Invited Review

Cellular and molecular mechanisms of fibrosis

TA Wynn*

Immunopathogenesis Section, Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA

*Correspondence to:
TA Wynn, Immunopathogenesis Section, Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 50 South Drive, Room 6154, MSC 8003, Bethesda, MD 20892, USA.
E-mail: twynn@niaid.nih.gov

No conflicts of interest were declared.

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.
Published in 2007 by John Wiley & Sons, Ltd.

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 nonredundant 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-13Rα2$^{-/-}$ 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-13Rα2$^{-/-}$ 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.

Acknowledgements

References

1. Wynn TA. Common and unique mechanisms regulate fibrosis in various fibroproliferative diseases. *J Clin Invest* 2007;**117**(3):524–529.

2. Tomasek JJ, Gabbiani G, Hinz B, Chaponnier C, Brown RA. Myofibroblasts and mechano-regulation of connective tissue remodelling. *Nat Rev Mol Cell Biol* 2002;**3**(5):349–363.

3. Friedman SL. Mechanisms of disease: mechanisms of hepatic fibrosis and therapeutic implications. *Nat Clin Pract Gastroenterol Hepatol* 2004;**1**(2):98–105.

4. Schuppan D, Ruehl M, Somasundaram R, Hahn EG. Matrix as a modulator of hepatic fibrogenesis. *Semin Liver Dis* 2001;**21**(3):351–372.

5. Kumar V, Abbas AK, Fausto N. Tissue renewal and repair: regeneration, healing, and fibrosis. In *Pathologic Basis of Disease*, Kumar V, Abbas AK, Fausto N (eds). Elsevier Saunders: Philadelphia, PA, 2005; 87–118.

6. Li MO, Wan YY, Sanjabi S, Robertson AK, Flavell RA. Transforming growth factor-beta regulation of immune responses. *Annu Rev Immunol* 2006;**24**:99–146.

7. Wynn TA. IL-13 effector functions. *Annu Rev Immunol* 2003;**21**:425–456.

8. Parsons CJ, Takashima M, Rippe RA. Molecular mechanisms of hepatic fibrogenesis. *J Gastroenterol Hepatol* 2007;**22**(suppl 1):S79–84.

9. Pardo A, Selman M. Matrix metalloproteases in aberrant fibrotic tissue remodelling. *Proc Am Thorac Soc* 2006;**3**(4):383–388.

10. Quan TE, Cowper SE, Bucala R. The role of circulating fibrocytes in fibrosis. *Curr Rheumatol Rep* 2006;**8**(2):145–150.

11. Zeisberg EM, Tarnavski O, Zeisberg M, Dorfman AL, McMullen JR, Gustafsson E, *et al*. Endothelial-to-mesenchymal transition contributes to cardiac fibrosis. *Nat Med* 2007;**13**(8):952–961. Epub: 29 July 2007.

12. Willis BC, du Bois RM, Borok Z. Epithelial origin of myofibroblasts during fibrosis in the lung. *Proc Am Thorac Soc* 2006;**3**(4):377–382.

13. Kalluri R, Neilson EG. Epithelial–mesenchymal transition and its implications for fibrosis. *J Clin Invest* 2003;**112**(12):1776–1784.

14. Bucala R, Spiegel LA, Chesney J, Hogan M, Cerami A. Circulating fibrocytes define a new leukocyte subpopulation that mediates tissue repair. *Mol Med* 1994;**1**(1):71–81.

15. Ebihara Y, Masuya M, Larue AC, Fleming PA, Visconti RP, Minamiguchi H, *et al*. Hematopoietic origins of fibroblasts: II. *In vitro* studies of fibroblasts, CFU-F, and fibrocytes. *Exp Hematol* 2006;**34**(2):219–229.

16. Brittan M, Hunt T, Jeffery R, Poulsom R, Forbes SJ, Hodivala-Dilke K, *et al*. Bone marrow derivation of pericryptal myofibroblasts in the mouse and human small intestine and colon. *Gut* 2002;**50**(6):752–757.

17. Direkze NC, Forbes SJ, Brittan M, Hunt T, Jeffery R, Preston SL, *et al*. Multiple organ engraftment by bone-marrow-derived myofibroblasts and fibroblasts in bone-marrow-transplanted mice. *Stem Cells* 2003;**21**(5):514–520.

18. Forbes SJ, Russo FP, Rey V, Burra P, Rugge M, Wright NA, *et al*. A significant proportion of myofibroblasts are of bone marrow origin in human liver fibrosis. *Gastroenterology* 2004;**126**(4):955–963.

19. Russo FP, Alison MR, Bigger BW, Amofah E, Florou A, Amin F, *et al*. The bone marrow functionally contributes to liver fibrosis. *Gastroenterology* 2006;**130**(6):1807–1821.

20. Phillips RJ, Burdick MD, Hong K, Lutz MA, Murray LA, Xue YY, *et al*. Circulating fibrocytes traffic to the lungs in response to CXCL12 and mediate fibrosis. *J Clin Invest* 2004;**114**(3):438–446.

21. Moore BB, Kolodsick JE, Thannickal VJ, Cooke K, Moore TA, Hogaboam C, *et al*. CCR2-mediated recruitment of fibrocytes to the alveolar space after fibrotic injury. *Am J Pathol* 2005;**166**(3):675–684.

22. Haudek SB, Xia Y, Huebener P, Lee JM, Carlson S, Crawford JR, *et al*. Bone marrow-derived fibroblast precursors mediate ischemic cardiomyopathy in mice. *Proc Natl Acad Sci USA* 2006;**103**(48):18284–18289. Epub: 17 November 2006.

