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Macrophages: Master Regulators of Inflammation and Fibrosis

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Abstract

Macrophages are found in close proximity with collagen-producing myofibroblasts and indisputably play a key role in fibrosis. They produce profibrotic mediators that directly activate fibroblasts, including transforming growth factor-β1 and platelet-derived growth factor, and control extracellular matrix turnover by regulating the balance of various matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases. Macrophages also regulate fibrogenesis by secreting chemokines that recruit fibroblasts and other inflammatory cells. With their potential to act in both a pro- and antifibrotic capacity, as well as their ability to regulate the activation of resident and recruited myofibroblasts, macrophages and the factors they express are integrated into all stages of the fibrotic process. These various, and sometimes opposing, functions may be performed by distinct macrophage subpopulations, the identification of which is a growing focus of fibrosis research. Although collagen-secreting myofibroblasts once were thought of as the master “producers” of fibrosis, this review will illustrate how macrophages function as the master “regulators” of fibrosis.

Keywords

Fibrosis; inflammation; collagen; wound healing; stellate cell; myofibroblasts; interleukin-13; transforming growth factor beta; tumor necrosis factor; interleukin-1; interleukin-17; arginase; Relm-alpha; chitinase

Fibrosis results when normal wound-healing responses persist or are not regulated properly, usually in response to some type of repeated injury. For example, the primary causes of liver fibrosis include persistent hepatitis C virus infection, chronic infections with the helminth parasites *Schistosoma mansoni* and *Schistosoma japonicum*, alcohol abuse, and nonalcoholic steatohepatitis. Following acute liver injury, a beneficial wound-healing mechanism regenerates damaged parenchymal cells, including hepatocytes, to replace necrotic tissue and apoptotic cells. But, when the cause of injury persists, extracellular matrix (ECM) components like fibrillar collagens accumulate to high levels, ultimately leading to advanced fibrosis or cirrhosis and hepatocellular dysfunction, as well as hepatic insufficiency and portal hypertension caused by increased intrahepatic resistance to blood flow. In diseased liver, most ECM components are produced by hepatic stellate cells (HSCs), also known as lipocytes, Ito cells, or perisinusoidal cells. HSCs respond to injury by differentiating into myofibroblast-like cells with contractile, proinflammatory, and potent fibrogenic activities. In addition, several groups have identified important roles for bone marrow–derived stem

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cells, circulating fibrocytes, and myofibroblasts derived from epithelial/endothelial mesenchymal transition.[1–4] Because the various types of myofibroblasts are the primary collagen-producing cells in the liver, not surprisingly, they have been the object of decades of research aimed at characterizing the origins and functions of these cells in the fibrotic process.

Recent studies have also identified macrophages as critical regulators of fibrosis. Like myofibroblasts,[1–5] these cells are derived from either resident tissue populations, like Kupffer cells, or from bone marrow immigrants.[6,7] Studies now suggest the pathogenesis of fibrosis is tightly regulated by distinct macrophage populations that exert unique functional activities throughout the initiation, maintenance, and resolution phases of fibrosis.

EVIDENCE MACROPHAGES CONTROL FIBROSIS PROGRESSION AND RESOLUTION

Macrophages are almost always found in close proximity with collagen-producing myofibroblasts,[8–10] and there is strong evidence that this interaction is reciprocal.[4] Activated HSCs attract and stimulate macrophages with multiple chemokines and macrophage colony stimulating factor (M-CSF), and macrophages produce profibrotic mediators that directly activate fibroblasts, including transforming growth factor (TGF)-β1 and platelet-derived growth factor (PDGF). TGF-β1 is well known as an important inducer of fibrosis in many tissues and organs. In the liver, TGF-β1 promotes fibrosis by prompting HSC differentiation into myofibroblasts, enhancing expression of tissue inhibitors of matrix metalloproteases (TIMPs) that block ECM degradation, and by directly promoting synthesis of interstitial fibrillar collagens.[1] PDGF also acts as a potent profibrotic signal by stimulating the proliferation of activated, collagen-producing HSCs.[11] Interestingly, although a variety of cell types produce both mediators, several studies have identified macrophages as a critical source of TGF-β1 and PDGF in fibrosis.[12,13] Macrophages also regulate fibrosis independently of direct interactions with myofibroblasts. Macrophages present antigens to propagate antigen-specific T-cell responses; produce their own matrix metalloproteases (MMPs) and TIMPs that control ECM turnover; secrete chemokines that recruit fibroblasts and other inflammatory cells; remove dead cells and debris by phagocytosis, which could otherwise trigger proinflammatory and profibrotic signals; and express immunoregulatory mediators like Relm-α/Fizz1/Retnla, chitinase-like proteins, and nitric oxide synthase (NOS)-2 or arginase-1 (Arg-1) that alter the magnitude and duration of the immune response.[14] In addition, a growing body of evidence suggests that macrophages and other mediators regulate matrix deposition independently of TGF-β1.[15–18] Finally, macrophages also play a distinct role in the resolution of fibrosis.[19]

