Advances in understanding the role of interleukins in pulmonary fibrosis (Review)

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Abstract. Pulmonary fibrosis (PF) is a progressive, irreversible disease characterized by heterogeneous interstitial lung tissue damage. It originates from persistent or repeated lung epithelial injury and leads to the activation and differentiation of fibroblasts into myofibroblasts. Interleukins (ILs) are a group of lymphokines crucial for immunomodulation that are implicated in the pathogenesis of PF. However, different types of ILs exert disparate effects on PF. In the present review, based on the effect on PF, ILs are classified into three categories: i) Promotors of PF; ii) inhibitors of PF; and iii) those that exert dual effects on PF. Several types of ILs can promote PF by provoking inflammation, initiating proliferation and transdifferentiation of epithelial cells, exacerbating lung injury, while other ILs can inhibit PF through suppressing expression of inflammatory factors, modulating the Th1/Th2 balance and autophagy. The present review summarizes the association of ILs and PF, focusing on the roles and mechanisms of ILs underlying PF.

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Abbreviations: AECs, alveolar epithelial cells; BLM, bleomycin; COPD, chronic obstructive pulmonary disease; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; IL, interleukin; MAPK, mitogen activated protein kinase; MPCs, mesenchymal progenitor cells; PF, pulmonary fibrosis

Key words: PF, IL, ECM, AECs

Contents

1. Introduction

Pulmonary fibrosis (PF) is a severe and irreversible consequence of various respiratory diseases, such as alveolitis and interstitial pneumonitis, which is characterized by excessive accumulation of extracellular matrix (ECM) and fibroblast proliferation (1). These pathological processes are accompanied by inflammatory responses and significant damage to the lung architecture (2,3). Subsequent to the injury of alveolar epithelial cells (AECs), multiple interconnected downstream profibrotic pathways are activated, and subsequent aberrant repair mechanisms can lead to harmful scarring in pulmonary tissues and severe impairment of lung function (4,5). Inflammatory responses (6), oxidative stress (7,8) and apoptosis (9) have been reported as possible pathological mechanisms underlying PF.

Globally, the number of patients with PF is increasing, which may be related to aging, increased awareness of the disease as well as improved diagnostic techniques and tools (10,11). The estimated incidence and prevalence of PF are 0.09-1.30/10,000 patients and 0.33-4.51/10,000 patients, respectively (12). Despite recent advances in the treatment of PF, the disease shows a poor prognosis and current available therapeutic options can only slow its progression (13).

Various cytokines have been implicated in the occurrence and development of PF (14), among which interleukins (ILs) have been extensively reported and are considered to be associated with PF (15,16). ILs are a type of proteins that promote interactions with immune and non-immune cells, and are essential in the activation, proliferation, migration and adhesion of immune cells (17). ILs were previously considered to be produced exclusively by leukocytes. However, monocytes, endothelial cells, macrophages, dendritic cells and T cells also express ILs (18,19). ILs can modulate cell proliferation, differentiation, and the initiation of inflammatory and immunological

responses (20,21). They also exert autocrine and paracrine effects (22). ILs have been identified as significant contributors to the pathology of PF (16,23). The present study reviews the current research on ILs in PF and summarizes the roles and mechanisms of ILs associated with PF.

2. Interleukins associated with PF

ILs belong to a large family that can be subdivided into numerous types and are critical mediators of PF pathogenesis (14). Recent studies have demonstrated that ILs contribute to PF development by modulating various biological processes, including inflammation (24,25), immune responses (26), autophagy (27), cellular senescence (28) and epithelial-mesenchymal transition (EMT) (29,30), as illustrated in Fig. 1. Notably, different types of ILs exert disparate effects on PF, as subsequently discussed in the present review.

ILs that promote PF

IL-1. IL-1, also termed lymphocyte-stimulating factor, belongs to the IL-1 family (31). IL-1 locally regulates immunity, promoting B lymphocyte proliferation and antibody production (32). In addition, IL-1 can also regulate the inflammatory response, which may cause fever, pyogenic arthritis, pyoderma gangrenosum, acne and Schnitzler syndrome (33).