23. Meneghin MD, Hogaboam C. Infectious disease, the innate immune response, and fibrosis. *J Clin Invest* 2007;**117**(3):530–538.

24. Otte JM, Rosenberg IM, Podolsky DK. Intestinal myofibroblasts in innate immune responses of the intestine. *Gastroenterology* 2003;**124**(7):1866–1878.

25. Akira S, Takeda K. Toll-like receptor signalling. *Nat Rev Immunol* 2004;**4**(7):499–511.

26. Coelho AL, Hogaboam CM, Kunkel SL. Chemokines provide the sustained inflammatory bridge between innate and acquired immunity. *Cytokine Growth Factor Rev* 2005;**16**(6):553–560. Epub: 20 June 2005.

27. Strehlow D, Korn JH. Biology of the scleroderma fibroblast. *Curr Opin Rheumatol* 1998;**10**(6):572–578.

28. Abraham DJ, Varga J. Scleroderma: from cell and molecular mechanisms to disease models. *Trends Immunol* 2005;**26**(11):587–595. Epub: 15 September 2005.

29. Varga J, Abraham D. Systemic sclerosis: a prototypic multisystem fibrotic disorder. *J Clin Invest* 2007;**117**(3):557–567.

30. Kaviratne M, Hesse M, Leusink M, Cheever AW, Davies SJ, McKerrow JH, *et al*. IL-13 activates a mechanism of tissue fibrosis that is completely TGFβ-independent. *J Immunol* 2004;**173**(6):4020–4029.

31. Moustakas A, Heldin CH. Non-Smad TGFβ signals. *J Cell Sci* 2005;**118**(16):3573–3584.

32. Markiewicz M, Smith EA, Rubinchik S, Dong JY, Trojanowska M, LeRoy EC. The 72-kDa IE-1 protein of human cytomegalovirus (HCMV) is a potent inducer of connective tissue growth factor (CTGF) in human dermal fibroblasts. *Clin Exp Rheumatol* 2004;**22**(3, suppl 33):S31–34.

33. Wang Y, Fan PS, Kahaleh B. Association between enhanced type I collagen expression and epigenetic repression of the *FLI1* gene in scleroderma fibroblasts. *Arthritis Rheum* 2006;**54**(7):2271–2279.

34. Hasegawa M, Fujimoto M, Takehara K, Sato S. Pathogenesis of systemic sclerosis: altered B cell function is the key linking systemic autoimmunity and tissue fibrosis. *J Dermatol Sci* 2005;**39**(1):1–7.

35. Wynn TA. Fibrotic disease and the T(H)1/T(H)2 paradigm. *Nat Rev Immunol* 2004;**4**(8):583–594.

36. Ong CJ, Ip S, Teh SJ, Wong C, Jirik FR, Grusby MJ, *et al*. A role for T helper 2 cells in mediating skin fibrosis in tight-skin mice. *Cell Immunol* 1999;**196**(1):60–68.

37. Lakos G, Melichian D, Wu M, Varga J. Increased bleomycin-induced skin fibrosis in mice lacking the Th1-specific transcription factor T-bet. *Pathobiology* 2006;**73**(5):224–237.

38. Aliprantis AO, Wang J, Fathman JW, Lemaire R, Dorfman DM, Lafyatis R, *et al*. Transcription factor T-bet regulates skin sclerosis through its function in innate immunity and via IL-13. *Proc Natl Acad Sci USA* 2007;**104**(8):2827–2830. Epub: 16 February 2007.

39. Smith RE, Strieter RM, Phan SH, Lukacs NW, Huffnagle GB, Wilke CA, *et al*. Production and function of murine macrophage inflammatory protein-1α in bleomycin-induced lung injury. *J Immunol* 1994;**153**(10):4704–4712.

40. Smith RE, Strieter RM, Zhang K, Phan SH, Standiford TJ, Lukacs NW, *et al*. A role for C–C chemokines in fibrotic lung disease. *J Leukoc Biol* 1995;**57**(5):782–787.

41. Lloyd CM, Minto AW, Dorf ME, Proudfoot A, Wells TN, Salant DJ, *et al*. RANTES and monocyte chemoattractant protein-1 (MCP-1) play an important role in the inflammatory phase of crescentic nephritis, but only MCP-1 is involved in crescent formation and interstitial fibrosis. *J Exp Med* 1997;**185**(7):1371–1380.

42. Belperio JA, Keane MP, Burdick MD, Lynch JP III, Xue YY, Berlin A, *et al*. Critical role for the chemokine MCP-1/CCR2 in the pathogenesis of bronchiolitis obliterans syndrome. *J Clin Invest* 2001;**108**(4):547–556.

43. Tokuda A, Itakura M, Onai N, Kimura H, Kuriyama T, Matsushima K. Pivotal role of CCR1-positive leukocytes in bleomycin-induced lung fibrosis in mice. *J Immunol* 2000;**164**(5):2745–2751.

44. Blease K, Mehrad B, Standiford TJ, Lukacs NW, Kunkel SL, Chensue SW, *et al*. Airway remodelling is absent in CCR1$^{-/-}$ mice during chronic fungal allergic airway disease. *J Immunol* 2000;**165**(3):1564–1572.

45. Anders HJ, Vielhauer V, Frink M, Linde Y, Cohen CD, Blattner SM, *et al*. A chemokine receptor CCR-1 antagonist reduces renal fibrosis after unilateral ureter ligation. *J Clin Invest* 2002;**109**(2):251–259.