MACROPHAGES REGULATE FIBROSIS BY FUNCTIONING AS PHAGOCYTIC CELLS

Macrophages have been described classically as cells that phagocytose (engulf and then digest) cellular debris and pathogens. This key activity of macrophages is critical to fibrogenesis; however, whether phagocytosis promotes or slows the progression of fibrosis depends on the type of dead cells that are being engulfed and removed. Tissue injury causes damaged parenchymal cells, like hepatocytes, to undergo either apoptotic or necrotic cell death. Macrophages clear the dead cells in both cases; however, they typically repress inflammation when phagocytosing apoptotic cells and promote inflammation during necrotic cell removal.[20,21] Because ingesting dying hepatocytes, and dead cells in general, increases TGF-β1 secretion,[20–23] in this case the phagocytic activity of macrophages is profibrotic. However, phagocytosis by macrophages can also aid in the regression or resolution of

fibrosis because clearing apoptotic myofibroblasts, hepatocytes, and cellular debris often eliminates the stimuli inducing TGF-β1 and other profibrotic factors.[2,24] The macrophage-dependent proinflammatory response to necrotic cells similarly holds both pro- and antifibrotic potential: first by recruiting inflammatory cells, which stimulate fibroblast activity and ECM deposition, and then by terminating inflammation by cleaning up tissue debris, including the dying inflammatory cells.[25] For example, the phagocytosis of erythrocytes by macrophages and Kupffer cells promotes oxidative stress, inflammation, and fibrosis by depositing iron derived from hemoglobin in the liver.[26] Conversely, the anti-fibrotic role of phagocytosis was illustrated nicely with the CCl_4-induced liver injury model in which macrophages and Kupffer cells were shown to phagocytose apoptotic hepatocytes and reduce the inflammatory response, thereby shortening the course of injury and preventing the development of fibrosis.[27] Likewise, macrophage-mediated phagocytosis of apoptotic cholangiocytes has been shown to promote the reversal of biliary fibrosis.[28] Excess matrix components also accumulate from a combination of increased synthesis and secretion of matrix proteins by fibroblasts and from the increased proliferation and accumulation of HSCs at sites of tissue injury. Consequently, the deposition of ECM components is also controlled by macrophages and Kupffer cells removing apoptotic myofibroblasts.[29] In addition to clearing apoptotic cells, macrophages can slow the progression of fibrosis by directly eliminating excess collagen from damaged tissues. A recent study suggested this mechanism is facilitated by milk fat globule epidermal growth factor 8 (Mfge8), which binds to and targets collagen for cellular uptake through Mfge8's discoidin domains.[30] Thus, macrophages' phagocytic activity impacts both the induction and resolution of fibrosis through multiple mechanisms.

ACTIVATED MACROPHAGES PRODUCE AND ACTIVATE TGF-β1

The TGF-β cytokines (TGF-β1, -β2, and -β3) are induced and activated in a variety of fibrotic diseases, with the TGF-β1 isoform suspected of playing a key role in liver fibrogenesis.[31] Early studies of liver fibrosis indicated that damaged hepatocytes and activated HSCs were likely the dominant sources of TGF-β1.[32,33] These findings suggested an autocrine effect of TGF-β in liver fibrogenesis—that is, the cells that are the primary target of the cytokine produce TGF-β selectively. Subsequent studies, however, revealed that a variety of cell types produce TGF-β1 following liver injury, including hepatocytes, sinusoidal endothelial cells, HSCs, Kupffer cells, $CD4^+$ T cells, bone marrow–derived monocytes, and monocyte-derived macrophages, with the type of cellular injury likely influencing the dominant source of TGF-β and its specific mechanism of action.[1,34,35] In addition to inducing fibrosis, TGF-β may also inhibit inflammation and induce apoptosis.[36] Thus, TGF-β both positively and negatively regulates fibrosis via pathways that are likely governed by the cells producing the cytokine. For example, TGF-β1-producing regulatory T cells were shown to ameliorate TGF-β1-mediated fibrosis through an interleukin (IL)-10-dependent mechanism.[37] In contrast, macrophage-derived TGF-β1 is typically profibrotic. Indeed, numerous studies have identified various macrophage subsets as key producers of TGF-β1,[34,35,38–40] with the profibrotic cytokine IL-13 playing a key role by both inducing and activating latent TGF-β1 through an MMP9-dependent mechanism.[41] Together, these data suggest TGF-β1 activity suppresses inflammation if produced by regulatory T cells but promotes fibrosis when derived from macrophages. The fact that TGF-β1 can simultaneously suppress inflammation but promote collagen synthesis in myofibroblasts likely explains the many contradictory findings reported for this cytokine. These observations present challenges for therapies geared toward TGF-β1 and its signaling pathway and may explain the lack of significant clinical progress with TGF-β-signaling inhibitors in the treatment of fibrotic diseases despite more than 20 years of research on the TGF-β pathway.[42,43] Suppressing the profibrotic macrophage, rather than globally attenuating TGF-β1, might provide a more rational approach to ameliorate fibrosis. Indeed,

