Beyond inflammation: alarmins as critical drivers of pulmonary fibrosis

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Clinical and pre-clinical studies reveal that epithelial alarmins play a key role in pulmonary fibrosis by promoting a type 2 cytokine environment and dynamically regulating fibroblast–macrophage interactions during lung injury https://bit.ly/3JF7nfX

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Abstract

Pulmonary fibrosis is a chronic respiratory disorder characterised by an overproduction and aberrant deposition of fibrotic tissue in the lungs. This narrative review focuses on the pivotal role played by epithelial alarmins, primarily thymic stromal lymphopoietin, interleukin (IL)-25 and IL-33, in the pathogenesis of idiopathic pulmonary fibrosis and connective tissue disease-associated interstitial lung disease. It considers their function as damage-associated molecular patterns and the attraction of both innate and adaptive immune cells that these patterns elicit, thereby playing a significant role in the immune response to fibrosis. Epithelial alarmins play a dynamic role in regulating fibroblast–macrophage interactions during lung injury and this process influences macrophage polarisation and drives the epithelial–mesenchymal transition. It is evident that these epithelial alarmins play a key role in activating the type 2 immune network and, given the established importance of type 2 inflammatory responses in pulmonary fibrosis, there is significant interest in the study of epithelial alarmins and their contribution to profibrotic type 2 immune responses. A deeper understanding of this area could result in the conceptualisation of new targeted therapies.

Introduction

The term "pulmonary fibrosis" includes several chronic respiratory diseases associated with a dysregulated production and deposition of fibrotic tissue in the lungs, leading to a progressive and irreversible architecture distortion with consequent loss of function.

Among these, the most severe and irreversible form is idiopathic pulmonary fibrosis (IPF). The aetiology of IPF is unknown; therefore, prior to diagnosis, it is essential to exclude secondary causes of fibrotic interstitial lung diseases (ILD), including, but not limited to, environmental exposures, connective tissue diseases (CTDs) and drug toxicity. Still, a plethora of studies have demonstrated an association between environmental risk factors (such as viral infections, micro aspiration, tobacco smoke, air pollution and occupational exposures) and the development of IPF, as well as individual predisposition related to genetic and/or epigenetic factors. However, with various degrees of probability, also other ILDs can display a progressive clinical course similar to IPF and are therefore defined as "progressive pulmonary fibrosis" (PPF) [1]. In such cases, they can present as a pulmonary complication of underlying autoimmune and connective tissue diseases (CTDs), more commonly rheumatoid arthritis (RA) and systemic sclerosis (SSc) [2].

Lessons for clinicians

- Pre-clinical studies indicate that epithelial alarmins initiate and amplify fibrotic pathways in the lung.
- Alarmins disrupt immune balance by promoting type 2 cytokine responses and modulating fibroblast–macrophage crosstalk, leading to macrophage polarisation and epithelial–mesenchymal transition.
- Idiopathic pulmonary fibrosis exhibits significantly elevated levels of thymic stromal lymphopoietin (TSLP) in the lungs and changes in TSLP dynamics during antifibrotic treatment are associated with functional stability.
- Interleukin-33 is the major cytokine of clinical relevance in connective tissue disease-associated interstitial lung disease (ILD), as it is linked to ILD development in both rheumatoid arthritis and systemic sclerosis.
- Future advancements in molecular and cellular technologies will enhance our understanding of the biology of alarmins in pulmonary fibrosis and their potential implications for therapeutic strategies.

To date, no curative treatment for IPF or PPF is available, except for lung transplantation. However, this represents a suitable option only for a minority of patients due to its high invasiveness and surgical complexity, not to mention the challenging management of lifelong immunosuppression and the relevant risk of infection or graft dysfunction. Pharmacological treatment with antifibrotics have demonstrated to significantly reduce the respiratory functional decline of IPF and PPF, but their impact on survival and quality of life is still to be fully clarified. Thus, there is still an urgent unmet need to develop more effective treatments, for which it is mandatory to improve our knowledge of the complex and multifaceted pathogenic pathways underlying the onset and the perpetuation of pulmonary fibrosis, particularly concerning the role of the immune system. This exploration will facilitate the identification of potential molecular targets, which could open a new chapter in the pharmacological treatment of pulmonary fibrosis [1, 3].

