. Immunolocalization of laminin in normal rat liver and biosynthesis of laminin by hepatic lipocytes in primary culture. Gastroenterology 1988;94:1053–1062. [PubMed: 3278941]

372. Maher JJ, Lozier JS, Scott MK. Rat hepatic stellate cells produce cytokine-induced neutrophil chemoattractant in culture and in vivo. Am J Physiol Gastrointest Liver Physiol 1998;275:G847–G853.

373. Maher JJ, Neuschwander-Tetri BA. Manipulation of glutathione stores in rat hepatic stellate cells does not alter collagen synthesis. Hepatology 1997;26:618–623. [PubMed: 9303491]

374. Maher JJ, Saito JM, Neuschwander-Tetri BA. Glutathione regulation in rat hepatic stellate cells Comparative studies in primary culture and in liver injury in vivo. Biochem Pharmacol 1997;53:637–641. [PubMed: 9113082]

375. Majack RA, Castle CK, Goodman LV, Weisgraber KH, Mahley RW, Shooter EM, Gebicke-Haerter PJ. Expression of apolipoprotein E by cultured vascular smooth muscle cells is controlled by growth state. J Cell Biol 1988;107:1207–1213. [PubMed: 2458361]

376. Mallat A, Preaux AM, Serradeil-Le G, Raufaste D, Gallois C, Brenner DA, Bradham C, Maclouf J, Iourgenko V, Fourassier L, Dhumeaux D, Mavier P, Lotersztajn S. Growth inhibitory properties of endothelin-A in activated human stellate cells: a cyclic adenosine monophosphate-mediated pathway. J Clin Invest 1996;98:2771–2778. [PubMed: 8981923]

377. Mallat A, Preaux AM, Serradeil-Le Gal C, Raufaste D, Gallois C, Brenner DA, Bradham C, Maclouf J, Iourgenko V, Fouassier L, Dhumeaux D, Mavier P, Lotersztajn S. Growth inhibitory properties of endothelin-1 in activated human hepatic stellate cells: a cyclic adenosine monophosphate-mediated pathway Inhibition of both extracellular signal-regulated kinase and c-Jun kinase and upregulation of endothelin B receptors. J Clin Invest 1996;98:2771–2778. [PubMed: 8981923]

378. Mancini R, Jezequel AM, Benedetti A, Paolucci F, Trozzi L, Orlandi F. Quantitative analysis of proliferating sinusoidal cells in dimethylnitrosamine-induced cirrhosis. An immunohistochemical study. J Hepatol 1992;15:361–366. [PubMed: 1447503]

379. Mann DA, Smart DE. Transcriptional regulation of hepatic stellate cell activation. Gut 2002;50:891–896. [PubMed: 12010897]

380. Mann J, Oakley F, Akiboye F, Elsharkawy A, Thorne AW, Mann DA. Regulation of myofibroblast transdifferentiation by DNA methylation and MeCP2: implications for wound healing and fibrogenesis. Cell Death Differ 2006;14:275–285. [PubMed: 16763620]

382. Mao TK, Kimura Y, Kenny TP, Branchi A, Gishi RG, Van de Water J, Kung HJ, Friedman SL, Gershwin ME. Elevated expression of tyrosine kinase DDR2 in primary biliary cirrhosis. Autoimmunity 2002;35:521–529. [PubMed: 12765478]

383. March S, Graupera M, Rosa Sarrias M, Lozano F, Pizcueta P, Bosch J, Engel P. Identification and functional characterization of the hepatic stellate cell CD38 cell surface molecule. Am J Pathol 2007;170:176–187. [PubMed: 17200192]

384. Marek CJ, Tucker SJ, Konstantinou DK, Elrick LJ, Haefner D, Sigalas C, Murray GI, Goodwin B, Wright MC. Pregnenolone-16alpha-carbonitrile inhibits rodent liver fibrogenesis via PXR (pregnane X receptor)-dependent and PXR-independent mechanisms. Biochem J 2005;387:601–608. [PubMed: 15595924]

385. Marra F. Chemokines in liver inflammation and fibrosis. Front Biosci 2002;7:d1899–1914. [PubMed: 12161342]

386. Marra F, Aleffi S, Bertolani C, Petrai I, Vizzutti F. Adipokines and liver fibrosis. Eur Rev Med Pharmacol Sci 2005;9:279–284. [PubMed: 16231590]

387. Marra F, Choudhury GG, Pinzani M, Abboud HE. Regulation of platelet-derived growth factor secretion and gene expression in human liver fat-storing cells. Gastroenterology 1994;107:1110–1117. [PubMed: 7926460]

388. Marra F, DeFranco R, Grappone C, Milani S, Pinzani M, Pellegrini G, Laffi G, Gentilini P. Expression of the thrombin receptor in human liver: up-regulation during acute and chronic injury. Hepatology 1998;27:462–471. [PubMed: 9462645]

389. Marra F, Efsen E, Romanelli RG, Caligiuri A, Pastacaldi S, Batignani G, Bonacchi A, Caporale R, Laffi G, Pinzani M, Gentilini P. Ligands of peroxisome proliferator-activated receptor gamma modulate profibrogenic and proinflammatory actions in hepatic stellate cells. Gastroenterology 2000;119:466–478. [PubMed: 10930382]

390. Marra F, Gentilini A, Pinzani M, Choudhury GG, Parola M, Herbst H, Dianzani MU, Laffi G, Abboud HE, Gentilini P. Phosphatidylinositol 3-kinase is required for platelet-derived growth factor's actions on hepatic stellate cells. Gastroenterology 1997;112:1297–1306. [PubMed: 9098016]

391. Marra F, Grandaliano G, Valente AJ, Abboud HE. Thrombin stimulates proliferation of liver fat-storing cells and expression of monocyte chemotactic protein-1: potential role in liver injury. Hepatology 1995;22:780–787. [PubMed: 7657283]

392. Marra F, Pastacaldi S, Romanelli RG, Pinzani M, Ticali P, Carloni V, Laffi G, Gentilini P. Integrin-mediated stimulation of monocyte chemotactic protein-1 expression. FEBS Lett 1997;414:221–225. [PubMed: 9315690]

393. Marra F, Pinzani M. Role of hepatic stellate cells in the pathogenesis of portal hypertension. Nefrologia 2002;22 5:34–40. [PubMed: 12107915]

394. Marra F, Romanelli RG, Giannini C, Failli P, Pastacaldi S, Arrighi MC, Pinzani M, Laffi G, Montalto P, Gentilini P. Monocyte chemotactic protein-1 as a chemoattractant for human hepatic stellate cells. Hepatology 1999;29:140–148. [PubMed: 9862860]

395. Marra F, Valente AJ, Pinzani M, Abboud HE. Cultured human liver fat-storing cells produce monocyte chemotactic protein-1. Regulation by proinflammatory cytokines. J Clin Invest 1993;92:1674–1680. [PubMed: 8408620]

396. Mars WM, Kim TH, Stolz DB, Liu ML, Michalopoulos GK. Presence of urokinase in serum-free primary rat hepatocyte cultures and its role in activating hepatocyte growth factor. Cancer Res 1996;56:2837–2843. [PubMed: 8665523]

397. Marsden ER, Hu Z, Fujio K, Nakatsukasa H, Thorgeirsson SS, Evarts RP. Expression of acidic fibroblast growth factor in regenerating liver and during hepatic differentiation. Lab Invest 1992;67:427–433. [PubMed: 1279268]

398. Martinez-Hernandez A. The hepatic extracellular matrix. I. Electron immunohistochemical studies in normal rat liver. Lab Invest 1984;51:57–74. [PubMed: 6376944]

399. Martinon F, Petrilli V, Mayor A, Tardivel A, Tschopp J. Gout-associated uric acid crystals activate the NALP3 inflammasome. Nature 2006;440:237–241. [PubMed: 16407889]

400. Mashiba S, Mochida S, Ishikawa K, Inao M, Matsui A, Ohno A, Ikeda H, Nagoshi S, Shibuya M, Fujiwara K. Inhibition of hepatic stellate cell contraction during activation in vitro by vascular endothelial growth factor in association with upregulation of FLT tyrosine kinase receptor family, FLT-1. Biochem Biophys Res Commun 1999;258:674–678. [PubMed: 10329444]

401. Mathew J, Geerts A, Burt AD. Pathobiology of hepatic stellate cells. Hepatogastroenterology 1996;43:72–91. [PubMed: 8682490]

402. Mathew J, Hines JE, James OF, Burt AD. Non-parenchymal cell responses in paracetamol (acetaminophen)-induced liver injury. J Hepatol 1994;20:537–541. [PubMed: 8051394]

403. Matsumoto K, Yoshitomi H, Rossant J, Zaret KS. Liver organogenesis promoted by endothelial cells prior to vascular function. Science 2001;294:559–563. [PubMed: 11577199]

404. Matsuoka M, Tsukamoto H. Stimulation of hepatic lipocyte collagen production by Kupffer cell-derived transforming growth factor beta: implication for a pathogenetic role in alcoholic liver fibrogenesis. Hepatology 1990;11:599–605. [PubMed: 2328954]

405. Matsuoka M, Zhang MY, Tsukamoto H. Sensitization of hepatic lipocytes by high-fat diet to stimulatory effects of Kupffer cell-derived factors: implication in alcoholic liver fibrogenesis. Hepatology 1990;11:173–182. [PubMed: 2307396]

406. Matsuura T, Nagamori S, Fujise K, Hasumura S, Homma S, Sujino H, Shimizu K, Niiya M, Kameda H, Hirosawa K. Retinol transport in cultured fat storing cells of rat liver. Quantitative analysis by anchored cell analysis and sorting system. Lab Invest 1989;61:107–115. [PubMed: 2747215]

407. Maubach G, Lim MC, Zhang CY, Zhuo L. GFAP promoter directs lacZ expression specifically in a rat hepatic stellate cell line. World J Gastroenterol 2006;12:723–730. [PubMed: 16521185]

408. Mazzocca A, Carloni V, Sciammetta S, Cordella C, Pantaleo P, Caldini A, Gentilini P, Pinzani M. Expression of transmembrane 4 superfamily (TM4SF) proteins and their role in hepatic stellate cell motility and wound healing migration. J Hepatol 2002;37:322–330. [PubMed: 12175627]

409. McGee JO, Patrick RS. The role of perisinusoidal cells in hepatic fibrogenesis. An electron microscopic study of acute carbon tetrachloride liver injury. Lab Invest 1972;264:429–440. [PubMed: 4336540]

410. Meijer DK, Beljaars L, Molema G, Poelstra K. Disease-induced drug targeting using novel peptide-ligand albumins. J Control Release 2001;72:157–164. [PubMed: 11389994]

411. Melgert BN, Olinga P, Van Der Laan JM, Weert B, Cho J, Schuppan D, Groothuis GM, Meijer DK, Poelstra K. Targeting dexamethasone to Kupffer cells: effects on liver inflammation and fibrosis in rats. Hepatology 2001;34:719–728. [PubMed: 11584368]

412. Melhem A, Muhanna N, Bishara A, Alvarez CE, Ilan Y, Bishara T, Horani A, Nassar M, Friedman SL, Safadi R. Anti-fibrotic activity of NK cells in experimental liver injury through killing of activated HSC. J Hepatol 2006;45:60–71. [PubMed: 16515819]

413. Melton AC, Datta A, Yee HF Jr. [Ca^{2+}]$_i$-independent contractile force generation by rat hepatic stellate cells in response to endothelin-1. Am J Physiol Gastrointest Liver Physiol 2006;290:G7–G13. [PubMed: 16123199]

414. Melton AC, Yee HF. Hepatic stellate cell protrusions couple platelet-derived growth factor-BB to chemotaxis. Hepatology 2007;45:1446–1453. [PubMed: 17465006]

415. Meneses-Lorente G, Watt A, Salim K, Gaskell SJ, Muniappa N, Lawrence J, Guest PC. Identification of early proteomic markers for hepatic steatosis. Chem Res Toxicol 2006;19:986–998. [PubMed: 16918237]

416. Meyer DH, Bachem MG, Gressner AM. Modulation of hepatic lipocyte proteoglycan synthesis and proliferation by Kupffer cell-derived transforming growth factors type beta 1 and type alpha. Biochem Biophys Res Commun 1990;171:1122–1129. [PubMed: 1699522]

417. Meyer DH, Krull N, Dreher KL, Gressner AM. Biglycan and decorin gene expression in normal and fibrotic rat liver: cellular localization and regulatory factors. Hepatology 1992;16:204–216. [PubMed: 1618472]

418. Midwood KS, Mao Y, Hsia HC, Valenick LV, Schwarzbauer JE. Modulation of cell-fibronectin matrix interactions during tissue repair. J Invest Dermatol Symp Proc 2006;11:73–78.

419. Mikula M, Proell V, Fischer AN, Mikulits W. Activated hepatic stellate cells induce tumor progression of neoplastic hepatocytes in a TGF-beta dependent fashion. J Cell Physiol 2006;209:560–567. [PubMed: 16883581]

420. Milani S, Herbst H, Schuppan D, Grappone C, Pellegrini G, Pinzani M, Casini A, Calabro A, Ciancio G, Stefanini F, Burroughs AK, Surrenti C. Differential expression of matrix-metalloproteinase-1 and -2 genes in normal and fibrotic human liver. Am J Pathol 1994;144:528–537. [PubMed: 8129038]

421. Minato Y, Hasumura Y, Takeuchi J. The role of fat-storing cells in Disse space fibrogenesis in alcoholic liver disease. Hepatology 1983;3:559–566. [PubMed: 6862368]

422. Miyahara T, Schrum L, Rippe R, Xiong S, Yee HF Jr, Motomura K, Anania FA, Willson TM, Tsukamoto H. Peroxisome proliferator-activated receptors and hepatic stellate cell activation. J Biol Chem 2000;275:35715–35722. [PubMed: 10969082]

423. Mizobuchi Y, Shimizu I, Yasuda M, Hori H, Shono M, Ito S. Retinyl palmitate reduces hepatic fibrosis in rats induced by dimethylnitrosamine or pig serum. J Hepatol 1998;29:933–943. [PubMed: 9875640]

424. Morishima C, Paschal DM, Wang CC, Yoshihara CS, Wood BL, Yeo AE, Emerson SS, Shuhart MC, Gretch DR. Decreased NK cell frequency in chronic hepatitis C does not affect ex vivo cytolytic killing. Hepatology 2006;43:573–580. [PubMed: 16496327]

425. Moriwaki H, Blaner WS, Piantedosi R, Goodman DS. Effects of dietary retinoid and triglyceride on the lipid composition of rat liver stellate cells and stellate cell lipid droplets. J Lipid Res 1988;29:1523–1534. [PubMed: 3241127]

426. Morrison N, Cochrane G, Faruque N, Tatusova T, Tateno Y, Hancock D, Field D. Concept of sample in OMICS technology. Omics 2006;10:127–137. [PubMed: 16901217]

427. Mullhaupt B, Feren A, Fodor E, Jones A. Liver expression of epidermal growth factor RNA. Rapid increases in immediate-early phase of liver regeneration. J Biol Chem 1994;269:19667–19670. [PubMed: 7519599]

428. Murakami K, Abe T, Miyazawa M, Yamaguchi M, Masuda T, Matsuura T, Nagamori S, Takeuchi K, Abe K, Kyogoku M. Establishment of a new human cell line, LI90, exhibiting characteristics of hepatic Ito (fat-storing) cells. Lab Invest 1995;72:731–739. [PubMed: 7540235]

429. Murphy FR, Issa R, Zhou X, Ratnarajah S, Nagase H, Arthur MJ, Benyon C, Iredale JP. Inhibition of apoptosis of activated hepatic stellate cells by tissue inhibitor of metalloproteinase-1 is mediated via effects on matrix metalloproteinase inhibition: implications for reversibility of liver fibrosis. J Biol Chem 2002;277:11069–11076. [PubMed: 11796725]