There are two subtypes of IL-1: i) IL-1α; and ii) IL-1β (31). IL-1α can be synthesized by hematopoietic and non-hematopoietic cell types, whereas IL-1β is synthesized primarily by mononuclear phagocytes (34). IL-1α promotes the conversion of fibroblasts into proinflammatory phenotypes, and IL-1β initiates the recruitment of neutrophils and lymphocytes, resulting in inflammation and lung fibrosis at the site of injury (34). It has been demonstrated that the molecular mechanism of lung fibrosis progression is improved by regulating the secretion of inflammatory factors such as IL-1β in lung tissue (25), and that the inhibition of IL-1 expression in lung fibrosis-related diseases can attenuate fibrosis, indicating that IL-1 is a key target in PF (24). IL-1R1 is a potential therapeutic target for the treatment of chronic obstructive pulmonary disease (COPD), and a relevant clinical trial has validated that monoclonal antibodies selectively bind to the receptor IL-1R1 and suppress the activation of IL-1α and IL-1β, and it can improve lung function as well as the quality of patients' lives (35). A recent study revealed that the combined inhibition of IL-1, IL-33 and IL-36 signaling by targeting the IL-1 receptor accessory protein could ameliorate lung fibrosis in preclinical models (36). Notably, this human phase I clinical trial concerning the anti-IL1RP antibody is currently ongoing (36), suggesting a promising method for treating PF in future clinical practice.

IL-6. IL-6 is a key cytokine in the acute-phase response and participates in the pathogenesis of a number of chronic inflammatory diseases including cancer (37-39). Monocytes and lymphocytes are the primary sources of IL-6 (40). In the early wound healing stage, M1 macrophages, lymphocytes and neutrophils infiltrate and play a pivotal role in wound healing by secreting various factors, including TNF-α and IL-6 (41). In the inflammation-terminating stage of injury repair, M2 macrophages regulate the inflammatory response and secrete TGF-β1 and platelet-derived growth factor to promote fibroblast proliferation, resulting in remodeling of the ECM and excessive deposition of collagen (42).

IL-6 can stimulate fibrosis by initiating chronic inflammation and activating the TGF-β pathway (43), whereas TGF-β1 is at present, the most potent profibrotic cytokine (44). In bleomycin (BLM)-induced mice with PF, the expression of fibrosis-related cytokine IL-6 and myofibroblast marker collagen type I in the lymphoid fibroblast supernatant, serum, blood and bronchoalveolar lavage fluid induced by TGF-β1 were significantly increased (45).

IL-6 promotes PF as a multifunctional cytokine involved in the inflammatory response and fibrosis. IL-6 induces the maturation of T and B lymphocytes and participates in acute inflammatory responses (46). IL-6 also induces collagen deposition and ECM accumulation and stimulates fibroblast proliferation, thereby promoting the development of fibrosis (45). Clinical studies demonstrated an association between serum IL-6 levels and lung function impairment in patients with PF (47,48). The detection of serum IL-6 levels in patients with PF could provide a basis for the clinical judgment of respiratory function (47). Moreover, results of a phase III clinical trial of an IL-6 receptor antagonist has indicated that IL-6 is a driver of PF, and inhibition of IL-6 could help restore lung function (49). To the best of our knowledge, there are no clinical studies that directly focus on IL-6 and PF, but the aforementioned findings indicate that targeting IL-6 may be a promising therapeutic approach against PF.

IL-8. IL-8, also termed chemokine CXCL8, is expressed during inflammation, tumors and allergies (50). IL-8 is involved in cellular immunity and delayed-type hypersensitivity inflammation, and its main biological roles include chemotaxis and activation of neutrophils, promotion of lysosomal enzyme activity and phagocytosis of neutrophils, mediation of cytotoxicity, and local inflammation-related immune responses to assist antibody production (51,52). Papiris *et al* (53) found that the amount of IL-8-secreting alveolar macrophages increases in patients with fibrosing alveolitis and that elevated levels of IL-6 and IL-8 are characteristics of early PF (43).