Pathogenesis of IPF

The role of alveolar damage

Despite the limited understanding of the mechanisms underlying pulmonary fibrosis, the prevailing concepts of its pathogenesis focus on the recurrent subclinical injury to a genetically predisposed alveolar epithelium, culminating in alveolar re-epithelialisation and repair failure [2]. Alveolar epithelial cells (AECs), particularly alveolar epithelial type 2 cells (AT2s), are considered as one of the main drivers in the pathogenesis of IPF. In the context of IPF, AT2s exhibit features such as genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence and alterations in intercellular communication. A prevailing concept is that AT2 depletion, due to repetitive micro-injuries, represents a crucial step in triggering dysregulated fibrogenic processes [4]. In the aftermath of lung injury, a series of events are initiated as the lung endeavours to minimise the extent of damage and restore its functional integrity [5]. Specifically, activated cells within the alveoli release a plethora of cytokines and growth factors promoting the recruitment, proliferation and differentiation of macrophages. Furthermore, these factors also promote impaired polarisation, unregulated proliferation of nonimmune cells, such as mesenchymal stem cells, and the differentiation of lung fibroblasts into myofibroblasts. Consequently, this leads to excessive collagen deposition, progressive scarring of the lung parenchyma and irreversible loss of function [2, 6].

A predominant phenomenon observed in AT2s in IPF is cellular senescence [7]. Cellular senescence is a mechanism involved in IPF pathogenesis, which is defined as a stable state of cell cycle arrest induced by various stressors (such as DNA damage, oxidative stress and telomere shortening) [7, 8]. A hallmark of this process is the senescence-associated secretory phenotype, whereby senescent cells secrete an array of pro-inflammatory cytokines, chemokines and growth factors [9]. This secretory profile has been demonstrated to promote chronic inflammation, in addition to disrupting normal tissue architecture and function. Consequently, this creates a self-perpetuating cycle of damage that contributes to the pathology of chronic lung disease [7]. The presence of biomarkers of cellular senescence, as well as the presence of senescent cells in lung tissue samples, has been demonstrated to correlate with the severity of the disease and impaired lung function [8].

The histological hallmark of IPF is the presence of “fibroblastic foci”, defined as aggregates of activated fibroblasts and myofibroblasts, typically associated with injured epithelial cells and adjacent mesenchymal compartments [10]. The intermittent and repetitive nature of many cellular crosstalk events has been shown to drive uncontrolled senescence, metabolism and other processes, resulting in aberrant wound repair [6, 11].

The role of immune response and type 2 inflammation

Both innate and adaptive immune responses play a pivotal role in the pathogenesis of pulmonary fibrosis, particularly the secretion of pro-fibrotic factors (such as transforming growth factor (TGF)-β) by a multitude of cells. Among these, macrophages are abundant in the lung and are usually classified in two phenotypes according to their activation pathway and related cytokine profile: classically activated (M1) and alternatively activated (M2) macrophages. M1 macrophages are mainly involved in pro-inflammatory immune defence, while M2 macrophages are activated following exposure to interleukin (IL)-4, IL-10 and IL-13, generally expressing anti-inflammatory and pro-fibrotic properties [3]. Macrophages secrete TGF-β, that on one side induces epithelial cell damage and apoptosis, on the other directly promotes extracellular matrix (ECM) deposition, fibroblast-to-myofibroblast differentiation and epithelial–mesenchymal transition (EMT). The progressive architectural distortion of lungs due to fibrosis accumulation is supported by the activity of myofibroblasts (the active form of fibroblasts that migrate to the damaged sites), which are considered to be responsible for synthesising ECM components *via* a TGF-β-dependent mechanism [3, 4].

In the context of immunological evaluation, it has been postulated that an imbalance between type 1 and 2 responses may constitute a significant contributing factor to the development of pulmonary fibrosis. Specifically, pulmonary fibrosis may be associated with an overactive pro-fibrotic type 2 response associated with a downregulation of type 1 response expressing antifibrotic properties. Indeed, type 1 cytokines have been demonstrated to inhibit the proliferation of fibroblasts and the formation of fibrotic tissue, whereas type 2 cytokines have the capacity to promote the activation and proliferation of fibroblasts, increase collagen synthesis and inhibit its degradation. Consequently, the deposition of matrix proteins and subsequent exaggerated fibrogenesis are the resultant outcomes of these processes [3].

