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Review article

Interleukin-17: Friend or foe in organ fibrosis

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ABSTRACT

Fibrosis affects all vital organs accounting for a staggering 45% of deaths worldwide and no effective therapies are currently available. Unresolved inflammation triggers downstream signaling events that lead to organ fibrosis. In recent years, proinflammatory cytokine Interleukin-17 (IL-17) has been implicated in several chronic inflammatory diseases that often culminate in organ damage followed by impaired wound healing and fibrosis. In this review, we outline the contribution of the IL-17 in mediating fibrotic diseases in various organs. A comprehensive understanding of the inflammatory events, and particularly the details of IL-17 signaling *in vivo*, could be beneficial in designing new therapeutic or preventive approaches to treat fibrosis. Additionally, understanding organ-specific differences in IL-17 activity could lead to targeted therapies and help spare other organs from unwanted side effects.

1. Introduction

The prevalence of chronic fibrosis related diseases is significantly rising and has amounted to a major public health issue [1]. Approximately 45% of deaths associated with diseases are attributed to fibrosis [1]. In the developed world fibrosis is a major cause of morbidity and mortality [1,2]. Although fibrosis is associated with almost every kind of organ damage, lack of information on the fundamental mechanisms underlying the fibrotic process act as a major challenge in developing targeted therapeutic approaches against fibrotic diseases.

Usually in an organ injury, repair mechanisms are preceded by a robust inflammatory response, which is crucial to counter the potential for infection at a site where a barrier is breached [2]. Abnormal tissue repair can lead to the formation of a fibrotic tissue upon wound healing. From recent studies, it is apparent that chronic inflammatory response may be, at least in part, responsible for aberrant tissue repair and fibrosis development at sites of tissue injury. Thus, fibrosis is a complex process that offers a conundrum of whether it is an inflammatory or a non-inflammatory response [2,3]. The reports of corticosteroids exacerbating symptoms in patients with pulmonary fibrosis raise the quandary of whether fibrosis is truly only an inflammatory disease. Various fibrotic diseases demonstrate shared features such as chronic inflammation associated with impaired wound healing and progression of the fibrotic conditions. The local fibrogenic response in injured organs includes the chemokine-mediated recruitment of immune cells such as macrophages. The infiltrating immune cells produce proinflammatory cytokines that trigger the activation of effector cells. These cells proceed to remodel and regenerate the injured tissue. However, in chronic fibrotic diseases there is a perturbation in the balance between production and degradation of extracellular matrix (ECM) components [2]. The continuously activated effector cells synthesize an excessive amount of ECM resulting in the deposition of connective tissue. This unabated pathogenic tissue remodeling contributes to the destruction of organ architecture and function. Since inflammation is a major contributor to the progression of fibrosis, strategies that target inflammatory pathways could offer therapeutic benefits. Thus, the aim of this review is to delineate the crucial events of organ fibrosis and to highlight the role of the members of Interleukin-17 (IL-17) cytokine family.

2. Immune players of organ fibrosis

There are four characteristic phases of the fibrogenic response-injury to the organ, activation of effector cells followed by the exacerbated production of extracellular matrix (ECM) and dynamic deposition of connective tissue. The inflammatory response constituting cells of innate and adaptive immune system and soluble factors such as cytokines, chemokines, proteases and growth factors regulate distinct phases of fibrogenic response following organ injury (Fig. 1).

