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REVIEW

Interleukin-17 pathways in systemic sclerosis-associated fibrosis

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Abstract

Fibrosis is unregulated tissue repair that may cause impairment of organ function, especially in end-organ damage. Systemic sclerosis (SSc) is the prototype systemic fibrosing disorder. Classical targets for fibrosis in SSc like transforming growth factor Beta (TGF-β), Interleukin-6 (IL-6), and multiple tyrosine kinases, have not yielded therapeutic benefit. There is multitude of evidence from across different tissues like the heart, lung, skin, liver, colon, and, to some extent, the kidney, that interleukin-17 (IL-17) and its downstream pathways are strongly associated with the initiation and propagation of fibrosis. Data from scleroderma patients, as well as from animal models of SSc, mirror these findings. Interestingly, hitherto unknown to be related to IL-17, newer molecules like Programmed Death-protein1 (PD-1), the phosphatase SHP2, along with known signal transducers like signal transducer and activator of transcription (STAT3), have been recently shown to be involved in the pathogenesis of fibrosis. Related molecules include the intracellular signalling molecules Ras/Erk, mammalian target organ of rapamycin (mTOR), and complement components. The biology of these pathways has not yet been fully elucidated to predict regulatory mechanisms, redundancies, and potential off-target effects. All these need to be better understood in the context of each other, in an effort to arrive at the optimal target to modulate fibrosis.

Keywords Interleukin 17 · T helper 17 · STAT3 · Fibrosis · Systemic sclerosis

Abbreviations

BAFF	B-cell activating factor
C3a	Complement component 3a
CCl4	Carbon tetrachloride
CCL5	Chemokine ligand 5
CTGF	Connective tissue growth factor
EMT	Epithelial-to-mesenchymal transition
ERK 1/2	Extracellular signal-regulated kinase 1/2
FGFR2	Fibroblast growth factor receptor 2
γδ T-cells	Gamma delta T cells
G-CSF	Granulocyte colony-stimulating factor
GD15	Growth/differentiation factor 15
GVHD	Graft versus host disease
IL	Interleukin
ITIM	Immunoreceptor tyrosine-based inhibitory motifs
MAPK	Mitogen-activated protein kinase
MMP-1	Matrix metalloproteinase-1
mRNA	Messenger ribonucleic acid
NET	Neutrophil extracellular traps
NLR	NOD-like receptor
NLRP-3	NOD-like receptor (NLR) family pyrin containing domain 3
NF-κB	Nuclear factor kappa B
PD-1	Programmed cell death 1
RANKL	Receptor activator of nuclear factor kappa B ligand
SH2	Src homology 2
SSc	Systemic sclerosis
Stat-3	Signal transduction and activator of transcription-3
TGF-β	Transforming growth factor beta
Th	T helper cell
TLR	Toll like receptor
TNF-α	Tumor necrosis factor alpha

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Treg	T regulatory cell
TSA	Trichostatin A
Tsk-1	Tight skin mouse 1

Introduction

Systemic sclerosis (SSc) or scleroderma is the prototype systemic fibrosing disorder [1]. The ensuing fibrosis of the skin can be disfiguring, affecting functionality and quality of life, whereas, fibrosis of internal organs and the associated vasculopathy can lead to severe morbidity and increased risk of mortality. Efforts have been ongoing for decades; however, we are yet to develop a drug that can halt the relentless claws of fibrosis in scleroderma. Normally, fibrosis is part of the healing process. At sites of injury, there is deposition of extracellular connective tissue (the most abundant being collagen). In SSc, there is an unregulated repair process in response to endothelial injury. Classically, the Transforming Growth Factor beta (TGF-β) pathways (both canonical and non-canonical) have been implicated in fibrosis, and numerous attempts have been made to target these pathways in SSc [2]. Though myriad preclinical experiments demonstrated benefit of blocking TGF-β in animal models of scleroderma, most human trials targeting this cytokine did not meet their primary end-points [3].