Several studies have demonstrated an association between lung fibrosis and the overexpression of type 2 cytokines (including IL-4, IL-5 and IL-13). This finding suggests that a shift towards a type 2 cytokine milieu may be a key event mediating abnormal epithelial–mesenchymal crosstalk [10].

Pathogenesis of CTD-ILD

IPF and CTD-ILD have been shown to share common fibrotic mechanisms, such as epithelial injury, fibroblast activation and ECM deposition, but there are significant differences in their underlying pathogenic drivers. IPF is regarded as a primary epithelial-driven disease, manifesting in genetically susceptible individuals without autoimmune diseases [12]. Conversely, CTD-ILDs manifest in the context of systemic autoimmune diseases and are driven by chronic immune activation, autoantibody production and dysregulated inflammation [13]. These distinct pathogenetic frameworks have important implications for diagnosis, treatment and prognosis. SSc is the most commonly associated ILD (34.7%), followed by RA (20%), overlap syndrome (13.3%), autoimmune myopathies (6.7%) and undifferentiated CTD (5.3%) [14].

The pathogenesis of CTD-ILD remains poorly understood due to the heterogeneity of the condition and the absence of specific pre-clinical models. It is evident that a variety of lung cell types are implicated in the process of lung fibrogenesis, particularly mesenchymal and AT2 cells, as evidenced in IPF. However, in CTD-ILD, the predominant mechanisms are immune-mediated processes [14]. Also, genetic abnormalities and environmental risk factors have been identified as key contributors to the dysregulation of regulatory pathways in inflammation. This leads to the dysfunction of AT2s, which in turn triggers several profibrotic pathways in the downstream process. These include inflammatory cascades, which promote the proliferation and activation of lung fibroblasts. This, in turn, causes abnormal lung remodelling and dysregulated repair, resulting in lung fibrosis [14].

The most extensively studied CTD-ILD is SSc-ILD. Similarly to IPF, it is characterised by an overactivation of macrophages with a prevalent M2 profibrotic phenotype. However, in contrast to IPF, SSc-ILD is distinguished by the accumulation and expansion of T-cell subsets, including T-helper 2 (Th2) regulatory T-cells (Tregs), Th22, Th17 and an increased ratio of cluster of differentiation (CD)4 to CD8. Moreover, B-cell profiles of patients with IPF and SSc-ILD differ, as do their T-cell chemokine profiles (IL-4, IL-5, IL-10 and IL-17 for IPF, and IL-4, IL-5, IL-6, IL-10, IL-13 and IL-22 for SSc-ILD). Of particular note in SSc-ILD is the role of IL-6, exploiting a potent enhancement of collagen production through fibroblast stimulation, myofibroblast differentiation and the inhibition of metalloproteinase secretion [2].

In the context of RA-ILD, similar to the findings observed in IPF and SSc-ILD, Th-17-cell-mediated immunity has been demonstrated to play a pivotal role in the pathogenesis process. However, a substantial increase in the numbers of B-cells and $CD4^+$ T-cells is observed in the lung tissue of individuals with

RA-ILD when compared to those with IPF. This finding indicates that immune dysregulation may be a more prevalent occurrence in patients with RA-ILD than in those with IPF [2].

Epithelial cell-derived cytokines

Epithelial alarmins is a broad term for endogenous mediators that are predominantly released from the epithelium and act as damage-associated molecular patterns (DAMPs), attracting cells of both adaptive and innate immune systems [15].

Among these, three epithelial cell-derived cytokines, namely thymic stromal lymphopoietin (TSLP), IL-25 and IL-33, have emerged as important initiators of immune activation in response to exogenous and endogenous danger signals [16] (table 1).

TSLP, a member of the IL-2 family, is released by a variety of cells including epithelial cells, dendritic cells and basophils. It signals through TSLP receptor (TSLPR), a heterodimer consisting of TSLPγ and IL-7Rα chains that is expressed by many cells from both innate and adaptive immunity as well as by airway epithelial cells [17].

