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Similarities and Differences in the Pathogenesis of Alcoholic and Nonalcoholic Steatohepatitis

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Abstract

Subpopulations of individuals with alcohol-induced fatty livers and nonalcoholic steatosis develop steatohepatitis. Steatohepatitis is defined histologically: increased numbers of injured and dying hepatocytes distinguish this condition from simple steatosis. The increased hepatocyte death is generally accompanied by hepatic accumulation of inflammatory cells and sometimes increases in myofibroblastic cells, leading to hepatic fibrosis and eventually, cirrhosis. The purpose of this review is to summarize similarities and differences in the pathogenesis of steatohepatitis in alcoholic fatty liver disease (AFLD) and nonalcoholic fatty liver disease (NAFLD).

Keywords

alcoholic; nonalcoholic; pathogenesis; steatohepatitis

Introduction

Steatohepatitis occurs in some, but not all, individuals who develop steatosis due to excessive consumption of alcohol [1,2]. It may also occur in some individuals with steatosis due to nonalcoholic fatty liver disease, a condition that is most commonly associated with obesity, insulin resistance and the metabolic syndrome [3–5]. Steatohepatitis differs from steatosis mainly in the degree of hepatocyte injury and death, both of which are much worse in steatohepatitis than simple steatosis [6,7]. Thus, although hepatocyte accumulation of triglyceride occurs in both steatosis and steatohepatitis, histological features of liver cell injury, such as hepatocyte ballooning and cytoskeletal condensation (Mallory-Denk bodies), and cell death (*e.g.*, apoptotic bodies), occur predominately in steatohepatitis and distinguish the condition from steatosis.

Hepatocyte injury in steatohepatitis is often accompanied by hepatic accumulation of inflammatory cells and myofibroblasts [8–10]. The latter sometimes results in deposition of excessive type 1 collagen (*i.e.*, fibrosis). The distribution of fibrosis in steatohepatitis differs somewhat from that of other types of chronic liver injury, with pericellular and sinusoidal

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fibrosis in acinar zone 3 being more common in steatohepatitis [9,11]. However, "typical" peri-portal fibrosis and bridging fibrosis between portal tracts and between portal tracts and central veins, also occur in steatohepatitis [9,12]. As in other types of chronic liver disease, bridging fibrosis may eventuate in cirrhosis. Hepatocellular carcinomas have also been demonstrated in rare individuals with steatohepatitis, and occur more commonly in steatohepatitis-related cirrhosis [13].

Evidence that cirrhosis and/or hepatocellular carcinoma are potential outcomes of steatohepatitis, but tend to occur relatively infrequently, if at all, in individuals with simple steatosis, supports the concept that steatohepatitis is a more serious form of liver damage than simple steatosis [14–16]. The purpose of this review is to summarize similarities and differences in the pathogenesis of steatohepatitis in alcoholic fatty liver disease (AFLD) and nonalcoholic fatty liver disease (NAFLD).

Pathogenesis of Hepatocyte Injury and Death in AFLD and NAFLD

The extent and severity of hepatocyte injury and death distinguish steatohepatitis from simple steatosis [6,7]. Regardless of the specific primary stimulus for steatosis, hepatocyte injury and death result from unsuccessful adaptations to that stimulus [17–19]. Ironically, both failure to sufficiently induce "coping" mechanisms and the coping mechanisms themselves can result in hepatocyte lethality. Thus, hepatic steatosis identifies a state of hepatocyte vulnerability [14]. Common mechanisms that promote progression from simple steatosis to steatohepatitis are discussed subsequently. It is important to emphasize that these mechanisms are interactive, redundant, and not specific for AFLD or NAFLD. Also, multiple mechanisms may be operative simultaneously within any given individual with either condition.

