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Role of Interleukin-6 Family Cytokines in Organ Fibrosis

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Abstract
Background: Organ fibrosis remains an important cause of high incidence rate and mortality worldwide. The prominent role of interleukin-6 (IL-6) family members represented by IL-6 in inflammation has been extensively studied, and drugs targeting IL-6 have been used clinically. Because of the close relationship between inflammation and fibrosis, researches on the role of IL-6 family members in organ fibrosis are also gradually emerging. ***Summary:*** In this review, we systematically reviewed the role of IL-6 family members in fibrosis and their possible mechanisms. We listed the role of IL-6 family members in organ fibrosis and drew two diagrams to illustrate the downstream signal transductions of IL-6 family members. We also summarized the effect of some IL-6 family members' antagonists in a table. ***Key Messages:*** Fibrosis contributes to organ structure damage, organ dysfunction, and eventually organ failure. Although IL-6 family cytokines have similar downstream signal pathways, different members play various roles in an organ-specific manner which might be partly due to their different target cell populations. The pathogenic role of individual member in various diseases needs to be deciphered carefully.

Introduction

Fibrosis which is characterized by excessive deposition of extracellular matrix occurs in various organs, including heart, liver, kidney, lung, skin, and so on. Fibrosis contributes to organ structure damage, organ dysfunction, and eventually organ failure [1]. Inflammation is an essential factor that triggers fibrosis, while fibrosis can be alleviated by inhibiting inflammatory factors [2].

Members of the classic interleukin-6 (IL-6) family which include IL-6, IL-11, IL-27, IL-35, IL-39, oncostatin M (OSM), leukemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF), cardiotrophin 1 (CT-1), and cardiotrophin-like cytokine have been found to act on stromal cells, monocytes, and inflammatory cells, and play an important role in the initiation, maintenance, and resolution of local and systemic inflammation. The receptors of IL-6 family cytokines are divided into signal transduction receptors (gp130, LIF receptor [LIFR], OSMR, WSX-1, IL-23R, and IL-12Rβ) which associate with Janus kinases (JAKs) and activate downstream JAK/signal transducer and activator of transcription (JAK/STAT) and mitogen-activated protein kinase (MAPK) cascades after binding with cytokine, and non-signal transduction receptors (IL-6R, IL-11R, CNTFR, and possibly CT-1R). All of IL-6 family cytokines rely on gp130 as a transduction subunit in the receptor complex (shown in Fig. 1). IL-6 and IL-11 first bind to their

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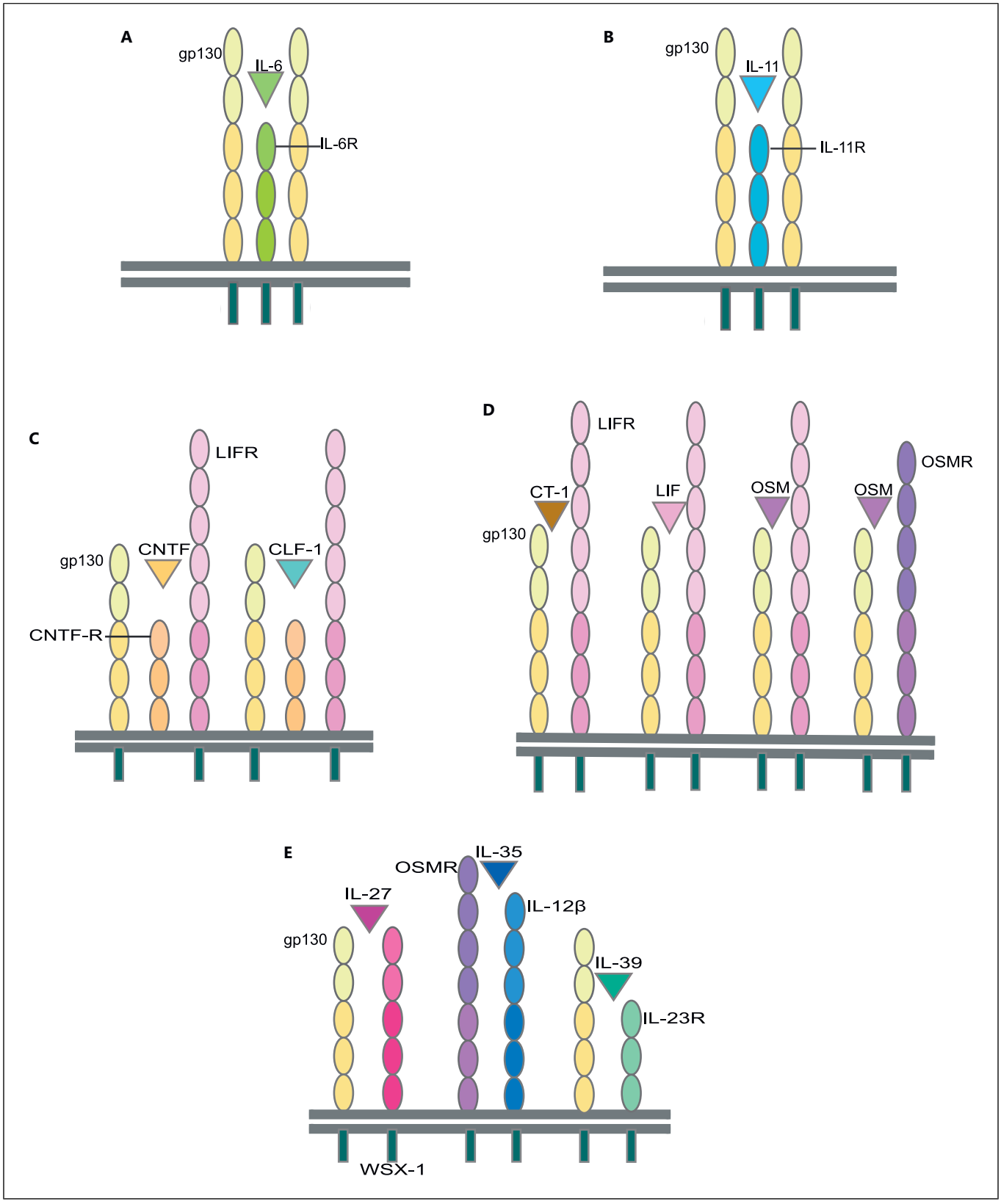