46. Moore BB, Paine R III, Christensen PJ, Moore TA, Sitterding S, Ngan R, *et al*. Protection from pulmonary fibrosis in the absence of CCR2 signalling. *J Immunol* 2001;**167**(8):4368–4377.

47. Zhu Z, Ma B, Zheng T, Homer RJ, Lee CG, Charo IF, *et al*. IL-13-induced chemokine responses in the lung: role of CCR2 in the pathogenesis of IL-13-induced inflammation and remodelling. *J Immunol* 2002;**168**(6):2953–2962.

48. Gao JL, Wynn TA, Chang Y, Lee EJ, Broxmeyer HE, Cooper S, *et al*. Impaired host defence, hematopoiesis, granulomatous inflammation and type 1-type 2 cytokine balance in mice lacking CC chemokine receptor 1. *J Exp Med* 1997;**185**(11):1959–1968.

49. Belperio JA, Dy M, Burdick MD, Xue YY, Li K, Elias JA, *et al*. Interaction of IL-13 and C10 in the pathogenesis of bleomycin-induced pulmonary fibrosis. *Am J Respir Cell Mol Biol* 2002;**27**(4):419–427.

50. Ma B, Zhu Z, Homer RJ, Gerard C, Strieter R, Elias JA. The C10/CCL6 chemokine and CCR1 play critical roles in the pathogenesis of IL-13-induced inflammation and remodelling. *J Immunol* 2004;**172**(3):1872–1881.

51. Wynn TA, Cheever AW, Jankovic D, Poindexter RW, Caspar P, Lewis FA, *et al*. An IL-12-based vaccination method for preventing fibrosis induced by schistosome infection. *Nature* 1995;**376**(6541):594–596.

52. Cheever AW, Williams ME, Wynn TA, Finkelman FD, Seder RA, Cox TM, *et al*. Anti-IL-4 treatment of *Schistosoma mansoni*-infected mice inhibits development of T cells and non-B, non-T cells expressing Th2 cytokines while decreasing egg-induced hepatic fibrosis. *J Immunol* 1994;**153**(2):753–759.

53. Chiaramonte MG, Donaldson DD, Cheever AW, Wynn TA. An IL-13 inhibitor blocks the development of hepatic fibrosis during a T-helper type 2-dominated inflammatory response. *J Clin Invest* 1999;**104**(6):777–785.

54. Pesce J, Kaviratne M, Ramalingam TR, Thompson RW, Urban JF Jr, Cheever AW, *et al*. The IL-21 receptor augments Th2 effector function and alternative macrophage activation. *J Clin Invest* 2006;**116**(7):2044–2055. Epub: 15 June 2006.

55. Reiman RM, Thompson RW, Feng CG, Hari D, Knight R, Cheever AW, *et al*. Interleukin-5 (IL-5) augments the progression of liver fibrosis by regulating IL-13 activity. *Infect Immun* 2006;**74**(3):1471–1479.

56. Gurujeyalakshmi G, Giri SN. Molecular mechanisms of antifibrotic effect of interferon-γ in bleomycin-mouse model of lung fibrosis: downregulation of TGFβ and procollagen I and III gene expression. *Exp Lung Res* 1995;**21**(5):791–808.

57. Keane MP, Belperio JA, Burdick MD, Strieter RM. IL-12 attenuates bleomycin-induced pulmonary fibrosis. *Am J Physiol Lung Cell Mol Physiol* 2001;**281**(1):L92–97.

58. Oldroyd SD, Thomas GL, Gabbiani G, El Nahas AM. Interferon-γ inhibits experimental renal fibrosis. *Kidney Int* 1999;**56**(6):2116–2127.

59. Poynard T, Yuen MF, Ratziu V, Lai CL. Viral hepatitis C. *Lancet* 2003;**362**(9401):2095–2100.

60. Hesse M, Cheever AW, Jankovic D, Wynn TA. NOS-2 mediates the protective anti-inflammatory and antifibrotic effects of the Th1-inducing adjuvant, IL-12, in a Th2 model of granulomatous disease. *Am J Pathol* 2000;**157**(3):945–955.

61. Hessel EM, Chu M, Lizcano JO, Chang B, Herman N, Kell SA, *et al*. Immunostimulatory oligonucleotides block allergic airway inflammation by inhibiting Th2 cell activation and IgE-mediated cytokine induction. *J Exp Med* 2005;**202**(11):1563–1573. Epub: 28 November 2005.

62. Hoffmann KF, McCarty TC, Segal DH, Chiaramonte M, Hesse M, Davis EM, *et al*. Disease fingerprinting with cDNA microarrays reveals distinct gene expression profiles in lethal type 1 and type 2 cytokine-mediated inflammatory reactions. *FASEB J* 2001;**15**(13):2545–2547.

63. Sandler NG, Mentink-Kane MM, Cheever AW, Wynn TA. Global gene expression profiles during acute pathogen-induced pulmonary inflammation reveal divergent roles for Th1 and Th2 responses in tissue repair. *J Immunol* 2003;**171**(7):3655–3667.

64. Zeeberg BR, Qin H, Narasimhan S, Sunshine M, Cao H, Kane DW, et al. High-throughput GoMiner, an 'industrial-strength' integrative gene ontology tool for interpretation of multiple-microarray experiments, with application to studies of common variable immune deficiency (CVID). BMC Bioinformat 2005;6:168.

65. Walker LS, Abbas AK. The enemy within: keeping self-reactive T cells at bay in the periphery. Nat Rev Immunol 2002;2(1):11–19.