Fibrotic mesenchymal progenitor cells (MPCs) in lung tissue are the original cells of PF fibroblasts (43). IL-8 derived from MPCs facilitates the proliferation, differentiation and migration of MPCs and induces macrophage migration to fibroblast foci via the receptor CXCR1/2 (54). Li *et al* (55) demonstrated that IL-8 production is induced in airway epithelial cells through the NF-κB pathway, and the induced IL-8 expression is not only involved in neutrophil recruitment in airway inflammation in lung diseases, but also associated with airway fibrosis and remodeling by provoking the proliferation and migration of lung fibroblasts and mesenchymal stem cells.

IL-13. IL-13 is produced mainly by Th2 lymphocytes, epithelial cells, and macrophages (56). IL-13 is functionally similar to IL-4 because their amino acid sequences share 20-25% homology (57). IL-13 is a proinflammatory cytokine and its role in allergic inflammation, asthma and inflammatory bowel disease has been well documented (58-60). IL-13 stimulates fibroblast activation and proliferation, increases smooth muscle cell contraction and ECM deposition, and facilitates mucus production (26,61). In addition, IL-13 can induce the production of profibrotic cytokines (such as TGF-β, PDGF,

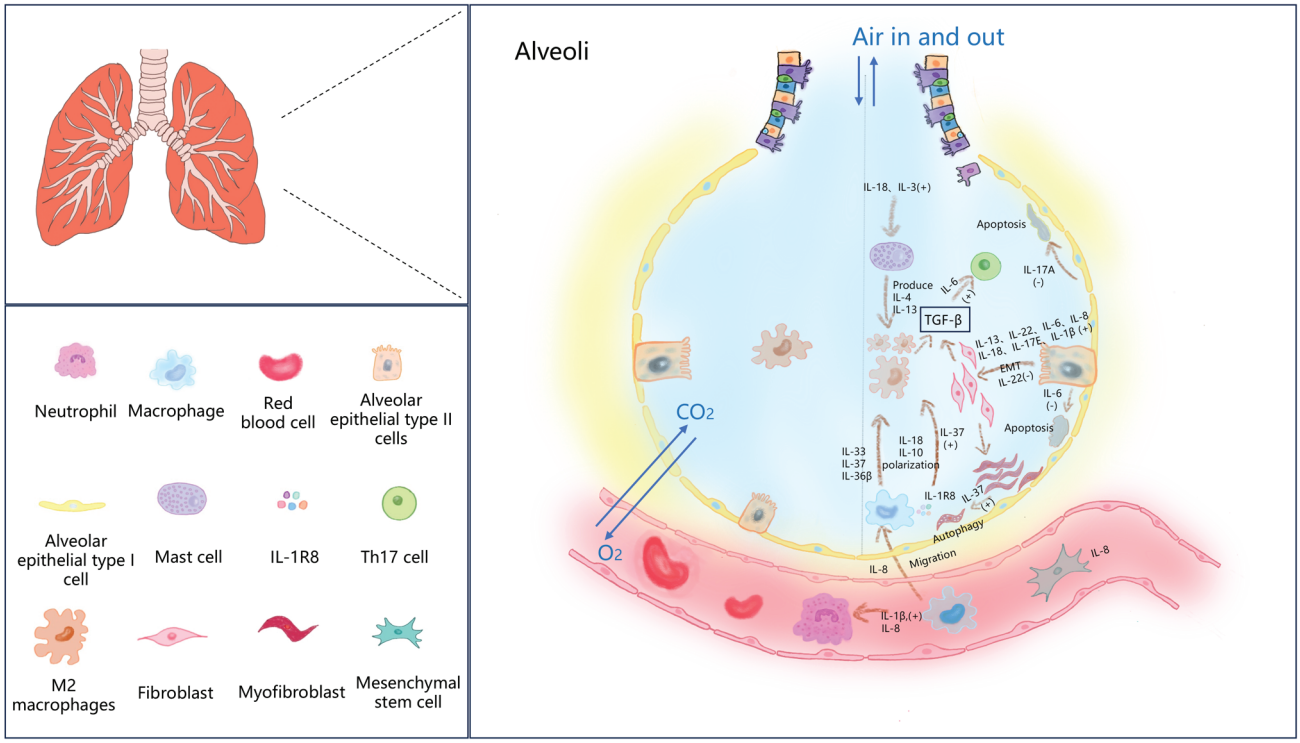

Figure 1. ILs are involved in the formation and development of pulmonary fibrosis through the regulation of inflammation, immune response, autophagy, senescence and EMT. IL, interleukin; EMT, epithelial-mesenchymal transition.

connective tissue growth factor and collagen type I) and fibronectin production (62). Clinical trials have confirmed that in patients with COPD and type 2 inflammation, dupilumab, which blocks both IL-4 and IL-13, showed improved lung function compared with patients treated with placebo (61,63). However, in patients with PF, blocking IL-13 did not achieve a satisfactory therapeutic effect (64), hence, the clinical role of IL-13 inhibitors in the treatment of PF still needs to be further studied.

IL-17. IL-17 is a proinflammatory cytokine involved in chronic inflammation that occurs in the pathogenesis of allergies, malignancies and autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and psoriasis (65). IL-17 regulates immune function by inducing the secretion of anti-inflammatory molecules such as cytokines, anti-pathogenic peptides and chemokines (66). IL-17 can act on a variety of cellular targets. For example, it induces inflammation when acting on endothelial cells (67) and induces cytokine and enzyme production when acting on epithelial cells and fibroblasts (68,69). In addition, IL-17 induces inflammation by increasing the production of proinflammatory cytokines when acting on monocytes and dendritic cells (70).

