
Review

Targeting Inflammation to Control Tissue Fibrosis

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Received: 17 November 2022

Accepted: 19 November 2022

Published: 21 December 2022

Abstract: Remodeling of the extracellular matrix (ECM) is an essential process in host defense against pathogens and tissue repair following injury. However, aberrant inflammatory responses could disturb ECM homeostasis leading to progressive disruption in tissue architecture and organ function. Fibrosis is the common outcome of a wide range of diseases, especially chronic inflammatory disorders, and represents the leading cause of morbidity and mortality globally. This review provides the current understanding of the pathogenesis of fibrosis, with particular emphasis on the role of inflammation in this process and the translational potential of targeting inflammation as a strategy to control fibrotic progression.

Keywords: inflammation; fibrosis; cytokines.

1. Introduction

Inflammation is the first response mechanism following tissue injury. Various inflammatory cells, especially neutrophils and monocytes, are activated and recruited to the injured tissue, which serves as rich sources of cytokines, chemokines, and growth factors. These damage-associated signals are also essential for activating different effector cells within the tissue microenvironment, such as residential fibroblasts, to promote their proliferation, contraction, and the production of collagenous and non-collagenous extracellular matrix (ECM) components [1]. Furthermore, inflammatory molecules have been reported to induce the myofibroblast transformation through epithelial-mesenchymal transition (EMT) [2] and endothelial-mesenchymal transition (EndMT) [3] process. Recently, infiltrating immune cells have been shown to contribute to the fibrotic progression by directly transforming into myofibroblasts, in a process called macrophage-to-myofibroblast transition (MMT), in the kidney [4] and the eye [5]. The acute inflammatory response is critical for limiting blood loss and preventing the pathogen spread and invasion [6]. Timely resolution of the inflammatory response is essential for restoring homeostasis and preserving tissue integrity and normal organ function. The persistent inflammatory response may trigger uncontrolled ECM remodeling and lead to permanent tissue damage and fibrosis which is associated with many chronic inflammatory diseases [7]. Although numerous factors have been reported to contribute to fibrotic progression, the underlying molecular mechanisms are poorly defined and effective management of fibrotic diseases remains a significant unmet medical need. In recent years, the importance of inflammation in fibrosis has attracted great attention. This review focuses on the role of common inflammatory molecules in fibrotic progression and the potential of targeting these pathways to control tissue fibrosis and restore tissue homeostasis.

2. Transforming Growth Factor-Beta (TGF- β)

Transforming growth factor-beta (TGF- β) is a multifunctional growth factor with potent inflammatory activity [8] and has been shown to regulate the function of T cells [9–13], natural killer (NK) cells [14], and dendritic cells (DC) [15]. At the same time, TGF- β serves as one of the most potent regulators of tissue fibrosis. Besides inducing the differentiation of fibroblasts into myofibroblasts [16], TGF- β promotes EMT in epithelial cells originating from the lung, liver, lens, or kidney [17] by regulating the activity of both canonical and non-canonical signaling transducers [18–20]. Deletion of receptor-mediated Smad [21] or introduction of exogenous inhibitory Smad [22] leads to attenuated EMT and fibrosis in mice. Inhibitors targeting PI3K/Akt [23] and MAPK [24] have also been shown to inhibit fibrosis in preclinical studies and clinical trials. TGF- β 's role in EndMT has also been extensively investigated and was shown to regulate EndMT through the canonical Smad signalling pathway [25,26]. Connective Tissue Growth Factor (CTGF) was reported to mediate, at least partially, the profibrotic effects of TGF- β . A functional Smad3 binding site has been identified in the CTGF promoter and TGF- β has been shown to induce the expression of CTGF in fibroblasts leading to the subsequent differentiation into myofibroblast [27]. On the other hand, CTGF has been reported to enhance the binding of TGF- β to its type II receptor T β RII leading to subsequent activation of downstream signalling transducers and potentiating the TGF- β -mediated fibrogenic actions [28]. Despite being recognized as a central pathway of fibrosis, TGF- β is not an ideal therapeutic targets due to its multifunctional role. Long-term inhibition of TGF- β has been shown to cause serious adverse effects.