430. Myung SJ, Yoon JH, Gwak GY, Kim W, Yang JI, Lee SH, Jang JJ, Lee HS. Bile acid-mediated thrombospondin-1 induction in hepatocytes leads to transforming growth factor-beta-dependent hepatic stellate cell activation. Biochem Biophys Res Commun 2007;353:1091–1096. [PubMed: 17204245]

431. Nagy NE, Holven KB, Roos N, Senoo H, Kojima N, Norum KR, Blomhoff R. Storage of vitamin A in extrahepatic stellate cells in normal rats. J Lipid Res 1997;38:645–658. [PubMed: 9144080]

432. Nakamura T, Arii S, Monden K, Furutani M, Takeda Y, Imamura M, Tominaga M, Okada Y. Expression of the Na^+/Ca^{2+} exchanger emerges in hepatic stellate cells after activation in association with liver fibrosis. Proc Natl Acad Sci USA 1998;95:5389–5394. [PubMed: 9560286]

433. Nakane PK. Ito's fat storing cell of the mouse liver. Anat Rec 1963;145:265–266.

434. Nakatani K, Okuyama H, Shimahara Y, Saeki S, Kim DH, Nakajima Y, Seki S, Kawada N, Yoshizato K. Cytoglobin/STAP, its unique localization in splanchnic fibroblast-like cells and function in organ fibrogenesis. Lab Invest 2004;84:91–101. [PubMed: 14647402]

435. Nakatani K, Seki S, Kawada N, Kobayashi K, Kaneda K. Expression of neural cell adhesion molecule (N-CAM) in perisinusoidal stellate cells of the human liver. Cell Tissue Res 1996;283:159–165. [PubMed: 8581955]

436. Nakatani K, Tanaka H, Ikeda K, Sakabe M, Kadoya H, Seki S, Kaneda K, Nakajima Y. Expression of NCAM in activated portal fibroblasts during regeneration of the rat liver after partial hepatectomy. Arch Histol Cytol 2006;69:61–72. [PubMed: 16609270]

437. Narla G, Difeo A, Reeves HL, Schaid DJ, Hirshfeld J, Hod E, Katz A, Isaacs WB, Hebbring S, Komiya A, McDonnell SK, Wiley KE, Jacobsen SJ, Isaacs SD, Walsh PC, Zheng SL, Chang BL, Friedrichsen DM, Stanford JL, Ostrander EA, Chinnaiyan AM, Rubin MA, Xu J, Thibodeau SN, Friedman SL, Martignetti JA. A germline DNA polymorphism enhances alternative splicing of the KLF6 tumor suppressor gene and is associated with increased prostate cancer risk. Cancer Res 2005;65:1213–1222. [PubMed: 15735005]

438. Narla G, DiFeo A, Yao S, Banno A, Hod E, Reeves HL, Qiao RF, Camacho-Vanegas O, Levine A, Kirschenbaum A, Chan AM, Friedman SL, Martignetti JA. Targeted inhibition of the KLF6 splice variant, KLF6 SV1, suppresses prostate cancer cell growth and spread. Cancer Res 2005;65:5761–5768. [PubMed: 15994951]

439. Narla G, Heath KE, Reeves HL, Li D, Giono LE, Kimmelman AC, Glucksman MJ, Narla J, Eng FJ, Chan AM, Ferrari AC, Martignetti JA, Friedman SL. KLF6, a candidate tumor suppressor gene mutated in prostate cancer. Science 2001;294:2563–2566. [PubMed: 11752579]

440. Natarajan SK, Thomas S, Ramachandran A, Pulimood AB, Balasubramanian KA. Retinoid metabolism during development of liver cirrhosis. Arch Biochem Biophys 2005;443:93–100. [PubMed: 16248980]

441. Neuschwander-Tetri BA, Brunt EM, Wehmeier KR, Sponseller CA, Hampton K, Bacon BR. Interim results of a pilot study demonstrating the early effects of the PPAR-gamma ligand rosiglitazone on insulin sensitivity, aminotransferases, hepatic steatosis and body weight in patients with nonalcoholic steatohepatitis. J Hepatol 2003;38:434–440. [PubMed: 12663234]

442. Neyzen S, Van de Leur E, Borkham-Kamphorst E, Herrmann J, Hollweg G, Gressner AM, Weiskirchen R. Cryopreservation of hepatic stellate cells. J Hepatol 2006;44:910–917. [PubMed: 16169118]

443. Nieto N, Friedman SL, Cederbaum AI. Cytochrome *P*450 2E1-derived reactive oxygen species mediate paracrine stimulation of collagen I protein synthesis by hepatic stellate cells. J Biol Chem 2002;277:9853–9864. [PubMed: 11782477]

444. Nieto N, Friedman SL, Cederbaum AI. Stimulation and proliferation of primary rat hepatic stellate cells by cytochrome P450 2E1-derived reactive oxygen species. Hepatology 2002;35:62–73. [PubMed: 11786960]

445. Nieto N, Friedman SL, Greenwel P, Cederbaum AI. CYP2E1-mediated oxidative stress induces collagen type I expression in rat hepatic stellate cells. Hepatology 1999;30:987–996. [PubMed: 10498651]

446. Nieto N, Greenwel P, Friedman SL, Zhang F, Dannenberg AJ, Cederbaum AI. Ethanol and arachidonic acid increase alpha 2(I) collagen expression in rat hepatic stellate cells overexpressing cytochrome P450 2E1. Role of H_2O_2 and cyclooxygenase-2. J Biol Chem 2000;275:20136–20145. [PubMed: 10770928]

447. Niiya M, Uemura M, Zheng XW, Pollak ES, Dockal M, Scheiflinger F, Wells RG, Zheng XL. Increased ADAMTS-13 proteolytic activity in rat hepatic stellate cells upon activation in vitro and in vivo. J Thromb Haemost 2006;4:1063–1070. [PubMed: 16689760]

448. Niki T, Pekny M, Hellemans K, Bleser PD, Berg KV, Vaeyens F, Quartier E, Schuit F, Geerts A. Class VI intermediate filament protein nestin is induced during activation of rat hepatic stellate cells. Hepatology 1999;29:520–527. [PubMed: 9918930]

448a. Hepatic stellate cell nomenclature. Hepatology 1996;23:193. No authors listed. [PubMed: 8550043]

449. Nollevaux MC, Guiot Y, Horsmans Y, Leclercq I, Rahier J, Geubel AP, Sempoux C. Hypervitaminosis A-induced liver fibrosis: stellate cell activation and daily dose consumption. Liver Int 2006;26:182–186. [PubMed: 16448456]

450. Novo E, Marra F, Zamara E, Valfre di Bonzo L, Caligiuri A, Cannito S, Antonaci C, Colombatto S, Pinzani M, Parola M. Dose dependent and divergent effects of superoxide anion on cell death, proliferation, migration of activated human hepatic stellate cells. Gut 2006;55:90–97. [PubMed: 16041064]

451. O'Brien CA, Pollett A, Gallinger S, Dick JE. A human colon cancer cell capable of initiating tumour growth in immunodeficient mice. Nature 2007;445:106–110. [PubMed: 17122772]

452. Oakley F, Mann J, Nailard S, Smart DE, Mungalsingh N, Constandinou C, Ali S, Wilson SJ, Millward-Sadler H, Iredale JP, Mann DA. Nuclear factor-kappaB1 (p50) limits the inflammatory and fibrogenic responses to chronic injury. Am J Pathol 2005;166:695–708. [PubMed: 15743782]

453. Oakley F, Meso M, Iredale JP, Green K, Marek CJ, Zhou X, May MJ, Millward-Sadler H, Wright MC, Mann DA. Inhibition of inhibitor of kappaB kinases stimulates hepatic stellate cell apoptosis and accelerated recovery from rat liver fibrosis. Gastroenterology 2005;128:108–120. [PubMed: 15633128]

454. Oakley F, Trim N, Constandinou CM, Ye W, Gray AM, Frantz G, Hillan K, Kendall T, Benyon RC, Mann DA, Iredale JP. Hepatocytes express nerve growth factor during liver injury: evidence for paracrine regulation of hepatic stellate cell apoptosis. Am J Pathol 2003;163:1849–1858. [PubMed: 14578185]

455. Oben JA, Roskams T, Yang S, Lin H, Sinelli N, Torbenson M, Smedh U, Moran TH, Li Z, Huang J, Thomas SA, Diehl AM. Hepatic fibrogenesis requires sympathetic neurotransmitters. Gut 2004;53:438–445. [PubMed: 14960531]

456. Oh SH, Cho KH, Yang BS, Roh YK. Natural compounds from Danshen suppress the activity of hepatic stellate cells. Arch Pharm Res 2006;29:762–767. [PubMed: 17024850]

457. Ohata M, Lin M, Satre M, Tsukamoto H. Diminished retinoic acid signaling in hepatic stellate cells in cholestatic liver fibrosis. Am J Physiol Gastrointest Liver Physiol 1997;272:G589–G596.

458. Ohnishi H, Miyata T, Yasuda H, Satoh Y, Hanatsuka K, Kita H, Ohashi A, Tamada K, Makita N, Iiri T, Ueda N, Mashima H, Sugano K. Distinct roles of Smad2-, Smad3-, ERK-dependent pathways in transforming growth factor-beta1 regulation of pancreatic stellate cellular functions. J Biol Chem 2004;279:8873–8878. [PubMed: 14688282]

459. Okanoue T, Burbige EJ, French SW. The role of the Ito cell in perivenular and intralobular fibrosis in alcoholic hepatitis. Arch Pathol Lab Med 1983;107:459–463. [PubMed: 6688340]

460. Okuno M, Moriwaki H, Imai S, Muto Y, Kawada N, Suzuki Y, Kojima S. Retinoids exacerbate rat liver fibrosis by inducing the activation of latent TGF-beta in liver stellate cells. Hepatology 1997;26:913–921. [PubMed: 9328313]

461. Okuno M, Sato T, Kitamoto T, Imai S, Kawada N, Suzuki Y, Yoshimura H, Moriwaki H, Onuki K, Masushige S, Muto Y, Friedman SL, Kato S, Kojima S. Increased 9,13-di-*cis*-retinoic acid in rat hepatic fibrosis: implication for a potential link between retinoid loss and TGF-beta mediated fibrogenesis in vivo. J Hepatol 1999;30:1073–1080. [PubMed: 10406186]

462. Olaso E, Ikeda K, Eng FJ, Xu L, Wang LH, Lin HC, Friedman SL. DDR2 receptor promotes MMP-2-mediated proliferation and invasion by hepatic stellate cells. J Clin Invest 2001;108:1369–1378. [PubMed: 11696582]

463. Olaso E, Ikeda K, Eng FJ, Xu L, Wang LH, Lin HC, Friedman SL. DDR2 receptor promotes MMP-2-mediated proliferation and invasion by hepatic stellate cells. J Clin Invest 2001;108:1369–1378. [PubMed: 11696582]

464. Olaso E, Salado C, Egilegor E, Gutierrez V, Santisteban A, Sancho-Bru P, Friedman SL, Vidal-Vanaclocha F. Proangiogenic role of tumor-activated hepatic stellate cells in experimental melanoma metastasis. Hepatology 2003;37:674–685. [PubMed: 12601365]

465. Olaso E, Santisteban A, Bidaurrazaga J, Gressner AM, Rosenbaum J, Vidal-Vanaclocha F. Tumor-dependent activation of rodent hepatic stellate cells during experimental melanoma metastasis. Hepatology 1997;26:634–642. [PubMed: 9303493]

466. Omary MB, Lugea A, Lowe AW, Pandol SJ. The pancreatic stellate cell: a star on the rise in pancreatic diseases. J Clin Invest 2007;117:50–59. [PubMed: 17200706]

467. Osawa Y, Seki E, Adachi M, Taura K, Kodama Y, Siegmund SV, Schwabe RF, Brenner DA. Systemic mediators induce fibrogenic effects in normal liver after partial bile duct ligation. Liver Int 2006;26:1138–1147. [PubMed: 17032415]

468. Otte C, Otte JM, Strodthoff D, Bornstein SR, Folsch UR, Monig H, Kloehn S. Expression of leptin and leptin receptor during the development of liver fibrosis and cirrhosis. Exp Clin Endocrinol Diabetes 2004;112:10–17. [PubMed: 14758566]

469. Ozaki I, Zhao G, Mizuta T, Ogawa Y, Hara T, Kajihara S, Hisatomi A, Sakai T, Yamamoto K. Hepatocyte growth factor induces collagenase (matrix metalloproteinase-1) via the transcription factor Ets-1 in human hepatic stellate cell line. J Hepatol 2002;36:169–178. [PubMed: 11830328]

470. Ozaki S, Sato Y, Yasoshima M, Harada K, Nakanuma Y. Diffuse expression of heparan sulfate proteoglycan and connective tissue growth factor in fibrous septa with many mast cells relate to unresolving hepatic fibrosis of congenital hepatic fibrosis. Liver Int 2005;25:817–828. [PubMed: 15998433]

471. Paik YH, Lee KS, Lee HJ, Yang KM, Lee SJ, Lee DK, Han KH, Chon CY, Lee SI, Moon YM, Brenner DA. Hepatic stellate cells primed with cytokines upregulate inflammation in response to peptidoglycan or lipoteichoic acid. Lab Invest 2006;86:676–686. [PubMed: 16619004]

472. Paik YH, Schwabe RF, Bataller R, Russo MP, Jobin C, Brenner DA. Toll-like receptor 4 mediates inflammatory signaling by bacterial lipopolysaccharide in human hepatic stellate cells. Hepatology 2003;37:1043–1055. [PubMed: 12717385]

473. Pan Q, Li DG, Lu HM, Lu LY, You HN, Xu QF. Relationship between somatostatin receptors and activation of hepatic stellate cells. Chin Med J 2004;117:1665–1669. [PubMed: 15569483]

474. Pan Q, Li DG, Lu HM, Wang YQ, Zhang WZ, Xu QF. A new immortalized rat cell line, hepatic stellate cell-PQ, exhibiting characteristics of hepatic stellate cell. Hepatobiliary Pancreat Dis Int 2005;4:281–284. [PubMed: 15908330]

475. Paradis V, Dargere D, Bonvoust F, Vidaud M, Segarini P, Bedossa P. Effects and regulation of connective tissue growth factor on hepatic stellate cells. Lab Invest 2002;82:767–774. [PubMed: 12065687]

476. Paradis V, Dargere D, Vidaud M, De Gouville AC, Huet S, Martinez V, Gauthier JM, Ba N, Sobesky R, Ratziu V, Bedossa P. Expression of connective tissue growth factor in experimental rat and human liver fibrosis. Hepatology 1999;30:968–976. [PubMed: 10498649]

477. Paradis V, Perlemuter G, Bonvoust F, Dargere D, Parfait B, Vidaud M, Conti M, Huet S, Ba N, Buffet C, Bedossa P. High glucose and hyperinsulinemia stimulate connective tissue growth factor

expression: a potential mechanism involved in progression to fibrosis in nonalcoholic steatohepatitis. Hepatology 2001;34:738–744. [PubMed: 11584370]

478. Parola M, Leonarduzzi G, Robino G, Albano E, Poli G, Dianzani MU. On the role of lipid peroxidation in the pathogenesis of liver damage induced by long-standing cholestasis. Free Radical Biol Med 1996;20:351–359. [PubMed: 8720905]

479. Parola M, Pinzani M, Casini A, Albano E, Poli G, Gentilini A, Gentilini P, Dianzani MU. Stimulation of lipid peroxidation or 4-hydroxynonenal treatment increases procollagen alpha 1 (I) gene expression in human liver fat-storing cells. Biochem Biophys Res Commun 1993;194:1044–1050. [PubMed: 8352762]

480. Parola M, Robino G, Bordone R, Leonarduzzi G, Casini A, Pinzani M, Neve E, Bellomo G, Dianzani MU, Ingelman-Sundberg M, Albano E. Detection of cytochrome P4503A (CYP3A) in human hepatic stellate cells. Biochem Biophys Res Commun 1997;238:420–424. [PubMed: 9299524]

481. Passino MA, Adams RA, Sikorski SL, Akassoglou K. Regulation of hepatic stellate cell differentiation by the neurotrophin receptor p75NTR. Science 2007;315:1853–1856. [PubMed: 17395831]

482. Patella S, Phillips DJ, Tchongue J, de Kretser DM, Sievert W. Follistatin attenuates early liver fibrosis: effects on hepatic stellate cell activation and hepatocyte apoptosis. Am J Physiol Gastrointest Liver Physiol 2006;290:G137–G144. [PubMed: 16123203]

483. Perri RE, Langer DA, Chatterjee S, Gibbons SJ, Gadgil J, Cao S, Farrugia G, Shah VH. Defects in cGMP-PKG pathway contribute to impaired NO-dependent responses in hepatic stellate cells upon activation. Am J Physiol Gastrointest Liver Physiol 2006;290:G535–G542. [PubMed: 16269521]

484. Petricoin E, Wulfkuhle J, Espina V, Liotta LA. Clinical proteomics: revolutionizing disease detection and patient tailoring therapy. J Proteome Res 2004;3:209–217. [PubMed: 15113096]

485. Pietrangelo A. Iron-induced oxidant stress in alcoholic liver fibrogenesis. Alcohol 2003;30:121–129. [PubMed: 12957296]

486. Pinzani M. PDGF and signal transduction in hepatic stellate cells. Front Biosci 2002;7:d1720–1726. [PubMed: 12133817]

487. Pinzani M, Abboud HE, Aron DC. Secretion of insulin-like growth factor-I and binding proteins by rat liver fat-storing cells: regulatory role of platelet-derived growth factor. Endocrinology 1990;127:2343–2349. [PubMed: 1699746]

488. Pinzani M, Abboud HE, Gesualdo L, Abboud SL. Regulation of macrophage colony-stimulating factor in liver fat-storing cells by peptide growth factors. Am J Physiol Cell Physiol 1992;262:C876–C881.