studies have already shown that decreasing the number of TGF-β1-producing macrophages significantly slows the progression of hepatic fibrosis.[44]

SEVERAL SECRETED FACTORS FROM MACROPHAGES CONTROL FIBROGENESIS

In addition to producing TGF-β1, activated macrophages and Kupffer cells regulate fibrosis by secreting a variety of chemokines, cytokines, and growth factors. Macrophages, like other innate immune cell types, are activated by pathogen-associated molecular patterns that engage an array of pattern-recognition receptors.[45] Once stimulated, macrophages secrete factors that recruit myofibroblasts and additional inflammatory cells to sites of tissue injury, and these recruited cells can also secrete a variety of chemokines, cytokines, and growth factors.[14,25,46–48] Thus, besides TGF-β1, activated macrophages amplify the fibrotic response indirectly by secreting numerous mediators that initiate and maintain the inflammatory cascade. Early studies showed the importance of monocyte chemotactic protein (MCP)-1 in recruiting CC chemokine receptor (CCR)2-expressing monocytes.[49] Activated monocytes in turn produce MCP-2 and -3, which have been shown to participate in the development of primary biliary cirrhosis and liver fibrosis by recruiting and activating myofibroblasts and by regulating the production of macrophage-derived MMPs, including MMP2 and MMP9.[34,50–52] The CC chemokines macrophage inflammatory protein (MIP)-1α, MIP-1β, and regulated upon activation, normal t-cell expressed and secreted (RANTES), together with their corresponding receptors CCR1 and CCR5, are also routinely up-regulated in models of liver fibrogenesis.[25] Furthermore, neutralization studies identified important roles for both CCR1- and CCR5-expressing Kupffer cells in the development of liver fibrosis.[53] MIP-2 also participates in fibrogenesis by regulating angiogenesis.[54] Another notable chemoattractant is osteopontin (OPN).[55,56] Studies have shown that OPN recruits macrophages to injured tissues,[57] and experiments with $OPN^{-/-}$ mice confirmed an important role for OPN in the development of kidney and liver fibrosis.[58,59] However, OPN can also protect mice from CCl_4-induced liver fibrosis.[60] Regardless of the exact mechanism of action of OPN, these studies nicely illustrate that macrophages regulate fibrosis via mechanisms that are distinct from TGF-β1.[61] Indeed, a complex interplay of chemokines and chemokine receptors, produced and expressed by macrophages (Kupffer cells), regulates fibrosis in part by promoting inflammation, angiogenesis, and the recruitment of macrophages and fibroblasts to sites of tissue injury.

Besides secreting TGF-β1 and chemoattractants, macrophages are an important source of yet other factors that regulate fibrosis. One is PDGF, which stimulates the proliferation, survival, and migration of myofibroblasts.[62,63] Imatinib mesylate (STI-571, Gleevec), a PDGF receptor tyrosine kinase inhibitor, is accordingly in preclinical development as a possible therapy for chronic hepatic fibrosis.[64] Macrophages produce significant amounts of IL-β1 in response to proinflammatory insults, and recent studies suggest that IL-1 myeloid differentiation primary response gene (88)(MyD88) signaling and the inflammasome are essential for fibrogenesis in the lung[15,65–67] and possibly, the liver.[68,69] Another factor is urokinase plasminogen activator, which generates plasmin to directly degrade ECM and assists in the activating MMPs.[70,71] Still other studies have shown that galectin-3, a β-galactoside-binding lectin produced by macrophages, is critically involved in the activation of renal fibroblasts. Depletion of galectin-3-positive macrophages reduced fibrosis severity after unilateral ureteric obstruction.[72] Macrophages also produce insulin-like growth factor-I, which stimulates the proliferation and survival of myofibroblasts and promotes collagen synthesis by these cells.[73] Finally, in some circumstances, macrophages and Kupffer cells secrete IL-4 and IL-13,[74,75] which (as discussed in the next section) are believed to function as potent profibrotic cytokines.[76]