IL-25, also known as IL-17E, is one of six members of the IL-17 family, including IL-17A, IL-17B, IL-17C, IL-17D and IL-17F. IL-25 receptor (IL-25R) is a heterodimer of IL-17RA and IL-17RB and is constitutively present on fibroblasts and airway smooth muscle cells [18].

IL-33 is a member of the IL-1 family and it can exert its effects in two ways, depending on its maturation status. The immature form of IL-33 (flIL-33), in its full-length form, acts as an intracellular gene regulator in the nucleus, leading to an increase in pro-inflammatory mediators. Upon release following inflammatory stimuli, flIL-33 can be processed by neutrophil-derived proteases into its mature form (mIL-33). mIL-33 functions as an extracellular cytokine signalled through the suppressor of tumorigenicity (ST2) receptor. An accessory receptor, IL-1 receptor accessory protein, is also needed for signal transduction. ST2 is expressed mostly on innate or adaptive immune cells and can be induced on structural cells [19].

DAMPs play a key role in physiological wound healing by re-establishing cell integrity and alerting adjacent cells to danger. Conversely, persistent and sustained stimulation of immune cells by epithelial-derived alarmins can result in dysregulation of normal wound healing dynamics, causing a pro-inflammatory milieu, cellular senescence and tissue destruction [20].

These epithelial alarmins are also crucial in activating the type 2 immune network and are considered as key regulators of the T2-skewed inflammatory phenotype in asthma. This is mainly achieved through the activation of group 2 innate lymphoid cells (ILC2s), which rapidly respond by generating type 2 cytokines [21]. The insights regarding the immunopathogenic role of alarmins in asthma have paved the way for the development of alarmin-targeted drugs; thus expanding the therapeutic options available for severe forms of asthma [22].

Since the type-2 inflammatory response plays an important role also in pulmonary fibrosis [23], a better understanding of the contribution of epithelial alarmins to profibrotic type 2 immune responses represents a challenge of great interest, as it may lead to the conceptualisation of new targeted therapies.

TABLE 1 Overview of epithelial alarmins interleukin (IL)-33, thymic stromal lymphopoietin (TSLP) and IL-25: sources, receptors and signalling pathways

Alarmins	Main cellular source	Receptor	Main signalling pathways
IL-33	Primarily epithelial cells (airway epithelium), endothelial cells, fibroblasts	ST2 (IL1RL1) receptor,	MyD88 → IRAK → TRAF6 → NF-κB and MAPK
TSLP	Epithelial cells, dendritic cells, basophils, fibroblasts, airway smooth muscle cells	TSLP receptor complex (TSLPR/IL-7Rα)	JAK1/2 → STAT5 activation; PI3K/AKT
IL-25 (IL-17E)	Airway epithelial cells, Th2 cells, mast cells	IL-17RB receptor	NF-κB, MAPK (ERK, JNK, p38)

AKT: protein kinase B; ERK: extracellular signal-regulated kinase; IRAK: interleukin-1 receptor-associated kinase; JAK1/2: Janus kinase 1 and 2; JNK: c-Jun N-terminal kinase; MAPK: mitogen-activated protein kinase; MyD88: myeloid differentiation primary response 88; NF-κB: nuclear factor-κB; p38: p38 mitogen-activated protein kinase; PI3K: phosphoinositide 3-kinase; ST2: suppressor of tumorigenicity 2; STAT5: signal transducer and activator of transcription 5; Th2: T-helper type 2; TRAF6: TNF receptor-associated factor 6.

Data collection and analysis

The systematic search was conducted on the Medline database through the PubMed search engine.

We included all clinical studies from 2013 to the present and limited the selection to those available in English.

For the study selection, we used the following keywords: “IL-33 and IPF”, “IL-33 and idiopathic pulmonary fibrosis”, “IL-33 and pulmonary fibrosis”, “IL-33 and CTD-ILD”, “IL-33 and SSc-ILD”, “IL-33 and AR-ILD”, “IL-25 and IPF”, “IL-25 and idiopathic pulmonary fibrosis”, “IL-25 and pulmonary fibrosis”, “IL-25 and CTD-ILD”, “IL-25 and SSc-ILD”, “IL-25 and AR-ILD”, “TSLP and IPF”, “TSLP and idiopathic pulmonary fibrosis”, “TSLP and pulmonary fibrosis”, “TSLP and CTD-ILD”, “TSLP and SSc-ILD”, “TSLP and AR-ILD”, “epithelial alarmins and IPF”, “epithelial alarmins and idiopathic pulmonary fibrosis”, “epithelial alarmins and pulmonary fibrosis”, “epithelial alarmins and CTD-ILD”, “epithelial alarmins and SSc-ILD” and “epithelial alarmins and AR-ILD”.