Lipotoxicity

Altered lipid homeostasis is an initiating force for both alcoholic fatty liver disease (AFLD) and nonalcoholic fatty liver disease (NAFLD) [20,21]. While hepatocyte accumulation of triglyceride is the hallmark of hepatic steatosis in both AFLD and NAFLD, it is important to emphasize that triglycerides themselves are not hepatotoxic [22] and, therefore, do not cause steatohepatitis. Rather, storage of fatty acids in triglycerides protects hepatocytes from various potentially noxious consequences of fatty acid accumulation. Before discussing mechanisms for fatty acid toxicity, a brief summary of the factors that influence triglyceride accumulation is justified, since failure to adequately dispose of excess fatty acids by converting them into triglyceride increases the risk for hepatocyte lipotoxicity.

Factors that regulate hepatocyte triglyceride content

Triglycerides are a natural end-product of fatty acid metabolism. Hepatocytes normally increase their rates of triglyceride synthesis when energy consumption exceeds energy utilization. Energy excess is a feature of obesity, because obese subjects typically consume more food energy than they utilize by doing physical activity. Hence, energy excess provides a major stimulus for hepatocyte triglyceride synthesis in NAFLD. It may also contribute to steatosis in AFLD because alcoholic beverages are calorically dense, and this may push energy intake above energy utilization in habitual heavy drinkers.

In both AFLD and NAFLD, triglycerides are ultimately synthesized from fatty acids. There are several potential sources of fatty acids that can be used to generate triglycerides. Dietary fatty acids are an important source of fatty acids in both conditions. In both AFLD and NAFLD, fatty acids derived from lipolysis of adipose tissue triglyceride depots are also delivered to the liver, taken up by hepatocytes, and converted into triglycerides [23,24].

Hepatocyte uptake of fatty acids from the diet and from lipid-containing particles that are released from endogenous lipid stores is regulated by several types of proteins, including fatty acid transport proteins (FATPs), fatty acid translocase [25] (also called CD36), and fatty acid binding proteins (FABPs). A detailed discussion of these proteins was recently published elsewhere [21], and is beyond the scope of this review. Briefly, targeted deletion of FATP [26], FAT [27,28] or FABP [29,30] in hepatocytes reduce hepatic lipid accumulation in animal models of diet-induced hepatic steatosis. Although not tested formally, it also seems likely that knock-down of these genes would afford some protection from alcohol-induced steatosis. To date, very little information has been published about whether or not polymorphisms of these genes play an important role in susceptibility to and/or progression of AFLD or NAFLD. However, hepatic expression of FAT/CD36 was reported to be increased and correlated with liver fat content in some patients with NAFLD [31]. On the other hand, there has been much discussion about the role of adipocytokines, such as adiponectin, in regulating hepatic fatty acid uptake (and *de novo* lipogenesis) in both AFLD and NAFLD [32]. Reduced adiponectin and/or defective adiponectin function have been demonstrated in both conditions, and are believed to contribute to hepatocyte fatty acid accumulation and increased triglyceride synthesis [33].

De novo lipogenesis (*i.e.*, increased fatty acid biosynthesis) is another factor that contributes to the development of steatosis in both AFLD and NAFLD. This process is regulated by transcription factors that are activated by insulin, particularly sterol regulatory element binding protein (SREBP)-1c [34]. Therefore, hyperinsulinemia is an important stimulus for de novo lipogenesis. Hyperinsulinemia is common in NAFLD, but may also occur in AFLD when inflammatory cytokines reduce insulin sensitivity [35,36]. SREBP-1 is also activated by endoplasmic reticulum (ER) stress, a condition that occurs in both AFLD and NAFLD [37–39] (see below). Hence, increased *de novo* lipogenesis may provide a stimulus for increased triglyceride synthesis in both NAFLD and AFLD.

Finally, fatty acids may also accumulate within hepatocytes because their metabolism is impaired. In healthy hepatocytes, fatty acids are oxidized by enzymes in peroxisomes, mitochondria, and the endoplasmic reticulum (microsomes) [21]. When fatty acid oxidation is inhibited, but mechanisms for triglyceride synthesis remain intact, the resultant accumulation of fatty acids provides a potent stimulus for triglyceride synthesis.