Thus, there is a need to understand the pathogenesis of SSc in greater depth, and identify more feasible targets to halt fibrosis. A drug successful in SSc may have far-reaching consequences, since fibrosis is the final common pathway associated with end-organ damage in almost all tissues, whether renal, hepatic (cirrhosis), neuronal (glial fibrosis), cardiac, or any other organ. Recent insights into the pathogenesis of SSc have demonstrated the role of neutrophil extracellular traps (NETosis), inflammasome activation, endosomal TLR (Toll like receptor) activation, leading to interferon production, and M2 polarized macrophages, and resultant fibrosis [4]. The roles of cytokine mediators such as interleukin-6 (IL-6), TGF-β and downstream pathways, serotonin (via serotonin receptor 2b), are already well known, and have been therapeutically explored with little success [5]. Similarly, evidences that interleukin (IL)-6 might drive TGF-β signalling culminated in the faSScinate trial in SSc [6]. Interestingly, IL-6 leads to the phosphorylation of the transcription factor STAT3 (signal transduction and activator of transcription-3), which, in turn, induces the polarization of naïve T cells towards a T helper 17 (Th17) phenotype. Skin biopsies from SSc patients have been reported to have high levels of expression of the cytokine IL-17 (a major source of which are Th17 cells), and its receptors [7]. Increased serum IL-17 levels have been reported in SSc patients, with higher levels in those having diffuse cutaneous involvement, and in those having interstitial lung disease [8]. Nevertheless, the exact role of IL-17, or the IL-6-STAT3-IL-17 axis has not yet been fully deciphered. Thus, we have reviewed the available literature on Interleukin-17 and fibrosis in different tissues as well as in animal models, and attempted to construct a hypothetical web of interlinked pathways leading to fibrosis.

Search strategy

A search of SCOPUS, MEDLINE, and Pubmed Central was carried out on the 28th of November 2018 with the keywords: interleukin-17, and fibrosis, as per previously published guidelines for writing narrative reviews [9]. The search was limited to articles in English, and preference was given to original articles published in the last 5 years. Reviews, abstracts and conference proceedings were not included. In addition, articles looking at possible mechanisms of action of proposed remedies were not included, unless specific blockers of IL-6, IL-17 or STAT3 were being used to explore these pathways. Of the 1032 search results thus derived, 70 were selected (Fig. 1). Based on the literature reviewed, we attempted to synthesize the different pathways identified into a single schematic to help identify nodes that could be potential future targets to inhibit fibrosis, including in the context of scleroderma.

Evidence for the involvement of IL-17 in human fibrotic disorders

It has been reported that the cytokine IL-27 can activate T lymphocytes from SSc patients to secrete IL-17, and this IL-17 further enhances the expression of the receptor for IL-27 on scleroderma fibroblasts, resulting in their stimulation by IL-27 to secrete greater amounts of extracellular matrix proteins [10]. Increased expression of messenger ribonucleic acid (mRNA), as well as protein levels of IL-17, has been reported in skin biopsies derived from SSc patients [7]. Furthermore, the IL-17A and IL-17F isoforms of IL-17 are elevated in scleroderma skin, when compared with skin

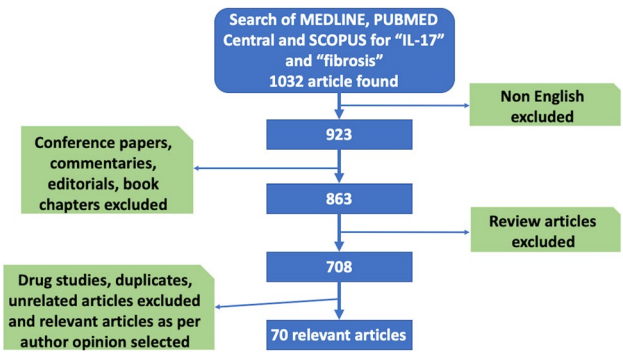

Fig. 1 Search strategy. Date of search: 28th November, 2018

biopsies from morphea patients [11]. Interleukin-35 has been reported in SSc patients—it increases the Th17–Treg ratio, and maybe a driver of the IL-17 fibrosis loop [12]. In the setting of keloids, a condition associated with exuberant, uncontrolled fibroblast proliferation, IL-17 has been reported to help maintain a niche of pro-fibrotic stem cells [13]. There is also indirect evidence of the role of IL-17 from patients with stem cell transplantation who develop scleroderma-like graft versus host disease (GVHD). In animal models of hematopoietic stem cell transplant, the use of granulocyte colony-stimulating factor (G-CSF), a potent stimulator of Th17 cell response with resultant IL-17A secretion, resulted in a scleroderma-like phenotype [14].