We included randomised controlled trials, observational retrospective and prospective studies, both multicentric and monocentric, focused on adults affected with IPF and CTD-ILD. We included only studies with available full text. We excluded case reports, reviews and pre-print reports.

We divided the studies into three groups based on their main outcomes:

1) epithelial alarmins and microenvironment of pulmonary fibrosis
2) epithelial alarmins and animal models of fibrotic lung disease
3) epithelial alarmins and pulmonary fibrosis: clinical studies

A flow diagram of study selection and final inclusion in this review, as well as an overview of the type of studies included, is shown in figure 1.

Epithelial alarmins and pulmonary fibrosis

Epithelial alarmins and the microenvironment of pulmonary fibrosis

Inflammatory phase of fibrolasts in pulmonary fibrosis

In pulmonary fibrosis models, fibroblasts seem to undergo an initial inflammatory phase, marked by the expression of immunoregulatory genes, before eventually differentiating into a fibrosis-promoting cell type [24]. The key factors driving these differentiation processes are still not fully understood. Epithelial alarmins released after lung injury may activate downstream pathways leading to fibroblastic differentiation

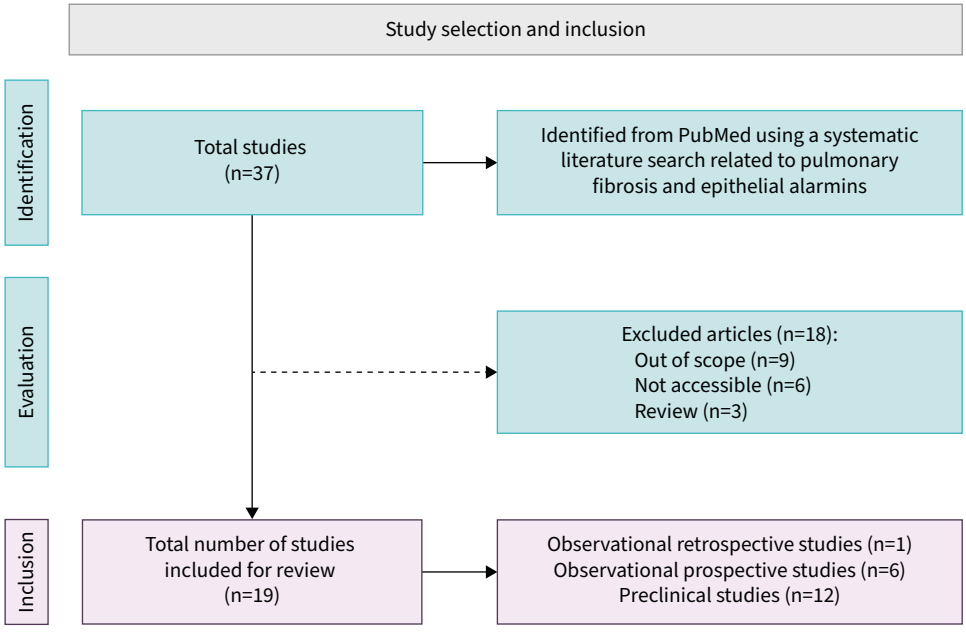

FIGURE 1 Flow diagram for study selection and inclusion for the review.

and activation. The expression of the main epithelial alarmins has been investigated in human lung fibroblasts as well as in the fibrotic lung microenvironment.

TSLP and STAT3 signalling

TSLP and its receptor (TSLPR) have been found to be highly expressed in the lungs of IPF patients. The expression of TSLP has been observed in epithelial cells, mononuclear cells and, though to a lesser extent and with weaker intensity, in fibroblasts. However, in healthy human lung tissue, TSLP has been detected exclusively in mast cells. Moreover, *in vitro* TSLP stimulation activates the fibroblast-driven STAT3 (signal transducer and activator of transcription 3) signalling pathway leading to the release of C-C motif chemokine ligand 2, a chemokine with chemotactic function for monocytes, known as key regulators of tissue repair and remodelling [25].