A ROLE FOR TH2 CYTOKINES AND ALTERNATIVELY ACTIVATED MACROPHAGES

The Th2 cytokines IL-4 and IL-13, like TGF-β1, directly stimulate collagen synthesis in mouse and human fibroblasts.[77–79] They also promote the development of the classic myofibroblast phenotype in human lung fibroblasts.[80] In support of these observations, early immune deviation studies during *Schistosoma* infection, using IL-12 to switch from a Th2 to a Th1 pattern of cytokines, demonstrated that a Th2 response was associated with significant liver fibrosis, and a Th1 response provided protection from fibrosis.[81] Similar findings were also observed with the CCl_4-induced liver fibrosis model.[82] Subsequent studies dissected the individual roles of Th2 cytokines and identified IL-13 as the dominant inducer of hepatic fibrosis in murine schistosomiasis,[77,83] although IL-4, IL-5, IL-10, and IL-21 all participate via distinct mechanisms.[77,84–86] IL-13 has also been linked with the development of liver fibrosis in chronic hepatitis C virus infection.[87] Although IL-13 can directly stimulate collagen synthesis in fibroblasts, at least one study suggested that IL-13 promotes fibrosis indirectly, by inducing and activating latent TGF-β1.[41] However, results from the schistosomiasis model indicated that IL-13 induces liver fibrosis independently of TGF-β1 signaling,[16] which is consistent with findings in humans developing liver fibrosis.[87] IL-13 and TGF-β1 have also been shown to cooperate in the activation of myofibroblasts.[79]

Like myofibroblasts, macrophages respond to Th2 cytokines, and numerous studies have implicated IL-4/IL-13-stimulated macrophages in the pathogenesis of fibrosis,[88,89] although their exact contribution remains controversial.[14,90–92] Gordon and colleagues first noted that macrophages treated with IL-4 developed an alternative activation state that is distinct from "classically activated macrophages" (CAMϕ) exposed to interferon-γ.[93–95] IL-13 was later shown to have equivalent effects as IL-4.[94] In vitro, this phenotype is characterized by elevated major histocompatibility complex class II, mannose receptor (CD206), Ym1, Fizz1/Relm-α, and arginase activity.[89,93–98] These cells are now commonly termed "alternatively activated macrophages" (AAMϕ) or M2 macrophages.[90,95] Studies of schistosomiasis-induced liver fibrosis found that AAMϕ compose 20 to 30% of egg-induced liver granulomas, suggesting that these cells are positioned to play an important regulatory role in hepatic fibrosis.[89] Indeed, infected mice treated with Th1-inducing IL-12 had many more nitric oxide (NO)-expressing CAMϕ and much less liver fibrosis than did control mice. Interestingly, however, fibrosis was restored when NO production was blocked, suggesting pro- and antifibrotic roles for AAMϕ and CAMϕ, respectively.[88,89] This model was also supported by findings with mice deficient in cationic amino transporter-2 (CAT-2), which imports L-arginine for use in NO production in macrophages.[99] CAT-$2^{-/-}$ mice developed exacerbated liver fibrosis following *Schistosoma* infection, associated with decreased NO production and increased Arg1 activity in AAMϕ and fibroblasts.[10] Together, these studies support the hypothesis that the phenotype of the macrophage (classically versus alternatively activated) plays an equal, if not more important, role in the pathogenesis of liver fibrogenesis than does the type of $CD4^+$ T-helper cell response (Th1 versus Th2).[76]

Several other fibrosis models have also implicated AAMϕ in the pathogenesis of fibrosis. As observed in schistosomiasis, latent herpes virus infection-induced fibrosis is associated with a large population of AAMϕ.[100] A silica-induced model of lung fibrosis also found that the IL-4Rα-dependent differentiation of AAMϕ is critical to the induction and maintenance of the $CD4^+$ Th2 response that is required to trigger fibrosis.[101] Still others have proposed that AAMϕ are needed for the activation of collagen-producing myofibroblasts, suggesting a positive feedback loop exists between these two cell types.[76,89,102] Given the presumably important contribution of AAMϕ to the development of fibrosis, a great deal of recent research has sought to identify the signals that regulate their activation and recruitment to sites of inflammation, with IL-4, IL-13, IL-10, granulocyte-macrophage colony-stimulating

factor, IL-21, prostaglandin E2 (PGE_2), and Toll-like receptor signaling all playing important roles.[85,89,97,103,104] There is also growing interest in understanding the functions of the unique set of genes that characterize alternative activation, including arginase-1 (*Arg1*), mannose receptor (*Mrc1*), FIZZ1 (Relm-α/hypoxia-induced mitogenic factor/ *Retnla*), and the large chitinase family of genes (Ym1 [*Chi3l3*], Ym2 [*Chi3l4*], acidic mammalian chitinase [*Chia*], and YKL-40/BRP-3).[105–107]