i. Innate mediators of organ fibrosis

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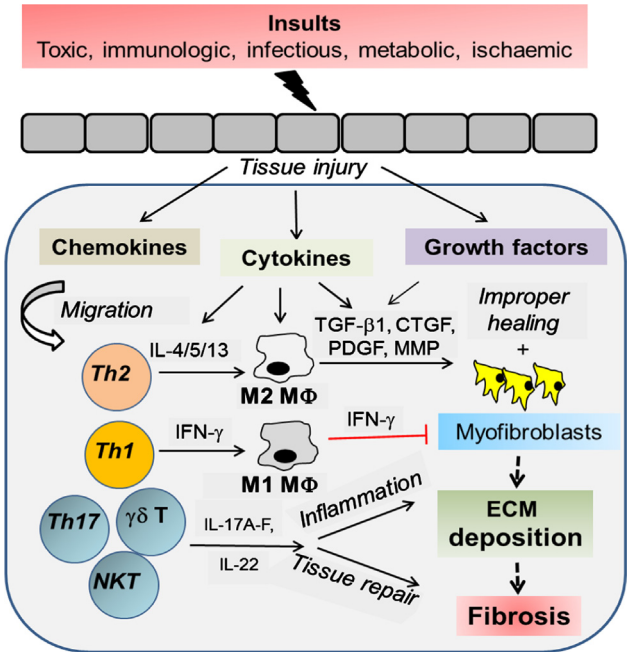

Fig. 1. The immunology of organ fibrosis: Cells respond to injury by secreting cytokines, chemokines and growth factors, setting the stage for inflammation that clears the insult and facilitate tissue repair and wound healing. In some cases chronic inflammation results in improper wound healing and initiates a cascade of profibrotic events in the organs. Chemokines recruit Th1, Th2 cells and Th17 and other IL-17 producing cells, as well as inflammatory monocytes. Th2 cytokines (IL-4, IL-5 and IL-13) convert monocytes to M2 macrophages. M2 macrophages are the major source of TGF-β and other growth factors required for trans-differentiation of tissue resident fibroblasts to ECM-secreting myofibroblasts. IFN-γ from Th1 cells converts monocytes to M1 macrophages. M1 macrophages inhibit myofibroblasts proliferation and facilitate the degradation of ECM proteins by producing matrix metalloproteinases (MMPs). Cytokines and growth factors secreted from tubular epithelial cells activate T cells, macrophages and myofibroblasts and aid in the process of ECM synthesis and deposition. The balance between ECM synthesis and degradation determines the outcome of the profibrotic cascade and eventually development of fibrosis. IL-17 produced from innate and adaptive IL-17 producing cells play both pro- or antifibrotic role depending on the organ affected and nature of initial insults.

Early events of fibrosis comprise inflammatory changes, including proliferation of ECM-producing cells and the influx of mononuclear inflammatory infiltrates in injured organs (Fig. 1). In this context, monocytes/macrophages and mast cells have been strongly implicated as important mediators of inflammatory processes involving fibrosis [4]. Activated monocytes/macrophages regulate ECM turnover through the release of cytokines, chemokines, reactive oxygen species (ROS), growth factors and ECM-degrading enzymes [4]. One of the most prominent activators of mononuclear cells and fibroblasts are hyaluronan fragments, which not only induce expression of various cytokines (IL-1, IL-12, and TNF-α), chemokines (MIP-1α, MCP-1, IL-8) and inducible nitric oxide synthase (iNOS), but also trigger the expression and secretion of macrophage-derived matrix metalloproteinases (MMPs). Accordingly, depletion of macrophages or mice deficient in MCP1 or CCR2 (mice unable to recruit monocytes/macrophages at the site of inflammation) display protective phenotypes in numerous fibrotic conditions [5,6]. Mast cells secrete tryptases which contribute to connective tissue breakdown and indirectly induce fibroblast proliferation through the synthesis of cyclooxygenase and prostaglandins [7,8]. In contrast, natural killer (NK) cells display predominantly antifibrotic properties in several fibrosis model systems. Mice lacking T-, B- and NK cells show increased susceptibility to chemically-induced liver and lung fibrosis [9]. NKT cell-deficient mice exhibit larger fibrotic lesions in lungs and skin and have worse clinical outcomes than controls following bleomycin (BLM)-induced injury [10]. Intriguingly, patients with chronic and acute liver disease also show impaired NK cell function in the target organs [11].