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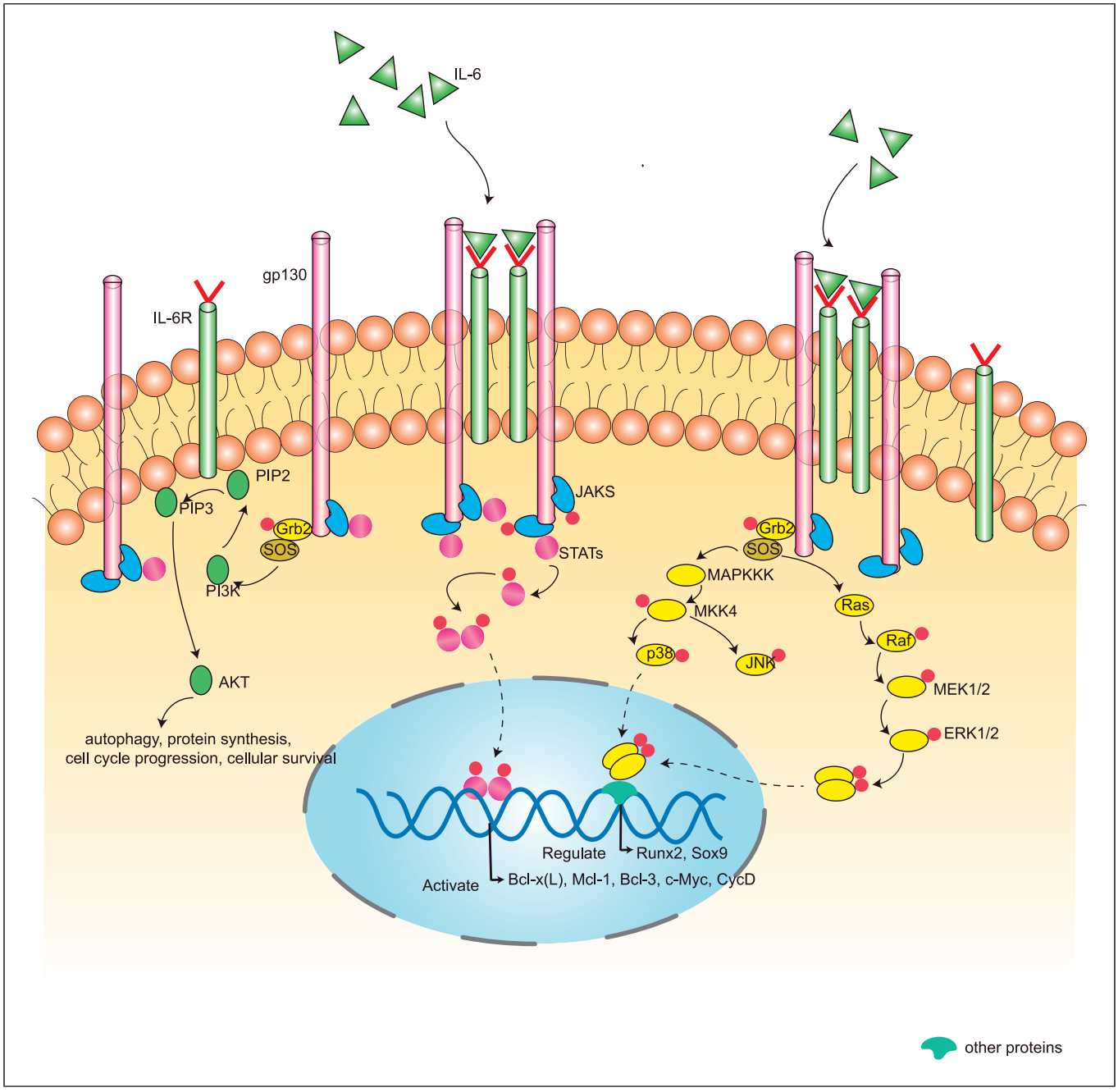

Fig. 2. IL-6 classical signal pathway: IL-6 binds to IL-6R (CD126) which has no kinase activity, and subsequently IL-6R dimerizes gp130, which leads to the activation of JAK/STAT and MAPK cascades. gp130, glycoprotein 130; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; PI3K, phosphatidylinositol 3-kinase; STAT, signal transducer and activator of transcription.

Fig. 1. Molecular construction of IL-6 family cytokine receptor complex. **A** In classical signal transduction, IL-6 binds to membrane binding receptor (IL-6R) and then to glycoprotein 130 (gp130) expressed on the same cell surface. **B** IL-11 binds to membrane binding receptor (IL-11R) and then to glycoprotein 130 (gp130) expressed on the same cell surface. **C** CNTF and CLF-1 use CNTF-R, LIFR, and gp130. **D** CT-1 and LIF signal through gp130 and LIFR. OSM can bind either to LIFR and gp130 or to OSMR and gp130. **E** IL-27 signals through gp130 and WSX-1. IL-35 binds to a heterodimer of receptor gp130 and IL-12Rβ, and IL-39 binds to a receptor comprising IL-23R and gp130.

Table 1. Antagonists of IL-6 family cytokines and their specificity

Cytokine	Antagonist	Role	Reference
IL-6	Sirukumab	A human anti-IL-6 monoclonal antibody that binds to IL-6 and prevents IL-6-mediated downstream effects	86
	Olokizumab		87
	Tocilizumab	A human monoclonal antibody that competitively inhibits the binding of IL-6 to its receptor (IL-6R)	88
	Sarilumab		89
	Olamkicept	Soluble human gp130 protein, targeting IL-6-sIL-6R complex to inhibit inflammatory signal pathway	43
IL-11	Anti-IL-11 Ab	A neutralizing IL-11 antibody	54
	Anti-IL-11Rα Ab	A neutralizing IL-11 Rα antibody	56
OSM	Anti-OSM Ab	Inhibit the phosphorylation and activation of STAT3, and improve tissue inflammation and fibrosis	69
LIF	LBP	A differentially spliced form of LIFR has been proved to improve the effects of LIF in goat radiocarpal joints in vivo	85
	LIF05		
	MH35BD	LIF mutant, which reduces the affinity to gp130 and retains the affinity to LIFR	