Regardless of the source of fatty acids that hepatocytes use to produce triglyceride, this triglyceride is normally packaged into lipoproteins in the hepatocyte endoplasmic reticulum, and then exported to adipose depots for storage. Therefore, in both AFLD and NAFLD, triglyceride accumulates within hepatocytes when these export mechanisms become overwhelmed [24]. This may occur due to inherited or acquired defects in lipoprotein assembly and secretion [40–42], including ER stress, homocysteinemia, abetaliproteinemia, and choline deficiency. These factors can occur in both AFLD and NAFLD.

Factors that control fatty acid oxidation

Variability in the efficiency of the different mechanisms for fatty acid oxidation, coupled with differences in the ability to cope with residual fatty acids and/or their metabolic by-products, is likely to explain some of the differences in the degree of hepatocyte triglyceride accumulation, and conversely, the severity of hepatocyte injury (*i.e.*, lipotoxicity) that occurs in any given individual over time, as well as among different individuals with AFLD or NAFLD. Lipotoxicity occurs because, unlike triglycerides which are relatively inert, fatty acids physically interact with lipid membranes and other cellular molecules [43,44]. Some of these interactions are directly damaging [45,46]. Others cause damage by initiating signaling events [47,48]. For example, fatty acids are endogenous ligands for certain nuclear hormone receptors, and thereby regulate cellular metabolism and differentiation [49] (see below). They

also alter lysosomal permeability in hepatocytes, promoting release of cathepsin B and triggering hepatocyte production of cytokines, such as tumor necrosis factor (TNF) α and interleukin-6 [50]. In addition, fatty acids are capable of interacting with certain toll like receptors and thus, modulate activation of down-stream kinases and transcription factors that are regulated by these receptors [51].

Fatty acids that are not incorporated into triglyceride are degraded by oxidation. This process may also be hepatotoxic. Fatty acid oxidation is catalyzed by enzymes that are localized within three discrete cellular compartments: mitochondria, peroxisomes and microsomes [52,53] (*i.e.*, smooth endoplasmic reticulum). Transcription of enzymes that catalyze β-oxidation of fatty acids in peroxisomes and mitochondria is regulated by the fatty acid-sensitive nuclear hormone receptor PPAR-α [54]. PPAR-α activity is inhibited by chronic consumption of alcohol, but may be more normal in NAFLD [55–57]. Changes in PPAR-α activity influence β-oxidation of fatty acids in both conditions. Mitochondrial oxidation of fatty acids generates superoxide (which is generally detoxified efficiently by mitochondrial superoxide dismutase), ATP, ketone bodies and acetyl CoA (which ultimately enters the tricarboxylic acid cycle and is converted to CO_2 and H_2O). Because mitochondrial damage is common in AFLD [58,59] and also occurs in NAFLD [60,61], the capacity for fatty acid oxidation in this organelle may become limiting, particularly in AFLD. This leads to increased peroxisomal (and microsomal) oxidation of fatty acids. Peroxisomal oxidation of fatty acids generates hydrogen peroxide, a potential source of oxidant stress [53,62]. Reactive oxygen species (ROS) are also produced when fatty acids undergo ω-oxidation by cytochrome P450 enzymes within microsomes [63–66]. In addition, microsomal ω-oxidation of fatty acids generates dicarboxcylic acids (DCA). DCA uncouple mitochondrial oxidative phosphorylation, reducing the mitochondrial membrane potential [63]. This decreases the efficiency of mitochondrial ATP production, and enhances vulnerability to other stresses that promote depolarization of mitochondrial membranes, including TNFα and various other pro-apoptotic signals [67]. DCA are also PPAR-α ligands [53], and thus, amplify expression of fatty acid oxidizing enzymes. This re-enforces expression of microsomal fatty acid oxidizing enzymes, such as Cyp2E1, and helps to explain why expression of Cyp2E1 and other microsomal enzymes are increased in both AFLD and NAFLD. Since Cyp2E1 also metabolizes ethanol [68,69], fatty acid-related induction of this enzyme contributes to generation of acetaldehyde, which forms immunogenic adducts [70] with various molecules, and exacerbates ROS production in AFLD.