ii. Pro-and antifibrotic growth factors

Among various profibrotic growth factors and inflammatory mediators, TGF-β1 is the key driver of fibrosis in most organs including the skin, kidney, liver, gastrointestinal tract, and lungs [12–14]. TGF-β1 is mainly produced by macrophages and fibroblasts; however, TGF-β1 production from other hematopoietic cells including Tregs, DCs, $CD8^+$ T cells has also been demonstrated [12–14]. Receptor engagement by TGF-β1 initiates the downstream signaling cascade including the phosphorylation of SMAD proteins. Activated phospho-SMAD proteins form complexes and translocate into the nucleus to activate target gene expression [14]. The activation of TGF-β1-mediated signaling pathway leads to the expression of molecules such as anti-smooth muscle actin (α-SMA), a classical marker for collagen secreting myofibroblasts [14]. In contrast to TGF-β1, TGF-β3 exhibits an antifibrotic effect in organ fibrosis [13]. The role of TGF-β2 in organ fibrosis is largely unexplored [13]. TGF-β1 in synergy with other pro-fibrotic growth factors, such as connective tissue growth factor (CTGF), osteopontin, insulin-like growth factor-2 (IGF-2) and epidermal growth factor (EGF) drives profibrotic events in chronic inflammatory diseases [15,16].

iii. Adaptive mediators of organ fibrosis

Cells and cytokines of the adaptive immune system play a prominent role in the initiation and progression of fibrosis. Th2 cell specific cytokines IL-4, IL-5, and IL-13 have been associated with the pathogenesis of fibrosis [2,17,18]. Amongst these, IL-13 has been identified to have a profibrotic effect in various fibrosis-related diseases [18]. The overexpression of IL-13 induced fibrosis in the airway in animal model of fibrosis [19]. Consequently, blockade of IL-13 with an anti-IL-13 antibody significantly decreased ECM deposition in a bleomycin (BLM)-induced lung fibrosis model [20]. IL-5 can amplify the profibrotic effect by inducing the production of IL-13 and the expression of its receptor [18]. In contrast, under inflammatory settings where IFN-γ (Th1 cytokine) dominates, organ fibrosis is attenuated [2,17,18]. Th1 and Th2 cytokines have been reviewed extensively elsewhere [18]. The focus of this review is on the role of Th17 cells and its secretory product IL-17 in organ fibrosis.

3. Characteristics of the IL-17 cytokine family

Apart from the cytokines and growth factors already investigated in fibrosis, recently members of the IL-17 cytokine family have been studied as mediators of fibrosis-related inflammation. Known functions of the IL-17 family include host defense against extracellular bacteria and fungi and driving chronic inflammation in autoimmune diseases. IL-17 is also essential for the maintenance of epithelial layer integrity and facilitating tissue healing [21].

IL-17 cytokine family consists of six related members: IL-17A (IL-17), IL-17B, IL- 17C, IL-17D, IL-17E (also known as IL-25), and IL-17F [21]. The IL-17R family has five receptor subunits, IL-17RA-IL-17RE and shows significant similarities in the structure of their receptor heterodimers [22]. While IL-17A and IL-17F homodimers as well as IL-17A-F heterodimer bind to IL-17RA/IL-17RC, IL-17C binds to IL-17RA/IL-17RE. IL-17B binds to IL-17RB and IL-17E to the IL-17RA/IL-17RB receptor complex. IL-17RA is ubiquitously expressed, with particularly increased expression on hematopoietic cells. Converse to IL-17RA, IL-17RC expression is lower in haemopoietic cells and high in the cells of non-hematopoietic origin such as cells of the kidney, liver, joints and thyroid [22]. Available evidence suggests that the major cell types responsive to IL-17 are non-hematopoietic cells including epithelial cells, endothelial cells and fibroblasts [22]. The differential expression of IL-

17RA and IL-17RC may provide a mechanism for the tissue-specific function by IL-17. The T-helper17 cells (Th17) subset produces IL-17, IL-17F, IL-21 and IL-22. Apart from adaptive Th17 cells, various innate immune cells have been identified as cellular sources for IL-17, including $\gamma\delta^+$ T, NK, NKT, 'natural' Th17 and group 3 innate lymphoid cells [22,23].