66. Hesse M, Modolell M, La Flamme AC, Schito M, Fuentes JM, Cheever AW, et al. Differential regulation of nitric oxide synthase-2 and arginase-1 by type 1/type 2 cytokines in vivo: granulomatous pathology is shaped by the pattern of L-arginine metabolism. J Immunol 2001;167(11):6533–6544.

67. Decitre M, Gleyzal C, Raccurt M, Peyrol S, Aubert-Foucher E, Csiszar K, et al. Lysyl oxidase-like protein localizes to sites of de novo fibrinogenesis in fibrosis and in the early stromal reaction of ductal breast carcinomas. Lab Invest 1998;78(2):143–151.

68. Akiri G, Sabo E, Dafni H, Vadasz Z, Kartvelishvily Y, Gan N, et al. Lysyl oxidase-related protein-1 promotes tumor fibrosis and tumor progression in vivo. Cancer Res 2003;63(7):1657–1666.

69. Wang S, Hirschberg R. BMP7 antagonizes TGFβ-dependent fibrogenesis in mesangial cells. Am J Physiol Renal Physiol 2003;284(5):F1006–1013.

70. Cheng S, Lovett DH. Gelatinase A (MMP-2) is necessary and sufficient for renal tubular cell epithelial–mesenchymal transformation. Am J Pathol 2003;162(6):1937–1949.

71. Underwood DC, Osborn RR, Bochnowicz S, Webb EF, Rieman DJ, Lee JC, et al. SB 239063, a p38 MAPK inhibitor, reduces neutrophilia, inflammatory cytokines, MMP-9, and fibrosis in lung. Am J Physiol Lung Cell Mol Physiol 2000;279(5):L895–902.

72. Heymans S, Lupu F, Terclavers S, Vanwetswinkel B, Herbert JM, Baker A, et al. Loss or inhibition of uPA or MMP-9 attenuates LV remodelling and dysfunction after acute pressure overload in mice. Am J Pathol 2005;166(1):15–25.

73. Kim H, Oda T, Lopez-Guisa J, Wing D, Edwards DR, Soloway PD, et al. TIMP-1 deficiency does not attenuate interstitial fibrosis in obstructive nephropathy. J Am Soc Nephrol 2001;12(4):736–748.

74. Vaillant B, Chiaramonte MG, Cheever AW, Soloway PD, Wynn TA. Regulation of hepatic fibrosis and extracellular matrix genes by the Th response: New insight into the role of tissue inhibitors of matrix metalloproteinases. J Immunol 2001;167(12):7017–7026.

75. Kaminski N, Allard JD, Pittet JF, Zuo F, Griffiths MJ, Morris D, et al. Global analysis of gene expression in pulmonary fibrosis reveals distinct programs regulating lung inflammation and fibrosis. Proc Natl Acad Sci USA 2000;97(4):1778–1783.

76. Kristensen DB, Kawada N, Imamura K, Miyamoto Y, Tateno C, Seki S, et al. Proteome analysis of rat hepatic stellate cells. Hepatology 2000;32(2):268–277.

77. Emura M, Nagai S, Takeuchi M, Kitaichi M, Izumi T, Nishimura K, et al. In vitro production of B cell growth factor and B cell differentiation factor by peripheral blood mononuclear cells and bronchoalveolar lavage T lymphocytes from patients with idiopathic pulmonary fibrosis. Clin Exp Immunol 1990;82(1):133–139.

78. Wallace WA, Ramage EA, Lamb D, Howie SE. A type 2 (Th2-like) pattern of immune response predominates in the pulmonary interstitium of patients with cryptogenic fibrosing alveolitis (CFA). Clin Exp Immunol 1995;101(3):436–441.

79. Booth M, Mwatha JK, Joseph S, Jones FM, Kadzo H, Ireri E, et al. Periportal fibrosis in human Schistosoma mansoni infection is associated with low IL-10, low IFNγ, high TNFα, or low RANTES, depending on age and gender. J Immunol 2004;172(2):1295–1303.

80. Buttner C, Skupin A, Reimann T, Rieber EP, Unteregger G, Geyer P, et al. Local production of interleukin-4 during radiation-induced pneumonitis and pulmonary fibrosis in rats: macrophages as a prominent source of interleukin-4. Am J Respir Cell Mol Biol 1997;17(3):315–325.

81. Fertin C, Nicolas JF, Gillery P, Kalis B, Banchereau J, Maquart FX. Interleukin-4 stimulates collagen synthesis by normal and scleroderma fibroblasts in dermal equivalents. Cell Mol Biol 1991;37(8):823–829.

82. Letterio JJ, Roberts AB. Regulation of immune responses by TGFβ. Annu Rev Immunol 1998;16:137–161.

83. Sempowski GD, Beckmann MP, Derdak S, Phipps RP. Subsets of murine lung fibroblasts express membrane-bound and soluble IL-4 receptors. Role of IL-4 in enhancing fibroblast proliferation and collagen synthesis. J Immunol 1994;152(7):3606–3614.

84. Doucet C, Brouty-Boye D, Pottin-Clemenceau C, Canonica GW, Jasmin C, Azzarone B. Interleukin (IL)-4 and IL-13 act on human lung fibroblasts. Implication in asthma. J Clin Invest 1998;101(10):2129–2139.

85. Ong C, Wong C, Roberts CR, Teh HS, Jirik FR. Anti-IL-4 treatment prevents dermal collagen deposition in the tight-skin mouse model of scleroderma. Eur J Immunol 1998;28(9):2619–2629.

86. Le Moine A, Flamand V, Demoor FX, Noel JC, Surquin M, Kiss R, et al. Critical roles for IL-4, IL-5, and eosinophils in chronic skin allograft rejection. J Clin Invest 1999;103(12):1659–1667.