IL-25/IL-17RB axis and profibrotic gene expression

IL-25 and its receptor (IL-17RB) have been detected in lung tissue of patients with IPF [26]. They are upregulated in damaged fibroblasts and AECs as the IL-25/IL-17RB axis may modulate their phenotype in favour of a profibrotic response to lung injury. *In vitro*, IL-25 stimulation directly activates lung fibroblasts and stimulates EMT process in AECs. This has resulted in a dose-dependent increase in the expression of pro-fibrotic genes, including collagen I and III [27].

IL-33 pathway and the ST2 receptor

Lastly, IL-33 expression is also increased in IPF lungs [28], despite the absence of any significant difference in IL-33 mRNA expression between non-IPF and IPF fibroblasts [29]. In accordance with the findings of the present report, the ST2 receptor has been observed to be absent in lung fibroblasts. Conversely, its expression has been detected in other cell types that have been demonstrated to be implicated in the IL-33 pathway, including M1 and M2 lung-resident macrophages and pulmonary artery endothelial cells [29].

Epithelial alarmins and ILC2 activation

In parallel with these findings, increased ILC2 counts have been reported in patients with lung fibrosis [23]. The gene expression of ILC2s from individuals with IPF exhibits a marked increase of type 2 pivotal mediators, including IL-13 and IL-5 [30]. Indeed, epithelial alarmins are effective activators of ILC2s, with the potential to trigger the activation of lung-resident ILC2s [31] and the onset of biased type 2 inflammation in fibrotic lungs [32].

Epithelial alarmins and animal models of fibrotic lung disease

Although it is hindered by many issues in terms of reliability and reproducibility of pathogenic processes, bleomycin (BLM)-induced pulmonary fibrosis remains the most accepted animal model of IPF [33]. Understanding the role of epithelial alarmins in BLM model may therefore be helpful to define the pathogenic mechanisms through which they contribute to fibrogenesis.

Insights into IL-33 function from bleomycin mouse models

The role of IL-33 in the pathogenesis of pulmonary fibrosis has been widely explored in the BLM model, but with conflicting results, probably due to different study designs. Overall, the mIL-33/ST2 axis appears to play a key role during the inflammatory phase subsequent BLM instillation, facilitating the shift from an acute pulmonary inflammatory state to an exuberant remodelling phase leading to a more extensive lung fibrosis development [34]. This is achieved by promoting the infiltration and activation of type 2 inflammatory cells, particularly ILC2s, as well as the polarisation of M2 macrophages.

In contrast, despite confirming the IL-33 expression by fibrotic fibroblasts and its susceptibility to TGF-β exposure, another study did not observe any significant pro-fibrotic effects on human lung fibroblasts treated with IL-33, suggesting that the IL-33/ST2 pathway is unlikely to play a critical role in the proliferation and overactivation of fibroblasts or myofibroblasts in IPF [29].

Still, IL-33 has the potential to exacerbate BLM-induced lung injury in an ST2- and Th2-independent manner, particularly through its immature form (flIL-33) [35], exerting its effects through a primarily post-translational pro-fibrotic mechanism, influencing the pulmonary inflammatory microenvironment [28, 35]. In BLM-treated mice, pharmacological inhibition of flIL-33 alleviated disease severity, underscoring the significance of IL-33 receptor binding-independent mechanisms in lung fibrogenesis [28, 35].

The mechanistic role of epithelial alarmins in pulmonary fibrosis has also been explored in the context of arthritis induction in animal models of murine disease. In this inflammatory setting, similar to RA,

repeated exposure to bacterial endotoxin drives the development of a pro-fibrotic/pro-inflammatory lung disease, marked by an amplified IL-33-mediated response [36].

Biphasic role of TSLP in BLM-induced lung fibrosis

Similarly to IL-33, TSLP showed a biphasic behaviour based on different phases of BLM-induced lung fibrosis. Macrophage-secreted TSLP contributes to the initiation of the fibrotic process upon lung injury by promoting the EMT of AECs [37]. By contrast, in acute tissue damage, TSLP appears to have a protective role by reducing the overall inflammation burden. This effect, as demonstrated both *in vitro* and *in vivo* (murine models), occurs through a dual mechanism, namely regulation of apoptosis and modulation of caspase-1 and caspase-3 activity, resulting in a decrease in the production of the pro-inflammatory IL-1β [38].