Upon stimulation by IL-17, the receptor complex consisting of two subunits IL-17RA and IL-17RC recruits the adaptor protein Act1. Act1 then associates with the downstream signaling molecules such as TRAF6 leading to activation of IKK and NF-κB. The IL-17-mediated Act1 signaling complex also activates MAPKs and induces C/EBP expression. IL-17 signaling cascades lead to the activation of transcription factors such as NF-κB, C/EBPs, and AP1 to induce gene transcription. An alternate signaling cascade includes the formation of another Act1 dependent complex through downstream mediators such as IKKi, TRAF2, TRAF5 and SF2. This signaling pathway mediates TRAF6-independent mRNA stability for IL-17 and TNFα driven expression of certain chemokines and cytokines [22,24]. IL-17 induces the expression of multiple IL-17 responsive genes via activation of transcription factors such as NF-κB and CEBPβ. Gene products induced by IL-17 include cytokines (IL-6, GM-CSF, TNFα), chemokines (CXCL1, CXCL2, CCL20) and inflammatory effectors (acute-phase proteins, complement), all of which can act as profibrotic factors in organ fibrosis [3,21]. IL-17 also drives the expression of downstream effectors such as MMPs, including MMP1, MMP3 and MMP9, which play crucial roles in extracellular matrix destruction and tissue damage [25–27]. Moreover, IL-17-driven nitric oxide synthase can play a significant role in the prevention of tissue damage, which is a common element of chronic fibrotic related diseases [28–30].

4. Role of IL-17 family in fibrotic diseases

Inflammation is a critical determinant of regeneration and fibrosis [2,3]. Tissue damage not only induces inflammation in general, it also determines the type and polarization of inflammation by recruiting and activating a variety of different cells types of the innate and adaptive immune system [2]. All fibrotic tissues display signs of a chronic immunologically-mediated inflammation during the earliest periods of their development. IL-17, a proinflammatory cytokine is linked to many autoinflammatory diseases. However, the impact of organ-specific and disease-specific factors on IL-17 function during organ fibrosis is poorly understood and will be systematically addressed here.

4.1. Pulmonary fibrosis

According to estimates by the CDC, some form of pulmonary fibrosis affects one in every 5 people in the United States (www.cdc.org). Pulmonary fibrosis is linked with a heterogenic group of diseases with varying etiology. It is associated with a vast array of clinical conditions such as radiation and chemotherapy-induced fibrosis, cystic lung disease, granulomatous lung disease, infection or autoimmune disease, environmental, and smoking-associated chronic obstructive pulmonary disease. It has also been shown to appear without any underlying cause, termed as idiopathic pulmonary fibrosis (IPF) [31]. Many of these pulmonary disorders are mostly characterized by the inflammation of the lung interstitium [32]. IPF, however, is mainly fibrotic and is caused when an excessive deposition of ECM results in the loss of the tissue architecture and destruction of the lung. Commonly, patients with known etiology of pulmonary fibrosis respond well to specific therapeutic approaches if the disease is inflammation dominated, but prove to be challenging when fibrosis drives the damage. Thus far, treatment options for IPF are limited; in severe cases lung transplantation is the only option available to patients [31].