489. Pinzani M, Carloni V, Marra F, Riccardi D, Laffi G, Gentilini P. Biosynthesis of platelet-activating factor and its 1O-acyl analogue by liver fat-storing cells. Gastroenterology 1994;106:1301–1311. [PubMed: 8174891]

490. Pinzani M, Failli P, Ruocco C, Casini A, Milani S, Baldi E, Giotti A, Gentilini P. Fat-storing cells as liver-specific pericytes. Spatial dynamics of agonist-stimulated intracellular calcium transients. J Clin Invest 1992;90:642–646. [PubMed: 1644929]

491. Pinzani M, Gentilini A, Caligiuri A, De FR, Pellegrini G, Milani S, Marra F, Gentilini P. Transforming growth factor-beta 1 regulates platelet-derived growth factor receptor beta subunit in human liver fat-storing cells. Hepatology 1995;21:232–239. [PubMed: 7806159]

492. Pinzani M, Gesualdo L, Sabbah GM, Abboud HE. Effects of platelet-derived growth factor and other polypeptide mitogens on DNA synthesis and growth of cultured rat liver fat-storing cells. J Clin Invest 1989;84:1786–1793. [PubMed: 2592560]

493. Pinzani M, Knauss TC, Pierce GF, Hsieh P, Kenney W, Dubyak GR, Abboud HE. Mitogenic signals for platelet-derived growth factor isoforms in liver fat-storing cells. Am J Physiol Cell Physiol 1991;260:C485–C491.

494. Pinzani M, Marra F. Cytokine receptors and signaling in hepatic stellate cells. Semin Liver Dis 2001;21:397–416. [PubMed: 11586468]

495. Pinzani M, Milani S, De FR, Grappone C, Caligiuri A, Gentilini A, Tosti GC, Maggi M, Failli P, Ruocco C, Gentilini P. Endothelin 1 is overexpressed in human cirrhotic liver and exerts multiple effects on activated hepatic stellate cells. Gastroenterology 1996;110:534–548. [PubMed: 8566602]

496. Pinzani M, Milani S, Grappone C, Weber FJ, Gentilini P, Abboud HE. Expression of platelet-derived growth factor in a model of acute liver injury. Hepatology 1994;19:701–707. [PubMed: 8119696]

497. Planaguma A, Claria J, Miquel R, Lopez-Parra M, Titos E, Masferrer JL, Arroyo V, Rodes J. The selective cyclooxygenase-2 inhibitor SC-236 reduces liver fibrosis by mechanisms involving non-parenchymal cell apoptosis and PPARgamma activation. FASEB J 2005;19:1120–1122. [PubMed: 15876570]

498. Poon TC, Hui AY, Chan HL, Ang IL, Chow SM, Wong N, Sung JJ. Prediction of liver fibrosis and cirrhosis in chronic hepatitis B infection by serum proteomic fingerprinting: a pilot study. Clin Chem 2005;51:328–335. [PubMed: 15590748]

499. Popper H. Distribution of vitamin A in tissue as visualized by flourescence microscopy. Physiol Rev 1944;24:205–224.

500. Porter FD, Drago J, Xu Y, Cheema SS, Wassif C, Huang SP, Lee E, Grinberg A, Massalas JS, Bodine D, Alt F, Westphal H. Lhx2, a LIM homeobox gene, is required for eye, forebrain, definitive erythrocyte development. Development 1997;124:2935–2944. [PubMed: 9247336]

501. Potter JJ, Womack L, Mezey E, Anania FA. Transdifferentiation of rat hepatic stellate cells results in leptin expression. Biochem Biophys Res Commun 1998;244:178–182. [PubMed: 9514867]

502. Poynard T, Mathurin P, Lai CL, Guyader D, Poupon R, Tainturier MH, Myers RP, Muntenau M, Ratziu V, Manns M, Vogel A, Capron F, Chedid A, Bedossa P. A comparison of fibrosis progression in chronic liver diseases. J Hepatol 2003;38:257–265. [PubMed: 12586290]

503. Promrat K, Lutchman G, Uwaifo GI, Freedman RJ, Soza A, Heller T, Doo E, Ghany M, Premkumar A, Park Y, Liang TJ, Yanovski JA, Kleiner DE, Hoofnagle JH. A pilot study of pioglitazone treatment for nonalcoholic steatohepatitis. Hepatology 2004;39:188–196. [PubMed: 14752837]

504. Purps O, Lahme B, Gressner AM, Meindl-Beinker NM, Dooley S. Loss of TGF-beta dependent growth control during HSC transdifferentiation. Biochem Biophys Res Commun 2007;353:841–847. [PubMed: 17204247]

505. Qamar A, Sheikh SZ, Masud A, Jhandier MN, Inayat IB, Hakim W, Mehal WZ. In vitro and in vivo protection of stellate cells from apoptosis by leptin. Dig Dis Sci 2006;51:1697–1705. [PubMed: 16957995]

506. Qiang H, Lin Y, Zhang X, Zeng X, Shi J, Chen YX, Yang MF, Han ZG, Xie WF. Differential expression genes analyzed by cDNA array in the regulation of rat hepatic fibrogenesis. Liver Int 2006;26:1126–1137. [PubMed: 17032414]

507. Rachfal AW, Brigstock DR. Connective tissue growth factor (CTGF/CCN2) in hepatic fibrosis. Hepatol Res 2003;26:1–9. [PubMed: 12787797]

508. Racine-Samson L, Rockey DC, Bissell DM. Expression of the collagen-binding integrins alpha1 beta1 and alpha 2 beta1 during activation of rat hepatic stellate cells in vivo. J Biol Chem. 1997

509. Racine-Samson L, Rockey DC, Bissell DM. The role of alpha1beta1 integrin in wound contraction. A quantitative analysis of liver myofibroblasts in vivo and in primary culture. J Biol Chem 1997;272:30911–30917. [PubMed: 9388237]

510. Radaeva S, Sun R, Jaruga B, Nguyen VT, Tian Z, Gao B. Natural killer cells ameliorate liver fibrosis by killing activated stellate cells in NKG2D-dependent and tumor necrosis factor-related apoptosis-inducing ligand-dependent manners. Gastroenterology 2006;130:435–452. [PubMed: 16472598]

511. Raddatz D, Henneken M, Armbrust T, Ramadori G. Subcellular distribution of glucocorticoid receptor in cultured rat and human liver-derived cells and cell lines: influence of dexamethasone. Hepatology 1996;24:928–933. [PubMed: 8855200]

512. Ramadori G, Knittel T, Schwogler S, Bieber F, Rieder H, Meyer ZBK. Dexamethasone modulates alpha 2-macroglobulin and apolipoprotein E gene expression in cultured rat liver fatstoring (Ito) cells. Hepatology 1991;14:875–882. [PubMed: 1718836]

514. Ramadori G, Veit T, Schwogler S, Dienes HP, Knittel T, Rieder H, Meyer zum Buschenfelde KH. Expression of the gene of the alpha-smooth muscle-actin isoform in rat liver and in rat fat-storing (ITO) cells. Virchows Arch B Cell Pathol Incl Mol Pathol 1990;59:349–357. [PubMed: 1705733]

515. Ramalho LN, Ramalho FS, Zucoloto S, Castro-e-Silva Junior O, Correa FM, Elias Junior J, Magalhaes JF. Effect of losartan, an angiotensin II antagonist, on secondary biliary cirrhosis. Hepatogastroenterology 2002;49:1499–1502. [PubMed: 12397717]

516. Ramm GA, Britton RS, O'Neill R, Bacon BR. Identification and characterization of a receptor for tissue ferritin on activated rat lipocytes. J Clin Invest 1994;94:9–15. [PubMed: 8040296]

517. Ramm GA, Britton RS, O'Neill R, Blaner WS, Bacon BR. Vitamin A-poor lipocytes: a novel desmin-negative lipocyte subpopulation, which can be activated to myofibroblasts. Am J Physiol Gastrointest Liver Physiol 1995;269:G532–G541.

518. Ramm GA, Crawford DH, Powell LW, Walker NI, Fletcher LM, Halliday JW. Hepatic stellate cell activation in genetic haemochromatosis. Lobular distribution, effect of increasing hepatic iron and response to phlebotomy. J Hepatol 1997;26:584–592. [PubMed: 9075666]

519. Ramm GA, Ruddell RG. Hepatotoxicity of iron overload: mechanisms of iron-induced hepatic fibrogenesis. Semin Liver Dis 2005;25:433–449. [PubMed: 16315137]

520. Reeves HL, Burt AD, Wood S, Day CP. Hepatic stellate cell activation occurs in the absence of hepatitis in alcoholic liver disease and correlates with the severity of steatosis. J Hepatol 1996;25:677–683. [PubMed: 8938545]

521. Reeves HL, Narla G, Ogunbiyi O, Haq AI, Katz A, Benzeno S, Hod E, Harpaz N, Goldberg S, Tal-Kremer S, Eng FJ, Arthur MJ, Martignetti JA, Friedman SL. Kruppel-like factor 6 (KLF6) is a tumor-suppressor gene frequently inactivated in colorectal cancer. Gastroenterology 2004;126:1090–1103. [PubMed: 15057748]

522. Reimann T, Hempel U, Krautwald S, Axmann A, Scheibe R, Seidel D, Wenzel KW. Transforming growth factor-beta1 induces activation of Ras, Raf-1, MEK and MAPK in rat hepatic stellate cells. FEBS Lett 1997;403:57–60. [PubMed: 9038360]

523. Resnick JM, Whitley CB, Leonard AS, Krivit W, Snover DC. Light and electron microscopic features of the liver in mucopoly-saccharidosis. Hum Pathol 1994;25:276–286. [PubMed: 8150458]

524. Reynaert H, Rombouts K, Vandermonde A, Urbain D, Kumar U, Bioulac-Sage P, Pinzani M, Rosenbaum J, Geerts A. Expression of somatostatin receptors in normal and cirrhotic human liver and in hepatocellular carcinoma. Gut 2004;53:1180–1189. [PubMed: 15247189]

525. Reynaert H, Thompson MG, Thomas T, Geerts A. Hepatic stellate cells: role in microcirculation and pathophysiology of portal hypertension. Gut 2002;50:571–581. [PubMed: 11889082]

526. Ricci-Vitiani L, Lombardi DG, Pilozzi E, Biffoni M, Todaro M, Peschle C, De Maria R. Identification and expansion of human colon-cancer-initiating cells. Nature 2007;445:111–115. [PubMed: 17122771]

527. Rimola A, Londono MC, Guevara G, Bruguera M, Navasa M, Forns X, Garcia-Retortillo M, Garcia-Valdecasas JC, Rodes J. Beneficial effect of angiotensin-blocking agents on graft fibrosis in hepatitis C recurrence after liver transplantation. Transplantation 2004;78:686–691. [PubMed: 15371669]

528. Rippe RA. Role of transcriptional factors in stellate cell activation. Alcohol Clin Exp Res 1999;23:926–929. [PubMed: 10371416]

529. Rippe RA, Brenner DA. From quiescence to activation: gene regulation in hepatic stellate cells. Gastroenterology 2004;127:1260–1262. [PubMed: 15481004]

530. Rivera CA, Bradford BU, Hunt KJ, Adachi Y, Schrum LW, Koop DR, Burchardt ER, Rippe RA, Thurman RG. Attenuation of CCl(4)-induced hepatic fibrosis by GdCl(3) treatment or dietary glycine. Am J Physiol Gastrointest Liver Physiol 2001;281:G200–G207. [PubMed: 11408273]

531. Rizzo G, Renga B, Mencarelli A, Pellicciari R, Fiorucci S. Role of FXR in regulating bile acid homeostasis and relevance for human diseases. Curr Drug Targets Immune Endocr Metabol Disord 2005;5:289–303. [PubMed: 16178789]

532. Rizzo S, Attard G, Hudson DL. Prostate epithelial stem cells. Cell Prolif 2005;38:363–374. [PubMed: 16300650]

533. Rockey D, Chung J. Inducible nitric oxide synthase in rat hepatic lipocytes and the effect of nitric oxide on lipocyte contractility. J Clin Invest 1995;95:1199–1206. [PubMed: 7533786]

534. Rockey DC. Cellular pathophysiology of portal hypertension and prospects for management with gene therapy. Clin Liver Dis 2001;5:851–865. [PubMed: 11565144]

535. Rockey DC. Characterization of endothelin receptors mediating rat hepatic stellate cell contraction. Biochem Biophys Res Commun 1995;207:725–731. [PubMed: 7864865]

536. Rockey DC. Hepatic blood flow regulation by stellate cells in normal and injured liver. Semin Liver Dis 2001;21:337–350. [PubMed: 11586464]

537. Rockey DC. Vascular mediators in the injured liver. Hepatology 2003;37:4–12. [PubMed: 12500181]

538. Rockey DC, Boyles JK, Gabbiani G, Friedman SL. Rat hepatic lipocytes express smooth muscle actin upon activation in vivo and in culture. J Submicrosc Cytol Pathol 1992;24:193–203. [PubMed: 1600511]

539. Rockey DC, Chung JJ. Endothelin antagonism in experimental hepatic fibrosis. Implications for endothelin in the pathogenesis of wound healing. J Clin Invest 1996;98:1381–1388. [PubMed: 8823303]

540. Rockey DC, Chung JJ. Inducible nitric oxide synthase in rat hepatic lipocytes and the effect of nitric oxide on lipocyte contractility. J Clin Invest 1995;95:1199–1206. [PubMed: 7533786]

541. Rockey DC, Chung JJ. Interferon gamma inhibits lipocyte activation and extracellular matrix mRNA expression during experimental liver injury: implications for treatment of hepatic fibrosis. J Invest Med 1994;42:660–670.

