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Invited Review

Cellular and molecular mechanisms of fibrosis

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Abstract

Fibrosis is defined by the overgrowth, hardening, and/or scarring of various tissues and is attributed to excess deposition of extracellular matrix components including collagen. Fibrosis is the end result of chronic inflammatory reactions induced by a variety of stimuli including persistent infections, autoimmune reactions, allergic responses, chemical insults, radiation, and tissue injury. Although current treatments for fibrotic diseases such as idiopathic pulmonary fibrosis, liver cirrhosis, systemic sclerosis, progressive kidney disease, and cardiovascular fibrosis typically target the inflammatory response, there is accumulating evidence that the mechanisms driving fibrogenesis are distinct from those regulating inflammation. In fact, some studies have suggested that ongoing inflammation is needed to reverse established and progressive fibrosis. The key cellular mediator of fibrosis is the myofibroblast, which when activated serves as the primary collagen-producing cell. Myofibroblasts are generated from a variety of sources including resident mesenchymal cells, epithelial and endothelial cells in processes termed epithelial/endothelial-mesenchymal (EMT/EndMT) transition, as well as from circulating fibroblast-like cells called fibrocytes that are derived from bone-marrow stem cells. Myofibroblasts are activated by a variety of mechanisms, including paracrine signals derived from lymphocytes and macrophages, autocrine factors secreted by myofibroblasts, and pathogen-associated molecular patterns (PAMPS) produced by pathogenic organisms that interact with pattern recognition receptors (i.e. TLRs) on fibroblasts. Cytokines (IL-13, IL-21, TGF-β1), chemokines (MCP-1, MIP-1β), angiogenic factors (VEGF), growth factors (PDGF), peroxisome proliferator-activated receptors (PPARs), acute phase proteins (SAP), caspases, and components of the renin–angiotensin–aldosterone system (ANG II) have been identified as important regulators of fibrosis and are being investigated as potential targets of antifibrotic drugs. This review explores our current understanding of the cellular and molecular mechanisms of fibrogenesis.

Keywords: fibrosis; myofibroblast; collagen; wound healing; liver; lung

Introduction

In contrast to acute inflammatory reactions, which are characterized by rapidly resolving vascular changes, oedema and neutrophilic inflammation, fibrosis typically results from chronic inflammation — defined as an immune response that persists for several months and in which inflammation, tissue remodelling and repair processes occur simultaneously. Despite having distinct aetiological and clinical manifestations, most chronic fibrotic disorders have in common a persistent irritant that sustains the production of growth factors, proteolytic enzymes, angiogenic factors and fibrogenic cytokines, which stimulate the deposition of connective tissue elements that progressively remodel and destroy normal tissue architecture [1–3].

Damage to tissues can result from various stimuli, including infections, autoimmune reactions, toxins, radiation and mechanical injury. The repair process typically involves two distinct phases: a regenerative phase, in which injured cells are replaced by cells of the same type, leaving no lasting evidence of damage; and a phase known as fibroplasia or fibrosis, in which connective tissues replaces normal parenchymal tissue. Although initially beneficial, the repair process becomes pathogenic when it is not controlled appropriately, resulting in substantial deposition of ECM components in which normal tissue is replaced with permanent scar tissue [4]. In some diseases, such as idiopathic pulmonary fibrosis, liver cirrhosis, cardiovascular fibrosis, systemic sclerosis and nephritis, extensive tissue remodelling and fibrosis can ultimately lead to organ failure and death (Table 1).

Wound healing versus fibrosis

When epithelial and/or endothelial cells are damaged, they release inflammatory mediators that initiate an

Table 1. Major tissues affected by fibrosis and possible contributing factors

- *Liver*—Viral hepatitis, schistosomiasis, and alcoholism are leading causes of cirrhosis worldwide.
- *Lung*—The interstitial lung diseases (ILDs) include a diverse set of disorders in which pulmonary inflammation and fibrosis are the final common pathological manifestations. There are more than 150 different causes of ILDs, including sarcoidosis, silicosis, drug reactions and infections, as well as collagen vascular diseases, such as rheumatoid arthritis and systemic sclerosis (scleroderma). Idiopathic pulmonary fibrosis, the most common type of ILD, has no known cause
- *Kidney disease*—Diabetes damages and scars the kidneys, which can lead to a progressive loss of function. Untreated hypertension can contribute
- *Heart and vascular disease*—Following a heart attack, scar tissue can impair the ability of the heart to pump blood. Hypertension, atherosclerosis and restenosis also contribute
- *Eye*—Macular degeneration, retinal and vitreal retinopathy can lead to blindness
- *Skin*—Including keloids and hypertrophic scars. Systemic sclerosis and scleroderma, burns and genetic factors may also contribute
- *Pancreas*—Poorly understood but possible autoimmune/hereditary causes
- *Intestine*—Crohn's disease/inflammatory bowel disease. Pathogenic orgnanisms
- *Brain*—Alzheimer's disease, AIDS
- *Bone marrow*—Cancer and ageing
- *Multi-organ fibrosis*—(a) Due to surgical complications; scar tissue can form between internal organs, causing contracture, pain and, in some cases, infertility; (b) chemotherapeutic drug-induced fibrosis; (c) radiation-induced fibrosis as a result of cancer therapy/accidental exposure; (d) mechanical injuries