receptors IL-6R or IL-11R, respectively, and then form complexes with gp130 dimers. CNTF, cardiotrophin-like cytokine, and possibly CT-1 bind to CNTFR or CT-1R first and then form complexes with gp130 and LIFR heterodimers. LIF, IL-27, IL-35, and IL-39 bind to gp130 and their respective specific receptors LIFR, WSX-1, IL-12Rβ, and IL-23R. OSM binds to IL-12Rβ and gp130 with high affinity, and LIFR and gp130 also mediate OSM-induced signal transduction [3]. As mentioned above, IL-6 family cytokines have similar ligand receptor binding patterns and share common signal transduction molecule gp130. They activate similar signal pathways (shown in Fig. 2) and have overlapping biologic activities. Although the involvement of IL-6 family members in inflammation is clear, their roles in organ fibrosis are complicated. Different members were likely to play different or even contradictory roles in different organ fibroses. Therefore, it is necessary to analyze the role of each member in the fibrosis of different organs. Table 1 summarizes the role and related research of IL-6 family cytokines.

IL-6 in Organ Fibrosis

IL-6 Signaling

The signal transduction of IL-6 can be divided into classic signaling and trans-signaling according to its binding receptors. IL-6 binds to IL-6R (CD126) which has no kinase activity, and subsequently IL-6R dimerizes gp130, which leads to the activation of JAK/STAT and MAPK cascades. There are two types of IL-6R. Membrane IL-6R, expressed only by a few cells (including hepatocyte and lymphocyte subsets), transmits the classic signaling. Therefore, the classical signal pathway transmitted by IL-6 is limited to specific cells. Another kind of IL-6R is soluble IL-6R (sIL-6R), which is released by proteolytic cleavage of membrane IL-6R or by translation from alternatively spliced mRNA, and transmits the trans-signaling. IL-6 binds to sIL-6Ra to form IL-6-sIL-6R complexes and then activates intracellular signaling through gp130. Since almost all cells express gp130, [4], the trans-signal of IL-6 can exist in nearly all cells.

IL-6-Mediated Organ Fibrosis and Possible Mechanisms

Some studies have demonstrated that trans-signaling of IL-6 plays a pro-inflammatory role, while others proved that it plays an anti-inflammatory role. Soluble signal transduction protein gp130 (sgp130) was detected in human plasma, which can bind to IL-6/sIL-6R complex and block IL-6 trans-signal transduction [5]. Sgp130fc showed significant anti-inflammatory effects in mouse models of arthritis and colon cancer [6, 7]. Some studies have proved that in the air pouch mouse model of acute inflammation, the infiltration of neutrophils and macrophages and the expression of MCP-1 in sgp130fc transgenic mice are lower than those in wild-type (WT) mice [5].

However, some scholars have proved that IL-6 plays an anti-inflammatory role. Xiaoling Jin et al. defined the in vivo effects of IL-6 on the intestinal tract by injecting CHO cells stably overexpressing IL-6 into female athymic nu/nu mice and implanting osmotic minipumps delivering recombinant murine IL-6 (1 ng/h) subcutaneously in 6–8-week-old male C57BL/6J mice. High-dose IL-6

administration over 7–10 days resulted in intestinal hyperplasia in small bowel mass and in intestinal villus height. Pulse bromodeoxyuridine labeling demonstrated prolonged enterocyte lifespan and slowed enterocyte migration rates in IL-6-treated mice. Furthermore, IL-6-treated mice showed less intestinal injury and improved barrier function following ischemia-reperfusion (IR) of the small bowel [8]. DnKO mice are an established model of colonic inflammation. Kuhn and his colleagues demonstrated that injection of IL-6 neutralizing monoclonal antibody into dnKO mice could induce mucosal damage because of diminished epithelial proliferation [9]. CCN1 is known to function in wound healing, $Ccn1^{dm/dm}$ knock-in mice expressing a CCN1 mutant, exhibited high mortality, impaired mucosal healing, and diminished IL-6 expression during the repair phase of dextran sodium sulfate-induced colitis compared with WT mice. In JS Choi's research, rIL-6-treated $Ccn1^{dm/dm}$ mice stimulate intestinal epithelial cell regeneration and inhibit epithelial cell apoptosis [8–10]. These studies prove that IL-6 plays a protective role in enteritis mainly by promoting epithelial cell proliferation. Nevertheless, no specific trans-signaling blocker or classic signaling activator was used in these studies. The different roles of two IL-6 signaling in inflammation suggest that they may also exert different functions in fibrosis.

A number of studies confirmed the profibrotic role of IL-6 in cardiac disease. Injection of IL-6 into male Sprague-Dawley rats for 7 days led to increased collagen expression in cardiac disease. Ventricular hypertrophy and fibrosis induced by pressure overload, high salt diet, or angiotensin II were reduced in IL-6 knockout (KO) mice [11, 12]. Myocardial remodeling induced by myocardial infarction was significantly alleviated in IL-6 KO mice, which may be related to the activation of M2 macrophages [13]. Another study also found that IL-6 promoted aldosterone-induced cardiac fibrosis by promoting macrophage infiltration [14]. Because IL-6 shows no measurable affinity to gp130, sgp130 did not affect IL-6 signaling via the membrane-bound IL-6R (classic signaling), but it efficiently blocked IL-6 trans-signaling [5]. Recombinant sgp130 can diminish myocardial fibrosis induced by aldosterone infusion, suggesting that the trans-signaling of IL-6 exerts its action in cardiac fibrosis [15]. These studies suggest that IL-6 plays a profibrotic role in cardiac fibrosis.