3. Tumor Necrosis Factor Alpha (TNF- α)

Tumor necrosis factor alpha (TNF- α) is a pleiotropic cytokine that is cleaved from the membrane-bound precursors into the soluble mature form by TNF- α -converting enzyme (TACE) [29]. Both precursor and mature TNF- α can activate downstream signalling transducers, through TNF α receptors. Although being named because of its role in promoting tumour necrosis, TNF- α is now believed to regulate diverse functions, including inflammation [30], angiogenesis [31–33], tumorigenesis [34] as well as tissue fibrosis [35]. Physiological, TNF- α plays a critical role in normal immune response, however, inappropriate activation of TNF- α contributes to the development of a variety of complications. In terms of tissue fibrosis, TNF- α 's role in liver fibrosis has been studied extensively. Hepatic stellate cells (HSCs) can differentiate into myofibroblasts and serve as the primary contributor to liver fibrosis [36]. Macrophages have been shown to serve as a major source of TNF- α [37] and macrophage-derived TNF- α promotes liver fibrosis by regulating the NF- κ B-mediated HSC survival [38]. The synergistic effect of TNF- α and TGF- β or other inflammatory factors on EMT and EndMT has also been reported [39–41]. On the other hand, TNF- α has been shown to reduce ECM deposition by reducing the expression of matrix metalloproteinase-9 (MMP9) [42] or inhibiting the synthesis of ECM components such as collagen I [43–47], through mediating the TGF- β -signalling [48–50]. Therefore, the role of TNF- α remains controversial.

4. Interleukins

Interleukins (ILs) are a group of cytokines that play important immunoregulatory functions. They regulate the immune system by promoting the proliferation and differentiation of immune cells and recruiting them to the injury sites [51–54]. Recently, ILs have been reported to govern fibrogenesis in several organ systems.

IL1 family of cytokines consists of members with both proinflammatory and anti-inflammatory properties [55]. Many of them have been implicated in tissue fibrosis. For example, IL-1 β is induced in the lungs of mice subjected to bleomycin-induced pulmonary fibrosis [56], in sputum and lung tissues of human patients with chronic obstructive pulmonary disease (COPD) [57], a disease characterized by fibrotic remodeling of the small airways [58], and in bronchoalveolar lavage (BAL) and lung biopsies of patients with idiopathic pulmonary fibrosis (IPF) [59]. Studies showed that IL-1 β deficient mice are protected from bleomycin-induced pulmonary fibrosis [56]. Consistent with this observation, administration of IL-1 β can lead to pulmonary fibrosis to a comparable magnitude to bleomycin [59]. Transient overexpressing IL-1 β in

rat lungs has also been reported to cause severe progressive tissue fibrosis [60], whereas neutralizing IL-1 β antibody can attenuate the silica-induced lung fibrosis by inhibiting the expression of TGF- β 1 [61]. EMT of alveolar epithelial cells into myofibroblasts contributes to fibrotic progression in the lung [62] and IL-1 β was reported to be actively involved in this process [63]. Besides the lung, IL-1 β was reported to regulate renal and hepatic fibrosis by mediating the EMT process, and neutralizing antibody targeting IL-1 β prevented the transformation of renal proximal tubular epithelial cells and hepatic stellate cells [64,65]. Therefore, targeting IL-1 β may offer an attractive strategy to control tissue fibrosis.

IL-6 is a pleiotropic cytokine with diverse biological functions. Its roles in inflammation and immunity are most well characterized. IL-6 was initially demonstrated to induce immunoglobulin production by directly affecting B cells [66] and STAT3 was reported to play a critical role in this process [67]. Consistent with this observation, IL-6 deficient mice are defective in immunoglobulin production [68,69]. Besides its role in B cells, IL-6 has also been reported in regulating T cell function in a STAT3-dependent manner [70, 71]. Interestingly, elevated IL-6 levels are observed in the injured skin tissues [72], patients with pulmonary fibrosis [73], systemic sclerosis [74], and liver cirrhosis [75], suggesting a potential disease-modifying role of IL-6 in tissue fibrosis. Indeed, IL-6 is shown to promote collagen synthesis and tissue fibrosis in the lung [76], kidney [77], heart [78], and skin [79]. Furthermore, increased IL-6 levels as a consequence of repeated inflammation are believed to regulate Th1 cell responses in peritoneal fibrosis, whereas IL-6 deficient mice are resistant to fibrosis [80]. Similarly, the genetic ablation of IL-6 leads to attenuated fibrosis in a bleomycin-induced murine model [81]. It was previously demonstrated that genetic or pharmacologic removal of IL-6 resulted in the attenuation of fibrosis [73]. Tocilizumab is a humanized monoclonal antibody against the IL-6 receptor. Blocking IL-6 trans signalling with Tocilizumab leads to improved skin scores in patients with diffuse systemic sclerosis [82]. These data provide evidence of IL-6 as an attractive therapeutic target for treating fibrosis.