542. Rockey DC, Chung JJ. Reduced nitric oxide production by endothelial cells in cirrhotic rat liver: endothelial dysfunction in portal hypertension. Gastroenterology 1998;114:344–351. [PubMed: 9453496]

543. Rockey DC, Chung JJ. Regulation of inducible nitric oxide synthase in hepatic sinusoidal endothelial cells. Am J Physiol Gastrointest Liver Physiol 1996;271:G260–G267.

544. Rockey DC, Fouassier L, Chung JJ, Carayon A, Vallee P, Rey C, Housset C. Cellular localization of endothelin-1 and increased production in liver injury in the rat: potential for autocrine and paracrine effects on stellate cells. Hepatology 1998;27:472–480. [PubMed: 9462646]

545. Rockey DC, Weisiger RA. Endothelin induced contractility of stellate cells from normal and cirrhotic rat liver: implications for regulation of portal pressure and resistance. Hepatology 1996;24:233–240. [PubMed: 8707268]

546. Rombouts K, Knittel T, Machesky L, Braet F, Wielant A, Hellemans K, De Bleser P, Gelman I, Ramadori G, Geerts A. Actin filament formation, reorganization and migration are impaired in hepatic stellate cells under influence of trichostatin A, a histone deacetylase inhibitor. J Hepatol 2002;37:788–796. [PubMed: 12445420]

547. Rosenbaum J, Blazejewski S. Regulation of Ito cell proliferation by soluble factors. J Hepatol 1995;22:65–70. [PubMed: 7545195]

548. Rosenbaum J, Blazejewski S, Preaux AM, Mallat A, Dhumeaux D, Mavier P. Fibroblast growth factor 2 and transforming growth factor beta 1 interactions in human liver myofibroblasts. Gastroenterology 1995;109:1986–1996. [PubMed: 7498665]

549. Roskams T. Different types of liver progenitor cells and their niches. J Hepatol 2006;45:1–4. [PubMed: 16723168]

550. Roskams T, Cassiman D, De Vos R, Libbrecht L. Neuroregulation of the neuroendocrine compartment of the liver. Anat Rec A Discov Mol Cell Evol Biol 2004;280:910–923. [PubMed: 15382010]

551. Ross AC, Zolfaghari R. Regulation of hepatic retinol metabolism: perspectives from studies on vitamin A status. J Nutr 2004;134:269S–275S. [PubMed: 14704332]

552. Roth-Eichhorn S, Eberheim A, Bode HP, Gressner AM. Transformation-dependent calcium influx by voltage-operated calcium channels in stellate cells of rat liver. J Hepatol 1999;30:612–620. [PubMed: 10207802]

553. Rubbia-Brandt L, Mentha G, Desmouliere A, Alto Costa AM, Giostra E, Molas G, Enzan H, Gabbiani G. Hepatic stellate cells reversibly express alpha-smooth muscle actin during acute hepatic ischemia. Transplant Proc 1997;29:2390–2395. [PubMed: 9270776]

554. Ruddell RG, Oakley F, Hussain Z, Yeung I, Bryan-Lluka LJ, Ramm GA, Mann DA. A role for serotonin (5-HT) in hepatic stellate cell function and liver fibrosis. Am J Pathol 2006;169:861–876. [PubMed: 16936262]

555. Rudolph R, McClure WJ, Woodward M. Contractile fibroblasts in chronic alcoholic cirrhosis. Gastroenterology 1979;76:704–709. [PubMed: 421998]

556. Ruhl CE, Everhart JE. Coffee and caffeine consumption reduce the risk of elevated serum alanine aminotransferase activity in the United States. Gastroenterology 2005;128:24–32. [PubMed: 15633120]

557. Ruhl CE, Everhart JE. Coffee and tea consumption are associated with a lower incidence of chronic liver disease in the United States. Gastroenterology 2005;129:1928–1936. [PubMed: 16344061]

558. Russo MW, Firpi RJ, Nelson DR, Schoonhoven R, Shrestha R, Fried MW. Early hepatic stellate cell activation is associated with advanced fibrosis after liver transplantation in recipients with hepatitis C. Liver Transplant 2005;11:1235–1241.

559. Safadi R, Ohta M, Alvarez CE, Fiel MI, Bansal M, Mehal WZ, Friedman SL. Immune stimulation of hepatic fibrogenesis by CD8 cells and attenuation by transgenic interleukin-10 from hepatocytes. Gastroenterology 2004;127:870–882. [PubMed: 15362042]

560. Sancho-Bru P, Bataller R, Colmenero J, Gasull X, Moreno M, Arroyo V, Brenner DA, Gines P. Norepinephrine induces calcium spikes and proinflammatory actions in human hepatic stellate cells. Am J Physiol Gastrointest Liver Physiol 2006;291:G877–G884. [PubMed: 16782692]

561. Sancho-Bru P, Bataller R, Gasull X, Colmenero J, Khurdayan V, Gual A, Nicolas JM, Arroyo V, Gines P. Genomic and functional characterization of stellate cells isolated from human cirrhotic livers. J Hepatol 2005;43:272–282. [PubMed: 15964095]

562. Sanz-Cameno P, Martin-Vilchez S, Lara-Pezzi E, Borque MJ, Salmeron J, Munoz de Rueda P, Solis JA, Lopez-Cabrera M, Moreno-Otero R. Hepatitis B virus promotes angiopoietin-2 expression in liver tissue: role of HBV x protein. Am J Pathol 2006;169:1215–1222. [PubMed: 17003480]

563. Sauvant P, Abergel A, Partier A, Alexandre-Gouabau MC, Rock E, Sion B, Motta C, Sapin V, Azais-Bresco V. Treatment of the rat hepatic stellate cell line, PAV-1, by retinol and palmitic acid leads to a convenient model to study retinoids metabolism. Biol Cell 2002;94:401–408. [PubMed: 12500946]

564. Sauvant P, Sapin V, Abergel A, Schmidt CK, Blanchon L, Alexandre-Gouabau MC, Rosenbaum J, Bommelaer G, Rock E, Dastugue B, Nau H, Azais-Braesco V. PAV-1, a new rat hepatic stellate cell line converts retinol into retinoic acid, a process altered by ethanol. Int J Biochem Cell Biol 2002;34:1017–1029. [PubMed: 12007639]

565. Saxena NK, Ikeda K, Rockey DC, Friedman SL, Anania FA. Leptin in hepatic fibrosis: evidence for increased collagen production in stellate cells and lean littermates of *ob/ob* mice. Hepatology 2002;35:762–771. [PubMed: 11915021]

566. Saxena NK, Titus MA, Ding X, Floyd J, Srinivasan S, Sitaraman SV, Anania FA. Leptin as a novel profibrogenic cytokine in hepatic stellate cells: mitogenesis and inhibition of apoptosis mediated by extracellular regulated kinase (Erk) and Akt phosphorylation. FASEB J 2004;18:1612–1614. [PubMed: 15319373]

567. Schaefer B, Rivas-Estilla AM, Meraz-Cruz N, Reyes-Romero MA, Hernandez-Nazara ZH, Dominguez-Rosales JA, Schuppan D, Greenwel P, Rojkind M. Reciprocal modulation of matrix metalloproteinase-13 and type I collagen genes in rat hepatic stellate cells. Am J Pathol 2003;162:1771–1780. [PubMed: 12759235]

568. Schirmacher P, Geerts A, Pietrangelo A, Dienes HP, Rogler CE. Hepatocyte growth factor/hepatopoietin A is expressed in fat-storing cells from rat liver but not myofibroblast-like cells derived from fat-storing cells. Hepatology 1992;15:5–11. [PubMed: 1530788]

569. Schmitt-Graeff A, Jing R, Nitschke R, Desmouliere A, Skalli O. Synemin expression is widespread in liver fibrosis and is induced in proliferating and malignant biliary epithelial cells. Hum Pathol 2006;37:1200–1210. [PubMed: 16938526]

570. Schmitt-Graff A, Chakroun G, Gabbiani G. Modulation of perisinusoidal cell cytoskeletal features during experimental hepatic fibrosis. Virchows Arch A Pathol Anat Histopathol 1993;422:99–107. [PubMed: 8465518]

571. Schmitt-Graff A, Desmouliere A, Gabbiani G. Heterogeneity of myofibroblast phenotypic features: an example of fibroblastic cell plasticity. Virchows Archiv 1994;425:3–24. [PubMed: 7921410]

572. Schmitt-Graff A, Kruger S, Bochard F, Gabbiani G, Denk H. Modulation of alpha smooth muscle actin and desmin expression in perisinusoidal cells of normal and diseased human livers. Am J Pathol 1991;138:1233–1242. [PubMed: 2024709]

573. Schnabl B, Choi YH, Hagedorn CH, Bataller R. DNA microarrays and data mining to study hepatic fibrosis. Methods Mol Med 2005;117:359–369. [PubMed: 16118462]

574. Schnabl B, Choi YH, Olsen JC, Hagedorn CH, Brenner DA. Immortal activated human hepatic stellate cells generated by ectopic telomerase expression. Lab Invest 2002;82:323–333. [PubMed: 11896211]

575. Schnabl B, Purbeck CA, Choi YH, Hagedorn CH, Brenner D. Replicative senescence of activated human hepatic stellate cells is accompanied by a pronounced inflammatory but less fibrogenic phenotype. Hepatology 2003;37:653–664. [PubMed: 12601363]

576. Schneiderhan W, Schmid-Kotsas A, Zhao J, Grunert A, Nussler A, Weidenbach H, Menke A, Schmid RM, Adler G, Bachem MG. Oxidized low-density lipoproteins bind to the scavenger receptor, CD36, of hepatic stellate cells and stimulate extracellular matrix synthesis. Hepatology 2001;34:729–737. [PubMed: 11584369]

577. Schuftan GG, Bachem MG. Alpha2-macroglobulin reduces paracrine- and autocrine-stimulated matrix synthesis of cultured rat hepatic stellate cells. Eur J Clin Invest 1999;29:519–528. [PubMed: 10354214]

578. Schulze-Krebs A, Preimel D, Popov Y, Bartenschlager R, Lohmann V, Pinzani M, Schuppan D. Hepatitis C virus-replicating hepatocytes induce fibrogenic activation of hepatic stellate cells. Gastroenterology 2005;129:246–258. [PubMed: 16012951]

579. Schuppan D, Ruehl M, Somasundaram R, Hahn EG. Matrix as a modulator of hepatic fibrogenesis. Semin Liver Dis 2001;21:351–372. [PubMed: 11586465]

580. Schwabe RF, Bataller R, Brenner DA. Human hepatic stellate cells express CCR5 and RANTES to induce proliferation and migration. Am J Physiol Gastrointest Liver Physiol 2003;285:G949–G958. [PubMed: 12829440]

581. Schwabe RF, Schnabl B, Kweon YO, Brenner DA. CD40 activates NF-kappa B and c-Jun N-terminal kinase and enhances chemokine secretion on activated human hepatic stellate cells. J Immunol 2001;166:6812–6819. [PubMed: 11359840]

582. Seifert WF, Bosma A, Brouwer A, Hendriks HF, Roholl PJ, van Leeuwen RE, van Thiel-de Ruiter GC, Seifert-Bock I, Knook DL. Vitamin A deficiency potentiates carbon tetrachloride-induced liver fibrosis in rats. Hepatology 1994;19:193–201. [PubMed: 8276355]

583. Seifert, WF.; Bosma, A.; Hendriks, HFJ.; de Ruiter, GCF.; van Leeuwen, REW.; Knook, DL.; Brouwer, A. Dual role of vitamin A in experimentally induced liver fibrosis. In: Wisse, E.; Knook, DL.; Decker, K., editors. Cells of the Hepatic Sinusoid. Rijswijk: The Kupffer Cell Foundation; 1989. p. 43-48.

584. Seki S, De Minicis S, Österreicher CH, Kluwe J, Osawa Y, Brenner DA, Schwabe RF. TLR4 mediates hepatic fibrosis by downregulating TGFβ pseudoreceptor BAMBI and enhancing TGFβ signaling. Nature Medicine. In press.

585. Senoo H, Imai K, Sato M, Kojima N, Miura M, Hata R. Three-dimensional structure of extracellular matrix reversibly regulates morphology, proliferation and collagen metabolism of perisinusoidal stellate cells (vitamin A-storing cells). Cell Biol Int 1996;20:501–512. [PubMed: 8931317]

586. Senoo H, Kojima N, Sato M. Vitamin A-storing cells (stellate cells). Vitam Horm 2007;75:131–159. [PubMed: 17368315]

587. Senoo H, Sato M, Imai K. Hepatic stellate cells—from the viewpoint of retinoid handling and function of the extracellular matrix. Kaibogaku Zasshi 1997;72:79–94. [PubMed: 9153961]

588. Senoo H, Wake K. Suppression of experimental hepatic fibrosis by administration of vitamin A. Lab Invest 1985;52:182–194. [PubMed: 2578584]

589. Serini G, Gabbiani G. Mechanisms of myofibroblast activity and phenotypic modulation. Exp Cell Res 1999;250:273–283. [PubMed: 10413583]

590. Shackel N, Rockey D. In pursuit of the "Holy Grail"—stem cells, hepatic injury, fibrogenesis and repair. Hepatology 2005;41:16–18. [PubMed: 15690475]

591. Shackel NA, McGuinness PH, Abbott CA, Gorrell MD, McCaughan GW. Insights into the pathobiology of hepatitis C virus-associated cirrhosis: analysis of intrahepatic differential gene expression. Am J Pathol 2002;160:641–654. [PubMed: 11839585]

592. Shackel NA, McGuinness PH, Abbott CA, Gorrell MD, McCaughan GW. Novel differential gene expression in human cirrhosis detected by suppression subtractive hybridization. Hepatology 2003;38:577–588. [PubMed: 12939584]

593. Shafiei MS, Rockey DC. The role of integrin-linked kinase in liver wound healing. J Biol Chem 2006;281:24863–24872. [PubMed: 16728409]

594. She H, Xiong S, Hazra S, Tsukamoto H. Adipogenic transcriptional regulation of hepatic stellate cells. J Biol Chem 2005;280:4959–4967. [PubMed: 15537655]

595. Shen H, Huang G, Hadi M, Choy P, Zhang M, Minuk GY, Chen Y, Gong Y. Transforming growth factor-beta1 downregulation of Smad1 gene expression in rat hepatic stellate cells. Am J Physiol Gastrointest Liver Physiol 2003;285:G539–G546. [PubMed: 12791600]

596. Shi YF, Fong CC, Zhang Q, Cheung PY, Tzang CH, Wu RS, Yang M. Hypoxia induces the activation of human hepatic stellate cells LX-2 through TGF-beta signaling pathway. FEBS Lett 2007;581:203–210. [PubMed: 17187782]

597. Shibata N, Watanabe T, Okitsu T, Sakaguchi M, Takesue M, Kunieda T, Omoto K, Yamamoto S, Tanaka N, Kobayashi N. Establishment of an immortalized human hepatic stellate cell line to develop antifibrotic therapies. Cell Transplant 2003;12:499–507. [PubMed: 12953924]

598. Shimizu I. Impact of oestrogens on the progression of liver disease. Liver Int 2003;23:63–69. [PubMed: 12640729]

599. Shin JY, Hur W, Wang JS, Jang JW, Kim CW, Bae SH, Jang SK, Yang SH, Sung YC, Kwon OJ, Yoon SK. HCV core protein promotes liver fibrogenesis via up-regulation of CTGF with TGF-beta1. Exp Mol Med 2005;37:138–145. [PubMed: 15886528]

600. Shlipak MG, Sarnak MJ, Katz R, Fried LF, Seliger SL, Newman AB, Siscovick DS, Stehman-Breen C. Cystatin C and the risk of death and cardiovascular events among elderly persons. N Engl J Med 2005;352:2049–2060. [PubMed: 15901858]