Type 2 inflammation and fibrosis induced by IL-25 in mice

IL-25 has been scarcely investigated in murine models, but it seems to contribute to the development of a biased inflammatory microenvironment, triggering excessive remodelling. In this context, intranasal administration of IL-25 to mice resulted in type 2 pulmonary inflammation driven by IL-5 and IL-13, leading to an increase in collagen deposition [27].

Limitations of current evidence in pre-clinical studies

It is important to acknowledge the limitations of studies conducted on animal models and the subsequent challenges in translating these results to human models.

BLM-induced models primarily reflect acute injury and do not recapitulate the chronic and heterogeneous nature of fibrotic ILDs, limiting the clinical relevance of the results. Furthermore, most murine studies have not systematically investigated the contribution of key immune cell populations, such as ILC2s, Tregs and alternatively M2 macrophages, which are increasingly recognised as central players in fibrotic pathogenesis [28].

Frequently, the available studies present small cohort sizes, which complicates the assessment of the relationship between alarmins and the clinical features of IPF. In addition, *in vitro* studies are not adequately designed to evaluate the efficacy of alarmins in inducing EMT of AECs. It is evident that the models employed in the studies lack the complexity inherent in human fibrotic models [27].

These general limitations are particularly evident in studies investigating IL-33, where conflicting results reflect not only biological variability but also methodological inconsistency.

Despite the growing interest in the role of IL-33 in fibrotic lung diseases, the available evidence presents a heterogeneous and sometimes conflicting picture. The role of IL-33 in experimental models of pulmonary fibrosis remains controversial, largely due to heterogeneity in study design and the molecular form of IL-33 employed. For instance, in BLM-models, the genetic deletion of IL-33 or ST2 reduces pulmonary fibrosis, as does Cre-induced IL-33 deficiency in response to acute or chronic BLM exposure. However, the transfer of flIL-33, but not mIL-33, *via* an adenovirus into the lungs of wild-type or ST2-deficient mice enhances the profibrotic effect of BLM without inducing a Th2 phenotype. In cultured mouse lung cells, flIL-33 overexpression induces moderate and distinct transcriptomic changes compared to the robust response induced by mIL-33. Meanwhile, ST2 deletion abrogates the effects of both IL-33 forms. Therefore, flIL-33 may contribute to fibrosis independently of ST2 and Th2 cells. This suggests that targeting both flIL-33 and mIL-33 pharmacologically may be an effective treatment for patients with pulmonary fibrosis [35]. The utilisation of different animal models complicates the translation of results to human models, given the complexity of pulmonary fibrosis and the differences between the human and animal immune systems. A particular point of interest is the inability of researchers to verify whether flIL-33 undergoes the same proteolytic process in human and mouse models [28].

Conversely, data derived from human studies have yielded less definitive results. While IL-33 expression is increased in the lungs of patients with IPF, *in vitro* studies using human precision-cut lung slices and primary fibroblasts have shown no significant pro-fibrotic response to IL-33 stimulation. This discrepancy may be partially explained by the absence or low expression of the IL-33 receptor ST2 on human fibroblasts, which limits their ability to respond to IL-33 *via* classical pathways.

Taken together, these observations highlight that the effects of IL-33 are highly context-specific, influenced by the cellular target, disease stage, model system used and the molecular form of IL-33 studied. The divergent results reported across pre-clinical and clinical studies underscore the need for more

standardised models and longitudinal human data to clarify whether and how IL-33 contributes to fibrogenesis in idiopathic and secondary ILDs (table 2).

Epithelial alarmins and IPF: clinical studies

Comparison of alarmin levels in IPF and other ILDs

The broad pre-clinical evidence of epithelial alarmins involvement in lung fibrosis needs to be compared to real-life settings to better address its clinical significance. On this regard, Lee *et al.* [39] measured IL-33, TSLP and IL-25 in bronchoalveolar lavage fluids obtained from patients with IPF, healthy controls and patients affected by other ILDs (including nonspecific interstitial pneumonia, hypersensitivity pneumonitis and sarcoidosis). IPF patients showed a significant increase in IL-33 and TSLP levels compared to other groups. However, isolated or concurrent increase in IL-33 and TSLP was not associated with clinical outcomes expressed as respiratory functional deterioration. The study was hindered by several limitations, including a short follow-up period and a small sample size, which likely conditioned a full understanding of the significance of these cytokines on the clinical outcomes of IPF. Moreover, since the currently available antifibrotic medications (nintedanib and pirfenidone) slow the functional decline of IPF, ongoing or discontinued use of these treatments may have biased the results.