The main subtypes of the IL-17 family are IL-17A to IL-17F, which bind to the IL-17 receptor (IL-17R) complex and consist of two chains: i) IL-17RA; and ii) IL-17RC (71). IL-17RA is expressed in almost every cell type, including epithelial and endothelial cells and fibroblasts (72,73). IL-17A expression levels are positively correlated with inflammation scores of skin and lung as well as skin fibrosis in PF mice and IL-17A inhibits autophagy in AECs (69). IL-17RC acts on numerous cell types, including CD4+ T cells, macrophages and neutrophils, and plays important roles in lung inflammation (74-76). IL-17E, often referred to as IL-25, is secreted by T2, epithelial, endothelial and T cells, alveolar macrophages, eosinophils and basophils, all of which are closely associated with the inflammatory response (77). In lung tissues from patients with PF, the levels of IL-17E and its receptor IL-17RB are increased, suggesting that they drive PF by mediating EMT in AECs and by recruiting and activating lung fibroblasts (29,30).

IL-18. IL-18 regulates innate and adaptive immunity (78). As a proinflammatory cytokine, IL-18 promotes the type I response and secretes inflammatory factors such as IL-1β and TNF-α, which exacerbates lung tissue injury at an early stage (79). Under the stimulation of IL-10, IL-18 induces the polarization of M2 macrophages (80). Notably, polarized M2 macrophages secrete TGF-β1 (81), which is the primary idiopathic dominant factor in ECM overproduction and deposition, fibroblast proliferation and differentiation into fibroblasts in PF (82). Zhang *et al* (28) found that IL-18 promotes lung fibroblast senescence and the senescence-associated secretory phenotype of fibroblasts by downregulating Klotho expression. IL-18 promotes inflammation, cell differentiation and cytokine production by regulating multiple cell signaling pathways (83). For example, IL-18 induces the expression of intercellular adhesion factor ICAM-1, promotes inflammatory cell recruitment, and upregulates the expression and activity of NF-κB, which is involved in the early stage of lung injury in lung fibrosis models and is associated with the modulation of the expression of multiple cytokines, including IL-1, IL-2, IL-6 and TNF-α (84).