87. Zurawski SM, Vega F Jr, Huyghe B, Zurawski G. Receptors for interleukin-13 and interleukin-4 are complex and share a novel component that functions in signal transduction. EMBO J 1993;12(7):2663–2670.

88. McKenzie GJ, Emson CL, Bell SE, Anderson S, Fallon P, Zurawski G, et al. Impaired development of Th2 cells in IL-13-deficient mice. Immunity 1998;9(3):423–432.

89. Zhu Z, Homer RJ, Wang Z, Chen Q, Geba GP, Wang J, et al. Pulmonary expression of interleukin-13 causes inflammation, mucus hypersecretion, subepithelial fibrosis, physiologic abnormalities, and eotaxin production. J Clin Invest 1999;103(6):779–788.

90. Donaldson DD, Whitters MJ, Fitz LJ, Neben TY, Finnerty H, Henderson SL, et al. The murine IL-13 receptor α2: molecular cloning, characterization, and comparison with murine IL-13 receptor α1. J Immunol 1998;161(5):2317–2324.

91. Blease K, Jakubzick C, Westwick J, Lukacs N, Kunkel SL, Hogaboam CM. Therapeutic effect of IL-13 immunoneutralization during chronic experimental fungal asthma. J Immunol 2001;166(8):5219–5224.

92. Kumar RK, Herbert C, Yang M, Koskinen AM, McKenzie AN, Foster PS. Role of interleukin-13 in eosinophil accumulation and airway remodelling in a mouse model of chronic asthma. Clin Exp Allergy 2002;32(7):1104–1111.

93. Keane MP, Gomperts BN, Weigt S, Xue YY, Burdick MD, Nakamura H, et al. IL-13 is pivotal in the fibro-obliterative process of bronchiolitis obliterans syndrome. J Immunol 2007;178(1):511–519.

94. Kolodsick JE, Toews GB, Jakubzick C, Hogaboam C, Moore TA, McKenzie A, et al. Protection from fluorescein isothiocyanate-induced fibrosis in IL-13-deficient, but not IL-4-deficient, mice results from impaired collagen synthesis by fibroblasts. J Immunol 2004;172(7):4068–4076.

95. Chiaramonte MG, Cheever AW, Malley JD, Donaldson DD, Wynn TA. Studies of murine schistosomiasis reveal interleukin-13 blockade as a treatment for established and progressive liver fibrosis. Hepatology 2001;34(2):273–282.

96. Fallon PG, Richardson EJ, McKenzie GJ, McKenzie AN. Schistosome infection of transgenic mice defines distinct and contrasting pathogenic roles for IL-4 and IL-13: IL-13 is a profibrotic agent. J Immunol 2000;164(5):2585–2591.

97. Rankin JA, Picarella DE, Geba GP, Temann UA, Prasad B, DiCosmo B, et al. Phenotypic and physiologic characterization of transgenic mice expressing interleukin 4 in the lung: lymphocytic and eosinophilic inflammation without airway hyperreactivity. Proc Natl Acad Sci USA 1996;93(15):7821–7825.

98. Webb DC, Mahalingam S, Cai Y, Matthaei KI, Donaldson DD, Foster PS. Antigen-specific production of interleukin (IL)-13 and IL-5 cooperate to mediate IL-4Rα-independent airway hyperreactivity. Eur J Immunol 2003;33(12):3377–3385.

99. Blease K, Schuh JM, Jakubzick C, Lukacs NW, Kunkel SL, Joshi BH, *et al*. Stat6-deficient mice develop airway hyperresponsiveness and peribronchial fibrosis during chronic fungal asthma. *Am J Pathol* 2002;**160**(2):481–490.

100. Fichtner-Feigl S, Strober W, Kawakami K, Puri RK, Kitani A. IL-13 signalling through the IL-13α2 receptor is involved in induction of TGFβ1 production and fibrosis. *Nat Med* 2006;**12**(1):99–106. Epub: 4 December 2005.

101. Wood N, Whitters MJ, Jacobson BA, Witek J, Sypek JP, Kasaian M, *et al*. Enhanced interleukin (IL)-13 responses in mice lacking IL-13 receptor α2. *J Exp Med* 2003;**197**(6):703–709.

102. Gharaee-Kermani M, Phan SH. Lung interleukin-5 expression in murine bleomycin-induced pulmonary fibrosis. *Am J Respir Cell Mol Biol* 1997;**16**(4):438–447.

103. Ochkur SI, Jacobsen EA, Protheroe CA, Biechele TL, Pero RS, McGarry MP, *et al*. Coexpression of IL-5 and eotaxin-2 in mice creates an eosinophil-dependent model of respiratory inflammation with characteristics of severe asthma. *J Immunol* 2007;**178**(12):7879–7889.

104. Williams TJ. The eosinophil enigma. *J Clin Invest* 2004;**113**(4):507–509.

105. Sher A, Coffman RL, Heiny S, Scott P, Cheever AW. Interleukin 5 is required for the blood and tissue eosinophilia but not granuloma formation induced by infection with *Schistosoma mansoni*. *Proc Natl Acad Sci USA* 1990;**87**:61–64.

106. Hao H, Cohen DA, Jennings CD, Bryson JS, Kaplan AM. Bleomycin-induced pulmonary fibrosis is independent of eosinophils. *J Leukoc Biol* 2000;**68**(4):515–521.

107. Gharaee-Kermani M, McGarry B, Lukacs N, Huffnagle G, Egan RW, Phan SH. The role of IL-5 in bleomycin-induced pulmonary fibrosis. *J Leukoc Biol* 1998;**64**(5):657–666.