It has also been suggested that increased IL-17A in SSc serum and skin maybe due to a negative feedback mechanism, as a consequence of downregulation of the receptor for IL-17A, since the increased IL-17A has also been reported to paradoxically reduce CTGF (connective tissue growth factor) and collagen expression in SSc fibroblasts [15]. When fibroblasts from SSc patients are stimulated with IL-17 and TGF-β together, compared to TGF-β alone, there is a synergistic effect on activation of the mitogen activated protein kinase (MAPK), with increased production of IL-6, which is known to promote fibrosis. However, a paradoxical reduction in type 1 collagen and fibronectin secretion from these same fibroblasts was also seen, when both IL-17 and TGF-β were used, compared to TGF-β alone. This suggests that IL-17 may have a dual role, both driving fibrosis as well as regulating it, in the context of scleroderma [16]. As we shall subsequently see, other fibrotic scenarios also highlight such a dual role of IL-17 in fibrosis.

From humans to preclinical models: role of IL-17

Preclinical models of scleroderma and skin fibrosis

In the bleomycin-induced murine model of scleroderma, it has been reported that administration of bleomycin increases the expression of adhesion molecules, and subsequent recruitment of Th17 cells, and the cytokine IL-17, to the skin and lung tissue of such mice [17]. This was validated in another animal model of scleroderma, the tight skin mouse 1 (TSK-1) model, wherein blockade of IL-17 could reduce the severity of fibrosis, and similar observations were noted in the bleomycin-induced fibrosis model also [18]. Furthermore, IL-17 knockout could also reduce the severity of fibrosis mediated by IL-1 knockout in lungs and skin, in bleomycin as well as GVHD murine models of scleroderma [19]. It has been reported that IL-21 is a key cytokine driving IL-17-mediated fibrosis in bleomycin-induced fibrosis, and the cytokine B-cell activating factor (BAFF) plays a role downstream to IL-17 in this model [20–23]. Exogenous administration of IL-17 promoted scar formation in an excision wound model of murine fibrosis, in part due to increased recruitment of macrophages to the site of the scar [24].

Preclinical models of cardiac fibrosis

In a rat model of heart failure induced by subcutaneous injection of isoproterenol, IL-17 was identified as a critical mediator of myocardial fibrosis, via further downstream activation of the RANKL [receptor activator of nuclear factor kappa B (NF-κB) ligand], and increased secretion of MMP-1 (matrix metalloproteinase-1) [25]. Furthermore, by blocking IL-17 signalling through a lentivirus carrying IL-17 receptor antagonist in spontaneous hypertension model of rats, a reduction in cardiac fibrosis was noted, along with improvement of cardiac contractile function and compliance [26]. The activation of cardiac myofibroblasts via IL-17 was, in part, mediated through the intracellular mediators p38 MAPK (mitogen associated protein kinase) [27] and ERK1/2 (extracellular signal regulated kinase 1/2) [28], causing downstream activation of the proinflammatory NF-κB. IL-17 induced activation of p38 MAPK enhanced cardiac myocyte apoptosis, and this could eventually result in cardiac fibrosis [29]. In another murine model of hypertension induced by angiotensin II infusion, IL-1β from monocytes further stimulated IL-17 secretion from gamma delta T cells (γδ T-cells), which in turn resulted in cardiac myofibroblast activation, with consequent fibrosis. In another ischemia-induced rabbit model of heart failure, Th17 cells, via secreted IL-17, activated p38 MAPK and enhanced cardiac fibrosis, as well as increased the subsequent risk of ventricular arrhythmia. These adverse scenarios could be ameliorated using a monoclonal antibody against IL-17 [30]. In a cardiac transplantation model, TGF-β, secreted by T lymphocytes, was a key player in cardiac fibrosis and allograft rejection, and this could be abrogated by knocking out IL-17 in these mice [31]. In yet another mouse model of sterile pericarditis induced by intra-pericardial talc injection, blocking IL-17 reduced atrial fibrosis, and the risk of resultant atrial fibrillation [32]. Thus, IL-17 has been demonstrated to play a role in different models of cardiac fibrosis. However, there is literature to suggest that the cytokine IL-23, which plays a role in maintaining the population of differentiated Th17 cells (source of IL-17), has a protective role following myocardial ischemia. In a murine model of ischemic cardiac injury, knocking out IL-23 signalling resulted in decreased Th17 cells in the infarcted area, with disruption of Th1/Th17 ratio, unchecked Th1 lymphocyte activity, and increased cardiac injury and fibrosis [33]. Thus, while abrogating harmful effects of increased IL-17 on the cardiac myocyte may protect against cardiac fibrosis, similar intervention upstream of the source of IL-17 may have counter-productive effects also.