Based on this discussion, it is evident that the ultimate “impact” of fatty acid oxidation is modulated by the capacity of various endogenous systems to buffer hepatocytes from noxious actions of by-products of fatty acid oxidation. Mitochondria themselves (which progressively degrade fatty acids and dicarboxylic acids to innocuous end-products), and various antioxidant enzymes (which detoxify superoxide anion and hydrogen peroxide that are generated during fatty acid oxidation) are particularly important in this regard [25,71–73]. These buffering systems act in concert with other factors that carefully regulate the net content of fatty acids within hepatocytes by controlling their uptake (*e.g.*, FATPs, FAT, FABPs), biosynthesis (*e.g.*, SREBP-1c), non-oxidative metabolism (*e.g.*, DGAT2-mediated conversion into triglyceride), and the availability/activity of fatty acid-sensitive signaling molecules (*e.g.*, PPARs, Toll-like receptors). Lipotoxicity (*i.e.*, hepatocyte injury and death) results when this delicate and complex equilibrium is disturbed.

Oxidative Stress

Increased generation of ROS occurs in both AFLD and NAFLD and this has long been considered to play an important role in progression to steatohepatitis in both conditions. As discussed above, hepatocyte metabolism of ethanol and lipids results in formation of ROS

within several intra-cellular compartments, including the mitochondria, peroxisomes, and the endoplasmic reticulum [65,74]. When ROS production exceeds the buffering/detoxifying capacity of antioxidant systems, various cellular macromolecules are subject to direct oxidative attack. This may result in DNA mutations, destruction of vital enzymes, peroxidation of lipid membranes, and generation of other toxic molecules such as peroxinitrite and reactive iron species [75,76]. At lower levels, ROS function as signaling intermediates, triggering the activation of redox-sensitive transcription factors, such as NF-κB [77,78], that control the transcription of genes that regulate hepatocyte viability, as well as the synthesis of inflammatory mediators, such as TNFα and other proinflammatory cytokines [79–81]. These cytokines, in turn, exert both autocrine and paracrine effects: autocrine activation of TNF receptors, for example, may initiate death receptor signaling within hepatocytes themselves [82,83]; paracrine activation of TNF receptors on neighboring macrophages, endothelial cells and stellate cells promotes inflammatory and fibrogenic responses [35,84–86].

Despite the compelling rationale that supports the importance of ROS in the pathogenesis of both ASH and NASH, it has been difficult to demonstrate consistent benefit of anti-oxidant therapies in either condition. For example, agents that increase intracellular stores of reduced glutathione (*e.g.*, betaine and S-adenosyl methionine) have been reported to improve ASH and NASH in some animal models, but similar improvements have not been observed reproducibly in patients with either condition [87,88]. To date, the benefits of vitamin E therapy have been similarly inconclusive [89,90]. In contrast, treatment with pharmacologic inhibitors of NADPH oxidase (the membrane-associated enzyme complex that generates ROS in macrophages and various other cell types, including hepatic stellate cells), as well as generalized knock-down of this enzyme, significantly protected mice from alcohol-induced steatohepatitis [79,81]. Conversely, mice that over-expressed a constitutively active mutant form of NADPH oxidase developed significantly more liver injury and fibrosis than wild type controls when treated with carbon tetrachloride [91]. Interestingly, in these NADPH oxidase transgenic mice, over-activation of NADPH oxidase was restricted to myofibroblastic cells because the transgene was under the control of α-smooth muscle actin regulatory elements. The latter finding raises the intriguing possibility that ROS production by myofibroblasts, rather than macrophages, is responsible for liver damage during steatohepatitis.

Endoplasmic Reticulum Stress

ER accumulation of proteins that are normally secreted evokes an unfolded protein response [92,93] that restrains the further synthesis of such proteins, while amplifying the production of ER membranes and membrane-associated factors [94,95]. It also induces other mechanisms (*e.g.*, autophagy) to cope with the burden of retained proteins. As mentioned above, such responses impact lipid homeostasis. They also have various other “off-target” effects that may be detrimental when superimposed upon hepatocytes that are already struggling to adapt to oxidative- and other forms of metabolic stress [96]. ER stress is believed to be an important mechanism of hepatotoxicity in both AFLD and NAFLD.