108. Blyth DI, Wharton TF, Pedrick MS, Savage TJ, Sanjar S. Airway subepithelial fibrosis in a murine model of atopic asthma: suppression by dexamethasone or anti-interleukin-5 antibody. *Am J Respir Cell Mol Biol* 2000;**23**(2):241–246.

109. Cho JY, Miller M, Baek KJ, Han JW, Nayar J, Lee SY, *et al*. Inhibition of airway remodelling in IL-5-deficient mice. *J Clin Invest* 2004;**113**(4):551–560.

110. Trifilieff A, Fujitani Y, Coyle AJ, Kopf M, Bertrand C. IL-5 deficiency abolishes aspects of airway remodelling in a murine model of lung inflammation. *Clin Exp Allergy* 2001;**31**(6):934–942.

111. Huaux F, Liu T, McGarry B, Ullenbruch M, Xing Z, Phan SH. Eosinophils and T lymphocytes possess distinct roles in bleomycin-induced lung injury and fibrosis. *J Immunol* 2003;**171**(10):5470–5481.

112. Mattes J, Yang M, Mahalingam S, Kuehr J, Webb DC, Simson L, *et al*. Intrinsic defect in T cell production of interleukin (IL)-13 in the absence of both IL-5 and eotaxin precludes the development of eosinophilia and airways hyperreactivity in experimental asthma. *J Exp Med* 2002;**195**(11):1433–1444.

113. Tanaka H, Komai M, Nagao K, Ishizaki M, Kajiwara D, Takatsu K, *et al*. Role of IL-5 and eosinophils in allergen-induced airway remodeling in mice. *Am J Respir Cell Mol Biol* 2004;**19**:19.

114. Frohlich A, Marsland BJ, Sonderegger I, Kurrer M, Hodge MR, Harris NL, *et al*. IL-21 receptor signalling is integral to the development of Th2 effector responses *in vivo*. *Blood* 2007;**109**(5):2023–2031. Epub: 31 October 2006.

115. Duffield JS, Forbes SJ, Constandinou CM, Clay S, Partolina M, Vuthoori S, *et al*. Selective depletion of macrophages reveals distinct, opposing roles during liver injury and repair. *J Clin Invest* 2005;**115**(1):56–65.

116. Sato M, Muragaki Y, Saika S, Roberts AB, Ooshima A. Targeted disruption of TGFβ1/Smad3 signalling protects against renal tubulointerstitial fibrosis induced by unilateral ureteral obstruction. *J Clin Invest* 2003;**112**(10):1486–1494.

117. Border WA, Noble NA, Yamamoto T, Harper JR, Yamaguchi Y, Pierschbacher MD, *et al*. Natural inhibitor of transforming growth factor-β protects against scarring in experimental kidney disease. *Nature* 1992;**360**(6402):361–364.

118. Clouthier DE, Comerford SA, Hammer RE. Hepatic fibrosis, glomerulosclerosis, and a lipodystrophy-like syndrome in PEPCK-TGFβ1 transgenic mice. *J Clin Invest* 1997;**100**(11):2697–2713.

119. Sime PJ, Xing Z, Graham FL, Csaky KG, Gauldie J. Adenovector-mediated gene transfer of active transforming growth factor-β1 induces prolonged severe fibrosis in rat lung. *J Clin Invest* 1997;**100**(4):768–776.

120. Gorelik L, Flavell RA. Transforming growth factor-β in T-cell biology. *Nat Rev Immunol* 2002;**2**(1):46–53.

121. Munger JS, Huang X, Kawakatsu H, Griffiths MJ, Dalton SL, Wu J, *et al*. The integrin αvβ6 binds and activates latent TGFβ1: a mechanism for regulating pulmonary inflammation and fibrosis. *Cell* 1999;**96**(3):319–328.

122. Roberts AB, Russo A, Felici A, Flanders KC. Smad3: a key player in pathogenetic mechanisms dependent on TGFβ. *Ann NY Acad Sci* 2003;**995**:1–10.

123. Flanders KC, Sullivan CD, Fujii M, Sowers A, Anzano MA, Arabshahi A, *et al*. Mice lacking Smad3 are protected against cutaneous injury induced by ionizing radiation. *Am J Pathol* 2002;**160**(3):1057–1068.

124. Bhowmick NA, Chytil A, Plieth D, Gorska AE, Dumont N, Shappell S, *et al*. TGFβ signalling in fibroblasts modulates the oncogenic potential of adjacent epithelia. *Science* 2004;**303**(5659):848–851.

125. Khalil N, Corne S, Whitman C, Yacyshyn H. Plasmin regulates the activation of cell-associated latent TGFβ1 secreted by rat alveolar macrophages after *in vivo* bleomycin injury. *Am J Respir Cell Mol Biol* 1996;**15**(2):252–259.

126. Ma LJ, Yang H, Gaspert A, Carlesso G, Barty MM, Davidson JM, *et al*. Transforming growth factor-β-dependent and -independent pathways of induction of tubulointerstitial fibrosis in β6−/− mice. *Am J Pathol* 2003;**163**(4):1261–1273.

127. Ashcroft GS, Yang X, Glick AB, Weinstein M, Letterio JL, Mizel DE, *et al*. Mice lacking Smad3 show accelerated wound healing and an impaired local inflammatory response. *Nat Cell Biol* 1999;**1**(5):260–266.

128. Lee CG, Homer RJ, Zhu Z, Lanone S, Wang X, Koteliansky V, *et al*. Interleukin-13 induces tissue fibrosis by selectively stimulating and activating transforming growth factor-β1. *J Exp Med* 2001;**194**(6):809–821.