IL-23. IL-23 is primarily produced by dendritic cells and macrophages (85). IL-17, IL-22 and IL-23 are significantly elevated in patients with combined lung cancer and PF, suggesting that IL-17, IL-22 and IL-23 are sensitive biomarkers for the early diagnosis of these diseases (86). Moreover, IL-23/Th17 cells are associated with the development of various inflammatory diseases, such as arthritis (87), psoriasis (88), inflammatory bowel disease (89) and asthma (90). Results of a paper published in 2021 suggested that IL-23 may be a new therapeutic strategy for acute exacerbations of PF (91), however, no clinical trials or research data are available to date.

IL-33. IL-33 expression is stimulated in non-lethal cell stretching, particularly in mechanosensitive cells such as fibroblasts (92). IL-33 drives disease pathology and promotes the reduction of inflammation under different inflammatory conditions and diseases (93,94). For example, a clinical trial has demonstrated that IL-33 plays a key role in the pathogenesis of atopic dermatitis (95), and monoclonal antibodies against IL-33 have been shown to reduce airway inflammation and associated tissue damage in a preclinical study (96). IL-33 promotes the polarization of M1 to M2 macrophages through IL-33/ST2 signaling, a pathological feature of PF (97). It has also been reported that IL-33 is expressed in the basal cells of the airway epithelium, endothelial cells and fibroblasts of the human lungs (98). Xiong *et al* (26) demonstrated that BLM induces IL-33 production *in vivo*, which triggers and promotes PF by activating macrophages and enhancing IL-13 and TGF-β production. Clinical trials have shown that neutralizing IL-33 has therapeutic and anti-inflammatory effects in lung diseases, including COPD and allergic asthma (99,100). At present, there are no clinical data on IL-33 inhibitors in the treatment of PF, and further research is needed for the confirmation of whether IL-33 could be targeted for treating PF.

IL-36. IL-36 is a new member of the IL-1 family (101). It includes three agonist proteins, IL-36α, IL-36β and IL-36γ, and the antagonist protein IL-36Ra (101). IL-36 is responsible for acute and chronic tissue inflammation in human diseases such as COPD, PF, asthma and arthritis (102). On the one hand, IL-36Ra antagonizes IL-36γ-mediated induction of NF-κB activation via IL-36R, and further inhibits inflammation in the lungs by suppressing massive accumulation of lung fibroblasts (103). On the other hand, IL-36 provokes the activation of macrophages, epithelial cells and keratinocytes to secrete inflammatory factors including IL-6, IL-1β, IL-12, IL-23 and TNF-α (104).

IL-36β activates M2 macrophages, and in bone marrow dendritic cells, IL-36 stimulation induces the production of proinflammatory cytokines (such as IL-1β, IL-6, IL-12, IL-23 and TNF) (105,106). The IL-36 receptor is expressed predominantly by initial CD4+ T cells, and promotes differentiation towards Th1 and Th17 cells, and facilitates their proliferation and inflammatory cytokine production (107).

ILs that inhibit PF

IL-10. IL-10, an inhibitory factor of human cytokine synthesis, is an anti-inflammatory cytokine (108,109). IL-10 is mainly produced by lymphocytes, macrophages and mast cells and has immunomodulatory effects such as the inhibition of monocytes/macrophages, Th1 cell function and enhancement of B lymphocyte function (110). IL-10 inhibits the expression of inflammatory factors, such as TNF-α, IL-6 and IL-1, through activating macrophages and can exert an immunostimulatory effect in numerous cell types (111).