IL-6 was upregulated in renal fibrotic tissues induced by aldosterone/salt in rat and unilateral ureteral obstruction (UUO) in mice [16, 17]. Similarly, elevated IL-6 expression was observed in the kidney of chronic kidney disease (CKD) patients [18]. However, unlike the heart, IL-6 depletion did not reduce renal fibrosis induced by the UUO in comparison with WT mice [17]. This outcome may be due to the elimination of both the anti-inflammatory effect of classic signaling and the pro-inflammatory effect of trans-signaling of IL-6. In IL-6 KO mice, loss of pro-inflammatory trans-signal may reduce fibrosis. However, in the meantime, removing anti-inflammatory effect of classic IL-6 signaling might exacerbate renal fibrosis. Sgp130Fc is produced by fusing the whole extracellular part of gp130 with the Fc region of human IgG1. It is an effective inhibitor of IL-6 trans-signal transduction and has a stronger blocking effect on IL-6 trans-signal compared with sgp130. Renal fibrosis and inflammation induced by UUO and IR in mice were significantly reduced after Sgp130Fc treatment via reducing the activity of JAK/STAT3 signaling [19]. These studies showed that the trans-signaling of IL-6 plays a critical role in the development of renal fibrosis.

Systemic sclerosis is an autoimmune disease that mainly involves skin and lung, which is characterized by fibrosis of skin and internal organs [20]. IL-6 deficiency reduced inflammatory cell infiltration and fibrosis induced by treatment with topo I and Freund's complete adjuvant in mice, which may be in connection with the decrease of Th17 cell accumulation and the increase of Treg cell number [21]. Lipid mediator lysophosphatidic acid (LPA) and LPA-producing enzyme autotaxin had a positive role in dermal fibrosis. IL-6 was found to form a malignant amplification ring with LPA and autotaxin, thereby promoting fibrosis [22]. Tocilizumab (TCZ) is an IL-6 receptor-α inhibitors widely used in the treatment of rheumatoid arthritis. After 24 weeks of TCZ treatment, the expression profile of skin fibroblasts in patients with SSc tended to be normal; especially, the fibrosis promoting signal mediated by TGF was significantly reversed [23].

The expression of IL-6 increased in a variety of animal models of pulmonary fibrosis and human pulmonary fibrosis-related diseases [24, 25]. IL-6 was upregulated in lung fibrosis induced by silica exposure, bleomycin treatment, and radiation in mice [26–28]. IL-6 level in bronchoalveolar lavage fluid (BALF) was higher in nonspecific interstitial pneumonia/fibrosis than those in normal control subjects [24]. Chronic lung allograft dysfunction is a disease closely related to pulmonary fibrosis after lung transplantation. The histopathological manifestations of chronic lung allograft dysfunction are monocyte infiltration, peribronchial fibrosis, and apparent fibroblast proliferation [29]. IL-6 and sIL-6R levels in the BALF of patients with CODL were significantly higher than those in healthy controls [30]. IL-4, IL-5, IL-6, and Stat3 mRNA expressions in BALF of silica-

exposed mice were suppressed significantly after IL-6Rα siRNA-treatment, indicating that IL-6 promotes silica-induced pulmonary inflammation and fibrosis [26].

In order to study the role of IL-6 downstream signals in pulmonary fibrosis, gp130 mutant mice were used. $Gp130^{757F}$ mice carry the Y757F and V760A mutations and destroy the $pY_{757}xxV_{760}$ SHP2-binding domain, thereby abolishing the associated activation of the SHP2-Ras-ERK signaling cascade in response to IL-6 [31]. $Gp130^{\Delta Stat}$ mice deleted all YxxQ STAT-binding sites in the cytosolic domain of gp130 and are incapable of transducing STAT1/3-mediated activation [31, 32]. The phosphorylation of STAT3 was stronger in the liver of $gp130^{757F}$ mice injected with IL-6 than that of WT mice. Similarly, the phosphorylation of ERK was stronger in the liver of $gp130^{\Delta Stat}$ mice injected with IL-6 than that of WT mice [31]. Bleomycin-induced pulmonary fibrosis was much more severe in $gp130^{757F}$ mice than in $gp130^{\Delta Stat}$ mice and WT mice. Thus, IL-6 promoted pulmonary fibrosis through its downstream STAT3 rather than ERK signaling pathway. Further research shows that trans-nasal administration of HYPER-IL-6 (the fusion protein of IL-6 and the sIL-6R) promoted higher transcription level of Col1a1 gene in lungs of $gp130^{757F}$ mice compared to lungs of Stat3+/− mice or WT mice [33]. These results suggest that trans-signaling mediated by sIL-6R activating STAT3 is related to bleomycin-induced pulmonary fibrosis. Hyper-IL-6 rather than IL-6 induced the activation of STAT3 in human BAL-derived mesenchymal cells [30], suggesting that IL-6 trans-signaling may play a role in pulmonary fibrosis as well. In conclusion, the mechanism of IL-6 in pulmonary fibrosis is still in question, but it may be related to IL-6 trans-signaling and the activation of its downstream STAT3.

Clinical studies found that a higher serum IL-6 level was associated with more severe liver cirrhosis [34]. IL-6 expression was upregulated in liver fibrosis induced by chronic intermittent injection of carbon tetrachloride (CCl_4). KO of IL-6 attenuated liver fibrosis induced by CCl_4 [35]. Another study illustrated that pretreatment of CCl_4-induced fibrotic liver with IL-6 improves hepatic microenvironment and primes it for mesenchymal stem cell transplantation leading to enhanced reduction of liver injury and fibrosis [36]. Specific deletion of IL-6Rα in myeloid cells ($Il6raMye^{-/-}$ mice) and IL-6 KO mice showed decreased inflammation but increased fibrosis after high-fat diet feeding [37]. These researches showed the contradictory role of IL-6 in liver fibrosis. This may be related to liver fibrosis caused by different mechanisms in different models. Besides, the balance of two kinds of IL-6 signaling should be taken into account in liver inflammation and fibrosis.

IL-6 As a Therapeutic Target in Inflammation and Fibrosis

Therapy targeting IL-6 has been developed, which is mainly used in inflammation and autoimmune-related diseases such as rheumatoid arthritis and Crohn's disease [38]. At first, IL-6 monoclonal antibody failed to be used in clinic for the reason that its complex formed with IL-6 accumulated in the circulation and caused serious side effects [39, 40]. TCZ, a humanized anti-IL-6 receptor antibody, has been developed [41]. Clinical trials have proved the efficacy of TCZ in patients with rheumatoid arthritis, juvenile idiopathic arthritis, Castleman's disease, Takayasu arteritis, and giant cell arteritis [42]. In addition, other IL-6 targeted therapeutic drugs have been developed like sarilumab targeting IL-6R, olokizumab targeting IL-6, and olamkicept targeting the trans-signaling [43]. These drugs still have side effects of severe infection [44]. Few studies focused on the treatment of targeted IL-6 in fibrosis, except that TCZ may alleviate the skin fibrosis in systemic sclerosis which is mentioned above. Though IL-6 is involved in the formation of fibrosis through different mechanisms in heart, lung, kidney, liver, and skin, its multifunctional feature makes its blocker effect not accurate. In order to enforce medicines targeting the IL-6 and their use in precision medicine in fibrosis, more precise targets downstream need to be explored.