Several studies have revealed an association between IL and 17 family of cytokines and pulmonary fibrosis [33–38]. In the murine model for pulmonary fibrosis induced by BLM, IL-17 level was markedly increased in the lung, draining thoracic lymph nodes and bronchoalveolar lavage (BAL) [33]. After exposure to BLM, but not *Schistosoma mansoni* eggs, IL-17 produced by $CD4^+$ and $\gamma\delta^+$ T cells induced significant neutrophilia and pulmonary fibrosis. Consequently, IL-$17^{-/-}$ mice had decreased pulmonary fibrosis after treatment with BLM than wild type animals [33]. Administration of an anti-IL-17A neutralizing antibody has also been shown to attenuate pulmonary fibrosis and ECM deposition, and increased survival in the BLM and silica-induced model of lung fibrosis [34,35,39]. Moreover, treatment with anti-IL-17 antibody also lessened radiation-induced pneumonitis and fibrosis and improved post-irradiation survival in mice, indicating a profibritic role for IL-17 in various mouse models of lung fibrosis [40].

In contrary, IL-17 producing $\gamma\delta^+$ T cells prevented BLM-induced pulmonary fibrosis by limiting interstitial inflammation and aiding regeneration of epithelial tissue [41]. In this setting, $\gamma\delta^{-/-}$ mice showed increased pulmonary inflammation and ECM deposition during BLM induced lung injury. Since IL-17 producing cells constitute ~5% of total $\gamma\delta^+$ T cells in the injured lung and $\gamma\delta^+$ T cells may be the source of other inflammatory cytokines, the role of IL-17 from these cell type is unclear and warrants careful future investigation.

Although these studies identified a critical role for IL-17 in fibrosis, the mechanism by which IL-17 is produced in the inflamed lung is poorly understood. Several reports have identified that BLM-induced IL-17 production was TGF-β and IL-1 dependent, suggesting cooperative roles for IL-17, TGF-β and IL-1 in the development of fibrosis [3,33]. More recently, B cell activating factor (BAFF) has been shown to be involved in a crosstalk with IL-17 in the pathogenesis of lung fibrosis [42]. Additionally, transglutaminase 2, a calcium-dependent enzyme that catalyzes the cross-linking of proteins, produced by lung epithelial and fibroblast cells is absolutely required for IL-17 production from lung infiltrating T cells during BLM-induced fibrosis [43,44]. In humans, elevated levels of IL-17 and IL-1β were seen in the BAL fluid of patients with IPF compared to healthy subjects [33]. Elevated pulmonary expression of IL-25, previously implicated in the *Schistosoma mansoni*-induced pulmonary fibrosis, was also noted in IPF patients [45].

4.2. Skin fibrosis

Skin fibrosis is the chief clinical manifestation of systemic sclerosis (SSc) and local forms of scleroderma including morphea [46,47]. SSc causes fibrosis of the skin and other internal organs. On the other hand, morphea is a fibrotic condition limited to the skin and subcutaneous tissues. While the pathogenesis of SSc remains unclear, the characteristic feature of this condition as characterized by thickened dermis is caused by excessive deposition of ECM [48]. The expression of components of the ECM, particularly type I collagen, is increased in the sclerotic lesions of SSc patients [48].

Cytokines have been associated with the pathogenesis of skin inflammation and fibrosis. However, our understanding of cytokine dysregulation in skin fibrosis lags far behind than other organs due to lack of reliable animal models of SSc. IL-17 is implicated in the pathogenesis of bleomycin-induced skin fibrosis [37,49–51]. These observations are in line with studies showing that IL-17 deficient mice display diminished fibrosis in inflammatory skin models [52]. In this system, IL-$17^{-/-}$ mice showed reduced infiltration of inflammatory cells in the skin in conjunction with reduced transcript expression of profibrotic growth factors including CTGF, TGF-β and ICAM-1. Overall, these data suggest that IL-17 acts as a profibrotic cytokine via augmenting inflammation and TGF-β-dependent enhanced collagen deposition in animal models of skin fibrosis.

Most but not all studies have noted increased number of Th17 cells and elevated level of IL-17 in the dermis of SSc individuals [53–58]. The dermal expression of high IL-17E and low IL-17C identifies a fibrosis-specific motif in patients with SSc and morphea [59]. How IL-17 contributes to skin fibrosis is poorly understood. Available evidence

suggests that IL-17 drives the proliferation of dermal fibroblasts and induces the expression of IL-6, IL-8, MCP-1 and MMP-1 [54,60].