anti-fibrinolytic coagulation cascade [5], which triggers blood-clot formation and formation of a provisional ECM. Platelets are exposed to ECM components, triggering aggregation, clot formation and haemostasis. Platelet degranulation also promotes vasodilation and increased blood vessel permeability, while myofibroblasts (activated collagen secreting, α-SMA$^+$ fibroblasts) and epithelial and/or endothelial cells produce MMPs, which disrupt the basement membrane, allowing inflammatory cells to be easily recruited to the site of injury. Growth factors, cytokines and chemokines are also produced, which stimulates the proliferation and recruitment of leukocytes across the provisional ECM. Some of the early responders include macrophages and neutrophils, which eliminate tissue debris, dead cells and any invading organisms. They also produce cytokines and chemokines, which are mitogenic and chemotactic for endothelial cells, which begin to surround the injured site. They also help form new blood vessels as epithelial/endothelial cells migrate towards the centre of the wound. During this period, lymphocytes and other cells become activated and begin secreting profibrotic cytokines and growth factors, such as TGFβ, IL-13 and PDGF [6–8], which further activate the macrophages and fibroblasts. Activated fibroblasts transform into α-SMA-expressing myofibroblasts as they migrate along the fibrin lattice into the wound. Following activation, the myofibroblasts promote wound contraction, the process in which the edges of the wound migrate towards the centre. Finally, epithelial and/or endothelial cells divide and migrate over the basal layers to regenerate the damaged tissue, which completes the wound-healing process. However, chronic inflammation and repair can trigger an excessive accumulation of ECM components, which leads to the formation of a permanent fibrotic scar. Collagen turnover and ECM remodelling is regulated by various MMPs and their inhibitors, which include the tissue inhibitors of metalloproteinases (TIMPs). Shifts in synthesis versus catabolism of the ECM regulate the net increase or decrease of collagen within the wound [9]. Fibrosis occurs when the synthesis of new collagen by myofibroblasts exceeds the rate at which it is degraded, such that the total amount of collagen increases over time.

The cellular origins of myofibroblasts

Local tissue myofibroblasts were originally believed to be the primary producers of ECM components following injury [5]; however, it is now thought that fibroblasts can be derived from multiple sources [10]. In addition to resident mesenchymal cells, myofibroblasts are derived from epithelial cells in a process termed epithelial–mesenchymal transition (EMT) [10–12]. More recently, it was suggested that a similar process occurs with endothelial cells, termed endothelial–mesenchymal transition (EndMT) [13]. Bucala and colleagues also identified a unique circulating fibroblast-like cell derived from bone marrow stem cells [14]. These blood-borne mesenchymal stem cell progenitors have a fibroblast/myofibroblast-like phenotype (they express CD34, CD45 and type I collagen) and are now commonly called fibrocytes [15–18]. Finally, in some tissues, resident fibroblasts are not the only source of myofibroblasts. For example, in liver fibrosis the resident hepatic stellate cell (HSC) appears to be the primary source of myofibroblasts, although bone-marrow-derived cells can also contribute [18,19]. Because it is now thought that fibrocytes and EMT-derived myofibroblasts participate with resident mesenchymal cells in the reparative process, there has been growing interest in dissecting the role of the various myofibroblast subpopulations in fibroproliferative disease [20]. Because bone marrow-derived fibrocytes must find their way to sites of tissue injury to participate in wound healing and fibrosis, there has been a great deal of interest in understanding the role of chemokines and acute phase proteins, such as serum amyloid P (SAP), in the development and recruitment of myofibroblasts [20–22]. Because fibrocytes and EMT-derived myofibroblasts produce a variety of factors that are involved in the fibrotic process [10], interrupting their development, recruitment and/or activation could provide a unique therapeutic approach to treat a variety of fibrotic diseases.