IL-10 inhibits the activation, migration and adhesion of inflammatory cells by downregulating the expression of the major histocompatibility antigen II on the surface of monocytes, decreasing its antigen-presenting effect and downregulating the activity of T lymphocytes (112,113). At the same time, IL-10 can reduce inflammatory cytokines, such as IL-2, INF-γ, TNF-α and CSF-GM, and thus attenuate the inflammatory response (114). Moreover, IL-10 inhibits the expression of cytokines, such as TNF-α, IL-1β and IL-8, and the expression of adhesion molecules (115).

IL-12. IL-12 is derived primarily from activated macrophages (116). IL-12 enhances cellular immunity and modulates immune responses (117). Previous studies have shown that early intervention with IL-12 promotes anti-inflammatory, immunomodulatory and antifibrotic effects in animal models of PF (118-120). In addition, IL-12 is a potent inducer of IFN-γ and it attenuates BLM-induced PF by modulating IFN-γ production (121).

The Th1/Th2 imbalance is crucial in the pathogenesis of PF, with Th1-type cells represented by IFN-γ, which may promote the repair of normal tissue structures, and Th2-type cytokines represented by IL-4, which may cause excessive damage repair, ECM deposition and fibrosis (122). When the balance of Th1/Th2 type cytokines shifts towards Th2 type cytokines, it can lead to the development of fibrosis (123). IL-12 induces the proliferation and differentiation of Th1 cells to produce Th1-type cytokines, and inhibits the proliferation and differentiation of Th2 cells (124).

IL-27. IL-27 is a member of the cytokine IL-12 family, produced primarily by dendritic cells and macrophages, and it comprises the subunit proteins IL-27p28 and Epstein Bar virus-inducible protein 3 (125). IL-27 is a multifunctional cytokine with anti-inflammatory and immunomodulatory properties (126). It has been suggested that IL-27 may play an antifibrotic role in lung fibroblast development, differentiation and collagen synthesis (127), and may alleviate TGF-β1-induced EMT in AECs (128). A recent study reported that IL-27 inhibits autophagy induced by the ERK/p38 signaling pathway and attenuates BLM-induced PF (129). Furthermore, mice deficient in IL-27RA show more severe collagen deposition in the lungs, suggesting that intact IL-27 signaling could limit PF progression (130).

IL-37. IL-37 was formerly defined as IL-1 family member 7, yet due to different functions from IL-1, it's now designated as an individual IL (22,131). IL-37 can either act directly inside the cell into the nucleus or be secreted outside the cell to act on its own membrane receptors or those of the surrounding cells to inhibit inflammation (132).

IL-37 and Smad3 are involved in the process of alveolitis and PF, and the IL-37b-Smad3 complex can suppress the phosphorylation of c-Jun N-terminal kinase and mitogen-activated protein kinase (MAPK), which is associated with IL-1-induced proinflammatory transcription factor AP-1 (133). Inhibition of MAPK phosphorylation can downregulate the expression of Th2-type factors in peripheral blood mononuclear cells (133).

IL-38 is a potential inhibitor of IL-1 and the Toll-like receptor family with potent anti-inflammatory effects (134). The anti-inflammatory effects of IL-38 are related to the inhibition of inflammatory signaling pathways in target cells, suppression of T lymphocyte function and reduction in the secretion of inflammatory factors, including IL-6, TNF, CCL5 and CXCL10 (135). IL-38 expression attenuates BLM-induced inflammatory and fibrotic injury in the lungs and reduces the production of proinflammatory and profibrotic cytokines (136).

Moreover, IL-38 has been reported to inhibit inflammatory processes by antagonizing IL-36R, similar to IL-36Ra or IL-1Ra (137). Furthermore, in a mouse model of BLM-induced PF, overexpression of IL-38 attenuated lung inflammation and fibrosis, reduced the production of inflammatory factors such as IL-1β, IL-6, IL-17A and TNF-α, and promoted the expression of the anti-inflammatory cytokine IL-1Ra (138).