601. Sicklick JK, Choi SS, Bustamante M, McCall SJ, Perez EH, Huang J, Li YX, Rojkind M, Diehl AM. Evidence for epithelial-mesenchymal transitions in adult liver cells. Am J Physiol Gastrointest Liver Physiol 2006;291:G575–G583. [PubMed: 16710052]

602. Sicklick JK, Li YX, Choi SS, Qi Y, Chen W, Bustamante M, Huang J, Zdanowicz M, Camp T, Torbenson MS, Rojkind M, Diehl AM. Role for hedgehog signaling in hepatic stellate cell activation and viability. Lab Invest 2005;85:1368–1380. [PubMed: 16170335]

603. Siegmund SV, Qian T, de Minicis S, Harvey-White J, Kunos G, Vinod KY, Hungund B, Schwabe RF. The endocannabinoid 2-arachidonoyl glycerol induces death of hepatic stellate cells via mitochondrial reactive oxygen species. FASEB J 2007;21:2798–2806. [PubMed: 17440119]

604. Siegmund SV, Seki E, Osawa Y, Uchinami H, Cravatt BF, Schwabe RF. Fatty acid amide hydrolase determines anandamide-induced cell death in the liver. J Biol Chem 2006;281:10431–10438. [PubMed: 16418162]

605. Siegmund SV, Uchinami H, Osawa Y, Brenner DA, Schwabe RF. Anandamide induces necrosis in primary hepatic stellate cells. Hepatology 2005;41:1085–1095. [PubMed: 15841466]

606. Skalli O, Schurch W, Seemayer T, Lagace R, Montandon D, Pittet B, Gabbiani G. Myofibroblasts from diverse pathologic settings are heterogeneous in their content of actin isoforms and intermediate filament proteins. Lab Invest 1989;60:275–285. [PubMed: 2644484]

607. Skrtic S, Wallenius V, Ekberg S, Brenzel A, Gressner AM, Jansson JO. Insulin-like growth factors stimulate expression of hepatocyte growth factor but not transforming growth factor beta1 in cultured hepatic stellate cells. Endocrinology 1997;138:4683–4689. [PubMed: 9348194]

608. Smart DE, Green K, Oakley F, Weitzman JB, Yaniv M, Reynolds G, Mann J, Millward-Sadler H, Mann DA. JunD is a profibrogenic transcription factor regulated by Jun N-terminal kinase-independent phosphorylation. Hepatology 2006;44:1432–1440. [PubMed: 17133482]

609. Smart DE, Vincent KJ, Arthur MJ, Eickelberg O, Castellazzi M, Mann J, Mann DA. JunD regulates transcription of the tissue inhibitor of metalloproteinases-1 and interleukin-6 genes in activated hepatic stellate cells. J Biol Chem 2001;276:24414–24421. [PubMed: 11337499]

610. Smith MW, Walters KA, Korth MJ, Fitzgibbon M, Proll S, Thompson JC, Yeh MM, Shuhart MC, Furlong JC, Cox PP, Thomas DL, Phillips JD, Kushner JP, Fausto N, Carithers RL Jr, Katze MG. Gene expression patterns that correlate with hepatitis C and early progression to fibrosis in liver transplant recipients. Gastroenterology 2006;130:179–187. [PubMed: 16401481]

611. Song SH, Leng XS, Li T, Qin ZZ, Peng JR, Zhao L, Wei YH, Yu X. Expression of subtypes of somatostatin receptors in hepatic stellate cells. World J Gastroenterol 2004;10:1663–1665. [PubMed: 15162546]

612. Sprenger H, Kaufmann A, Garn H, Lahme B, Gemsa D, Gressner AM. Induction of neutrophil-attracting chemokines in transforming rat hepatic stellate cells. Gastroenterology 1997;113:277–285. [PubMed: 9207288]

613. Srinivas PR, Verma M, Zhao Y, Srivastava S. Proteomics for cancer biomarker discovery. Clin Chem 2002;48:1160–1169. [PubMed: 12142368]

614. Stamm S, Ben-Ari S, Rafalska I, Tang Y, Zhang Z, Toiber D, Thanaraj TA, Soreq H. Function of alternative splicing. Gene 2005;344:1–20. [PubMed: 15656968]

615. Starkel P, Sempoux C, Leclercq I, Herin M, Deby C, Desager JP, Horsmans Y. Oxidative stress, KLF6 and transforming growth factor-beta up-regulation differentiate non-alcoholic steatohepatitis progressing to fibrosis from uncomplicated steatosis in rats. J Hepatol 2003;39:538–546. [PubMed: 12971963]

616. Stedman C, Liddle C, Coulter S, Sonoda J, Alvarez JG, Evans RM, Downes M. Benefit of farnesoid X receptor inhibition in obstructive cholestasis. Proc Natl Acad Sci USA 2006;103:11323–11328. [PubMed: 16844773]

617. Stefanovic B, Hellerbrand C, Brenner DA. Regulatory role of the conserved stem-loop structure at the 5′ end of collagen alpha1(I) mRNA. Mol Cell Biol 1999;19:4334–4342. [PubMed: 10330174]

618. Stefanovic B, Hellerbrand C, Holcik M, Briendl M, Aliebhaber S, Brenner DA. Posttranscriptional regulation of collagen alpha1(I) mRNA in hepatic stellate cells. Mol Cell Biol 1997;17:5201–5209. [PubMed: 9271398]

619. Stefanovic B, Stefanovic L, Schnabl B, Bataller R, Brenner DA. TRAM2 protein interacts with endoplasmic reticulum Ca^{2+} pump Serca2b and is necessary for collagen type I synthesis. Mol Cell Biol 2004;24:1758–1768. [PubMed: 14749390]

620. Steiling H, Muhlbauer M, Bataille F, Scholmerich J, Werner S, Hellerbrand C. Activated hepatic stellate cells express keratinocyte growth factor in chronic liver disease. Am J Pathol 2004;165:1233–1241. [PubMed: 15466389]

621. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function—measured and estimated glomerular filtration rate. N Engl J Med 2006;354:2473–2483. [PubMed: 16760447]

622. Stroebel P, Mayer F, Zerban H, Bannasch P. Spongiotic pericytoma: a benign neoplasm deriving from the perisinusoidal (Ito) cells in rat liver. Am J Pathol 1995;146:903–913. [PubMed: 7717457]

623. Suematsu M, Goda N, Sano T, Kashiwagi S, Egawa T, Shinoda Y, Ishimura Y. Carbon monoxide: an endogenous modulator of sinusoidal tone in the perfused rat liver. J Clin Invest 1995;96:2431–2437. [PubMed: 7593631]

624. Suskind DL, Muench MO. Searching for common stem cells of the hepatic and hematopoietic systems in the human fetal liver: CD34+ cytokeratin 7/8+ cells express markers for stellate cells. J Hepatol 2004;40:261–268. [PubMed: 14739097]

625. Svegliati Baroni G, D'Ambrosio L, Ferretti G, Casini A, Di Sario A, Salzano R, Ridolfi F, Saccomanno S, Jezequel AM, Benedetti A. Fibrogenic effect of oxidative stress on rat hepatic stellate cells. Hepatology 1998;27:720–726. [PubMed: 9500700]

626. Svegliati-Baroni G, Di Sario A, Casini A, Ferretti G, D'Ambrosio L, Ridolfi F, Bolognini L, Salzano R, Orlandi F, Benedetti A. The Na^+/H^+ exchanger modulates the fibrogenic effect of oxidative stress in rat hepatic stellate cells. J Hepatol 1999;30:868–875. [PubMed: 10365814]

627. Tacke F, Trautwein C, Yagmur E, Hellerbrand C, Wiest R, Brenner DA. Up-regulated eotaxin plasma levels in chronic liver disease patients indicate hepatic inflammation, advanced fibrosis and adverse clinical course. J Gastroenterol Hepatol 2007;22:1256–1264. [PubMed: 17688666]

628. Tahashi Y, Matsuzaki K, Date M, Yoshida K, Furukawa F, Sugano Y, Matsushita M, Himeno Y, Inagaki Y, Inoue K. Differential regulation of TGF-beta signal in hepatic stellate cells between acute and chronic rat liver injury. Hepatology 2002;35:49–61. [PubMed: 11786959]

629. Taimr P, Higuchi H, Kocova E, Rippe RA, Friedman S, Gores GJ. Activated stellate cells express the TRAIL receptor-2/death receptor-5 and undergo TRAIL-mediated apoptosis. Hepatology 2003;37:87–95. [PubMed: 12500193]

630. Taipale J, Beachy PA. The Hedgehog and Wnt signalling pathways in cancer. Nature 2001;411:349–354. [PubMed: 11357142]

631. Takahara T, Smart DE, Oakley F, Mann DA. Induction of myofibroblast MMP-9 transcription in three-dimensional collagen I gel cultures: regulation by NF-kappaB, AP-1 and Sp1. Int J Biochem Cell Biol 2004;36:353–363. [PubMed: 14643899]

632. Takeji M, Moriyama T, Oseto S, Kawada N, Hori M, Imai E, Miwa T. Smooth muscle alpha-actin deficiency in myofibroblasts leads to enhanced renal tissue fibrosis. J Biol Chem 2006;281:40193–40200. [PubMed: 17090535]

633. Takeji M, Moriyama T, Oseto S, Kawada N, Hori M, Imai E, Miwa T. Smooth muscle alpha-actin deficiency in myofibroblasts leads to enhanced renal tissue fibrosis. J Biol Chem 2006;281:40193–40200. [PubMed: 17090535]

634. Takemura S, Kawada N, Hirohashi K, Kinoshita H, Inoue M. Nucleotide receptors in hepatic stellate cells of the rat. FEBS Lett 1994;354:53–56. [PubMed: 7957901]

635. Tanaka Y, Nouchi T, Yamane M, Irie T, Miyakawa H, Sato C, Marumo F. Phenotypic modulation in lipocytes in experimental liver fibrosis. J Pathol 1991;164:273–278. [PubMed: 1890552]

636. Tang M, Potter JJ, Mezey E. Leptin enhances the effect of transforming growth factor beta in increasing type I collagen formation. Biochem Biophys Res Commun 2002;297:906–911. [PubMed: 12359239]

637. Tao J, Mallat A, Gallois C, Belmadani S, Mery PF, Nhieu JT, Pavoine C, Lotersztajn S. Biological effects of C-type natriuretic peptide in human myofibroblastic hepatic stellate cells. J Biol Chem 1999;274:23761–23769. [PubMed: 10446136]

638. Teixeira-Clerc F, Julien B, Grenard P, Tran Van Nhieu J, Deveaux V, Li L, Serriere-Lanneau V, Ledent C, Mallat A, Lotersztajn S. CB1 cannabinoid receptor antagonism: a new strategy for the treatment of liver fibrosis. Nat Med 2006;12:671–676. [PubMed: 16715087]

639. Theret N, Lehti K, Musso O, Clement B. MMP2 activation by collagen I and concanavalin A in cultured human hepatic stellate cells. Hepatology 1999;30:462–468. [PubMed: 10421655]

640. Theret N, Musso O, L'Helgoualc'h A, Clement B. Activation of matrix metalloproteinase-2 from hepatic stellate cells requires interactions with hepatocytes. Am J Pathol 1997;150:51–58. [PubMed: 9006321]

641. Thirunavukkarasu C, Uemura T, Wang LF, Watkins SC, Gandhi CR. Normal rat hepatic stellate cells respond to endotoxin in LBP-independent manner to produce inhibitor(s) of DNA synthesis in hepatocytes. J Cell Physiol 2005;204:654–665. [PubMed: 15828022]

642. Thirunavukkarasu C, Watkins S, Harvey SA, Gandhi CR. Superoxide-induced apoptosis of activated rat hepatic stellate cells. J Hepatol 2004;41:567–575. [PubMed: 15464236]

643. Thirunavukkarasu C, Watkins SC, Gandhi CR. Mechanisms of endotoxin-induced NO, IL-6, TNF-alpha production in activated rat hepatic stellate cells: role of p38 MAPK. Hepatology 2006;44:389–398. [PubMed: 16871588]

644. Thompson K, Maltby J, Fallowfield J, McAulay M, Millward-Sadler H, Sheron N. Interleukin-10 expression and function in experimental murine liver inflammation and fibrosis. Hepatology 1998;28:1597–1606. [PubMed: 9828224]

645. Thompson KC, Trowern A, Fowell A, Marathe M, Haycock C, Arthur MJ, Sheron N. Primary rat and mouse hepatic stellate cells express the macrophage inhibitor cytokine interleukin-10 during the course of activation in vitro. Hepatology 1998;28:1518–1524. [PubMed: 9828215]

646. Tiggelman AM, Boers W, Linthorst C, Brand HS, Sala M, Chamuleau RA. Interleukin-6 production by human liver (myo) fibroblasts in culture. Evidence for a regulatory role of LPS, IL-1 beta and TNF alpha. J Hepatol 1995;23:295–306. [PubMed: 8550994]

647. Tillmann HL, Manns MP, Rudolph KL. Merging models of hepatitis C virus pathogenesis. Semin Liver Dis 2005;25:84–92. [PubMed: 15732000]

648. Tomita K, Azuma T, Kitamura N, Nishida J, Tamiya G, Oka A, Inokuchi S, Nishimura T, Suematsu M, Ishii H. Pioglitazone prevents alcohol-induced fatty liver in rats through up-regulation of c-Met. Gastroenterology 2004;126:873–885. [PubMed: 14988841]

649. Torimura T, Ueno T, Inuzuka S, Kin M, Ohira H, Kimura Y, Majima Y, Sata M, Abe H, Tanikawa K. The extracellular matrix in hepatocellular carcinoma shows different localization patterns depending on the differentiation and the histological pattern of tumors: immunohistochemical analysis. J Hepatol 1994;21:37–46. [PubMed: 7963419]

650. Trigueiro de Araujo MS, Gerard F, Chossegros P, Guerret S, Barlet P, Adeleine P, Grimaud JA. Cellular and matrix changes in drug abuser liver sinusoids: a semiquantitative and morphometric ultrastructural study. Virchows Archiv A 1993;422:145–152.