Innate and adaptive immune mechanisms regulate myofibroblast activity

Many fibrotic disorders are thought to have an infectious aetiology, with bacteria, viruses, fungi and multicellular parasites driving chronic inflammation and the development of fibrosis. It was recently suggested that conserved pathogen-associated molecular patterns (PAMPs) found on these organisms help maintain myofibroblasts at a heightened state of activation [23]. Bacteria living in the gut can also contribute to the activation of myofibroblasts [24]. PAMPs are pathogen byproducts, such as lipoproteins, bacterial DNA and double-stranded RNA, which are recognized by pattern recognition receptors (PRRs) found on a wide variety of cells, including fibroblasts [25]. The interaction between PAMPs and PRRs serves as a first line of defence during infection and activates numerous proinflammatory cytokine and chemokine responses. In addition, because fibroblasts express a variety of PRRs, including Toll-like receptors (TLRs), Toll ligands can directly activate fibroblasts and promote their differentiation into collagen-producing myofibroblasts [23,24,26]. Thus, inhibiting TLR signalling might represent a novel approach to treat fibrotic disease.

Nevertheless, pathogenic organisms are not responsible for all fibrotic disorders. Therefore, additional mechanisms must also participate in the activation of myofibroblasts. For example, in the case of systemic sclerosis (SSc), fibroblasts obtained from lesional skin or fibrotic lungs have a constitutively activated myofibroblast-like phenotype, characterized by enhanced ECM synthesis, constitutive secretion of cytokines and chemokines and increased expression of cell surface receptors [27–29]. Because most of the characteristics of fibroblasts from patients with SSc are reproduced in normal human fibroblasts following stimulation with TGFβ, it is thought that the SSc fibroblast phenotype is maintained by an autocrine TGFβ signal. However, TGFβ/SMAD3-independent mechanisms have also been proposed [30,31], including a role for viruses such as CMV, which stimulate the production of auto-antibodies and connective tissue growth factor (CTGF), both of which are known to participate in the activation of myofibroblasts [28,32]. Epigenetic changes may also contribute to the persistent activation of myofibroblasts [33]. B cells have also been implicated, either by producing autoantibodies or by secreting IL-6, a well-known fibroblast growth factor [34]. Still other studies have argued that Th2-type cytokines derived from a variety of cellular sources are critically involved in the mechanism of fibrosis [35–38]. Therefore, paracrine signals derived from activated lymphocytes, autocrine factors produced by fibroblasts, as well as molecules derived from pathogenic organisms can cooperate to initiate and maintain myofibroblast activation.

Chemokines regulate fibrogenesis by controlling myofibroblast recruitment

Chemokines are leukocyte chemoattractants that cooperate with profibrotic cytokines in the development of fibrosis by recruiting myofibroblasts, macrophages and other key effector cells to sites of tissue injury. Although a large number of chemokine signalling pathways are involved in the mechanism of fibrogenesis, the CC- and CXC-chemokine receptor families have consistently exhibited important regulatory roles. Specifically, CCL3 (macrophage inflammatory protein 1α) and CC-chemokines such as CCL2 (monocyte chemoattractant protein-1), which are chemotactic for mononuclear phagocytes, were identified as profibrotic mediators. Macrophages and epithelial cells are believed to be the key sources of CCL3, and studies in the bleomycin model of pulmonary fibrosis showed that anti-CCL3 antibodies could significantly reduce the development of fibrosis [39,40]. Similar results were obtained when CCL2 was neutralized, suggesting that a variety of CC-chemokines are involved [41,42]. Subsequent studies with CC-chemokine receptor 1 (CCR1)- and CCR2-deficient mice produced similar results, confirming critical roles for CCL3/CCL2-mediated signalling pathways in fibrogenesis [43–47]. Interestingly, in several of these blocking studies, the absence of fibrosis was associated with decreased IL-4/IL-13 expression [44,48], suggesting a direct link between CC-chemokine activity and the production of profibrotic cytokines such as IL-13. IL-13 is a potent inducer of several CC-chemokines, including CCL3, CCL4 (MIP-1β), CCL20 (MIP-3α), CCL2, CCL11, CCL22 (macrophage-derived chemokine) and CCL6 (C10), among others, suggesting that a positive feedback mechanism exists between IL-13 and the CC-chemokine family [49,50]. As seen with anti-CCL3 and anti-CCL2 antibody treatment, antibodies to CCL6 significantly attenuated lung remodelling responses in IL-13-transgenic mice [50] as well as in mice challenged with bleomycin [49], indicating non-redundant roles for a variety of CC-chemokines in the pathogenesis of fibrosis. In mice, CXC chemokine receptor 4 (CXCR4), CC chemokine receptor 7 (CCR7) and CCR2 have also been shown to regulate the recruitment of fibrocytes to the lung [20,21]. Thus, interrupting specific chemokine signalling pathways could have a significant impact on the treatment of a variety of fibroproliferative diseases.