IL-11 in Organ Fibrosis

IL-11-Mediated Organ Fibrosis and Possible Mechanisms

In recent years, more and more scholars paid attention to the role of IL-11 in organ fibrosis. The research of IL-11 in cardiac fibrosis was carried out earlier. IL-11 level was elevated in the heart of mice with myocardial infarction induced by ligation of left coronary artery [45], in the heart of rat with cardiac fibrosis induced by high salt diet [46], and in the heart of mice with fibrosis induced by Ang II [47]. Serum IL-11 levels were elevated in patients with congestive heart failure, coronary heart disease, and thoracic aortic dissection [48–50]. These findings suggest that IL-11 plays an important role in cardiac fibrosis. However, animal experiments showed that IL-11 played a contradictory role in cardiac fibrosis, which is caused by species-specific recombinant IL-11 used. Administration of recombinant human IL-11 reduced the cardiac injury

in mice induced by myocardial IR [45]. Administration of recombinant mouse IL-11 (rmIL-11) to mice can aggravate cardiac injury and fibrosis caused by myocardial ischemia, while deletion of IL-11Ra1 gene in mice reduced such fibrosis. Recombinant human IL-11 showed a strong profibrotic effect on primary human myofibroblasts, while rmIL-11 showed a strong profibrotic effect on mouse fibroblasts [49]. Surface plasmon resonance experiments and competition ELISA showed that rhIL11 binds to the mouse IL11ra1 with a higher affinity than rmIL11 without activating mouse signaling pathways; thus, rhIL11 is an effective blocker of mouse IL11. These may explain the protective effect of rhIL11 in rodent models [51]. Interestingly, different from the classical signal pathway downstream of IL-6 family members, STAT3 is mildly and transiently phosphorylated after IL-11 stimulation in primary fibroblasts, while ERK is activated and required to induce profibrotic phenotypes [49].

Similarly, elevated levels of IL-11 were found in animal models related to renal injury and fibrosis and human renal diseases. Endogenous IL-11 was elevated in the early stage in two different models of renal fibrosis, UUO and IR injury [52]. The expression of IL-11 increased significantly in the injured kidney induced by renovascular hypertension rat, which was related to the markers of fibrosis [53]. As the same in the heart, rmIL-11 promoted fibrosis. The deletion of IL11ra1 in mice attenuated folic acid-induced renal fibrosis [49]. These results confirmed the fibrotic effect of IL-11 in kidney.

IL-11 also plays a promoting role in pulmonary fibrosis. Fibroblast-specific IL-11 transgene or subcutaneous injection of rmIL-11 induced pulmonary fibrosis. The deletion of IL11ra1 reduced the pulmonary fibrosis induced by bleomycin [54]. IL-11 promoted the activation of lung fibroblasts into myofibroblasts and stimulated the secretion of inflammatory factors and chemokines like IL-6, CCL2, CXCL1. IL-11 worked dependently on the phosphorylation of ERK [55].

IL-11 as a Therapeutic Target in Inflammation and Fibrosis

It has been proved that neutralizing IL-11 antibody can reduce lung inflammation and improve fibrosis by preventing the activation of lung fibroblasts and inhibiting the activation of ERK and SMAD in mice [54]. For liver fibrosis, intraperitoneal injection of anti-IL11 (x203) and anti-IL1RA (X209) in mice reduced nonalcoholic steatohepatitis and liver fibrosis caused by high-fat methionine and choline-deficient diet [56]. The research and development of IL-11 drugs will contribute to the treatment of fibrosis diseases [57].

In conclusion, IL-11 exerts consistent profibrotic effect in a variety of organs. It should be noted that the signal mechanism of IL-11 promoting organ fibrosis seems to be different from IL-6. IL-6 promotes fibrosis mainly by activating STAT3. However, the activation of ERK seems to be more important for IL-11.

OSM in Organ Fibrosis

OSM-Mediated Organ Fibrosis and Possible Mechanisms

OSM is mainly expressed in immune cells, including macrophages, neutrophils, and activated mast cells. Among the members of IL-6 family, OSM has the most extensive signal transduction spectrum, including JAK/STAT, MAPK, phosphatidylinositol 3-kinase/Akt. In human body, OSM combines to its specific type I receptor complex (LIFRβ/gp130) or type II receptor complex (OSMRβ/gp130) to activate the downstream signal. The important item should be noticed that human OSM can only bind murine LIFRβ and murine OSM can only bind its specific murine OSMRβ [58]. Therefore, inconsistent results often occur when mice are treated with human OSM or mouse OSM. For example, administration of human OSM mitigated the inflammation of RA in mice [59], while administration of the murine OSM in the synovial space resulted in increased infiltration of mononuclear cells [60].

OSM was elevated in some animal models related to renal fibrosis and human renal diseases. OSM expression was elevated in human obstructive kidney due to stones or carcinoma, suggesting a correlation between OSM expression and urinary obstruction-mediated renal fibrosis. The level of OSM and its receptor OSMR increased gradually with time in the early 12 h after UUO in mice [61]. Besides, in the kidney of OSMR$\beta^{-/-}$ mice, the crystal formation induced by glyoxylate was significantly reduced, together with downregulation of inflammatory cytokines and fibrosis markers (TGF-β, collagen1A2, and α-smooth muscle actin) [62]. These studies suggest that OSM is involved in the process of renal interstitial fibrosis. Extracellular experiments provide some possible mechanisms by which OSM promoted renal fibrosis. OSM inhibited the N-cadherin expression in human proximal tubular cells through ERK1/2 signaling, so as to promote the mesenchymal transformation of renal tubular epithelial cells [63]. OSM directly induced the expression of fibrosis markers and inflammation factors in renal fibroblasts [62]. However, it has been reported that OSM reduced the extracellular matrix expressed by