Preclinical models of renal fibrosis

Different types of insults, including obstructive uropathy, ischemic injury and toxic injury, can lead on to renal damage and resultant fibrosis. In an animal model of renal injury due to ureteric obstruction, Il-17, secreted by CD4+ T lymphocytes and γδ T lymphocytes, intensified the inflammatory infiltrate in the kidney, by increasing expression of the chemokine ligand 5 (CCL5 or RANTES), and resulted in greater severity of renal fibrosis [34]. Similar findings were observed in a rat model of ischemia reperfusion injury, wherein IL-17 secreted by CD4+ T lymphocytes and natural killer cells promoted renal fibrosis, which could be ameliorated by blocking this cytokine [35]. In a murine model of obstructive uropathy, the pro-inflammatory cytokine IL-36 was reported to activate the Nod-like receptor (NLR) family pyrin containing domain 3 (NLRP-3) inflammasome complex, an innate immune mechanism, which further resulted in increased activation of dendritic cells, stimulation of Th17 cells, expression of IL-23 and IL-17, and resultant interstitial fibrosis in the kidneys [36]. In the same disease model, the complement component 3a (C3a) could result in activation of T lymphocytes and subsequent IL-17 production, with resultant tubulointerstitial fibrosis [37].

The relationship between IL-17 and renal fibrosis is not as clear as in other models of end-organ damage. Despite an increase in renal expression of IL-17A in a murine model of ischemia–reperfusion injury, blocking this cytokine did not affect the consequent renal fibrosis [38]. Knocking out IL-17 in a murine obstructive uropathy model paradoxically exacerbated renal fibrosis, and in this particular model, IL-17 inhibited downstream effects of TGF-β on renal fibroblasts [39]. Similarly, in mouse models of diabetic nephropathy, knocking out IL-17 increased the severity of renal injury and fibrosis. Use of low-dose IL-17 had a preventative as well as therapeutic effect on diabetic nephropathy in such mice [40]. A possible reason for the protective effects seen with IL-17 in renal fibrosis could be explained by another set of experiments, wherein the histone deacetylase inhibitor Trichostatin A (TSA) was demonstrated to be therapeutic in a mouse model of obstructive uropathy. The use of TSA resulted in a decrease in renal fibrosis, with a reduction in the number of Th17 cells (which normally secrete IL-17), but an increase in the number of CD4+ FoxP3+ secreting IL-17, with demonstrable plasticity between these subsets further adding to the complexity of the role of IL-17 in renal fibrosis [41].

Preclinical models of peritoneal and gastrointestinal tract fibrosis

In a murine model of peritonitis, IL-17 was demonstrated to play a synergistic role along with TGF-β in driving peritoneal adhesions, and blocking IL-17 (but not TGF-β) helped reduce the severity of such peritoneal fibrosis [42]. It was further demonstrated in another mouse model that CD4+ T lymphocytes were the predominant source of such IL-17 in peritoneal fibrosis [43]. Two agents which reduced peritoneal dialysis induced fibrosis in animal models, paricalcitol (a stimulator of vitamin D receptor) and alanyl-glutamine peptide, did so in part by reducing levels of IL-17 [44, 45]. In a model of chronic colitis in rats induced by 2,4,6-trinitrobenzene sulfonic acid, the reparative phase was associated with increased fibrosis and colonic expression of IL-17 [46], and reduction of colonic fibrosis in this model by blocking TGF-β1 was associated with reduced numbers of Th17 cells, and decreased expression of IL-17 in the colon [47]. Thus, IL-17 plays a role in driving fibrosis in the peritoneal cavity, as well as the gastrointestinal tract also.