IL-7 is a member of the IL-2 superfamily and signals through IL-7R [83]. IL-7/IL-7R signalling is essential for the development of T cells and mouse B cells, the differentiation and survival of naive T cells, and the generation and maintenance of memory T cells [83]. Unlike IL-1 β , IL7's role in tissue fibrosis is less understood. However, it was reported to downregulate TGF- β production in macrophages in an IFN- γ -independent manner [84]. Consistent with these *in vitro* observations, recombinant IL-7 has been shown to reduce bleomycin-induced pulmonary fibrosis in mice by suppressing the expression of TGF- β in a JAK1/STAT1-dependent manner [85]. In addition, IL-7-mediated inhibition of TGF- β signaling was associated with an increase in the expression of an inhibitory Smad, Smad7 [85]. Similarly, IL-7 was also reported to attenuate high-glucose-induced activation of the TGF- β signaling pathway, EMT of renal proximal tubule epithelial cells and renal fibrosis [86]. Consistent with the observations in pulmonary fibroblasts, high-glucose-induced inhibition of Smad7 is significantly reversed by IL-7 [86]. In liver fibrosis, the IL7RA rs6897932 polymorphism was reported to be associated with an increased risk of liver fibrosis progression in HCV-infected patients [87], and regulating IL7R expression by targeting miR-122-5p can inhibit HBV-related liver fibrosis [88].

5. Chemokines

Chemokines are soluble, membrane-bound proteins that act on the superfamily of G-protein coupled serpentine receptors expressed on various target cells [89]. They act synergistically with other cytokines to recruit and activate various effector cells, such as myofibroblasts, endothelial cells, neutrophils, and monocytes, within the tissue microenvironment in response to tissue injury [90]. Based on the number of amino acids located between the N-terminal cysteine residues, chemokines could be divided into four groups, C, CC, CXC, and CX₃C [91].

5.1. CXCL

The CXC family of chemokines are important mediators of inflammatory response and their main function is to guide the neutrophils to the site of infection [92] and activates them [93]. Besides its important roles in inflammation, CXCLs also participate in tissue fibrosis. CXCL8 is induced in patients with IPF [94,95],

pneumoconiosis [96], liver fibrosis [97], and cystic fibrosis [98]. Mesenchymal progenitor cell (MPC)-derived CXCL8 promotes pulmonary fibrosis by increasing MPC proliferation and recruiting activated macrophages in the lung. CXCL8's role in EMT has also been reported [99], however, how whether it is involved in EMT-mediated tissue fibrosis remains to be investigated. A similar role of CXCL10 has also been reported. CXCL10 is induced in severe hepatitis C virus (HCV)-induced liver fibrosis [100] and the deletion of CXCL10 leads to reduced liver fibrosis [101]. CXCL4 is another pro-fibrotic chemokine and it regulates liver fibrosis by inhibiting the migration of CD8⁺T cells [102]. CXC chemokines are also involved in pulmonary fibrosis, primarily through their action on T helper 1 and Natural Killer T cells [103]. Blocking CXCLs, such as CXCL2, significantly attenuates the development of pulmonary fibrosis [103]. However, other CXCLs, including CXCL10 and CXCL11, serve as potent inhibitors of pulmonary fibrosis [104,105].