Table 2. Summary of studies with data on the role of IL-6 family in organ fibrosis

Cytokine	Organ	Experimental design	Findings	Promotes fibrosis	Reference
IL-6	Heart	Male C57BL/6J and interleukin-6-knockout (KO) mice were implanted with telemetry devices for blood pressure (BP) measurements, fed a 4% NaCl diet, and infused with either vehicle or Ang II (90 ng/min per mouse subcutaneously) for 8 weeks	Absence of interleukin-6 did not alter the development of Ang II-high salt-induced hypertension and cardiac hypertrophy, but it prevented the development of cardiac dysfunction, myocardial inflammation, and fibrosis	√	11
		Blockade of aldosterone by eplerenone and IL-6 Ab in an aldosterone infusion mouse model	IL-6 promoted aldosterone-induced cardiac fibrosis by promoting macrophage infiltration	√	14
	Lung	Allogeneic transplants were created by transplanting the left lung of a B6D2F1/J donor mouse (first-generation offspring between a DBA/2J and C57BL/6J) into a C57BL/6J or C57BL/6J IL6−/− recipient	The use of an IL-6-deficient recipient in a murine orthotopic transplant model of CLAD reduces allograft fibrosis by over 50%	√	30
	Liver	IL-6 KO and IL-6 receptor A (Il6ra) conditional KO mice with high-fat diet (HFD) feeding	Specific deletion of IL-6Rα in myeloid cells (Il6raMye−/− mice) and IL-6 KO mice showed decreased inflammation but increased fibrosis after HFD feeding	×	37
	Kidney	Male wild-type (WT) or IL-6KO mice aged 8–10 weeks were anesthetized by intraperitoneal injection of ketamine (80 mg/kg) and methylthiazide (10 mg/kg)	Targeted disruption of IL-6 has no significant effect on myofibroblast formation and a-SMA expression, and the severity of renal fibrosis	×	17
		Fc-gp130 was used to specifically block IL-6 trans-signaling. Unilateral ureteral occlusion (UUO) and ischemia-reperfusion (IR) mouse models were constructed to investigate the therapeutic effect of Fc-gp130 on renal fibrosis	Blockade of IL-6 trans-signaling with Fc-gp130 also reduced inflammation levels, immune cell infiltration, and profibrotic cytokine expression in renal tissue, with decreased STAT3 phosphorylation and reduced fibroblast accumulation in the renal tissue	IL-6 trans-signaling promotes renal fibrosis	19
IL-11	Heart	Twenty-four hours after coronary ligation, human IL-11 was administered intravenously for 5 days consecutively and was administered intravenously, followed by consecutive administration every 24 h for 4 days	IL-11 attenuated cardiac fibrosis after MI through STAT3	×	45
		Ten-week-old male mice and transgenic Col1a1-green fluorescent protein (GFP) reporter mice23 were subjected to daily subcutaneous injection with either 100 μg/kg of recombinant mouse IL-11 (rmIL-11) or an identical volume of saline for 21 days	Il-11 injection causes heart and kidney fibrosis and organ failure, whereas genetic deletion of Il11ra1 protects against disease	√	49
	Lung	rmIl-11 (100 μg/kg) was administered daily subcutaneously into transgenic mice that express GFP under the control of a Col1a1 promoter. Bleomycin was administered to Il11ra1−/− mice to examine the role of IL-11 in the progression of lung fibrosis	IL-11 receptor subunit alpha-1 (Il11ra1)-deleted mice, whose lung fibroblasts are unresponsive to profibrotic stimulation, are protected from fibrosis in the bleomycin mouse model of pulmonary fibrosis	√	54

Table 2 (continued)

Cytokine	Organ	Experimental design	Findings	Promotes fibrosis	Reference
	Kidney	Ten-week-old male mice and transgenic Col1a1-GFP reporter mice23 were subjected to daily subcutaneous injection with either 100 μg/kg of rmIL-11 or an identical volume of saline for 21 days	Il-11 injection causes heart and kidney fibrosis and organ failure, whereas genetic deletion of Il11ra1 protects against disease	√	49
		Two-kidney, one-clip renovascular hypertension (2K1C) was induced in rats. IL-11 expression was measured by real-time polymerase chain reaction in the left ventricle and the right kidney	Renal IL-11 expression of renovascular hypertensive rats is markedly increased and correlates with profibrotic markers and loss of function and might therefore serve as a biomarker for the severity of hypertensive nephrosclerosis	-	53
OSM	Lung	Mice were endotracheally administered 5 × 107 PFUs of either the replication-deficient adenovirus encoding OSM (AdOSM) or control vector AdDl70. Samples were collected after 5, 7, 14, and 28 days	AdOSM-treated BALB/c mice showed increased percentages of neutrophils and lymphocytes relative to naive and AdDl70-treated BALB/c mice. AdOSM induces mRNA for collagen in BALB/c mice in vivo	√	67
	Liver	For a mouse model of liver fibrosis, thioacetamide (TAA) was administered with drinking water (0.03% v/v) for 12 weeks. OSM KO mice were used	Genetic ablation of the OSM gene alleviated fibrosis in a mouse model of chronic hepatitis	√	68
	Kidney	A mouse model of renal crystal was formed by intraperitoneal injection of GOx using OSM receptor β (OSMRβ)-deficient mice (OSMRβ−/− mice)	Fibrosis markers (TGF-β, collagen 1a2, and α-smooth muscle actin) were decreased in the kidneys of OSMRβ−/− mice compared with those in WT mice	√	62
LIF	Heart	In vitro	Short-term LIF stimulation (24 h) had no effect on fibroblast proliferation and/or cell differentiation. Longer term LIF stimulation (48±72 h) increased fibroblast proliferation and significantly inhibited cardiac fibroblast differentiation into myofibroblasts	-	77
	Lung	For intratracheal instillations, a 24-gauge angiocatheter was placed into surgically exposed tracheas and guided into the left bronchus. A 50-μL bolus of saline con_x005f_x0002_taining ~10̊6 CFU *Escherichia coli* or 25 ng recombinant murine LIF was instilled through the angiocatheter into the left lung lobe	Anti-LIF completely eliminated lung LIF detection and markedly exacerbated lung injury compared with control mice	-	79
	Kidney	Kidney IR injury model and in vitro experiment	LIF participates in the regeneration process after tubular injury	-	81
		KM mice; one group received LIF (25 μg/kg sc daily) from days 0–6 after ligation and the other group received physiological saline solution as a control	LIF inhibited collagen type 1 and collagen type 3 expression in mice with UUO	×	80