Preclinical models of cirrhosis

Cirrhosis is the end-result of fibrosis in the liver occurring due to hepatocyte damage, irrespective of the etiology of such damage. Animal models of liver cirrhosis attempt to replicate this scenario through multiple routes, such as direct exposure to toxin, or biliary obstruction. In a mouse model of liver cirrhosis induced by administration of the toxin carbon tetrachloride (CCl_4), the ensuing fibrosis could be reduced by co-administering 1, 25-dihydroxy Vitamin D3, and this acted in part by the reduction of infiltrating Th17 cells and decreased secretion of IL-17 [48]. In another murine model of excessive activation of the NLRP3 inflammasome causing liver fibrosis, genetic knockdown of IL-17A partially ameliorated fibrosis [49]. In murine cirrhosis induced by bile duct ligation, similar increases in IL-17 in the liver, along with the fibrogenic cytokines TGF-β1 and TGF-β2, were noted [50]. The proposed mechanisms by which IL-17 may drive liver cirrhosis in the CCl_4 injury and the bile duct ligation models include the induction of inflammatory cytokines IL-1, IL-6 (causing activation of the transcription factor STAT3) and tumor necrosis factor alpha (TNF-α), as well as of TGF-β1, with consequent stellate cell activation, which secrete collagen and result in fibrosis [51]. Blocking the receptor for IL-17A reduces the severity of inflammatory infiltrate and resultant liver fibrosis in the CCl4 injury model [52]. Apart from T lymphocytes, mast cells and neutrophils have also been proposed to be sources of the IL-17 responsible for the induction of fibrosis in models of cirrhosis [53].

Preclinical models of pulmonary fibrosis

Fibrosis plays a role in airway remodeling associated with the chronicity of asthma. In patients with moderate-to-severe asthma, there is increased expression of IL-17 and TGF-β in

the bronchial mucosa. While the former cytokine is reduced by oral corticosteroid therapy, this is not the case with TGF-β, resulting in ongoing collagen deposition and fibrosis despite therapy [54]. Eosinophils have been demonstrated to play a role in asthma, and when such eosinophils from asthmatic patients are stimulated ex vivo with IL-17, there is increased production of TGF-β, a process mediated by p38MAPK [55]. In in vitro cultures of human small airway epithelial cells, a synergistic effect of the cytokine IL-17 and growth/differentiation factor 15 (GD15) in driving epithelial-to-mesenchymal transition (EMT) in the presence of cigarette smoke extract has been demonstrated. Such EMT is a precursor to fibrosis, and higher levels of IL-17 and GD15 have also been demonstrated in the lungs of smokers with COPD [56]. NETs are extrusions from activated neutrophils which contain inflammatory mediators, and these have recently been recognised to play a role in fibrosis, including lung fibrosis. It was demonstrated that NETs secreted by neutrophils stimulated with toxins such as cigarette smoke contained IL-17. While IL-17 alone could not differentiate lung fibroblasts into myofibroblasts, it could do so when present along with deoxyribonucleic acid and histones in the NETs generated by such neutrophils [57]. Lung injury and resultant fibrosis can also occur following bone marrow transplant. In a murine model of post-bone marrow transplant pneumonitis and lung fibrosis, blocking IL-17 had beneficial effects on lung fibrosis [58]. A recent study described an association between pulmonary fibrosis and increased expression of the programmed cell death 1 (PD-1) molecule on CD4+ lymphocytes (mainly Th17 cells), leading to STAT3 activation that further leads to increased TGF-β and IL-17A production [59]. Such cells were identified in patients of idiopathic pulmonary fibrosis and sarcoidosis, as well as in the bleomycin-induced murine model of lung fibrosis. Co-culturing human PD-1 + CD4+ cells with human lung fibroblasts resulted in increased deposition of collagen and other extracellular matrix proteins. Furthermore, knocking out PD-1 in these mice ameliorated the severity of lung fibrosis. These experiments identified PD-1 as a potential new target to reduce fibrosis [59].

Exploring new therapeutic targets for fibrosis along the IL-17 pathway

Having looked at the evidence for the role of IL-17 pathway in driving fibrosis in different disease states, it is reasonable to conclude that this cytokine has been implicated as a player of fibrosis in most organs of the body, except for the kidney. In the latter, there are evidences both for and against the role of IL-17 pathway in driving renal fibrosis, and, probably, the IL-17 secreted at a lower concentration, possibly from FoxP3 positive cells, may be anti-fibrotic [40, 41]. This is not at all surprising, since redundancy of biological pathways is a common occurrence. Therefore, there may be a need to explore molecules and transcription factors that lie before and after IL-17, or work in synergism with the same, as therapeutic targets.