Th1 and Th2 cells differentially regulate organ fibrosis

Chronic inflammatory reactions are typically characterized by a large infiltrate of mononuclear cells, including macrophages, lymphocytes, eosinophils and plasma cells. Lymphocytes are mobilized to sites of injury and become activated following contact with various antigens, which stimulate the production of lymphokines that further activate macrophages and other local inflammatory cells. Thus, there is significant activation of the adaptive immune response in many chronic inflammatory diseases. Although inflammation typically precedes the development of fibrosis, results from a variety of experimental models suggest that fibrosis is not always characterized by persistent inflammation, implying that the mechanisms regulating fibrosis are to a certain extend distinct from those controlling inflammation. Findings from our own studies of schistosomiasis-induced liver fibrosis support this theory [35]. In this model, fibrosis develops progressively in response to schistosome eggs that are deposited in the liver, which induce a chronic granulomatous response. As in many other experimental models of fibrosis, $CD4^+$ T cells play a prominent role in the progression of the disease. Studies conducted with multiple cytokine-deficient mice have demonstrated that liver fibrosis is strongly linked with the development of a $CD4^+$ Th2 cell response (involving IL-4, IL-5, IL-13 and IL-21) [51–55].

Several experimental models of fibrosis in addition to our own have also documented potent antifibrotic activities for the Th1-associated cytokines IFNγ and IL-12. In schistosomiasis, while treatment with IFNγ or IL-12 has no effect on the establishment of infection, collagen deposition associated with chronic granuloma formation is substantially decreased [51]. Similar results have been obtained in models of pulmonary, liver and kidney fibrosis [56–59]. These findings suggest that it might be possible to develop an antifibrosis vaccine based on immune deviation [51,60], in which the profibrotic effects of the Th2 response are switched off in favour of an antifibrotic Th1 response. Indeed, similar approaches have been proposed for individuals suffering from allergic airway inflammation [61], which is also driven by Th2-type responses. Studies investigating the gene expression patterns of fibrotic tissues found that markedly different gene expression profiles are induced during Th1 and Th2 polarized responses [62, 63]. As might be expected, a large number of IFNγ-induced genes are upregulated in the tissues of mice exhibiting Th1-polarized responses, with no evidence of significant activation of the fibrosis-associated genes in this setting [62–64]. Instead, two major groups of genes were identified in Th1-polarized mice: those associated with the acute-phase reaction and apoptosis (cell death), findings which may explain the extensive tissue damage that is commonly observed when Th1 responses continue unchecked [65]. By contrast, several genes known to be involved in the mechanisms of wound healing and fibrosis were upregulated in animals exhibiting Th2-polarized inflammation [62,63]. The regulation and function of a few of the genes, including procollagens I, III and VI, arginase-1 [66], lysyl oxidase [67,68], matrix metalloproteinase-2 (MMP-2) [69,70], MMP-9 [71,72] and tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) [73,74], have been investigated in some detail. Several additional Th2-linked genes [62,63], including haem oxygenase, procollagen III, secreted phosphoprotein 1, procollagen V, reticulocalbin and fibrillin 1 have also been reported in the fibrotic lungs of bleomycin-treated mice [75] and in CCl_4-stimulated rat hepatic stellate cells (collagen-producing cells in the liver) [76], providing further evidence that fibrosis is often associated with the development of Th2-type responses.

Unique roles for the Th2 cytokines IL-4, IL-5, IL-13 and IL-21 in fibrosis

The Th2 cytokines IL-4, IL-5, IL-13 and IL-21 each have distinct roles in the regulation of tissue remodelling and fibrosis. IL-4 is found at increased levels in the bronchoalveolar lavage fluids of patients with idiopathic pulmonary fibrosis (IPF) [77], in the pulmonary interstitium of individuals with cryptogenic fibrosing alveolitis [78] and in peripheral blood mononuclear cells (PBMCs) of those suffering from periportal fibrosis [79]. Development of post-irradiation fibrosis is also associated with increased production of IL-4 [80]. Although the extent to which IL-4 participates in fibrosis varies in different diseases, it has long been considered a potent profibrotic mediator. In fact, studies have suggested that IL-4 is nearly twice as effective as TGFβ [81], another potent profibrotic cytokine that has been extensively studied [82]. Receptors for IL-4 are found on many mouse [83] and human fibroblast subtypes [84] and *in vitro* studies showed the synthesis of the extracellular matrix proteins, types I and III collagen and fibronectin, following IL-4 stimulation. One of the first *in vivo* reports to investigate the contribution of IL-4 was a study of schistosomiasis in mice, in which neutralizing antibodies to IL-4 were shown to significantly reduce the development of hepatic fibrosis [52]. Inhibitors of IL-4 were also found to reduce dermal fibrosis in a chronic skin graft rejection model and in a mouse model of scleroderma [85,86].