129. Lanone S, Zheng T, Zhu Z, Liu W, Lee CG, Ma B, *et al*. Overlapping and enzyme-specific contributions of matrix metalloproteinases-9 and -12 in IL-13-induced inflammation and remodelling. *J Clin Invest* 2002;**110**(4):463–474.

130. Elias JA, Zhu Z, Chupp G, Homer RJ. Airway remodelling in asthma. *J Clin Invest* 1999;**104**(8):1001–1006.

131. Nakao A, Miike S, Hatano M, Okumura K, Tokuhisa T, Ra C, *et al*. Blockade of transforming growth factor beta/Smad signalling in T cells by overexpression of Smad7 enhances antigen-induced airway inflammation and airway reactivity. *J Exp Med* 2000;**192**(2):151–158.

132. Hansen G, McIntire JJ, Yeung VP, Berry G, Thorbecke GJ, Chen L, *et al*. CD4+ T helper cells engineered to produce latent TGFβ1 reverse allergen-induced airway hyperreactivity and inflammation. *J Clin Invest* 2000;**105**(1):61–70.

133. Kitani A, Fuss I, Nakamura K, Kumaki F, Usui T, Strober W. Transforming growth factor (TGF)-β1-producing regulatory T cells induce Smad-mediated interleukin 10 secretion that facilitates coordinated immunoregulatory activity and amelioration of TGFβ1-mediated fibrosis. *J Exp Med* 2003;**198**(8):1179–1188. Epub: 13 October 2003.

134. Daniels CE, Wilkes MC, Edens M, Kottom TJ, Murphy SJ, Limper AH, *et al*. Imatinib mesylate inhibits the profibrogenic activity of TGFβ and prevents bleomycin-mediated lung fibrosis. *J Clin Invest* 2004;**114**(9):1308–1316.

135. Oriente A, Fedarko NS, Pacocha SE, Huang SK, Lichtenstein LM, Essayan DM. Interleukin-13 modulates collagen homeostasis in human skin and keloid fibroblasts. *J Pharmacol Exp Ther* 2000;**292**(3):988–994.

136. Del Papa N, Quirici N, Soligo D, Scavullo C, Cortiana M, Borsotti C, et al. Bone marrow endothelial progenitors are defective in systemic sclerosis. Arthritis Rheum 2006;54(8):2605–2615.

137. Wilkinson-Berka JL. Angiotensin and diabetic retinopathy. Int J Biochem Cell Biol 2006;38(5–6):752–765. Epub: 1 September 2005.

138. Rattner A, Nathans J. Macular degeneration: recent advances and therapeutic opportunities. Nat Rev Neurosci 2006;7(11):860–872. Epub: 11 October 2006.

139. Friedlander M. Fibrosis and diseases of the eye. J Clin Invest 2007;117(3):576–586.

140. Strieter RM, Gomperts BN, Keane MP. The role of CXC chemokines in pulmonary fibrosis. J Clin Invest 2007;117(3):549–556.

141. Watanabe T, Barker TA, Berk BC. Angiotensin II and the endothelium: diverse signals and effects. Hypertension 2005;45(2):163–169. Epub: 3 January 2005.

142. Mezzano SA, Ruiz-Ortega M, Egido J. Angiotensin II and renal fibrosis. Hypertension 2001;38(3, Pt 2):635–638.

143. Rosenkranz S. TGFβ1 and angiotensin networking in cardiac remodelling. Cardiovasc Res 2004;63(3):423–432.

144. Bataller R, Schwabe RF, Choi YH, Yang L, Paik YH, Lindquist J, et al. NADPH oxidase signal transduces angiotensin II in hepatic stellate cells and is critical in hepatic fibrosis. J Clin Invest 2003;112(9):1383–1394.

145. Rosenkranz S, Flesch M, Amann K, Haeuseler C, Kilter H, Seeland U, et al. Alterations of β-adrenergic signalling and cardiac hypertrophy in transgenic mice overexpressing TGFβ1. Am J Physiol Heart Circ Physiol 2002;283(3):H1253–1262.

146. Li RK, Li G, Mickle DA, Weisel RD, Merante F, Luss H, et al. Overexpression of transforming growth factor-β1 and insulin-like growth factor-I in patients with idiopathic hypertrophic cardiomyopathy. Circulation 1997;96(3):874–881.

147. Berk BC, Fujiwara K, Lehoux S. ECM remodelling in hypertensive heart disease. J Clin Invest 2007;117(3):568–575.

148. Iwano M, Neilson EG. Mechanisms of tubulointerstitial fibrosis. Curr Opin Nephrol Hypertens 2004;13(3):279–284.

149. Moore KW, de Waal Malefyt R, Coffman RL, O'Garra A. Interleukin-10 and the interleukin-10 receptor. Annu Rev Immunol 2001;19:683–765.

150. Thompson K, Maltby J, Fallowfield J, McAulay M, Millward-Sadler H, Sheron N. Interleukin-10 expression and function in experimental murine liver inflammation and fibrosis. Hepatology 1998;28(6):1597–1606.

151. Louis H, Van Laethem JL, Wu W, Quertinmont E, Degraef C, Van den Berg K, et al. Interleukin-10 controls neutrophilic infiltration, hepatocyte proliferation, and liver fibrosis induced by carbon tetrachloride in mice. Hepatology 1998;28(6):1607–1615.

152. Arai T, Abe K, Matsuoka H, Yoshida M, Mori M, Goya S, et al. Introduction of the interleukin-10 gene into mice inhibited bleomycin-induced lung injury in vivo. Am J Physiol Lung Cell Mol Physiol 2000;278(5):L914–922.