STAT3/PD-1 as targets for fibrosis

STAT3, upstream of IL-17, can be potentially a target for ameliorating fibrosis. It is induced by the canonical pathway of TGF-β, and numerous pathways driving fibrosis, including those involving the kinases JAK, JNK, c-ABL and SRC, converge on STAT-3. Furthermore, increased STAT-3 signalling has been demonstrated in activated fibroblasts of patients with scleroderma [60]. But it should be remembered that STAT3 is central in various processes like cellular proliferation, therefore, caution should be exercised while inhibiting this transcription factor due to fear of off-target effects. Strategies to selectively target STAT-3 in activated fibroblasts may need future exploration.

PD-1 has been classically described as a marker of T lymphocyte "exhaustion", wherein the PD-1-expressing T cell loses most of its proliferative and pro-inflammatory properties. But recent literature has uncovered functions of PD-1 beyond exhaustion [61]. It is increasingly being recognised that PD-1 + T cells have been switched from an pro-inflammatory into a reparative role (as opposed to the previous thought of them roaming around "exhausted"). This makes sense in the light of the data mentioned earlier in the review that PD-1 is linked to fibrosis. The success stories of PD-1 inhibition are exemplified the 2018 Nobel prize in Physiology or Medicine being awarded for negative checkpoint inhibition. However, PD-1 inhibitors only have demonstrable favourable effects in a specific population of patients with refractory malignancies, and can precipitate autoimmune disease in almost one-half of them [62]. This brings to light an ethical concern, i.e., whether, for non-malignant conditions like fibrosis, is it worth risking a new autoimmune or endocrine disease? Thus, PD-1 may not be a favourable molecule for non-selective targeting, and future therapeutic strategies exploring PD-1 inhibition in fibrotic states might require optimisation for specific targeting of this molecule at sites of fibrosis. Furthermore, PD-1 is upstream of SHP2 and it is logical to assume similar or more redundant pathways and off-target effects.

SHP2 as an anti-fibrotic target

It is noteworthy that PD-1 works through Immunoreceptor tyrosine-based inhibitory motifs (ITIMs) that recruit SHP2, a ubiquitous tyrosine phosphatase containing Src Homology 2 (SH2) domains, amongst others. Recently, Zehender et al. demonstrated that SHP2 controls STAT3-induced

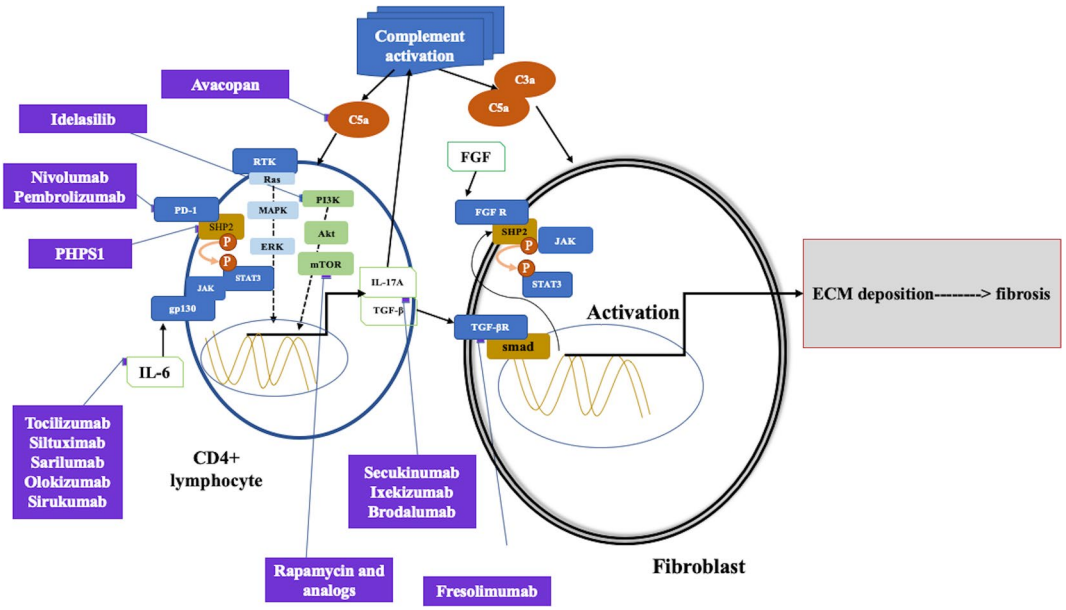

Fig. 2 Various pathways driving fibrosis in different human disease states and potential targets for anti-fibrotic therapy [3, 62, 76–82]