IL-13 shares many functional activities with IL-4 because both cytokines exploit the same IL-4Rα/Stat6 signalling pathways [87]. However, with the development of IL-13 transgenic and knockout mice [88,89], as well as IL-13 antagonists [53,90], unique and non-redundant roles for IL-13 and IL-4 have been revealed in numerous models. When IL-4 and IL-13 were inhibited independently, IL-13 was identified as the dominant effector cytokine of fibrosis in several experimental models of fibrosis [38,53,91–94]. In schistosomiasis, although the egg-induced inflammatory response was unaffected by IL-13 blockade, collagen deposition decreased by more than 85% [53,95], despite continued and undiminished production of IL-4 [53,96]. Related studies have also shown a dominant role for

IL-13 in the pathogenesis of pulmonary fibrosis. Over-expression of IL-13 in the lung triggered significant subepithelial airway fibrosis in mice in the absence of any additional inflammatory stimulus [89], while treatment with anti-IL-13 antibody markedly reduced collagen deposition in the lungs of animals challenged with *A. fumigatus* conidia [91] or bleomycin [49]. In contrast, transgenic mice that over-expressed IL-4 displayed little evidence of subepithelial airway fibrosis, despite developing an intense inflammatory response in the lung [97]. Interestingly, two recent studies suggested that IL-13-regulated responses [98], including lung fibrosis [99], could develop in the absence of IL-4Rα or Stat6-mediated signalling, suggesting that IL-13 can exploit an additional signalling mechanism that is distinct from the IL-4Rα/Stat6-signalling pathway. Indeed, a recent report suggested that TGFβ1-driven pulmonary fibrosis might in some cases be dependent on IL-13-mediated signalling through the IL-13Rα2 chain [100], which was originally thought to operate exclusively as a decoy receptor for IL-13 and as an inhibitor of fibrosis [53,101].

IL-5 and eosinophils have also been shown to regulate tissue fibrogenesis. The differentiation, activation and recruitment of eosinophils is highly dependent on IL-5, and eosinophils are an important source of fibrogenic cytokines, including TGFβ1 and IL-13. IL-5 and tissue eosinophils have been observed in a variety of diseases, including skin allograft rejection and pulmonary fibrosis [86,102,103]. However, studies with neutralizing anti-IL-5 antibodies and IL-5 knockout mice have often yielded conflicting results [104]. Early experiments with neutralizing anti-IL-5 monoclonal antibodies showed no reduction in liver fibrosis following *S. mansoni* infection, even though tissue eosinophil responses were markedly reduced [105]. Although negative findings were also reported in some of the skin and lung fibrosis models [105,106], other studies observed significant reductions in fibrosis when IL-5 activity was neutralized [86,107–110]. A recent study demonstrated that although excessive amounts of IL-5 can exacerbate bleomycin-induced fibrosis, IL-5$^{-/-}$ mice showed no impairment in fibrosis [111], suggesting that IL-5 and/or eosinophils act as amplifiers rather than as direct mediators of fibrosis. In mice deficient in IL-5 and/or CCL11 (eotaxin), tissue eosinophilia was abolished and the ability of CD4^{+} Th2 cells to produce the profibrotic cytokine IL-13 was significantly impaired [112]. Eosinophils were also found to be an important source of IL-13 in the schistosomiasis-induced model of liver fibrosis [55]. IL-5 and eosinophils can also regulate the TGFβ response in the lungs of mice [109,113]. Thus, one of the key roles of IL-5 and eosinophils may be to facilitate production of important profibrotic cytokines like IL-13 and/or TGFβ, which function as the key mediators of fibrosis.

Finally, similar to IL-5 [55], IL-21/IL-21R signalling was recently shown to promote fibrosis by facilitating the development of the CD4^{+} Th2 response [54]. IL-21R-signalling was also critical for Th2-cell survival and for the migration Th2 cells to the peripheral tissues [114]. In addition to supporting the development of Th2 responses, IL-21 also increased IL-4 and IL-13 receptor expression on macrophages [54], which enhances the development of alternatively activated macrophages that are believed to be important regulators of fibrosis [66,115].