REGULATION OF FIBROSIS BY MACROPHAGE-ASSOCIATED RELM-α/ FIZZ1

The functions of Relm-α in fibrosis are a topic of ongoing research and some controversy. Relm-α (*Retnla*) is a member of a family of cysteine-rich secreted proteins referred to as *resistin-like molecules* or *found in inflammatory zone*, originally identified in the lung.[108] The resistin-like family consists of four members: Retnla/Relm-α/FIZZ1, Relm-β/FIZZ2, Resistin/FIZZ3, and Relm-γ/FIZZ4.[109] Relm-α is expressed by bronchial epithelial cells and in the walls of the large and small bowel, and was originally hypothesized to regulate obesity and type-2 diabetes.[110] Relm-α increases during allergic responses in the lung, as well as in the lung, liver, and/or gut during most helminth infections, largely due to IL-4, IL-13, and Stat6-dependent signaling.[107,111,112] Relm-α is also induced in AAMϕ, serving as a useful biomarker of alternative activation.[113–115] Studies with the bleomycin model of fibrosis revealed that Relm-α is highly induced in the lung during fibrogenesis.[116,117] Relm-α-expressing cells activate α-smooth muscle actin and type I collagen expression in fibroblasts via a notch1-dependent but TGF-β1-independent mechanism in vitro.[116,117] Relm-α also exerts an antiapoptotic effect on mouse lung fibroblasts. Together, these findings provided evidence that macrophage-derived Relm-α might be involved in fibrogenesis by promoting the differentiation and survival of myofibroblasts.[118] A similar hypothesis was also proposed for Relm-β (Retnlb).[119] Thus, Relm-α and -βwere both predicted to be important mediators of wound repair and fibrosis at sites of Th2-mediated inflammation.

In addition to the injured lung, Relm-α is also found in abundance following infection with a variety of metazoan parasites.[85,107,120–123] In schistosomiasis, liver fibrosis and portal hypertension are the primary causes of chronic morbidity and mortality, and Th2 cytokines are essential to the development of fibrosis.[83,124] Relm-α is markedly induced in the granulomatous gut, liver, and lungs of *S. mansoni*-infected and egg-challenged mice[85,107] with expression depending on the Th2 immune response.[107] Surprisingly, although studies with other helminth parasites linked Relm-α expression with AAMϕ,[85,121,125] eosinophils appeared to be the predominant producers of Relm-α during schistosome infection.[126] Experiments with Relm-α knockout/reporter mice revealed that Relm-α is not required for the development of helminth-induced $CD4^+$ Th2 responses in the lung, liver, or gut.[126] On the contrary, ablating Relm-α facilitated the development of a much stronger Th2 response to *S. mansoni* eggs, leading to exacerbated liver fibrosis mediated by IL-13. Relm-α similarly reduced inflammation in the lungs of egg-challenged mice.[126,127] Therefore, instead of inducing fibrosis, as might have been predicted by prior in vitro studies with recombinant Relm-α/Fizz1 protein,[111,116] in vivo Relm-α exhibits protective activity in schistosomiasis-induced fibrosis by functioning as a negative regulator of the Th2 response.[126,127] The specific contribution of macrophage-derived Relm-α, however, remains unclear. Conditional deletion of Relm-α in macrophages could help clarify its role in fibrosis. It will also be important to investigate the role of Relm-α in other fibrotic diseases.[111]

CHITINASES AND CHITOLECTINS REGULATE FIBROSIS

Like Relm-α, chitin-binding proteins are induced in fibrotic lesions, are associated with AAMϕ, and remain an active topic of investigation, yet are inconclusively understood. Active chitinases hydrolyze chitin, an oligosaccharide polymer found in the exoskeletons of insects, crustaceans, fungal cell walls, and in some parasitic helminths, but not vertebrates. Eight human chitinases have been identified, but only two have preserved their chitinase activity, chitotriosidase (*CHIT1*) and acidic mammalian chitinase (*CHIA*). Due to mutations in the catalytic domain, the other chitinases have lost their chitinolytic activity and are termed *chitolectins*.[128] Interestingly, expression of the chitinases and chitolectins increases during infectious and inflammatory responses and exhibits important regulatory activity in Th2-type immunity,[107,129] although the exact function of the active chitinases remains debated.[130,131] Acidic mammalian chitinase (AMCase) is induced in epithelial cells and macrophages by IL-13. Neutralization of AMCase activity has been shown to ameliorate Th2-dependent inflammation, AAMϕ development, airway remodeling, and airway hyperresponsiveness in an aeroallergen asthma model, in part by inhibiting activation of the IL-13 pathway.[131] A similar effect was also recently ascribed to the mouse chitolectin breast regression protein-39 (BRP-39; *Chi3l1*) and its human homologue YKL-40.[132] Although AMCase and BRP-39 were both identified as critical mediators of IL-13-induced responses, other studies have shown that IL-4/13-induced AMCase activity inhibits chitin from promoting Th2, AAMϕ, and allergic responses.[130] Further study is clearly warranted to better understand the role of AM-Case and the entire chitinase-like family in the development of Th2-driven pathologies.