651. Tseng TL, Shih YP, Huang YC, Wang CK, Chen PH, Chang JG, Yeh KT, Chen YM, Buetow KH. Genotypic and phenotypic characterization of a putative tumor susceptibility gene, GNMT, in liver cancer. Cancer Res 2003;63:647–654. [PubMed: 12566309]

652. Tsukada S, Parsons CJ, Rippe RA. Mechanisms of liver fibrosis. Clin Chim Acta 2006;364:33–60. [PubMed: 16139830]

653. Tsukamoto H. Adipogenic phenotype of hepatic stellate cells. Alcohol Clin Exp Res 2005;29:132S–133S. [PubMed: 16344597]

654. Tsukamoto H. Epigenetic mechanism of stellate cell trans-differentiation. J Hepatol 2007;46:352–353. [PubMed: 17161490]

655. Tsukamoto H, She H, Hazra S, Cheng J, Miyahara T. Anti-adipogenic regulation underlies hepatic stellate cell transdifferentiation. J Gastroenterol Hepatol 2006;21 3:S102–S105. [PubMed: 16958658]

656. Uemura M, Swenson ES, Gaca MD, Giordano FJ, Reiss M, Wells RG. Smad2 and Smad3 play different roles in rat hepatic stellate cell function and α-smooth muscle actin organization. Mol Biol Cell. 2005

657. Ueno H, Sakamoto T, Nakamura T, Qi Z, Astuchi N, Takeshita A, Shimizu K, Ohashi H. A soluble transforming growth factor beta receptor expressed in muscle prevents liver fibrogenesis and dysfunction in rats. Hum Gene Ther 2000;11:33–42. [PubMed: 10646637]

658. Ueno T, Sata M, Sakata R, Torimura T, Sakamoto M, Sugawara H, Tanikawa K. Hepatic stellate cells and intralobular innervation in human liver cirrhosis. Hum Pathol 1997;28:953–959. [PubMed: 9269832]

659. Ulven SM, Natarajan V, Holven KB, Lovdal T, Berg T, Blomhoff R. Expression of retinoic acid receptor and retinoid X receptor subtypes in rat liver cells: implications for retinoid signalling in parenchymal, endothelial, Kupffer and stellate cells. Eur J Cell Biol 1998;77:111–116. [PubMed: 9840460]

660. Unanue ER. Ito cells, stellate cells, myofibroblasts: new actors in antigen presentation. Immunity 2007;26:9–10. [PubMed: 17241956]

661. Uyama N, Zhao L, Van Rossen E, Hirako Y, Reynaert H, Adams DH, Xue Z, Li Z, Robson R, Pekny M, Geerts A. Hepatic stellate cells express synemin, a protein bridging intermediate filaments to focal adhesions. Gut 2006;55:1276–1289. [PubMed: 16484507]

662. Valencia-Sanchez MA, Liu J, Hannon GJ, Parker R. Control of translation and mRNA degradation by miRNAs and siRNAs. Genes Dev 2006;20:515–524. [PubMed: 16510870]

663. Valentino KL, Gutierrez M, Sanchez R, Winship MJ, Shapiro DA. First clinical trial of a novel caspase inhibitor: anti-apoptotic caspase inhibitor, IDN-6556, improves liver enzymes. Int J Clin Pharmacol Ther 2003;41:441–449. [PubMed: 14703949]

664. Van de Bovenkamp M, Groothuis GM, Draaisma AL, Merema MT, Bezuijen JI, van Gils MJ, Meijer DK, Friedman SL, Olinga P. Precision-cut liver slices as a new model to study toxicity-induced hepatic stellate cell activation in a physiologic milieu. Toxicol Sci 2005;85:632–638. [PubMed: 15728706]

665. Van de Bovenkamp M, Groothuis GM, Meijer DK, Slooff MJ, Olinga P. Human liver slices as an in vitro model to study toxicity-induced hepatic stellate cell activation in a multicellular milieu. Chem Biol Interact 2006;162:62–69. [PubMed: 16815347]

666. Vassy J, Rigaut JP, Briane D, Kraemer M. Confocal microscopy immunofluorescence localization of desmin and other intermediate filament proteins in fetal rat livers. Hepatology 1993;17:293–300. [PubMed: 7679087]

667. Velculescu VE, Zhang L, Vogelstein B, Kinzler KW. Serial analysis of gene expression. Science 1995;270:484–487. [PubMed: 7570003]

668. Verrill C, Davies J, Millward-Sadler H, Sundstrom L, Sheron N. Organotypic liver culture in a fluid-air interface using slices of neonatal rat and adult human tissue—a model of fibrosis in vitro. J Pharmacol Toxicol Methods 2002;48:103–110. [PubMed: 14565567]

669. Viglianti GA, Lau CM, Hanley TM, Miko BA, Shlomchik MJ, Marshak-Rothstein A. Activation of autoreactive B cells by CpG dsDNA. Immunity 2003;19:837–847. [PubMed: 14670301]

670. Vinas O, Bataller R, Sancho-Bru P, Gines P, Berenguer C, Enrich C, Nicolas JM, Ercilla G, Gallart T, Vives J, Arroyo V, Rodes J. Human hepatic stellate cells show features of antigen-presenting cells and stimulate lymphocyte proliferation. Hepatology 2003;38:919–929. [PubMed: 14512879]

671. Vogel S, Piantedosi R, Frank J, Lalazar A, Rockey DC, Friedman SL, Blaner WS. An immortalized rat liver stellate cell line (HSC-T6): a new cell model for the study of retinoid metabolism in vitro. J Lipid Res 2000;41:882–893. [PubMed: 10828080]

672. Voss B, Rauterberg J, Pott G, Brehmer U, Allam S, Lehmann R, von Bassewitz DB. Nonparenchymal cells cultivated from explants of fibrotic liver resemble endothelial and smooth muscle cells from blood vessel walls. Hepatology 1982;2:19–28. [PubMed: 7033099]

673. Vyas SK, Leyland H, Gentry J, Arthur MJ. Rat hepatic lipocytes synthesize and secrete transin (stromelysin) in early primary culture. Gastroenterology 1995;109:889–898. [PubMed: 7657119]

674. Wake K. Cell-cell organization and functions of "sinusoids" in liver microcirculation system. J Electron Microsc 1999;48:89–98.

675. Wake K. Development of vitamin A-rich lipid droplets in multivesicular bodies of rat liver stellate cells. J Cell Biol 1974;63:683–691. [PubMed: 4421899]

676. Wake, K. Liver perivascular cells revealed by gold and silver impregnation methods and electron microscopy. In: Motta, PM., editor. Biopathology of the Liver, an Ulrastructural Approach. Dordrecht: Kluwer; 1988. p. 23-36.

677. Wake K. Perisinusoidal stellate cells (Fat-storing cells, interstitial cells, lipocytes) their related structure in and around liver sinusoids, vitamin A storing cells in extrahepatic organs. Int Rev Cytol 1980;66:303–353. [PubMed: 6993411]

678. Wake K. "Sternzellen" in the liver: perisinuosidal cells with special reference to storage of vitamin A. Am J Anat 1971;132:429–462. [PubMed: 4942297]

679. Wake, K. Structure of the sinusoidal wall in the liver. In: Wisse, E.; Knook, DL.; Wake, K., editors. Cells of the Hepatic Sinusoid. Leiden: The Kupffer Cell Foundation; 1995. p. 241-246.

680. Wake, K.; Motomatsu, K.; Ekataksin, W. Postnatal development of the perisinusoidal stellate cells in the rat liver. In: Wisse, E.; Knook, DL.; McCuskey, RS., editors. Cells of the Hepatic Sinusoid. Leiden: Kupffer Cell Foundation; 1991. p. 269-275.

681. Wake K, Motomatsu K, Senoo H. Stellate cells storing retinol in the liver of adult lamprey, *Lampetra japonica*. Cell Tissue Res 1987;249:289–299. [PubMed: 3621303]

682. Wake K, Sato T. Intralobular heterogeneity of perisinusoidal stellate cells in porcine liver. Cell Tissue Res 1993;273:227–237. [PubMed: 7689937]

683. Wandzioch E, Kolterud A, Jacobsson M, Friedman SL, Carlsson L. Lhx2−/− mice develop liver fibrosis. Proc Natl Acad Sci USA 2004;101:16549–16554. [PubMed: 15536133]

684. Wang L, Tankersley LR, Tang M, Potter JJ, Mezey E. Regulation of the murine alpha(2)(I) collagen promoter by retinoic acid and retinoid X receptors. Arch Biochem Biophys 2002;401:262–270. [PubMed: 12054477]

685. Wang SC, Ohata M, Schrum L, Rippe RA, Tsukamoto H. Expression of interleukin-10 by in vitro and in vivo activated hepatic stellate cells. J Biol Chem 1998;273:302–308. [PubMed: 9417080]

686. Wang YJ, Wang SS, Bickel M, Guenzler V, Gerl M, Bissell DM. Two novel antifibrotics, HOE 077 and Safironil, modulate stellate cell activation in rat liver injury: differential effects in males and females. Am J Pathol 1998;152:279–287. [PubMed: 9422545]

687. Watanabe T, Shibata N, Westerman KA, Okitsu T, Allain JE, Sakaguchi M, Totsugawa T, Maruyama M, Matsumura T, Noguchi H, Yamamoto S, Hikida M, Ohmori A, Reth M, Weber A, Tanaka N, Leboulch P, Kobayashi N. Establishment of immortalized human hepatic stellate scavenger cells to develop bio-artificial livers. Transplantation 2003;75:1873–1880. [PubMed: 12811248]

688. Wei H, Lu H, Li D, Zhan Y, Wang Z, Huang X. The expression of AT1 receptor on hepatic stellate cells in rat fibrosis induced by CCl4. Chin Med J 2001;114:583–587. [PubMed: 11780431]

689. Wei HS, Li DG, Lu HM, Zhan YT, Wang ZR, Huang X, Zhang J, Cheng JL, Xu QF. Effects of AT1 receptor antagonist, losartan, on rat hepatic fibrosis induced by CCl(4). World J Gastroenterol 2000;6:540–545. [PubMed: 11819643]

690. Wei HS, Lu HM, Li DG, Zhan YT, Wang ZR, Huang X, Cheng JL, Xu QF. The regulatory role of AT 1 receptor on activated HSCs in hepatic fibrogenesis:effects of RAS inhibitors on hepatic fibrosis induced by CCl(4). World J Gastroenterol 2000;6:824–828. [PubMed: 11819703]

691. Weill FX, Blazejewski S, Blanc JF, Huet S, Gauthier JM, Neaud V, Olaso E, Dubuisson L, Azais-Braesco V, Vidal-Vanaclocha F, Balabaud C, Bioulac-Sage P, Rosenbaum J. Characterization of a new human liver myofibroblast cell line: transcriptional regulation of plasminogen activator inhibitor type I by transforming growth factor beta 1. Lab Invest 1997;77:63–70. [PubMed: 9251679]

692. Weiner FR, Blaner WS, Czaja MJ, Shah A, Geerts A. Ito cell expression of a nuclear retinoic acid receptor. Hepatology 1992;15:336–342. [PubMed: 1310477]

693. Wells RG. Fibrogenesis V. TGF-beta signaling pathways. Am J Physiol Gastrointest Liver Physiol 2000;279:G845–G850. [PubMed: 11052979]

694. Wells RG. The role of matrix stiffness in hepatic stellate cell activation and liver fibrosis. J Clin Gastroenterol 2005;39:S158–S161. [PubMed: 15758652]

695. Weng H, Mertens PR, Gressner AM, Dooley S. IFN-gamma abrogates profibrogenic TGF-beta signaling in liver by targeting expression of inhibitory and receptor Smads. J Hepatol 2007;46:295–303. [PubMed: 17125875]

696. Whalen R, Rockey DC, Friedman SL, Boyer TD. Activation of rat hepatic stellate cells leads to loss of glutathione *S*-transferases and their enzymatic activity against products of oxidative stress. Hepatology 1999;30:927–933. [PubMed: 10498644]

697. Wickert L, Abiaka M, Bolkenius U, Gressner AM. Corticosteroids stimulate selectively transforming growth factor (TGF)-beta receptor type III expression in transdifferentiating hepatic stellate cells. J Hepatol 2004;40:69–76. [PubMed: 14672616]

698. Wiercinska E, Wickert L, Denecke B, Said HM, Hamzavi J, Gressner AM, Thorikay M, ten Dijke P, Mertens PR, Breitkopf K, Dooley S. Id1 is a critical mediator in TGF-beta-induced transdifferentiation of rat hepatic stellate cells. Hepatology 2006;43:1032–1041. [PubMed: 16628634]

699. Win KM, Charlotte F, Mallat A, Cherqui D, Martin N, Mavier P, Preaux AM, Dhumeaux D, Rosenbaum J. Mitogenic effect of transforming growth factor-beta 1 on human Ito cells in culture: evidence for mediation by endogenous platelet-derived growth factor. Hepatology 1993;18:137–145. [PubMed: 8325605]

700. Winau F, Hegasy G, Weiskirchen R, Weber S, Cassan C, Sieling PA, Modlin RL, Liblau RS, Gressner AM, Kaufmann SH. Ito cells are liver-resident antigen-presenting cells for activating T cell responses. Immunity 2007;26:117–129. [PubMed: 17239632]

701. Wolf AM, Wolf D, Avila MA, Moschen AR, Berasain C, Enrich B, Rumpold H, Tilg H. Up-regulation of the anti-inflammatory adipokine adiponectin in acute liver failure in mice. J Hepatol 2006;44:537–543. [PubMed: 16310276]

702. Wong L, Yamasaki G, Johnson RJ, Friedman SL. Induction of beta-platelet-derived growth factor receptor in rat hepatic lipocytes during cellular activation in vivo and in culture. J Clin Invest 1994;94:1563–1569. [PubMed: 7929832]

703. Xu JW, Gong J, Chang XM, Luo JY, Dong L, Hao ZM, Jia A, Xu GP. Estrogen reduces CCL(4)-induced liver fibrosis in rats. World J Gastroenterol 2002;8:883–887. [PubMed: 12378635]

704. Xu L, Hui AY, Albanis E, Arthur MJ, O'Byrne SM, Blaner WS, Mukherjee P, Friedman SL, Eng FJ. Human hepatic stellate cell lines, LX-1 and LX-2: new tools for analysis of hepatic fibrosis. Gut 2005;54:142–151. [PubMed: 15591520]

705. Xu XQ, Leow CK, Lu X, Zhang X, Liu JS, Wong WH, Asperger A, Deininger S, Eastwood Leung HC. Molecular classification of liver cirrhosis in a rat model by proteomics and bioinformatics. Proteomics 2004;4:3235–3245. [PubMed: 15378689]

706. Yamada M, Blaner WS, Soprano DR, Dixon JL, Kjeldbye HM, Goodman DS. Biochemical characteristics of isolated rat liver stellate cells. Hepatology 1987;7:1224–1229. [PubMed: 2824313]

707. Yamada T, Imaoka S, Kawada N, Seki S, Kuroki T, Kobayashi K, Monna T, Funae Y. Expression of cytochrome *P*450 isoforms in rat hepatic stellate cells. Life Sci 1997;61:171–179. [PubMed: 9217276]

708. Yamamoto K, Ogawa K. Fine structure and cytochemistry of lysosomes in the Ito cells of the rat liver. Cell Tissue Res 1983;233:45–57. [PubMed: 6616565]

709. Yamano T, Hirai R, Hato S, Uemura T, Shimizu N. Delayed liver regeneration with negative regulation of hepatocyte growth factor and positive regulation of transforming growth factor-beta1 mRNA after portal branch ligation in biliary obstructed rats. Surgery 2002;131:163–171. [PubMed: 11854694]

710. Yamauchi M, Potter JJ, Mezey E. Characteristics of alcohol dehydrogenase in fat-storing (Ito) cells of rat liver. Gastroenterology 1988;94:163–169. [PubMed: 3335287]

711. Yanagisawa M, Kurihara H, Kimura S, Tomobe Y, Kobayashi M, Mitsui Y, Yazaki Y, Goto K, Masaki T. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. Nature 1988;332:411–415. [PubMed: 2451132]

712. Yang Y, Nemoto EM, Harvey SA, Subbotin VM, Gandhi CR. Increased hepatic platelet activating factor (PAF) and PAF receptors in carbon tetrachloride induced liver cirrhosis. Gut 2004;53:877–883. [PubMed: 15138217]

713. Yasuda M, Shimizu I, Shiba M, Ito S. Suppressive effects of estradiol on dimethylnitrosamine-induced fibrosis of the liver in rats. Hepatology 1999;29:719–727. [PubMed: 10051473]

714. Yavrom S, Chen L, Xiong S, Wang J, Rippe RA, Tsukamoto H. Peroxisome proliferator-activated receptor gamma suppresses proximal alpha1(I) collagen promoter via inhibition of p300-facilitated NF-I binding to DNA in hepatic stellate cells. J Biol Chem 2005;280:40650–40659. [PubMed: 16216869]

715. Yee HF Jr. Rho directs activation-associated changes in rat hepatic stellate cell morphology via regulation of the actin cytoskeleton. Hepatology 1998;28:843–850. [PubMed: 9731582]

716. Yin L, Lynch D, Ilic Z, Sell S. Proliferation and differentiation of ductular progenitor cells and littoral cells during the regeneration of the rat liver to CCl4/2-AAF injury. Histol Histopathol 2002;17:65–81. [PubMed: 11813887]

717. Yin L, Lynch D, Sell S. Participation of different cell types in the restitutive response of the rat liver to periportal injury induced by allyl alcohol. J Hepatol 1999;31:497–507. [PubMed: 10488710]