Distinct and overlapping roles for TGFβ and Th2-type cytokines in fibrosis

TGFβ has been the most intensively studied regulator of the ECM and has been linked with the development of fibrosis in a number of diseases [116–119]. There are three isotypes of TGFβ in mammals, TGFβ1, -2 and -3, all exhibiting similar biological activity [120]. Although a variety of cell types produce and respond to TGFβ [82], tissue fibrosis is primarily attributed to the TGFβ1 isoform, with circulating monocytes and tissue macrophages being the predominant cellular sources. In macrophages, the primary level of control is not in the regulation of TGFβ1 mRNA expression, but in the regulation of both the secretion and activation of latent TGFβ1. TGFβ1 is stored inside the cell as a disulphide-bonded homodimer, non-covalently bound to a latency-associated protein (LAP), which keeps TGFβ inactive. Binding of the cytokine to its receptors requires dissociation of the LAP, a process that is catalysed by several agents, including cathepsins, plasmin, calpain, thrombospondin, integrin-αvβ6 and matrix metalloproteinases [82,120,121], many of which have become potential targets of antifibrotic drugs. Once activated, TGFβ signals through transmembrane receptors that trigger signalling intermediates known as Smad proteins, which modulate transcription of important target genes, including procollagen I and III [122]. Dermal fibrosis following irradiation [123] and renal interstitial fibrosis induced by unilateral ureteral obstruction [116] are both reduced in Smad3-deficient mice, confirming an important role for the TGFβ signalling pathway. Macrophage-derived TGFβ1 is thought to promote fibrosis by directly activating resident mesenchymal cells including epithelial cells, which differentiate into collagen-producing myofibroblasts via EMT. Interestingly, a recent paper showed that the loss of TGFβ signalling in fibroblasts triggers intraepithelial neoplasia, suggesting that TGFβ1 signalling critically regulates the activity of fibroblasts as well as the oncogenic potential of neighbouring epithelial cells [124]. In the bleomycin model of fibrosis, alveolar macrophages are thought to produce nearly all of the active TGFβ that promotes pulmonary fibrosis [125]. Nevertheless, Smad3/TGFβ1-independent mechanisms of fibrosis have also been demonstrated in the lung and other tissues [30,126,127], suggesting that profibrotic mediators such as IL-4, IL-5, IL-13 and IL-21 can act separately from the

TGFβ/Smad-signalling pathway to stimulate collagen deposition.

There is also evidence that Th2 cytokines cooperate with TGFβ to induce fibrosis. IL-13 induces the production of latent TGFβ1 in macrophages and can also serve as an indirect activator of TGFβ by upregulating expression of proteins that cleave the LAP [128,129]. Indeed, IL-13 is a potent stimulator of both MMP and cathepsin-based proteolytic pathways that activate TGFβ [74,129]. Thus, the significant tissue remodelling associated with polarized Th2 responses may involve a pathway wherein IL-13-expressing CD4$^+$ Th2 cells trigger macrophage production of TGFβ1, which then serves as the major stimulus for fibroblast activation and collagen deposition [100,128,130]. In support of this hypothesis, when TGFβ1 activity was neutralized in the lungs of IL-13-transgenic mice, development of subepithelial fibrosis was significantly reduced [128]. However, related studies observed enhanced pulmonary pathology when the TGFβ/Smad signalling pathway was blocked [131,132], suggesting that TGFβ suppresses rather than induces tissue remodelling in some settings. The source of TGFβ1 appears to be critical, since macrophage-derived TGFβ1 is often profibrotic [128], while T cell-derived TGFβ1 appears to play a suppressive role [133]. Some studies investigating the mechanisms of IL-13-driven fibrosis also reported no reduction in fibrosis in MMP-9-, Smad3- and TGFβ1-deficient mice, suggesting that IL-13 can operate independently from TGFβ1 [30]. This may explain the unexpected failure of Smad/TGFβ inhibitors in some blocking studies [126,127]. Thus, it remains unclear to what extent IL-13 must act through TGFβ1 to trigger fibrosis. Given that numerous antifibrotic therapies are focused on inhibiting the TGFβ1 signalling pathway [82,134], it will be important to determine whether the collagen-inducing activity of IL-13 is dependent on TGFβ1 or whether IL-13 and other profibrotic mediators [135] can also operate independently, as has been suggested in some studies [30,53,135].

Vascular changes often accompany the development of fibrosis

In addition to fibroproliferation and deposition of ECM components, the pathogenesis of IPF, systemic sclerosis (SSc), liver fibrosis and many other fibrotic diseases, including many fibrotic diseases of the eye, are characterized by substantial vascular remodelling, which often occurs prior to the development of fibrosis. In the case of systemic sclerosis, vascular changes are a prominent and early manifestation of the disease, with impaired angiogenesis leading to the progressive disappearance of blood vessels [28,29]. It has been suggested that reduced numbers of circulating bone marrow-derived CD34$^+$ endothelial progenitor cells, as well as their impaired differentiation into mature endothelial cells, might be contributing to the early vascular defects in SSc [136]. In contrast to SSc, where fibrosis is associated with the loss of blood vessels, fibrosis and traction retinal detachments associated with advanced diabetic retinopathy (DR) are characterized by uncontrolled vascular proliferation [137]. Indeed, the common pathway for many fibrotic eye diseases, including age-related macular degeneration (ARMD) [138], is injury to the cornea and/or retina, which results in inflammatory changes, tissue oedema, hypoxia-driven neovascularization and ultimately fibrosis. Once new blood vessels begin to grow in the eye, they are prone to haemorrhage, leading to further activation of the wound-healing response, and ultimately development of severe fibrosis [139]. Therefore, prevention of the primary vascular abnormality has been the most promising therapeutic strategy for many diseases of the eye. Because various members of the CXC-chemokine family exhibit potent angiogenic or angiostatic activity [140], targeting the CXC-chemokine family might offer a unique approach to regulate angiogenesis and fibrosis.