In addition to allergic-type inflammation, chitinases and chitolectins have been linked with the development of fibrosis in several organs including the liver, likely because of their association with Th2-type immune responses. For example, human chitotriosidase, produced mainly by activated macrophages and Kupffer cells,[133] is elevated in patients with nonalcoholic steato-hepatitis.[134–136] Macrophage-derived chitotriosidase is also overexpressed in lung lavage samples taken from patients with idiopathic pulmonary fibrosis or sarcoidosis, especially from those with progressing disease and significant lung involvement, suggesting that this enzyme plays a role in the pathogenesis of diffuse lung disease-associated fibrosis.[137,138] The plasma levels of YKL-40 increase in parallel with the degree of liver fibrosis and so might be useful as a serum biomarker of disease severity.[139] However, YKL-40 is also increased in the serum of patients with sarcoidosis, endotoxemia, and some types of cancer,[140–142] suggesting it may better mark tissue damage, active inflammation, and fibrosis in general rather than distinguishing liver fibrosis, a pattern consistent with YKL-40's presumed role as a growth factor for fibroblasts and vascular endothelial cells.[142] AMCase, chitotriosidase, and BRP-39 are also increased in the lungs and livers of mice embedded with *S. mansoni* eggs, suggesting that the chitinase family may play an important role in the development IL-13-dependent fibrosis mediated by infections.[107,143] Detailed mechanistic studies are needed to elucidate the unique contributions of the chitinases and chitolectins in the pathogenesis of fibrosis.

ARGINASE-1-EXPRESSING MACROPHAGES NEGATIVELY REGULATE FIBROSIS

Although a variety of proteins are differentially expressed between AAMϕ and CAMϕ,[105,122,144] the enzymes Arg-1 and NOS-2, respectively, are the key inducible genes commonly used to differentiate these two populations.[97,145,146] IL-13-activated macrophages produce the amino acid proline via a mechanism that is highly regulated by Arg-1.[89] Because collagen synthesis requires proline,[147] this pathway might explain how AAMϕ account for critical steps in wound healing and fibrosis.[76,100,107,148–150] Indeed, it

has been suggested that the profibrotic activity of IL-13 depends on the activation of Arg-1 in macrophages[89] However, this hypothesis was recently challenged by a key study conducted with LysM^{Cre} IL-4Rα $^{-/flox}$ mice, in which macrophages cannot recognize IL-4 or IL-13 and so cannot become alternatively activated.[151] If deprived of AAMϕ, schistosome-infected mice responded by increasing Th1 cytokine production and NOS-2 activity, which exaggerated hepatic and intestinal pathology, impaired egg expulsion, and led to sepsis at the acute stage of infection. However, egg-induced granulomas and liver fibrosis developed normally in the absence of AAMϕ. Therefore, at least in the context of schistosomiasis, AAMϕ are not strictly required for the development of hepatic fibrosis or granuloma formation, but instead avert acute morbidity and mortality by down-regulating proinflammatory cytokine expression in the intestine.[151] The specific contribution of macrophage-associated Arg-1, however, could not be discerned in these studies.

Recent studies have tested the function of arginine metabolism in various Th2 disease models using RNA interference, macrophage depletion, and the arginase inhibitors, [120,152,153] yet relatively few investigations have examined the role of macrophage-associated Arg-1 in the regulation of fibrosis. Because Arg-1 is predominantly expressed by macrophages[85,89] the newly created LysM^{Cre} Arg-1$^{-/flox}$ mouse provided an ideal tool to define the role of arginase in the schistosomiasis model of liver fibrosis by selectively deleting *ARG1* in macrophages.[103] In contrast to the findings with LysM^{Cre} IL-4Rα $^{-/flox}$ mice,[151] depleting arginase-1 activity specifically in AAMϕ exacerbated the development of liver fibrosis and increased the Th2 immune response without altering the development of AAMϕ.[91] The macrophage-specific Arg1 knockout mice also failed to develop endotoxemia or hepatotoxicity and survived acute infection, indicating that Arg-1 expression by AAMϕ is not required to suppress Th1- and NOS-2-mediated morbidity and mortality. Instead, LysM^{Cre} Arg-1$^{-/flox}$ mice died at an accelerated rate during the chronic stage of infection and displayed markedly increased granuloma size (i.e., inflammation), liver fibrosis, and portal hypertension. Blood was also frequently found in the intestine, suggesting that bleeding from collateral vessels was contributing to their morbidity and mortality. Thus, although Arg-1 was originally hypothesized to promote fibrosis and portal hypertension, studies with LysM^{Cre} Arg-1$^{-/flox}$ mice suggested that the primary role of Arg1-expressing AAMϕ is to slow the progression of schistosomiasis-induced liver disease.[91]