718. Yokoi Y, Namihisa T, Kuroda H, Komatsu I, Miyazaki A, Watanabe S, Usui K. Immunocytochemical detection of desmin in fat-storing cells (Ito cells). Hepatology 1984;4:709–714. [PubMed: 6204917]

719. Yokomori H, Oda M, Ogi M, Sakai K, Ishii H. Enhanced expression of endothelial nitric oxide synthase and caveolin-1 in human cirrhosis. Liver 2002;22:150–158. [PubMed: 12028410]

720. Yoshiji H, Kuriyama S, Yoshii J, Ikenaka Y, Noguchi R, Hicklin DJ, Wu Y, Yanase K, Namisaki T, Yamazaki M, Tsujinoue H, Imazu H, Masaki T, Fukui H. Vascular endothelial growth factor and receptor interaction is a prerequisite for murine hepatic fibrogenesis. Gut 2003;52:1347–1354. [PubMed: 12912869]

721. Yoshiji H, Kuriyama S, Yoshii J, Ikenaka Y, Noguchi R, Nakatani T, Tsujinoue H, Yanase K, Namisaki T, Imazu H, Fukui H. Tissue inhibitor of metalloproteinases-1 attenuates spontaneous liver fibrosis resolution in the transgenic mouse. Hepatology 2002;36:850–860. [PubMed: 12297832]

722. Yoshikawa K, Imai K, Seki T, Higashi-Kuwata N, Kojima N, Yuuda M, Koyasu K, Sone H, Sato M, Senoo H, Irie T. Distribution of retinylester-storing stellate cells in the arrowtooth halibut, *Atheresthes evermanni*. Comp Biochem Physiol A Mol Integr Physiol 2006;145:280–286. [PubMed: 16891138]

723. Yoshino R, Miura K, Segawa D, Hirai Y, Goto T, Ohshima S, Mikami K, Yoneyama K, Shibuya T, Watanabe D, Kataoka E, Takeuchi S, Endoh A, Sato W, Watanabe S. Epimorphin expression and stellate cell status in mouse liver injury. Hepatol Res 2006;34:238–249. [PubMed: 16480920]

724. Yu C, Wang F, Jin C, Huang X, Miller DL, Basilico C, McKeehan WL. Role of fibroblast growth factor type 1 and 2 in carbon tetrachloride-induced hepatic injury and fibrogenesis. Am J Pathol 2003;163:1653–1662. [PubMed: 14507672]

725. Yu MC, Chen CH, Liang X, Wang L, Gandhi CR, Fung JJ, Lu L, Qian S. Inhibition of T-cell responses by hepatic stellate cells via B7–H1-mediated T-cell apoptosis in mice. Hepatology 2004;40:1312–1321. [PubMed: 15565659]

726. Yu Y, Fuhr J, Boye E, Gyorffy S, Soker S, Atala A, Mulliken JB, Bischoff J. Mesenchymal stem cells and adipogenesis in hemangioma involution. Stem Cells 2006;24:1605–1612. [PubMed: 16456130]

727. Zamora-Valdes D, Ponciano-Rodriguez G, Chavez-Tapia NC, Mendez-Sanchez N. The endocannabinoid system in chronic liver disease. Ann Hepatol 2005;4:248–254. [PubMed: 16432489]

728. Zaret KS. Regulatory phases of early liver development: paradigms of organogenesis. Nat Rev Genet 2002;3:499–512. [PubMed: 12094228]

729. Zeisberg M, Hanai J, Sugimoto H, Mammoto T, Charytan D, Strutz F, Kalluri R. BMP-7 counteracts TGF-beta1-induced epithelial-to-mesenchymal transition and reverses chronic renal injury. Nat Med 2003;9:964–968. [PubMed: 12808448]

730. Zhan SS, Jiang JX, Wu J, Halsted C, Friedman SL, Zern MA, Torok NJ. Phagocytosis of apoptotic bodies by hepatic stellate cells induces NADPH oxidase and is associated with liver fibrosis in vivo. Hepatology 2006;43:435–443. [PubMed: 16496318]

731. Zhang LP, Takahara T, Yata Y, Furui K, Jin B, Kawada N, Watanabe A. Increased expression of plasminogen activator and plasminogen activator inhibitor during liver fibrogenesis of rats: role of stellate cells. J Hepatol 1999;31:703–711. [PubMed: 10551395]

732. Zhao C, Chen W, Yang L, Chen L, Stimpson SA, Diehl AM. PPARgamma agonists prevent TGFbeta1/Smad3-signaling in human hepatic stellate cells. Biochem Biophys Res Commun 2006;350:385–391. [PubMed: 17010940]

733. Zhao R, Duncan SA. Embryonic development of the liver. Hepatology 2005;41:956–967. [PubMed: 15841465]

734. Zheng S, Chen A. Disruption of transforming growth factor-beta signaling by curcumin induces gene expression of peroxisome proliferator-activated receptor-gamma in rat hepatic stellate cells. Am J Physiol Gastrointest Liver Physiol 2007;292:G113–G123. [PubMed: 16959952]

735. Zhou X, Murphy FR, Gehdu N, Zhang J, Iredale JP, Benyon RC. Engagement of alphavbeta3 integrin regulates proliferation and apoptosis of hepatic stellate cells. J Biol Chem 2004;279:23996–24006. [PubMed: 15044441]

736. Zhou X, Zhang Y, Zhang J, Zhu H, Du W, Zhang X, Chen Q. Expression of fibronectin receptor, integrin alpha 5 beta 1 of hepatic stellate cells in rat liver fibrosis. Chin Med J 2000;113:272–276. [PubMed: 11775263]

737. Zindy F, Lamas E, Schmidt S, Kirn A, Brechot C. Expression of insulin-like growth factor II (IGF-II) and IGF-II, IGF-I and insulin receptors mRNAs in isolated non-parenchymal rat liver cells. J Hepatol 1992;14:30–34. [PubMed: 1310705]

738. Znoyko I, Trojanowska M, Reuben A. Collagen binding alpha2beta1 and alpha1beta1 integrins play contrasting roles in regulation of Ets-1 expression in human liver myofibroblasts. Mol Cell Biochem 2006;282:89–99. [PubMed: 16317516]

739. Zou Z, Ekataksin W, Wake K. Zonal and regional differences identified from precision mapping of vitamin A-storing lipid droplets of the hepatic stellate cells in pig liver: a novel concept of addressing the intralobular area of heterogeneity. Hepatology 1998;27:1098–1108. [PubMed: 9537451]
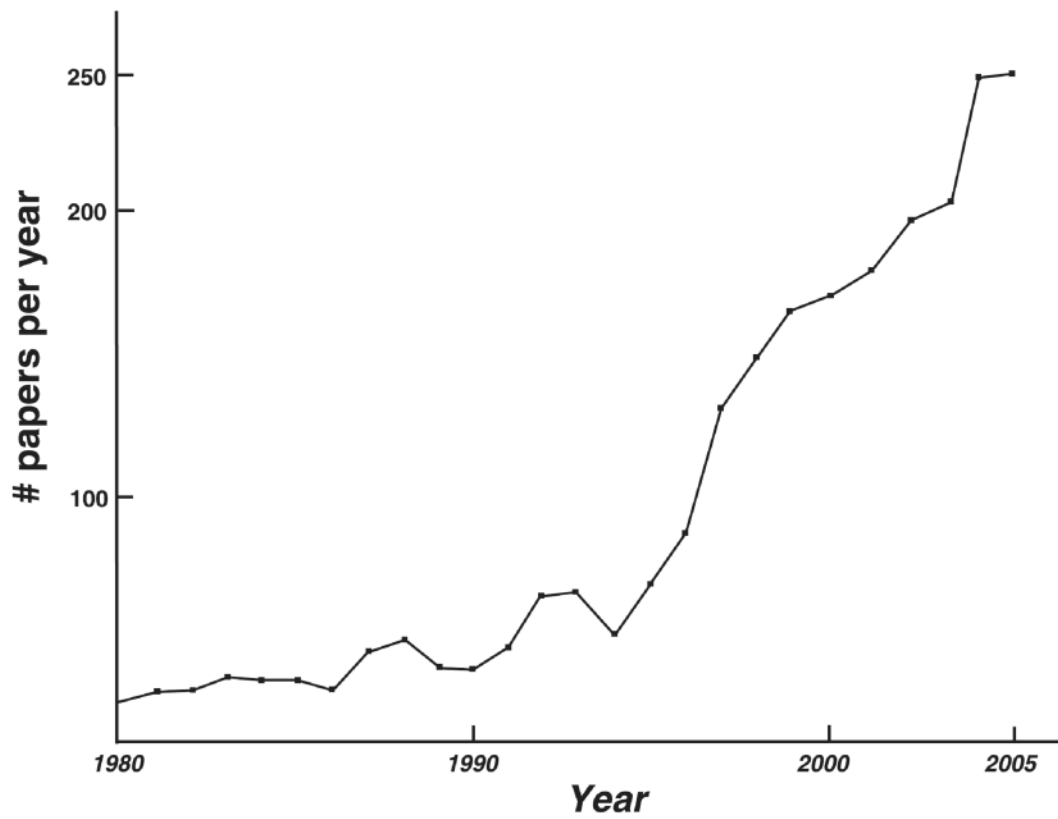
Fig. 1.
Growth of the hepatic stellate cell field in 25 years. This graph illustrates the number of citations per year between 1980 and 2005 in Medline using the search terms of either hepatic stellate cell, Ito cell, lipocyte, fat storing cell, or perisinusoidal cell.
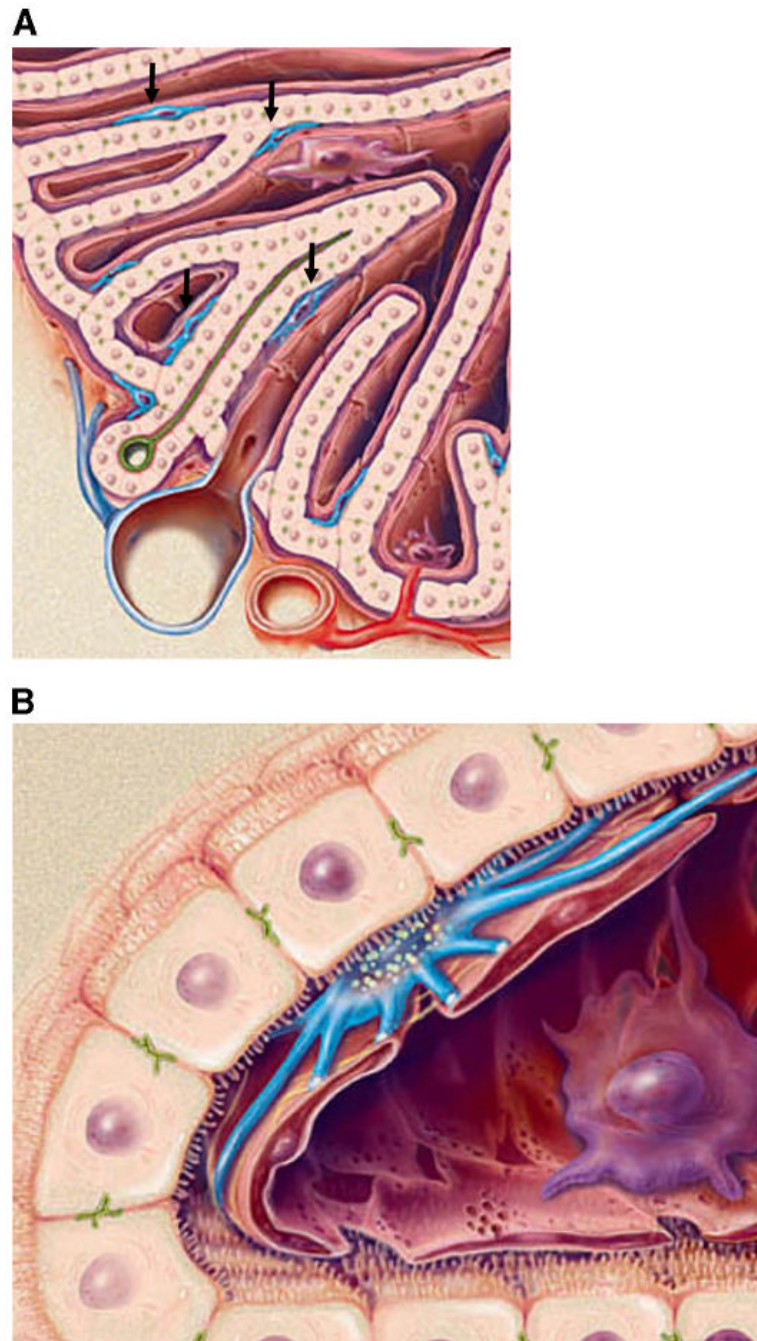
Fig. 2.
Morphology of hepatic stellate cells in normal liver. *A*: diagram of the hepatic sinusoid demonstrating the relative orientation of stellate cells (in blue, indicated with arrows) within the sinusoidal architecture. *B*: higher resolution drawing of stellate cells situated within the subendothelial space. [From Friedman and Arthur (169).]
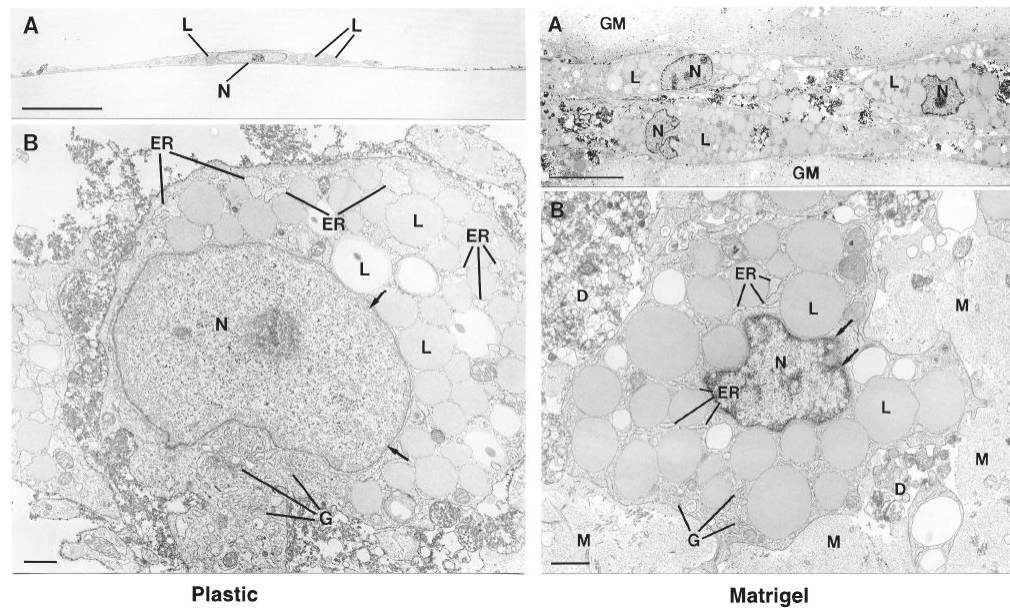
Fig. 3.
Ultrastructure of cultured stellate cells. Primary rat hepatic stellate cells cultured for 7 days on either uncoated plastic (*left panel*) or Matrigel (*right panel*). Cells on plastic become activated and are flat, with well-developed endoplasmic reticulum (ER) and some lipid droplets (L). In contrast, cells on Matrigel (GM, gel matrix) remain quiescent with condensed nuclear chromatin (N) and a high density of vitamin A-containing lipid droplets. Acellular debris (D) and secreted matrix (M) are trapped within the Matrigel surrounding the cell (bar = 10 μm). [From Friedman et al. (173).]
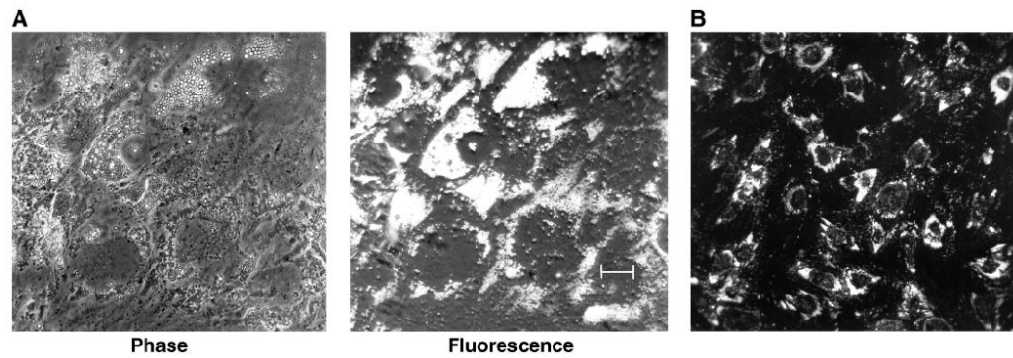
Fig. 4.
Cultured hepatic stellate cells in primary culture. *A*: high-power phase (*left panel*) and fluorescence (*right panel*) micrograph of primary cultured rat stellate cells, demonstrating cytoplasmic vitamin A droplets that fluorescence when excited by ultraviolet light (bar = 20 μm). *B*: low-power fluorescence micrograph of rat hepatic stellate cells in primary culture on plastic for 1 wk, photographed under ultraviolet light (bar = 80 μm). [From Friedman et al. (174).]
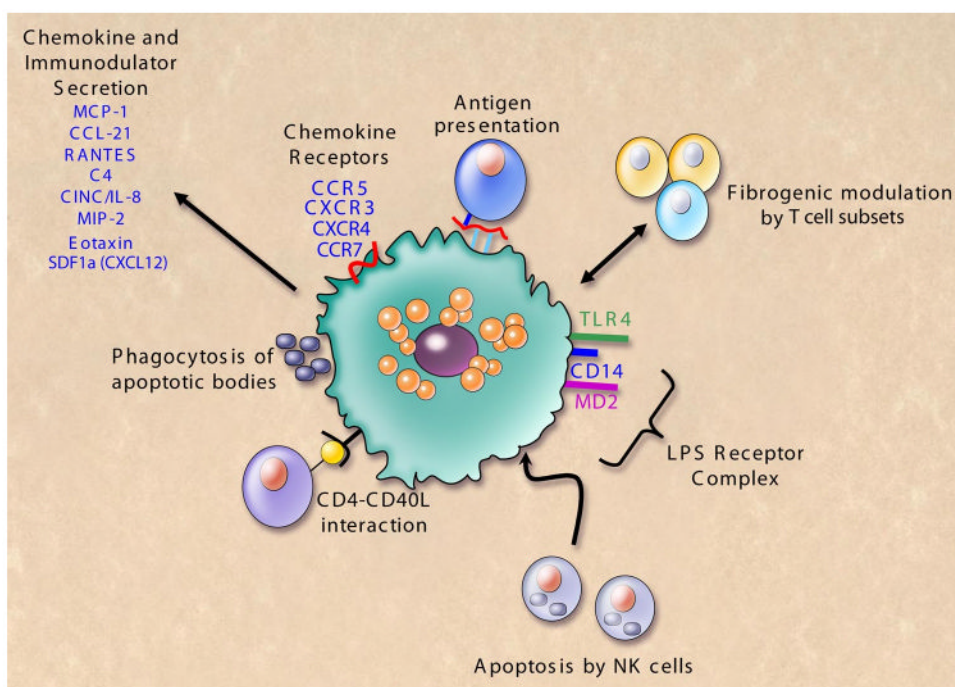
Fig. 5.
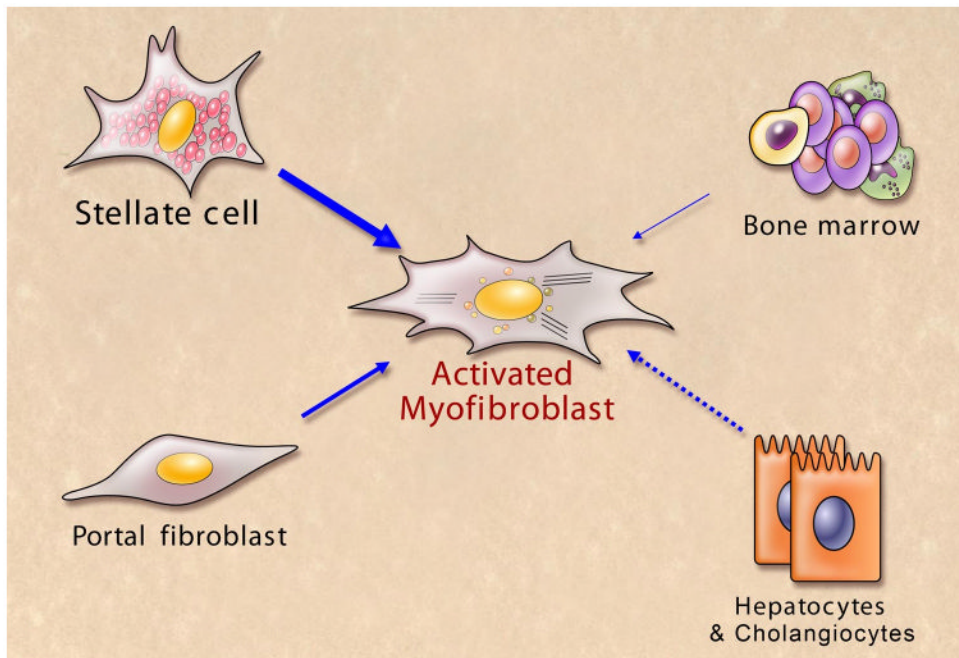Immunoregulatory roles of stellate cells (see text).