153. Demols A, Van Laethem JL, Quertinmont E, Degraef C, Delhaye M, Geerts A, et al. Endogenous interleukin-10 modulates fibrosis and regeneration in experimental chronic pancreatitis. Am J Physiol Gastrointest Liver Physiol 2002;282(6):G1105–1112.

154. Wangoo A, Laban C, Cook HT, Glenville B, Shaw RJ. Interleukin-10- and corticosteroid-induced reduction in type I procollagen in a human ex vivo scar culture. Int J Exp Pathol 1997;78(1):33–41.

155. Wang SC, Ohata M, Schrum L, Rippe RA, Tsukamoto H. Expression of interleukin-10 by in vitro and in vivo activated hepatic stellate cells. J Biol Chem 1998;273(1):302–308.

156. Nelson DR, Tu Z, Soldevila-Pico C, Abdelmalek M, Zhu H, Xu YL, et al. Long-term interleukin 10 therapy in chronic hepatitis C patients has a proviral and anti-inflammatory effect. Hepatology 2003;38(4):859–868.

157. Wynn TA, Cheever AW, Williams ME, Hieny S, Caspar P, Kühn R, et al. IL-10 regulates liver pathology in acute murine schistosomiasis mansoni but is not required for immune down-modulation of chronic disease. J Immunol 1998;160:5000–5008.

158. Hoffmann KF, Cheever AW, Wynn TA. IL-10 and the dangers of immune polarization: excessive type 1 and type 2 cytokine responses induce distinct forms of lethal immunopathology in murine schistosomiasis. J Immunol 2000;164(12):6406–6416.

159. Wilson MS, Elnekave E, Mentink-Kane M, Hodges MG, Pesce JT, Ramalingam TR, et al. IL-13Ra2 and IL-10 coordinately suppresss airway inflammation, airway-hyperreactivity, and fibrosis in mice. J Clin Invest 2007;117:2941–2951.

160. Taube C, Duez C, Cui ZH, Takeda K, Rha YH, Park JW, et al. The role of IL-13 in established allergic airway disease. J Immunol 2002;169(11):6482–6489.

161. Mattes J, Yang M, Siqueira A, Clark K, MacKenzie J, McKenzie AN, et al. IL-13 induces airways hyperreactivity independently of the IL-4R α chain in the allergic lung. J Immunol 2001;167(3):1683–1692.

162. Feng N, Lugli SM, Schnyder B, Gauchat JF, Graber P, Schlagenhauf E, et al. The interleukin-4/interleukin-13 receptor of human synovial fibroblasts: overexpression of the nonsignalling interleukin-13 receptor α2. Lab Invest 1998;78(5):591–602.

163. Chiaramonte MG, Mentink-Kane M, Jacobson BA, Cheever AW, Whitters MJ, Goad ME, et al. Regulation and function of the interleukin 13 receptor α2 during a T helper cell type 2-dominant immune response. J Exp Med 2003;197(6):687–701.

164. Mentink-Kane MM, Cheever AW, Thompson RW, Hari DM, Kabatereine NB, Vennervald BJ, et al. IL-13 receptor α2 down-modulates granulomatous inflammation and prolongs host survival in schistosomiasis. Proc Natl Acad Sci USA 2004;101(2):90–586. Epub: 29 December 2003.

165. Issa R, Zhou X, Constandinou CM, Fallowfield J, Millward-Sadler H, Gaca MD, et al. Spontaneous recovery from micronodular cirrhosis: evidence for incomplete resolution associated with matrix cross-linking. Gastroenterology 2004;126(7):808–1795.

166. Iredale JP. Models of liver fibrosis: exploring the dynamic nature of inflammation and repair in a solid organ. J Clin Invest 2007;117(3):539–548.

167. Fallowfield JA, Kendall TJ, Iredale JP. Reversal of fibrosis: no longer a pipe dream? Clin Liver Dis 2006;10(3):481–497.

168. Vennervald BJ, Dunne DW. Morbidity in schistosomiasis: an update. Curr Opin Infect Dis 2004;17(5):439–447.

169. Lund RD, Wang S, Klimanskaya I, Holmes T, Ramos-Kelsey R, Lu B, et al. Human embryonic stem cell-derived cells rescue visual function in dystrophic RCS rats. Cloning Stem Cells 2006;8(3):189–199.

170. Iredale JP, Benyon RC, Pickering J, McCullen M, Northrop M, Pawley S, et al. Mechanisms of spontaneous resolution of rat liver fibrosis. Hepatic stellate cell apoptosis and reduced hepatic expression of metalloproteinase inhibitors. J Clin Invest 1998;102(3):538–549.

171. Thannickal VJ, Toews GB, White ES, Lynch JP, 3rd, Martinez FJ. Mechanisms of pulmonary fibrosis. Annu Rev Med 2004;55:395–417.

172. Wright MC, Issa R, Smart DE, Trim N, Murray GI, Primrose JN, et al. Gliotoxin stimulates the apoptosis of human and rat hepatic stellate cells and enhances the resolution of liver fibrosis in rats. Gastroenterology 2001;121(3):685–698.

173. Caplan AI, Dennis JE. Mesenchymal stem cells as trophic mediators. J Cell Biochem 2006;98(5):1076–1084.

174. Huang H, Shiffman ML, Friedman S, Venkatesh R, Bzowej N, Abar OT, et al. A seven gene signature identifies the risk of developing cirrhosis in patients with chronic hepatitis C. Hepatology 2007;46(2):297–306.