ILs with dual effects on PF

IL-4. IL-4 is a pleiotropic cytokine that is primarily produced by activated T lymphocytes, mast cells, basophils and eosinophils cells (139). IL-4 exerts immunomodulatory effects on B lymphocytes, T and mast cells, macrophages and hematopoietic cells, and also exerts anti- and pro-inflammatory effects (61).

On the one hand, IL-4 attenuates PF by inhibiting macrophage infiltration, M2 polarization and collagen deposition, and the pharmacological treatment enhances IL-4-induced autophagy in macrophages and lung tissue in BLM-treated rats (27). On the other hand, IL-4 increases in the serum of patients with PF and in bronchoalveolar lavage fluid of mice after BLM intoxication (140). The primary role of IL-4 includes the induction of Th2 responses and the alternative activation of dendritic cell stimulation to present antigens to other immune cells and macrophages (141). In addition, the synergistic effect of IL-24 and IL-4 promotes M2-type polarization of macrophages, which further promotes the development of PF (140). However, M2 macrophages can have an anti-inflammatory and pro-wound healing phenotype; when this process is dysregulated, the overactivation of these responses can lead to the development of fibrosis (142). Notably, a previous study confirmed that the development of fibrosis is closely related to the production of Th2-type cytokines, mainly IL-4-mediated macrophage activation, fibroblast proliferation and differentiation, and ECM deposition, ultimately leading to PF formation (143).

IL-22. IL-22 is expressed by different types of lymphocytes, including CD4+ T cells, especially Th17, δγ T and NK cells (144). These cellular subpopulations express IL-22 with similar characteristics and unique mechanisms of expression (145). IL-22 differs from most ILs in that it does not directly regulate immune cell functions. Instead, IL-22 targets cells on extracorporeal barriers, such as the skin and tissues of the digestive and respiratory systems (146,147), as well as the pancreas, liver, kidneys and joints (148-151). IL-22 induces them to produce antimicrobial proteins and specific chemokines, whereas IL-17, TNF-α and IL-1β amplify this effect (152,153).

IL-22 exerts anti-inflammatory and antifibrotic effects (154). Cellular regeneration, tissue remodeling and homeostasis between commensal gut bacteria and the host immune system are the anti-inflammatory hallmarks of IL-22 (155,156). IL-22 is also important in intrinsic and adaptive immunity and is involved in various pathophysiological processes (157,158). For example, in mice infected with *Klebsiella pneumoniae*, IL-22 promotes epithelial repair and inhibits epithelial damage, thereby suppressing the inflammatory response (159). The antifibrotic effect of IL-22 is related to the protection of epithelial cells in *in vivo* and *in vitro* studies of PF, and it is an essential (155) immunomodulatory molecule in the lungs (159). It has been suggested that inhibition of the TGF-β pathway and collagen production by IL-22 reduces activation of Smad2/3 signaling *in vitro* (160). The mechanisms involved may not be clear, but it has been found that IL-22 mainly affects fibroblasts and epithelial cells (161), and it represents the main communication channel between specific tissue cell types and the immune system (162).

Notably, IL-22 was also reported to be a proinflammatory and profibrotic factor (163). IL-22 is capable of activating collagen production and deposition by stimulating fibroblast proliferation and secretion of profibrotic cytokines, which promote subepithelial fibrosis and lead to the remodeling of asthmatic airways (164).

3. Conclusion

ILs are a group of cytokines originating from diverse cell types and are known for their diverse effects. ILs can exert either antifibrotic or profibrotic effects and rarely exhibit dual actions by influencing the structure and functionality of various cell types involved in PF predominantly by targeting fibroblasts, macrophages and epithelial cells, which are closely associated with PF progression. The majority of the studies described in the present review still have some controversies. Therefore, a full understanding of ILs and their association with PF remains to be elucidated.

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Availability of data and materials

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Authors' contributions

SN and KZ contributed to the study conception and design. Material preparation, and data collection and analysis were performed by YH, XS, KZ and SN. The draft of the manuscript was written by YH, and all authors commented on previous versions of the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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