Fig. 6.
Sources of myofibroblasts in liver injury. Multiple sources of fibrogenic myofibroblasts are likely in liver injury depending on the site and nature of the injury. While resident stellate cells appear to be the most likely source, periportal fibroblasts may be especially prominent in biliary injury, whereas bone marrow and possible epithelial-mesenchymal transition may contribute as well.
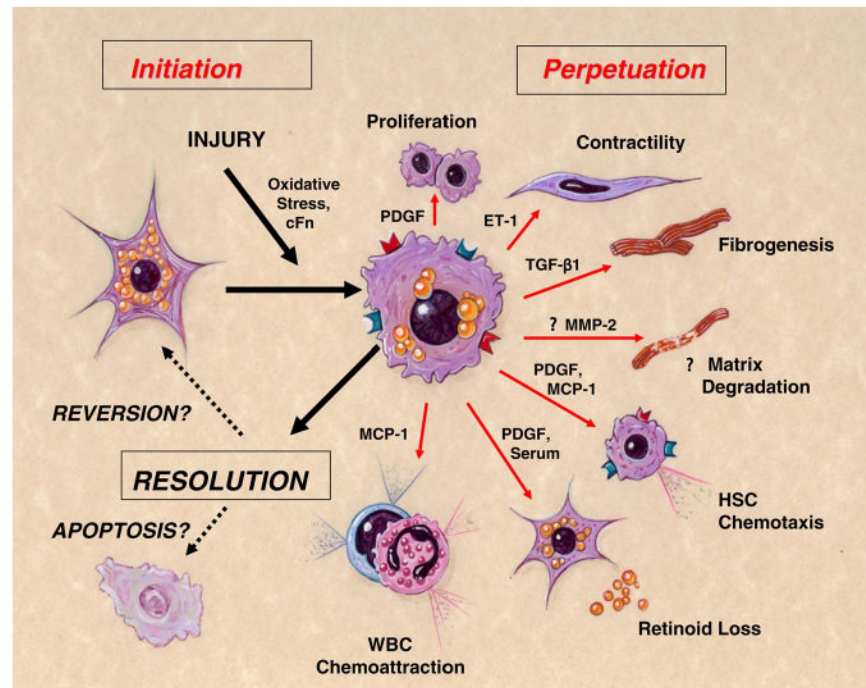
Fig. 7.
Pathways of stellate cell activation and resolution. Following liver injury, hepatic stellate cells undergo "activation," which connotes a transition from quiescent vitamin A-rich cells into proliferative, fibrogenic, and contractile myofibroblasts. The major phenotypic changes after activation include proliferation, contractility, fibrogenesis, matrix degradation, chemotaxis, retinoid loss, and WBC chemoattraction. Key mediators underlying these effects are shown. The fate of activated stellate cells during resolution of liver injury is uncertain but may include reversion to a quiescent phenotype and/or selective clearance by apoptosis. [From Friedman (165).]
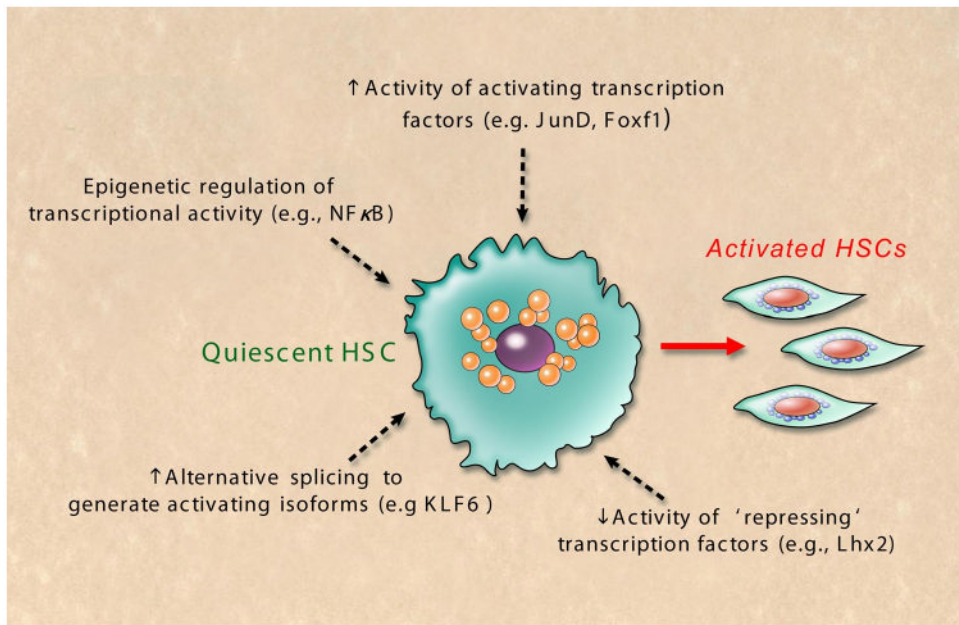
Fig. 8.
Mechanisms of transcriptional regulation of stellate cell activation (see text).

Table 1

Repertoire of cytokines and membrane receptors associated with hepatic stellate cells

Cytokine Family	Cytokines	Receptor(s)
Proliferative or fibrogenic		
Transforming growth factors	TGF-β1/TGF-α, BMP4 and BMP6	TGF-β receptor types I, II and III; mannose-6-phosphate receptor
Platelet-derived growth factors	PDGF-B	β-PDGF-R and α-PDGF-R
Epidermal growth factor	NR	EGF receptor
Stem cell factor	Stem cell factor	NR
Hepatocyte growth factor	HGF	c-met
Connective tissue growth factor (CCN2)	CTGF (CCN2)	αvβ3-Integrin, low-density lipoprotein receptor-related protein (LRP)
Fibroblast growth factors	aFGF and bFGF	FGF receptor-2 (flg)
Endothelin-1	ET-1, ECE	ET-A and ET-B receptors
Leptin	Leptin	OB-Ra and OB-Rb
Plasminogen	UPA/PAI-1	uPAR
Vascular endothelial cell growth factor	VEGF	VEGFR-1 (Flt1) and VEGFR-2 (Flk1)
Insulin-like growth factors	IGF-I and IGF-II	IGF-IR
Thrombin	NR	Thrombin receptor
RGD containing and integrin ligands	Fibronectin, tenascin	Integrins α1β1, α2β1, α6β4, α5β1, α8β1, αvβ1 αvβ3, integrin-linked kinase
Fibrillar collagens	Collagens I, II	Discoidin domain receptors 1 and 2
Cannabinoids	NR	CB1 receptor
Purines	Ubiquitous	P2Y receptors
Adenosine	Ubiquitous	A(2a) adenosine receptor
Renin-angiotensin	Angiotensin II, renin, ACE	Angiotensin II types 1 and 2 receptors
Serotonin	NR	SSR2, SSR3, and SSR5 receptors
Hedgehog	Indian hedgehog and sonic hedgehog	Patched
Galectins	Galectin-3	NR
Chemotactic/inflammatory		
Advanced glycation end products (AGE)	NR	Receptors for AGE (RAGE)
Macrophage colony stimulating factor	M-CSF	NR
Endothelin	ET-1, ECE	ET-A and ET-B
Platelet activating factor	PAF	PAF receptor
CD40	CD40 ligand	NR
Tumor necrosis factor-α	TNF-α	TNFR1, p75NTR
Chemokines	CXCL1, MCP-1 RANTES, MIP-1, eotaxin, IL-8	CXCR3
Opioids	NR	Delta 1 and Delta 2 opioid receptors
Oxidized LDL	NR	CD36
Toll like receptor ligands	NR	TLR4, CDl4
Regenerative		
Interleukin-6	IL-6	NR
Neurotrophins	NGF, BDNF, NT-4, NT-4/5	P75-NTR; Trk-B, Trk-C

Cytokine Family	Cytokines	Receptor(s)
Hepatocyte growth factor	HGF	c-met
Antifibrogenic		
Interleukin-10	IL-10	IL-10 receptor
Cannabinoids	NR	CB2 receptor
Adiponectin	Adiponectin	NR
Hepatocyte growth factor	HGF	c-met
Follistatin	Follistatin	NR
Apoptotic		
Fas signaling	NR	Fas
Miscellaneous		
Cystatin	Cystatin	NR
Catecholamines	Norepinephrine	α1A- and β-adrenergic receptors
5-Hydroxytamine	NR	5-Hydroxytamine receptor subtypes 1A, 2A, and 2B
Adrenomedullin	Adrenomedullin	NR
Complement cascade	NR	C5a receptor
Natriuretic peptides	NR	Natriuretic peptide receptor B

Shown is a compilation of data reported from all mammalian species describing expression of either mRNA or protein for a broad range of cytokines and soluble factors, and/or their cognate receptors associated with hepatic stellate cells. The table is organized according to their main activity reported, although most of these molecules have many activities. The table does not distinguish whether these molecules are associated with quiescent or activated stellate cells. See text for details. NR, not reported.

Table 2
Transcription factors expressed by hepatic stellate cells

Factor	Function or Target Gene(s)
NF-$\kappa\beta$	Regulates inflammation and apoptosis survival
AP-1 (c-Jun, JunB, Jun D, and c-Fos; Fra1, Fra2, and Fos-B)	TGF-β1, TIMP-1, and IL-6 gene regulation
AP-2	Collagen gene regulation
Ets-1	Activation
NF-1	Collagen gene regulation
Smads	Collagen gene regulation, growth arrest
C/EBP	Collagen gene regulation
MEF2	Activation
E-box factors	Regulate mannose-6-phosphate/IGF-II receptor
c-myb	α-Smooth muscle actin
CREB	Activation
CRP2	Quiescence
SREBP	Quiescence
Lhx2	Quiescence
Kruppel-like zinc finger factors	
KLF6	Varied
Sp1, Sp3	Collagen gene regulation
BTEB	Collagen gene regulation
ZNF 267	MMP-10
Egr1	Activation
Nuclear hormone receptors	
FXR	Quiescence
PPARγ	Quiescence
LXR	Quiescence
PXR	Quiescence
Vitamin D Receptor	Activation
RAR-α, β/RXR	Varied
Forkhead factors	
Foxf1	Activation
FoxO1	Activation

Those transcription factors identified to date in hepatic stellate cells from any mammalian species are listed, along with their general function and/or specific transcriptional targets in stellate cells.