fibroblast activation and fibrosis [63]. Thus, SHP2 is present both upstream (in CD4+ lymphocytes) and downstream (in fibroblasts) of TGF-β signalling. Logically, this makes it an attractive target for therapy. Inhibition of SHP2 will also inhibit fibroblast activation via fibroblast growth factor receptor 2 (FGFR2) [64]. This simplistic viewpoint needs to be modified in the light of knowledge that, in the presence of TNF-α, SHP2 attenuates the IL-6 induced STAT3 activation via gp130 [65]. Thus, SHP2 inhibition may paradoxically increase STAT3 activation if TNF-α is present in the milieu. Though another recent paper has demonstrated that SHP2 upregulates STAT3 via dephosphorylation of JAK2, in the setting of Noonan syndrome, activated SHP2 downregulates phosphorylation of STAT3 [66]. While downregulation of STAT3 should decrease cellular proliferation, it must also be kept in mind that SHP2 also acts as a protooncogene in breast cancer [67]. SHP2 inhibits both Ras/ERK [68] and Akt/mTOR pathways both of which are implicated in fibrosis. SHP2 has also been observed to be involved in DNA repair pathways including damage checkpoints [69]. Thus at present, understanding regarding SHP2 mediated actions is far from perfect. Though it appears to be a potentially viable target, a more in-depth exploration of all of its regulatory mechanisms, of parallel redundant pathways, and all of its targets is required before targeting of this molecule can be translated clinically.

Complement anaphylatoxins and IL-17

In SSc, complement activation is well known, but is often ascribed to vasculopathy. But the role, if any, of complement activation in fibrosis is still unknown. It has been reported that both TGF-β [70] and IL-17A [71] activate complement during lung fibrosis. IL-17 knockout or blockade reduces bleomycin induced complement activation in the mouse model [71]. C3a and C5a are complement components that can instigate an inflammatory reaction, and hence are often referred to as the anaphylatoxins. C5a has been reported to induce plasticity of CD4+ cells into a Th17 phenotype, in a background of chronic graft versus host disease [72]. Blockade of C3a and C5a receptors have been reported to abrogate endothelial to myofibroblast transition [73] and reduce interstitial fibrosis [74] in diabetic renal fibrosis. Similar blockade of C3a and C5a attenuates lung fibrosis in the murine bleomycin model [75]. The oral C5a receptor antagonist, Avacopan, was successful in a phase 2/3 clinical trial in ANCA associated vasculitis and is being explored in other conditions [76]. Thus, C5a pathway blocking agents safe for human use are already available. Their role may need further exploration in fibrotic states.

Conclusion

The review has identified the following nodal points related to IL-17 and fibrosis: IL-6, PD-1, SHP2, STAT3, IL-17A, and C5a/C3a. In the case of renal fibrosis, there is conflicting evidence, since low-dose Il-17 has also been reported to reduce renal fibrosis [40]. Most of the literature, however, makes a strong case in favour of the role of IL-17 in fibrosis. The associated pathways have been summarised in Fig. 2 [3, 62, 76–82], with possible points of interventions with

currently available drugs also mentioned. However, the biology, control mechanisms, redundant pathways and potential off-target effects of PD-1, SHP2, STAT3, IL-17A, or C5a/C3a need to be better understood to have a clinically relevant and viable remedy to break the mesh of fibrosis. We may be tantalizingly close! However, one needs to be cautious in drawing comfort from targeting only IL-17 pathways. We know that TGF-β, the most potent pro-fibrotic cytokine, mediates fibrosis through canonical (Smad2/3 dependent) as well as non-canonical pathways (ERK1/2, STAT3, MAPK etc.) [82]. Targeting non-canonical pathways may thus have potential to ameliorate fibrosis to some extent but not fully. Thus, targeting more than one node should also be explored, in the future search of the elusive holy grail of an anti-fibrotic agent.

Author contributions The conception and design of the study, acquisition of data, analysis and interpretation of data—SA, DPM, VA. Drafting the article—SA; Revising it critically for important intellectual content—DPM, VA. Final approval of the version to be submitted—SA, DPM, VA. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved—SA, DPM, VA.

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Compliance with ethical standards

Conflict of interest Sakir Ahmed declares that he has no conflict of interest, including no relationship with pharmaceutical companies. Durga Prasanna Misra declares that he has no conflict of interest, including no relationship with pharmaceutical companies. Vikas Agarwal declares that he has no conflict of interest, including no relationship with pharmaceutical companies.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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