Angiotensin II plays a critical role in fibrosis

Although all major components of the renin–angiotensin–aldosterone system exhibit profibrotic activity, ANG II appears to be the dominant hormone responsible for cardiac fibrosis in hypertensive heart disease [141]. ANG II also plays an important role in the development of renal and hepatic fibrosis [142]. ANG II, produced locally by activated macrophages and fibroblasts, is thought to exert its effects by directly inducing NADPH oxidase activity, stimulating TGFβ1 production and triggering fibroblast proliferation and differentiation into collagen-secreting myofibroblasts [143,144]. In addition to its effects on TGFβ1 secretion and activation, ANG II also enhances TGFβ1 signalling by increasing SMAD2 levels and by augmenting the nuclear translocation of phosphorylated SMAD3. TGFβ1, in turn, augments the production of interstitial collagens, fibronectin and proteoglycans by cardiac myofibroblasts [2]. It also stimulates its own production in myofibroblasts, thereby establishing an autocrine cycle of myofibroblast differentiation and activation. Studies have shown that overexpression of TGFβ1 in transgenic mice can lead to cardiac hypertrophy, characterized by both interstitial fibrosis and hypertrophic growth of cardiac myocytes [145]. Patients suffering from idiopathic hypertrophic cardiomyopathy and dilated cardiomyopathy also have increased levels of TGFβ1 in the left ventricular myocardium [146]. Therefore, therapies that target the renin–angiotensin–aldosterone system or TGFβ1 pathways might provide effective strategies to slow the progression of fibrosis in hypertensive heart disease, progressive renal disease and hepatic fibrosis [144,147,148].

Endogenous mechanisms that slow the progression of fibrosis

Regulatory T cells (Tregs) and IL-10

IL-10 functions as a general immunosuppressive cytokine, which down-regulates chronic inflammatory responses through many mechanisms [149]. Consistent with its role as a suppressive cytokine, IL-10 has been shown to inhibit fibrosis in numerous models. Mice treated with IL-10 develop significantly less liver, lung and pancreatic fibrosis when challenged with carbon tetrachloride (CCl4), bleomcyin and cerulein, respectively [150–153]. In contrast, IL-10-deficient mice are much more susceptible to these fibrosis-inducing compounds. IL-10 has also been shown to significantly suppress the synthesis of type I collagens in human scar tissue-derived fibroblasts [154], indicating that it can directly inhibit fibrosis [155]. The severity of liver fibrosis in a subset of patients chronically infected with hepatitis C virus was also reduced by IL-10 treatment [156]. However, despite its success in some clinical studies, the mechanism by which IL-10 confers protection from fibrosis remains unclear. In the schistosomiasis model, IL-10 deficiency alone has little effect on the progression of hepatic fibrosis [157]. However, when IL-$10^{-/-}$ mice were crossed with IFN$\gamma^{-/-}$, IL-$12^{-/-}$ or IL-13R$\alpha 2^{-/-}$ animals, liver fibrosis developed at a highly accelerated rate, suggesting that IL-10 cooperates with Th1 cytokines and the IL-13 decoy receptor to suppress collagen deposition [74,158,159]. In support of these findings, a study of human *S. mansoni* infection found that most cases of severe periportal fibrosis are associated with low IL-10 and IFNγ production [79].

The IL-13 decoy receptor (IL-13Rα2)

Soluble IL-13Rα2-Fc is a highly effective inhibitor of IL-13 [90], which can ameliorate the progression of established fibrotic disease [53,95,160]. IL-13Rα2 inhibits IL-13 by blocking its interaction with the signalling type II IL-4R complex [90,98,161]. Consistent with its proposed activity as a decoy receptor [162], mice with targeted deletion of IL-13Rα2 displayed enhanced IL-13 activity [101]. When the IL-13Rα2-deficient mice were infected with *S. mansoni*, the development of IL-13-dependent liver fibrosis increased significantly [163]. Fibrosis increased despite the fact that there was no change in the inflammatory response. These findings suggested that IL-13Rα2 directly inhibits the ECM-remodelling activity of IL-13. However, the decoy receptor did play a significant role in the down-regulation of the inflammatory response in chronically infected animals [164]. In fact, the chronically infected IL-13R$\alpha 2^{-/-}$ mice showed a marked exacerbation in granulomatous inflammation. They also developed severe liver fibrosis and portal hypertension, which led to their rapid death following infection. Thus, the IL-13 decoy receptor was identified as a critical life-sustaining inhibitor of Th2-driven inflammation and fibrosis.