Cytokines

Production of pro-inflammatory cytokines, particularly TNFα and IL-1, and TNF-inducible cytokines such as interleukin (IL)-6 and IL-8, is increased in both AFLD and NAFLD [97,98]. Multiple cell types likely contribute to this process because hepatocytes, cholangiocytes, macrophages, stellate cells, endothelial cells, and adipocytes are all capable of producing cytokines when challenged. In animal models of either AFLD or NAFLD, various strategies that inhibit expression and/or activity of TNFα generally improve steatohepatitis [99–101].

This is not surprising because there are multiple mechanisms by which increased TNFα is likely to promote progression from steatosis to steatohepatitis. For example, TNFα inhibits the expression and activity of adiponectin [102] and this exacerbates hepatocyte accumulation of fatty acids, contributing to lipotoxicity (see above). In addition, TNFα increases mitochondrial ROS production and promotes the mitochondrial membrane transition, effects that contribute to oxidant and apoptotic stress [35,103]. TNFα also activates down-stream kinases that interfere with insulin-signaling and this promotes hepatic (and systemic) insulin-resistance, hyperinsulinemia, and the consequent perturbations in lipid and glucose metabolism [35,104]. Finally, TNFα is a potent inducer of IL-8 and other chemokines and chemokine receptors that promote the hepatic recruitment and accumulation of various types of inflammatory cells [105].

However, despite all of these potentially dangerous effects of TNFα and the apparent benefit that accrues when TNFα signaling is blocked in animal and cell culture models of steatohepatitis, it is critical to acknowledge that specific antagonism of TNFα has not been proven to improve the outcomes in patients with ASH. Indeed, in at least two trials that were performed in patients with severe ASH, TNFα antagonism led to increased morbidity and mortality [106,107]. The reasons for the discrepant outcomes in experimental models and patients with ASH are not well-understood, but may relate to differences in the severity of liver injury and/or fibrosis in animals and people with alcohol-related steatohepatitis. Because specific TNFα antagonists are expensive and potentially toxic and patients with NASH seldom, if ever, manifest the same florid features of hepatic decompensation that occur in patients with acute alcoholic hepatitis, specific TNFα antagonists have not been evaluated in humans with NASH.

Interestingly, however, another “anti-cytokine” agent, pentoxifylline, has proven to improve outcomes in both ASH and NASH patients [108,109]. Although pentoxifylline inhibits TNFα, it also suppresses production of other cytokines and inhibits phosphodiesterases [110]. The latter effect has been linked to its anti-fibrotic actions, including its ability to block stellate cell activation [86,111]. Therefore, it is difficult to know which (if any) of these actions underlie the observed benefits of pentoxifylline in patients with steatohepatitis. Corticosteroids are another ASH therapy that is presumed to mediate its benefits by blocking the negative actions of inflammatory cytokines [112]. However, because prednisone and prednisolone are known to promote adiposity and exacerbate insulin resistance, and both conditions are risk factors for NASH, these agents have not been evaluated as therapies for NASH. Given evidence that corticosteroids improve mortality in patients with ASH [113], but would likely worsen insulin resistance, which constitutes a major risk factor for NASH, it is curious that certain insulin sensitizing agents improve both ASH and NASH [114,115].