Table 2 (continued)

Cytokine	Organ	Experimental design	Findings	Promotes fibrosis	Reference
		RNA-seq data from chronic kidney disease (CKD) patients were used to analyze transcript levels of IL6 family members. The UUO and the IR injury (IRI) were employed to validate the finding. To assess the role of LIF in vivo, short hairpin RNA, lenti-GFP-LIF was used to knock down LIF receptor (LIFR) and overexpress LIF, respectively. LIF-neutralizing antibody was used in therapeutic studies	The LIF-neutralizing antibody attenuated TIF induced by UUO and UIRI	√	83
IL-27	Skin	Serum levels of IL-27 in 91 patients with SSc and the production of IL-27 by isolated monocytes were examined by ELISA. The expression of IL-27 receptor in the skin fibroblasts, B cells, and T cells was quantified by real-time PCR	IL-27 stimulation increased proliferation and collagen synthesis of fibroblasts in patients with SSc compared with those in healthy controls	√	86
	Lung	For the pulmonary fibrosis model, 5 mg/kg bleomycin was dissolved in phosphate-buffered saline (PBS) buffer and administered to the mice intratracheally Either the mouse IL-27 recombinant protein (1 μg per mouse for 7 days) or anti-mouse IL-27 p28 functional grade purified antibody (200 μg per mouse for 1 day) was injected hypodermically	IL-27 potentially attenuates BLM-induced pulmonary fibrosis	×	88
	Kidney	UUO was performed on WT and IL-27Ra2/2 mice for 14 days	After UUO, IL-27 deficiency resulted in increased tissue injury and collagen deposition associated with higher levels of chemokine mRNA and increased numbers of M2 macrophages. Loss of the IL-27Ra led to increased infiltration of activated CD4+ T cells that coproduced IL-17A and TNF-a	√	87
IL-31	Skin and lung	A mini ALZA osmotic pump implanted in the skin pumped one of the following treatments continuously over 14 days: saline control, 200 ng of IL-31 per day, 800 ng TGFb per day, or IL-31 with TGFb	In mice, IL-31 induced skin and lung fibrosis	√	89
CT-1	Kidney	CT-1(100 μg/kg or 400 μg/kg) administration in CT-1−/− mice after 3 or 15 days of UUO	Obstructed kidneys from CT-1−/− mice show higher fibrosis than obstructed kidneys from WT mice. Administration of exogenous CT-1 prevents the increased fibrosis resulting from the genetic KO of CT-1 upon UUO	×	91
CLF-1	Lung	A volume of 200L of LIF 2.5 μg, PBS, or CLF-1/CLC 5 μg was instilled by a sterile 18-gauge catheter inserted in the trachea. After 15 min, the animal was euthanized and the lungs were inflation-fixed	Administration of CLF-1/CLC to both uninjured and bleomycin-injured mice led to the pulmonary accumulation of CD4(+) T cells. We also found that CLF-1/CLC administration increased inflammation but decreased pulmonary fibrosis	×	92

renal tubular epithelial cells treated with TGF-β in vitro. The author considered that OSM might play different roles under different conditions [64]. OSM participated in the inflammatory microenvironment in tumors through paracrine. About 70% clear cell renal cell carcinoma is related to the inactivation of von Hippel Lindau (VHL) tumor suppressor gene. In mice with VHL conditional KO in renal tubular, the kidney produced severe inflammation and fibrosis. VHL-deficient renal tubular cells expressed OSM and stimulated endothelial cells to produce inflammatory factor [65]. In general, OSM seems to have a dual role in the regulation of cellular mechanisms associated with renal tubulointerstitial fibrogenesis; the role and mechanism of OSM in renal fibrosis remain to be elucidated.

OSM was increased in the lung of patients with scleroderma-associated interstitial lung disease or idiopathic pulmonary fibrosis, both of which are characterized by extracellular matrix accumulation [66]. Both mice received intranasal administration of rmOSM and intratracheal injection of OSM overexpression; adenovirus showed more severe pulmonary fibrosis. Current research showed that the mechanism of OSM in pulmonary fibrosis may be related to the effect of OSM on macrophages and the activation of STAT3 [66, 67].

The promotion of liver fibrosis by OSM may also be related to macrophages. Overexpression of OSM in the liver directly induced liver fibrosis, while eliminating macrophages using clodronate liposome reduced OSM-induced liver fibrosis and the expression of profibrotic genes [68].

Anti-OSM Antibody in Organ Inflammation and Fibrosis

OSM expression level was markedly elevated in the kidneys of MRL/lpr mice, and injection with OSM neutralizing antibody attenuated the inflammation and fibrosis in the kidney [69]. In addition, the clinical symptoms of mice were improved and the cell infiltration of synovium was significantly reduced by using anti-OSM antibody in two kinds of mouse arthritis models [70].Specific KO of OSMR in cardiac fibroblast induced cardiac fibrosis, while intravenously injection of neutralizing antibody to OSM aggravated cardiac fibrosis after transverse coarctation of aorta operation [71].

OSM plays a consistent role in promoting fibrosis in the kidney, liver, and lung, but may play a protective role in the heart. This reminds us that OSM or other IL-6 family members may not have a consistent effect in all organs, which may be due to the cells' different responses to the same factors in different organs.

LIF in Organ Fibrosis

LIF-Mediated Organ Fibrosis and Possible Mechanisms

LIF is involved in many important physiological processes, such as maintaining the totipotency of embryonic stem cells, bone remodeling, and cardiomyocyte survival. LIF binds preferentially to LIFR with high affinity and then binds to gp130 to form a complex to activate downstream signaling [72].