However, nagging discrepancies exist regarding the role of IL-17 in skin fibrosis in patients with SSc. An inverse correlation was demonstrated between IL and 17^+ cell numbers and skin thickness of SSc patients, indicating an antifibrotic role for IL-17 [61]. IL-17 reduces collagen production and α-SMA expression induced by TGF-β1 [61]. Moreover, the antifibrotic function of IL-17 is relied on the upregulation of miR-129-5p and the down-regulation of CTGF and type I collagen [58]. The reason for these discrepancies between these findings in patients with SSc is currently unclear. Genetic predisposition, patient heterogeneity and environmental factors including the differences in skin microbiota content may account for the inconsistencies observed between studies in SSc subjects.

4.3. Liver fibrosis

Liver fibrosis is one of the primary causes for morbidity and mortality with about 1.5 million deaths per year reported worldwide [62]. The key etiologies for liver fibrosis include fatty liver, chronic viral infection, biliary track disease, autoimmune disease, and toxic exposure [62]. One of the primary event in the initiation of hepatic fibrosis is the activation of hepatic stellate cells (HSCs) [63], which results in the overproduction of ECM. The activation of HSC is a highly regulated process involving multiple cytokines and growth factors produced by liver infiltrating immune cells and hepatic cells [64,65].

Data from multitude of studies have implicated IL-17 in the promotion of liver fibrosis in numerous mouse models of hepatic diseases including cholestatic liver disease, non-alcoholic fatty liver disease and schistosomiasis [66–72]. In these settings, levels of IL-17 and IL-17RA were increased in the injured liver compared to control animals. The increased level of IL-17 facilitates the influx of inflammatory cells, drives the expression of profibrogenic growth factors and activates hepatic stellate cells in the liver [66–72]. The liver infiltrating inflammatory cells in turn induce the production of profibrotic cytokines such as TNF-α, IL-6, IL-1 and TGF-β1. IL-17 dependent hepatic stellate cells activation is primarily mediated by the $IL\text{-}17^+$ T cells and neutrophils in the liver. IL-17 also drives the production of type I collagen in hepatic stellate cells in a Stat3 dependent manner [66]. Similarly, elevated levels of IL-17 were also found in the fibrotic livers of patients with Hepatitis B virus and cirrhosis related liver damage [73]. Overall, these reports suggest IL-17 as a profibrotic cytokine following various forms of liver injury.

4.4. Renal fibrosis

The incidence of chronic kidney diseases (CKD) is increasing worldwide (estimated 8–16% of individuals affected by CKD) in an alarming rate (www.cdc.gov). The prevalent etiologies of CKD progressing to end stage renal diseases are hypertension and diabetes mellitus in adults and obstructive nephropathy in children [74]. Moreover, CKD are associated with an inflammatory component, displaying a robust correlation with the progression of renal fibrosis and the eventual decline in the kidney function.

Recently a connection between renal fibrosis and IL-17 has been suggested. IL-17 produced by kidney-infiltrating $\gamma\delta^+$ T and Th17 cells drives renal fibrosis in a mouse model of unilateral ureteral obstruction (UUO) [75]. In this setting, IL-17 contributes significantly to the pathogenesis of renal fibrosis by regulating RANTES-mediated inflammatory cell infiltration in the renal parenchyma. Accordingly, neutralization of IL-17 in wild type mice yielded similar benefit confirming the pathogenic role for IL-17 in the development of fibrosis in CKD. This observation is in line with a previous finding showing that IL-17R expression in monocytes and macrophages is required for ECM deposition in the obstructed kidney [76]. However, this report failed to assess the role of IL-17R signaling in non-hematopoietic cells, where IL-17 signaling dominates.