Arguments that these agents are beneficial because they inhibit TNFα may need to be reconsidered in light of emerging evidence that TNFα antagonism is actually harmful in patients with severe ASH. This, in turn, re-directs attention towards other common targets. Thiazolidenediones, for example, increase activity of PPAR-γ. In addition to improving insulin sensitivity, inhibiting inflammatory signaling, and preventing TNFα production, PPAR-γ also suppresses transformation of quiescent stellate cells into activated myofibroblasts [116], and this is likely to be beneficial in both ASH and NASH. Another insulin sensitizing agent, metformin, has also been reported to provide some benefit in both NASH and ASH [117,118]. Metformin increases the activity of adenosine monophosphate-activated protein (AMP) kinase [119]. This is expected to promote PPAR-α activation, and thus, might promote fatty acid disposal. Increased AMP kinase activity is also expected to improve ATP regeneration. Recent evidence also suggests that increasing AMP kinase activity prevents stellate cell activation [120,121]. Thus, like pentoxifylline, two commonly prescribed insulin-sensitizing agents that seem to improve ASH and NASH have TNFα

independent effects that may reduce hepatocyte injury, including important actions on liver non-parenchymal cells.

Adipose tissues are also a rich source of cytokines that modulate the biology of various types of liver cells. In addition to TNFα and IL6 (which are thought to be produced by macrophages that accumulate in adipose tissues), adipocytes themselves also produce adipocytokines [102,122]. Two of the most extensively studied factors are leptin and adiponectin. Leptin reduces steatosis and lipotoxicity mainly by improving peripheral insulin sensitivity and thereby reducing hepatic exposure to adipose-derived fatty acids [123]. It also has significant anti-inflammatory actions [124]. However, leptin promotes myofibroblastic activation of hepatic stellate cells and thus, may contribute to fibrogenesis in NASH (and ASH) [125,126]. Adiponectin, on the other hand, seems to have generally beneficial effects, inhibiting steatosis, lipotoxicity, and fibrogenesis in both conditions [32,33,127].

Endotoxin and other products of gut bacteria

The healthy liver receives most of its afferent blood supply from the portal venous system and consequently, it is routinely exposed to commensal flora and their products. Intestinal permeability increases significantly in ASH [128,129]. It has also been reported to be increased in experimental animals and patients with NASH [130,131]. Thus, in both ASH and NASH, hepatic exposure to gut-derived bacterial products increases [100,101,132]. Evidence that such factors contribute to the pathogenesis of steatohepatitis was first demonstrated in animal models of ASH [133]. Treatment with poorly absorbed oral antibiotics, particularly agents that bound lipopolysaccharide, significantly protected rodents from alcohol-induced liver injury [101]. Subsequent studies demonstrated similar protection by deleting cell-surface receptors that promote LPS signaling [134,135]. Some benefits were also observed in rodent models of NAFLD/NASH when the mice were treated with probiotics [136]. Oral antibiotic therapy also improved liver damage in patients with total parenteral nutrition-related steatohepatitis [137]. More recent, elegant studies in germ-free mice proved that the gut flora modulates hepatic lipid homeostasis, and thus, influences lipotoxicity [138]. Multiple mechanisms are likely to be involved given that resident intestinal bacteria release various factors that interact with different pathogen-associated molecular pattern (PAMP) recognition receptors on the surface of resident liver cells, including hepatocytes, macrophages, and stellate cells. Ligation of Toll-like receptor 4, for example, activates inflammatory signaling in hepatocytes [139,140]. It is also known to play a critical role in activation of hepatic stellate cells [141].

Ethanol and its metabolites

Perhaps the biggest difference in ASH and NASH pertains to the relative exposure to ethanol and its metabolites, which occur at significant levels in the former, but presumably not the latter, condition. On the other hand, it is important to emphasize that ethanol and acetaldehyde can be generated endogenously, albeit in much lower levels than are typically observed in actively drinking alcohol abusers [142,143]. Ethanol, for example, is produced by gut bacteria during carbohydrate metabolism. Acetaldehyde is also a by-product of normal intermediary metabolism. The fact that ASH and NASH share many similar histologic features despite the fact that the two conditions clearly differ in the degree to which the liver is exposed to ethanol and acetaldehyde suggests either that these factors are unimportant in the pathogenesis of ASH or that their hepatotoxic effects may be mimicked by (or result from) other molecules. On the other hand, evidence that the natural history of ASH appears to be much more “aggressive” than that of NASH suggests that ethanol and/or acetaldehyde may, indeed, have unique roles in steatohepatitis progression. For example, acetaldehyde