5.2. CCL

Hepatic stellate cells (HSC) express a multitude of CCLs, such as CCL2, CCL3, CCL5, and CCL21 [106,107]. Inhibition of CCL2 and CCL21 indeed attenuates liver fibrosis *in vivo* [107, 108]. CCLs have also been implicated in the pathogenesis of pulmonary fibrosis. CCL2 mRNA and protein expression are highly induced in lung epithelial cells and bronchoalveolar fluid from human patients with IPF [109], and the profibrotic role of CCL2 has been demonstrated in various animal models of pulmonary fibrosis [110–112]. However, clinical trial results on the CCL2 neutralizing antibody in patients with IPF was rather disappointing [113]. CCR7 is a cognate receptor of CCL21 and it is expressed in IPF but not normal fibroblasts [114]. Furthermore, CCL21 can activate CCR7 on fibroblasts isolated from patients with IPF to promote their proliferation migration and chemokine expression in a mitogen-activated protein kinase (MAPK) 1/2-dependent manner [114]. Indeed, the CCL21 neutralizing antibody has been shown to attenuate pulmonary fibrosis *in vivo* [115]. Besides the lung, CCL21 is involved in the fibrotic progression in different organs and tissues, including the lymph nodes [116], heart [117], and kidney [118]. For example, CCL21 is expressed by high endothelial venules in lymph nodes and Peyer's patches and by stromal cells in the T-cell areas of secondary lymphoid organs [119]. The binding between CCL21 and its receptor CCR7 is essential in the organization of normal lymphoid tissue during development [119]. CCL21 can also stimulate the recruitment of CCR7⁺ dendritic cells (DCs) and lymphocytes into both renal draining lymph nodes (RDLNs) and spleen, resulting in a systemic lymphocyte expansion, which plays a critical role in driving fibrosis following renal injury. Consistently, Injury-induced intrarenal inflammation and fibrosis could be attenuated by blocking the recruitment of CCR7⁺ cells into RDLN and spleen or inhibiting lymphangiogenesis [116]. In addition, blockading CCL21/CCR7 signaling using a neutralizing CCL21 antibody effectively attenuates renal fibrosis by reducing the recruitment of macrophages and renal transcripts of monocyte chemoattractant protein-1 (MCP-1/CCL2) [116]. It is worthy highlighting that the CCL21-induced migration of fibrocytes is chemotactic but not chemokinetic [120].

6. Future Directions

Despite the advances in understanding the pathophysiological mechanisms of fibrosis, effective management of fibrotic diseases remains challenging. At the site of tissue injury or infection, recruited and activated inflammatory cells contribute to fibrotic progression by interacting with resident cells within the tissue microenvironment [121]. Targeting inflammatory regulators may serve as an attractive approach for developing novel anti-fibrotic therapeutics. However, the complex role of inflammation molecules and the heterogeneity of different fibrotic disease contexts warrant further investigation in the search for novel therapeutic targets for a specific type of fibrotic disease. Recent single-cell multi-omics approaches looking at molecular changes in distinct cell populations of healthy and diseased tissue samples with unprecedented resolution revolutionized our understanding of disease pathogenesis [122,123]. These approaches offer a powerful exploration of cell states and types at the single-cell level, helping us to generate new insights into the disease mechanisms associated with fibrosis.

Author Contributions: Writing-original draft preparation, W.S., W.S., Z.W., K.Y.C.T, C.M.G.C., and X.W; Writing-review and editing, W.S., W.S., Z.W., K.Y.C.T, C.M.G.C., and X.W; Funding acquisition: C.M.G.C, K.Y.C.T and X.W.

All authors have read and agreed to the published version of the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This research is funded by NMRC-LCG grant Translational Asian Age-related Macular Degeneration Programme (TAAP): NMRC/LCG/2018/004.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: This work was supported by grants from National Medical Research Council Singapore Large Collaborative Grant TAAP (NMRC/OFLCG/004/2018) to GCMC and XMW.

Conflicts of Interest: The authors declare no conflict of interest.

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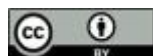
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Citation: Song W. H.; Sun W.; Wang Z. L.; et al. (2022). Targeting inflammation to control tissue fibrosis. *International Journal of Drug Discovery and Pharmacology*, *1*(1),6. <https://doi.org/10.53941/ijddp.v1i1.206>.

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