Immediately, injection of LIF plasmid DNA into mouse thigh muscle after myocardial infarction increased LIF level in circulation and significantly reduced myocardial fibrosis compared with mice injected with control vector [73]. Pretreatment of adult or neonatal cardiac myocytes with LIF protected against hypoxia/reoxygenation and doxorubicin-induced injury [74, 75]. These results showed that LIF has protective effects on acute cardiac injury. However, the long-term effects of LIF on the heart are uncertain. Carlos Zgheib et al. injected 2 μg LIF per 30 g body weight intraperitoneally in male C57BL/6 mice for 10 days which did not lead to cardiac fibrosis, but improved cardiac function [76], while, in vitro, LIF promoted the proliferation of cardiac fibroblasts, but inhibited the differentiation of cardiac fibroblasts into myofibroblasts and reduced the secretion of collagen in fibroblast [77]. Thus, the role of LIF in cardiac fibrosis and relevant mechanism remains to be explored.

IL-1β induced the rapid accumulation of LIF mRNA and protein release in pulmonary epithelial cells, lung fibroblasts, and airway smooth muscle cells, and IL-6 induced the expression of LIF in airway smooth muscle cells [78]. LIF neutralization markedly exacerbated the lung injury and inflammation in mice with pneumonia induced by intratracheal instillations of *Escherichia coli* [79]. These results suggest that similar to acute cardiac injury, LIF is protected against the early inflammation of pulmonary injury.

In kidney, KM mice received LIF (25 μg/kg sc daily) from days 0–6 after UUO showed decreased type I and type III collagen expression [80], suggesting an anti-fibrotic role of LIF in kidney. However, in days 0–6 after UUO, renal injury may be in the transition from acute phase to chronic phase. Since LIF was reported to promote tubular regeneration in AKI [81], administrating LIF on day 1 after UUO might attenuate acute renal tubular injury and subsequently leads to reduced TIF. Another team reported that subcapsular administration of LIF did not show obviously effect on the degree of TIF in both UUO and folic acid nephropathy models since the dosage of recombinant LIF protein might be not enough to achieve any obvious effect [82].

Most recently, we systemically analyzed the expression profile of IL-6 family members in both human and mouse

renal fibrotic lesions. Surprisingly, we found that, among IL-6 family members, LIF is the most upregulated one in both human and mouse renal fibrotic lesions. LIF levels in renal biopsies of human CKD patients were correlated with the extent of TIF. Importantly, baseline urinary concentrations of LIF in CKD patients predict the risk of CKD progression to end-stage kidney disease. Mechanistically, LIF promoted the proliferation and activation of fibroblasts via ERK and STAT3 signaling. LIF-LIFR-EGR1 axis and sonic hedgehog signaling formed a vicious cycle between fibroblasts and proximal tubular cells to augment LIF expression and promote the profibrotic response. The LIF-neutralizing antibody attenuated TIF induced by UUO and UIRI. Our study provides evidence that LIF might be a potential therapeutic target of TIF [83]. In addition, our study suggests systemic analysis of the expression of whole family members is needed to identify the most critical member in certain disease state.

LIF Antagonists

LIF binding protein (LBP) is a differential spliced form of LIFR. Bell et al. studied the ability of mouse LBP to attenuate the effect of LIF in goat radiocarpal joints in vivo. They showed that taking 5 μg of mouse LBP 1 h after intra-articular injection of 0.5 μg of rhLIF significantly reduced joint swelling, cartilage proteoglycan loss, and inhibition of proteoglycan synthesis in vitro [84]. LIF-05 and MH35BD are human LIF mutants, which reduce the affinity of gp130 and improve the affinity of LIFR [85].

Obviously, there is a growing body of evidence that IL-6 family cytokines play an important role in organ fibrosis. Therefore, IL-6 family cytokines are regarded as excellent new targets for the treatment of inflammatory and fibrosis diseases. Table 2 summarizes the currently developed drugs for IL-6 and IL-6R and antagonists for IL-11, OSM, and LIF.

Other IL-6 Family Cytokines in Organ Fibrosis

Serum IL-27 level was elevated in patients with CKD [86, 87]. IL-27Ra deficiency resulted in more severe renal fibrosis after UUO, which is associated with an increase in M2 macrophages, IL-17, and TNF-a [87], suggesting that endogenous IL-27 may limit the extent of immune-mediated renal damage. Consistently, hypodermical injection of rmIL-27 alleviated bleomycin-induced pulmonary fibrosis [88]. However, IL-27 promoted the proliferation of SSc fibroblasts and the secretion of extracellular matrix type I collagen [86].

A high level of IL-31 was detected in plasma and fibrotic skin and lung in patients with scleroderma. Injection of IL-31 induced skin and pulmonary fibrosis in mice, which may be related to fibroblast proliferation and collagen secretion [89]. The loss of IL-31RA attenuated pulmonary fibrosis induced by bleomycin [90].

Obstructed kidneys from $CT1^{-/-}$mice have a higher degree of fibrosis than kidneys from WT mice, and supplementation of exogenous CT-1 in WT mice further reduced the renal fibrosis induced by UUO. The protective effect of CT-1 in renal fibrosis may be related to inhibition of inflammation and collagen secretion by fibroblasts [91]. Administration of CLF-1 to uninjured and bleomycin-injured mice resulted in increased inflammation but reduced pulmonary fibrosis [92]. Thus, CT-1 and CLF-1 may protect organs from fibrosis, but more evidence is needed.

Conclusion

In this review, we systemically reviewed the role of IL-6 family members in fibrosis and the possible mechanisms. According to these results, we can conclude that although IL-6 family cytokines have many similarities in function and signal transduction, different members play different roles in organ fibrosis. Part of the reasons is that different cytokines activate distinct target cell populations depending on the distribution of its specific receptors, though gp130, a common receptor of all IL-6 members, is expressed in almost all cells. In addition, the same cytokine may act on different cell populations in different organs. Single-cell RNA-sequencing data are helpful to determine the distribution of the receptors in various cell types. The pathogenic role of individual member in various diseases needs to be deciphered carefully. In order to clarify the role of IL-6 family members in human diseases, more human studies are needed.

Conflict of Interest Statement

All authors declare that there is no conflict of interest.

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Author Contributions

Ying Chen, Jiaxin Zhou, and Shihui Xu drafted the manuscript; Nie Jing revised the manuscript.

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