interacts with various molecules to form adducts that have immunogenic properties [70]. Acetaldehyde has also been shown to directly activate collagen gene expression in hepatic stellate cells [144,145]. Ethanol itself disorders lipid membranes. Its (non-oxidative) metabolism also generates fatty acid ethyl esters that may be cytotoxic [146]. Therefore, chronic exposure to ethanol and/or its metabolites may further challenge livers that are concomitantly experiencing stresses related to lipotoxicity, oxidative and ER stress, and exposure to cytokines and PAMP recognition receptors, exacerbating hepatocyte injury and related inflammation and fibrogenesis.

Summary

Steatohepatits occurs in subpopulations of individuals with either alcoholic or nonalcoholic fatty liver disease. Steatohepatitis differs from simple steatosis mainly with regard to the severity of hepatocyte injury and extent of hepatocyte death, both being much worse in steatohepatitis than steatosis. A number of common mechanisms contribute to hepatocyte injury in ASH and NASH (Figure 1), including lipotoxicity, oxidant and ER stress, and increased exposure to various cytokines and factors that activate PAMP recognition receptors. Patients with ASH are also chronically exposed to relatively high concentrations of ethanol and its metabolite, acetaldehyde, which superimpose additional toxicities. The latter may help to explain why a greater proportion of patients with ASH than NASH appear to develop cirrhosis and liver-related mortality. Nevertheless, ASH and NASH are generally improved by treatments that reduce hepatocyte fatty acid accumulation and/or that block inflammatory signaling and activation of hepatic stellate cells. This suggests that these shared mechanisms drive the pathogenesis and progression of steatohepatitis in both conditions.

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Abbreviations

AFLD	alcoholic fatty liver disease
AMP	adenosine monophosphate-activated protein
ASH	alcoholic steatohepatitis
ATP	adenosine triphosphate
CYP2E1	cytochrome P450 2E1
DCA	dicarboxylic acids
DGAT	diacylglycerol acyltransferase
ER	endoplasmic reticulum
FABP	fatty acid binding protein
FAT	fatty acid translocase
FATP	fatty acid transport protein
HCC	hepatocellular carcinoma
IL	interleukin
LPS	lipopolysaccharide

NADPH	nicotinamide adenine dinucleotide phosphate
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NFkB	nuclear factor kappa B
PAMP	pathogen-associated molecular pattern
PPAR	peroxisome proliferator-activated receptor
ROS	reactive oxygen species
SREBP	sterol regulatory element binding protein
TLR	toll-like receptor
TNF	tumor necrosis factor