In contrary, a recent study has linked IL-17 deficiency to exaggerated fibrosis following UUO [77]. In this report, IL-17 was shown to inhibit TGF-β-induced renal fibroblast activation and ECM synthesis, and sequentially kidney fibrosis, *via* downregulation of SMAD-independent pathway. Study from our group observed a similar protective function of IL-17RA signaling in the obstructed kidney. In this system, IL-17 mediated antifibrotic effect can be attributed to the increased expression of renal protective Kallikrein-kinin system in the UUO kidney (data not shown). The obvious disagreement between Peng et al. and our findings cannot be ascribed to a difference in IL-17 producers-driving gut microbiota, as antibiotic treatment showed minimal impact on TF development during uretral obstruction UUO. The antifibrotic role for IL-17 was further supported by a study in deoxycorticosterone acetate plus angiotensinII-induced hypertension induced progressive renal fibrosis model. In this system, IL-23/Th17-axis activation protects kidney against fibrotic changes [78,79].

Diabetes mellitus is one of the primary cause for renal failure, with estimates of > 45% of new cases requiring dialysis [80]. Diabetic nephropathy is generally characterized by chronic inflammation and fibrosis [81,82]. Diminished IL-17 levels were observed in urine and plasma samples of patients with advanced diabetic nephropathy [83]. Administration of a low dose therapy of IL-17 prevented and reversed established nephropathy in genetic models of diabetes. Additionally, renal tubular epithelial cells-specific overexpression of IL-17 suppressed the diabetic nephropathy in a Stat3-dependent manner. The protective effect of IL-17 was also noted with the administration of low doses of IL-17F but not with IL-17C or IL-17E. Interestingly, treatment of streptozotocin (STZ)-induced diabetic mice with mycophenolate mofetil selectively suppresses renal IL-17 producing cells and ameliorates renal fibrosis [84].

4.5. Intestinal fibrosis

Intestinal fibrosis is a grave complication in inflammatory bowel disease (IBD) in adults and children [85]. IBD comprise Crohn's disease (CD) and ulcerative colitis (UC), that are mainly characterized by localized chronic inflammatory response followed by fibrosis [86]. In CD, fibrosis is seen in the mucosa and submucosal layers of the entire gastrointestinal tract. Whereas, fibrosis is restricted to the mucosal and submucosal layers of only the large bowel in UC. The increase in deposition of fibronectin or collagen leads to the formation of intestinal strictures and causes obstruction in the GI tract of IBD patients [85,86].

Despite the surprising protective function of IL-17 in mouse model of colitis [87–89], several clinical and experimental studies have indicated a potential pathogenic role for the members of IL-17 cytokine family in intestinal fibrosis. Studies have reported upregulation of IL-17 in the strictured gut of CD patients [90]. Also patients with active CD exhibited elevated level of fecal IL-17 and an increased frequency of IL-17 producing cells in the lamina propria [90]. Several studies have suggested that IL-17 directly interacts with colonic IL-17R expressing myofibroblasts and contributes significantly for stricture development in CD [91–93]. Accordingly, gut-resident fibroblasts exhibit reduced migration capacities and produce increased levels of collagen and TIMP1 in response to IL-17 stimulation. Another recent study demonstrated an increased expression of heat shock protein 47 (HSP47) and IL-17 in the intestine of CD patients [94]. *In vitro* stimulation of IL-17 induced HSP47 as well as type I collagen in human intestinal myofibroblasts. Consistently, knocking down HSP47 lowered the IL-17 driven type I collagen expression in these cell types. In normal intestinal tissue constitutive expression of IL-23 and IL-17 is required for the protection of epithelial barriers and tight regulation of bacterial colonization of the gut [95]. Interestingly, in a TNBS-induced murine model of acute and chronic colitis, it was shown that a p40 targeting peptide vaccine against IL-23 resulted in a marked decrease in collagen deposition [96].