Can progressive fibrosis be reversed and normal tissue architecture restored?

Although the ability to repair damaged tissues without scarring would be ideal, in most chronic inflammatory diseases repair cannot be accomplished solely by the regeneration of parenchymal cells, even in tissues where significant regeneration is possible, such as the liver. Repair of damaged tissues must then occur by replacing non-regenerated parenchymal cells with connective tissues, which in time leads to significant fibrosis and scarring. Thus, development of therapeutic strategies that limit the progression of fibrosis without adversely affecting the overall repair process would represent an important technological advance.

It is controversial whether advanced fibrosis can be reversed to the extent that normal tissue architecture is restored completely. Indeed, there is substantial evidence that, if fibrosis is sufficiently advanced, reversal is no longer possible. Because advanced fibrosis is often hypocellular, it has been suggested that incomplete ECM degradation (irreversible fibrosis) develops when the appropriate cellular mediators (the source of MMPs) are no longer present [165]. Thus, ongoing inflammation might be required for the successful resolution of fibrotic disease [166]. Not surprisingly, the source and identity of key MMPs that mediate the resolution of fibrosis are being intensively investigated. Recent studies demonstrated that macrophage depletion at the onset of fibrosis resolution could retard ECM degradation and the loss of activated HSCs [115]. This suggests that macrophages are essential for initiating ECM degradation, perhaps by producing MMPs. Therefore, it might be possible to reverse what was once thought to be irreversible fibrosis [167]. Successful elimination of HBV and HCV in chronically infected individuals is often associated with marked regression of disease, providing evidence that human hepatic fibrosis is at least partially reversible [167]. Similar observations have also been reported in schistosomiasis patients following treatment with praziquantel, a drug that eliminates the causative pathogen [168]. Current approaches aimed at treating fibrosis are primarily directed at inhibiting cytokines (TGFβ1, IL-13), chemokines, specific MMPs, adhesion molecules (integrins) and inducers of angiogenesis, such as VEGF [138]. Although many of these treatments could prove highly successful, ideally, the best therapy would lead to the complete restoration of the damaged tissue, or minimally, restore homeostasis to the areas that drive the fibrotic response [169]. One way to restore homeostasis would be to eliminate the collagen-producing cell. Indeed, apoptosis of hepatic stellate cells (HSCs) have been observed during the resolution of liver fibrosis [170]. Thus, methods that inhibit fibroblast proliferation and activation or actively induce myofibroblast apoptosis could help slow the progression of fibrosis [8,171,172]. Cell-based therapies using adult bone marrow-derived progenitor/stem cell technologies might also prove highly successful for the treatment of fibrosis. Stem cell therapies have already proved successful at restoring cardiac function in injured hearts [173], therefore they might prove successful for a wide variety of fibroproliferative disorders.

Moving experimental antifibrotic strategies into the clinic

As discussed in this review, there is a growing list of novel mediators and pathways that could be exploited in the development of antifibrotic drugs. These include cytokine, chemokine and TLR antagonists, angiogenesis inhibitors, anti-hypertensive drugs, TGFβ signalling modifiers, B cell-depleting antibodies and stem/progenitor cell transplantation strategies, to name just a few. As there are many potential targets and strategies, what we need now is a well thought-out plan for translating the available experimental information into clinically effective drugs. However, there are challenging roadblocks ahead that must be overcome before any treatment can reach the clinic. The most difficult obstacle will be to design effective clinical trials with well-defined clinical endpoints. Non-invasive techniques, such as serum markers, improved imaging techniques or other clinical features that can quickly quantify changes in the natural history of the disease (rate of disease progression, etc.) are desperately needed. Host genetic factors, such as single nucleotide polymorphisms (SNPs), may also be exploited to determine the relative risk of developing fibrosis. Recently, a predictive seven-gene signature was identified in chronic hepatitis C patients at high risk of developing cirrhosis [174]. In future studies, it will be important to explore what impact these or other SNPs have on fibrosis in other organ systems. Nearly 45% of all deaths in the developed world are attributed to some type of chronic fibroproliferative disease. Therefore, the demand for antifibrotic drugs that are both safe and effective is great and will likely continue to increase in the coming years.

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