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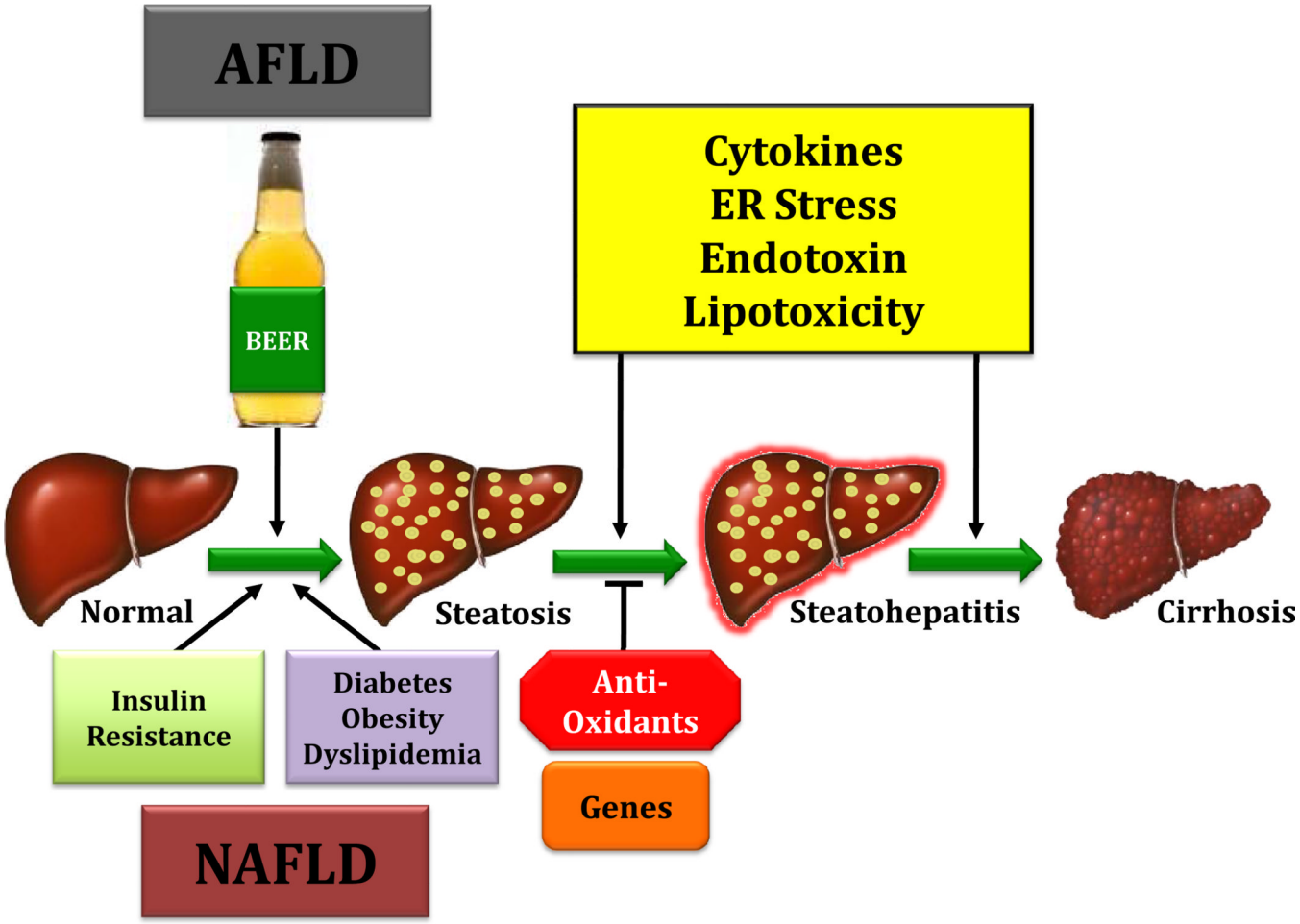

Figure 1.

Under normal conditions, cells respond to increased fatty acid load by up regulating oxidation pathways, increase cellular export of VLDL and suppress fatty acid synthesis. In NAFLD and AFLD, triglyceride accumulation results from excess energy because obese subjects typically consume more food energy than they utilize by doing physical activity and because alcoholic beverages are calorically dense pushing energy intake above energy utilization in habitual heavy drinkers respectively. Hepatic steatosis then occurs when the influx of fatty acids to the liver is coupled with repressed fatty acid oxidation, triglyceride export (VLDL) and dysregulated fatty acid synthesis. When increased fatty acid load exceeds metabolic oxidation pathways, accumulation of potentially toxic by-products and reactive oxygen species (ROS), including hydrogen peroxide results. ROS trigger lipid, protein and DNA peroxidation, and are immunogenic, which lead to the production of proinflammatory cytokines (such as TNFα). When persistent, these cellular stresses overwhelm intrinsic detoxification mechanisms (antioxidants and unfolded protein response), and promote hepatocyte cell death, a hallmark of steatohepatitis. Compounding the problem, obesity, diabetes and chronic ethanol intake are associated with increased gut epithelial permeability and bacterial overgrowth, resulting in endotoxemia (*i.e.*,lipopolysaccharide, LPS) which activate hepatic stellate cells and Kupffer cells. This triggers the production of additional TNFα and ROS, both of which are pro-apoptotic and promote the inflammatory milieu that drives progressive fibrosis.