4.6. Atherosclerosis

Chronic vascular inflammation plays a vital role in the pathogenesis of atherosclerosis [97]. IL-17 controls atherosclerosis by triggering numerous signaling pathways in the endothelial and smooth muscle cells of blood vessels leading to chronic vascular inflammation. Existing studies document both atherogenic and atheroprotective role for IL-17 in the pathogenesis of atherosclerosis. Mice deficient in ApoE and fed high fat diet showed elevated levels of IL-17 and increased frequency of IL-17 producing cells in the atherosclerotic plaque. $ApoE^{-/-}$ mice lacking IL-17 signaling demonstrated an atherogenic role for IL-17 in atherosclerosis [98–100]. IL-17 induced the expression of cytokines, chemokines and MMPs from endothelial cells, essential for the infiltration of pathogenic neutrophils and monocytes/macrophages in the aorta [26,98–101]. Moreover, IL-17 drives the apoptosis of endothelial cells and augments endothelium-mediated von Willebrand factor production, which promote endothelial cell dysfunction and platelets adhesion and aggregation, respectively [98]. Supporting the mouse model studies, higher level of IL-17 is noted in the atherosclerotic tissue of symptomatic patients with carotid stenosis than asymptomatic patients and healthy individuals [102]. The patients with stable angina also exhibit increased number of peripheral Th17 cells and levels of Th17 related cytokines than healthy volunteers [103].

A single report showed that, $ApoE^{-/-}$ mice deficient in IL-17 developed larger atherosclerotic lesion in the aortic arch following high fat diet, indicating that IL-17 had a site-specific effect [104]. The atheroprotective effect was attributed to the ability of IL-17 to maintain the stability of plaque by inducing the proliferation of smooth muscle cells and inhibiting monocyte adherence to the plaque by down-regulating VCAM1 expression in the endothelial cells. Likewise, in a study including 981 patients with myocardial infarction (MI), high IL-17 serum levels were linked with low risk of mortality and recurrent myocardial infarction [105]. Importantly, VCAM1, a potential biomarker for atherosclerosis, was also diminished in these patients [106]. The atherogenic *vs*. atheroprotective effects of IL-17 may depend on the variable expression of IL-17 at different stages of the disease with highest expression at the very early stages followed by a reduction in the IL-17 level at the advanced stages of atherosclerosis. Moreover, the role of other IL-17 family cytokines needs to be addressed in the pathogenesis of atherosclerosis. Overall, a complicated and least understood role for IL-17 has been reported in these studies where IL-17 can have both protective and exacerbating effect on atherosclerosis development. More investigations are needed to explain these disparities.

5. Concluding remarks

Despite the unmet medical need there is no effective therapy to treat or hinder organ fibrosis, the leading cause of mortality in developed countries. However, the recently available treatments of fibrosis are insufficient, and new therapeutic approaches are needed. Since IL-17 demonstrate an antifibrotic function in an some organs, therapeutic avenues to block IL-17 signaling in these fibrosis related diseases can be tailored to target this pathway. An anti-IL-17 biologic (secukinumab) has recently been approved for the treatment of moderate to severe psoriasis [107–109]. Currently, ~90 clinical trials are ongoing to test IL-17 blockade clinically (clinicaltrials.gov). There are also other clinical trials planned or underway targeting other IL-17 pathway molecules such as IL-23p19 subunit, which is an important subunit of the IL-23R [110]. However, these clinical trials are underway in treatment strategies for autoimmune conditions such as psoriasis and multiple sclerosis amongst others. Thus far there are no reports of clinical trials using anti-IL-17 biologic for the treatment of fibrotic diseases. IL-17 has been shown to have both profibrotic as well as an antifibrotic role depending on the organ involved. Thus, extreme caution must be taken to treat autoinflammatory conditions with anti-IL-17 biologics in organs where IL-17 has an antifibrotic function. Moreover, thorough characterization of disease phenotypes is required to divide patients into those that may receive anti-IL-17 therapy and those patients where anti-IL-17 biologics may be contraindicated.

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