Th2 cytokine-activated macrophages have often been described as “suppressor” cells.[154] Nevertheless, most studies have focused on “myeloid-derived suppressor cells” that are associated with cancers and that cross-regulate type-1 immunity and inhibit the function of classically activated macrophages.[155–157] Results from the schistosomiasis model suggested that AAMϕ slow the progression of IL-13-dependent liver fibrogenesis by specifically reducing the proliferation and/or activation of CD4^{+} Th2 cells,[91] although an inhibitory effect on myofibroblasts could not be ruled out. Wild-type macrophages activated with IL-13 promoted minimal antigen-specific T-cell proliferation, and macrophages obtained from Arg-1 knockout mice promoted robust T-cell proliferation both before and after stimulation with IL-13.[91] T-cell proliferation could also be restored if wild-type AAMϕ were supplemented with exogenous L-arginine, suggesting the suppressive activity of Arg1-expressing AAMϕ was mediated by L-arginine depletion.[91,155] The inhibitory cytokines IL-10 and TGF-β1 were not involved, further confirming that L-arginine depletion by AAMϕ was serving as the primary suppressive mechanism. Thus, Arg1-expressing AAMϕ slowed the development of liver fibrosis, at least in part, by suppressing the antigen-specific CD4^{+} Th2-cell response. This conclusion contrasts with previous reports suggesting AAMϕ are required to induce Th2-cell responses.[75,93,158] Given these new findings, it will be important to investigate whether Arg1-expressing macrophages impede ECM deposition in other fibrotic diseases.[159,160]

A ROLE FOR MACROPHAGES IN THE RESOLUTION AND REVERSAL OF FIBROSIS

Although for many years fibrosis was thought to be a progressive and irreversible process, recent studies have challenged this theory. Perhaps counterintuitively, ongoing inflammation may be the key to reversing fibrosis because inflammatory cells, in particular activated macrophages, are the key sources of MMPs (collagenases) that facilitate ECM degradation. Recruited macrophages and resident Kupffer cells also phagocytose apoptotic myofibroblasts and clean up cellular debris that otherwise perpetuates the fibrotic process. Although the identity and source of the key collagenases that resolve fibrosis remain unclear, accumulating evidence strongly implicates macrophages and the interstitial collagenases MMP1, MMP2, MMP8, MMP9, and MMP13 in the reversal of fibrosis. Experimental depletion of macrophages at the onset of fibrosis resolution (recovery phase) has been shown to retard ECM degradation and the loss of activated HSCs.[19] Conversely, transferring macrophages into mice undergoing unilateral ureteral obstruction attenuates the development of renal fibrosis.[161] Hepatic macrophages may also play an indirect role in the resolution of fibrosis by recruiting neutrophils, whose collagenases effectively digest ECM components.[162] Together, these observations argue that macrophages regulate the resolution and reversal fibrosis through multiple mechanisms, producing MMPs that degrade the ECM, recruiting and/or activating additional collagenase-producing cells and phagocytosing cellular debris. Given that macrophages exert both pro- and antifibrotic activity,[19,163] identifying the phenotype, subpopulation, and/or soluble mediator(s) that preferentially activate antifibrotic macrophages will be an important advance in the goal of developing the “holy grail” therapy that can reverse established and progressive fibrosis. The heterogeneity and plasticity of macrophages poses a formidable obstacle to this goal and likely explains why depleting macrophages globally has often yielded conflicting results.[164,165] Manipulating distinct macrophage subpopulations may prove critical to understanding the contributions of macrophages to the initiation, maintenance, and resolution phases of fibrosis.[19,163]

A logical starting point for reversing fibrosis is to identify MMPs and other enzymes able to break down the ECM components that make up fibrotic lesions. Scar-associated macrophages are a major source of MMP13, and studies have shown that the resolution of CCl_4-induced hepatic fibrosis is substantially retarded in MMP13-deficient mice.[166] Results from the schistosomiasis model also revealed an important antifibrotic role for MMP13 in the development of infection-induced liver fibrosis. In this study, IL-13-mediated fibrosis was dependent on MMP12 (macrophage metalloelastase) and associated with markedly increased expression of collagenases MMP2, MMP9, and MMP13, suggesting that MMP12 was promoting fibrosis by limiting the expression of the ECM-degrading MMPs.[167] These findings were consistent with recent studies showing overexpressing MMP9 in macrophages can attenuate pulmonary fibrosis induced by bleomycin,[168] and MMP13 produced by Kupffer cells inhibits pig serum-induced liver fibrosis.[169] Although numerous investigations have suggested antifibrotic roles for the collagenases, a few have provided conflicting results. Indeed, one study showed that cholestasis-induced liver fibrosis, caused by bile duct ligation, is attenuated in the absence of MMP13. These authors suggested that macrophage-derived MMP13 regulates HSC proliferation and activation, thus identifying a critical profibrotic role for MMP13.[170] A similar protective effect was observed when macrophage infiltration was blocked during the induction of liver fibrogenesis in rats.[171] These findings reinforce the key point that macrophages and Kupffer cells exhibit both pro- and antifibrotic activity, with the specific experimental model, type of MMP, and phase of the response likely dictating the overall contribution of macrophages to the progression, resolution, and reversal of fibrosis. Together, these observations suggest that instead of shutting down

inflammation entirely, the currently favored approach,[172–174] manipulating the macrophage population or the character of the inflammatory response,[2,25,91] might offer a more cogent strategy to treat progressive and advanced fibrotic disease.

SUMMARY AND FUTURE GOALS

It is clear that macrophages are critically involved in both the induction and resolution of fibrosis. Seemingly slight modifications in the pattern of MMP expression can dramatically affect outcomes, with macrophage-derived MMP12 enhancing fibrosis whereas MMP1 and MMP13 display potent antifibrotic activity.[166,167] To promote fibrosis, macrophages produce specific MMPs, like MMP9, that degrade the basement membrane and allow inflammatory cells and recruited fibroblasts to enter sites of injury. They also secrete a variety of profibrotic mediators including TGF-β1, PDGF, and many chemokines that recruit and activate inflammatory cells. To negatively regulate fibrosis, macrophages secrete factors that induce myofibroblast apoptosis, remove cellular debris that otherwise perpetuates inflammation, engulf and digest ECM components, and stimulate the production of collagen-degrading MMPs in other cell types including stellate cells, myofibroblasts, and neutrophils. Macrophage-mediated changes in the ECM can also affect the survival of myofibroblasts and so facilitate the termination of progressive fibrosis.[175] By expressing Arg-1, macrophages also deplete an essential amino acid that $CD4^+$ T cells and myofibroblasts require to proliferate, thereby facilitating the down-regulation of profibrotic immune responses.[91] These observations are consistent with many recent studies that have suggested macrophages are essential to the resolution of fibrosis.

Therefore, although myofibroblasts are typically thought of as the “master mediators” of fibrosis because they synthesize collagen and other ECM components, macrophages play an equally important role by serving as the “master regulators” of myofibroblast function and ECM degradation. A key goal of future research will be to determine when and how distinct subpopulations of macrophages control these disparate functions or whether the same macrophage population can adjust its phenotype over time in coordination with new stimuli found in the local milieu. It will be especially important to test whether recovering from fibrosis requires recruiting a new class of macrophage from the bone marrow.[51] In addition to specifying which macrophage subpopulations promote, inhibit, or reverse fibrosis, future research should also elucidate the signals that regulate macrophage phenotypic conversion, differentiation, and recruitment. With our growing appreciation of the complex role of macrophages in fibrogenesis, the global depletion of macrophages no longer seems a viable option to treat highly progressive and established disease.[19] Instead, future efforts should focus on identifying the specific macrophage subpopulations that facilitate the resolution and reversal fibrosis as well as their specific mechanism of action.

ABBREVIATIONS

AAMϕ	alternatively activated macrophages
AMCase	acidic mammalian chitinase
Arg-1	arginase-1
BRP-39	breast regression protein-39
CAMϕ	classically activated macrophages
CCR	CC chemokine receptor
CAT-2	cationic amino transporter-2

ECM	extracellular matrix
HSC	hepatic stellate cell
IL	interleukin
MCP	monocyte chemotactic protein
M-CSF	macrophage colony stimulating factor
Mfge8	milk fat globule epidermal growth factor 8
MIP	macrophage inflammatory protein
MMP	matrix metalloprotease
NO	nitric oxide
NOS	nitric oxide synthase
OPN	chemoattractant is osteopontin
PDGF	platelet-derived growth factor
TGF	transforming growth factor
TIMP	tissue inhibitors of matrix metalloprotease

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