Alarmin dynamics before and after antifibrotic treatment

Based on the above assumptions, Majewski *et al.* [40, 41] prospectively evaluated IL-25, IL-33 and TSLP concentrations in systemic circulation and lung compartments in patients with IPF before and after 1 year of antifibrotic treatment. Exhaled breath condensate (EBC) was used for sampling airway epithelial lining fluid. At baseline, serum and EBC concentrations of TSLP serum resulted elevated in patients with IPF compared to controls, while no significant differences of IL-25 or IL-33 values were observed. Notably, the authors observed a significant decrease of both IL-25 and TSLP in lung compartment after 1 year of antifibrotic treatment. Therefore, to better assess the mechanistic link between antifibrotic efficacy and epithelial alarmins reduction, patients were classified into progressors and nonprogressors according to functional decline rate. IL-25 and TSLP levels in EBC significantly decreased over the study period in stable IPF patients, while in progressors, a significant reduction was observed only in IL-25 EBC levels [40, 41].

Potential role of TSLP and IL-25 as treatment response markers

The interconnection between TSLP kinetics and functional stability supports the hypothesis of a clinical relevance of TSLP-driven immune responses in IPF development and progression, which may also be influenced by antifibrotic treatment, suggesting TSLP and IL-25 as potential markers of response to treatment. On the other hand, despite the aforementioned evidence of IL-33 role in lung fibrosis development in murine model, the concentration or expression of this cytokine appeared not to be associated with the most valuable outcomes usually implemented in the clinical management of IPF [39, 40].

TABLE 2 Epithelial alarmins in pre-clinical studies of fibrotic lung disease: main findings and study limitations

Alarmin	Main experimental evidence	Pro-fibrotic mechanisms	Limitations
IL-33	IL-33/ST2 axis promotes type 2 inflammation (ILC2, M2 macrophages) flIL-33 exacerbates fibrosis independently of ST2	Enhances Th2-type immune response Modifies inflammatory microenvironment post-translationally Favours chronic remodelling phase	Contradictory findings (flIL-33 *versus* mIL-33) *In vitro* human studies show limited fibroblast response Inconsistent expression of ST2 in human fibroblasts Unclear proteolytic processing in humans *versus* mice
TSLP	Shows biphasic effect in BLM models Promotes EMT in AECs Reduces inflammation during acute damage	Induces EMT *via* macrophage signalling Modulates caspase-1 and -3 Reduces IL-1β levels	Phase-dependent effects make interpretation complex Data limited mostly to early or acute phases
IL-25	Few studies available Intranasal administration leads to type 2 inflammation and collagen deposition	Drives IL-5/IL-13 axis Increases collagen synthesis and tissue remodelling	Poorly investigated in animal models Lack of mechanistic and longitudinal studies

AEC: alveolar epithelial cell; BLM: bleomycin; EMT: epithelial-to-mesenchymal transition; flIL-33: full-length interleukin-33; IL: interleukin; ILC: innate lymphoid cell; mIL-33: mature interleukin-33; ST2: suppressor of tumorigenicity 2; Th2: T-helper type 2; TSLP: thymic stromal lymphopoietin.

Epithelial alarmins and CTD-ILDs: clinical studies

IL-33/IL-13 axis in SSc-ILD

Regarding the clinical significance of epithelial alarmins in CTD-ILDs, most of the studies available in literature focused on the prognostic and diagnostic role of IL-33, while TSLP and IL-25 have been scarcely explored. Versace *et al*. [42] assessed serum levels of IL-33 and IL-13 in patients with diffuse SSc-ILD, comparing them to SSc patients without ILD and healthy controls. Their goal was to validate the pre-clinical hypothesis of an IL-33/IL-13 signalling axis driving SSc-associated ILD. Both IL-13 and IL-33 levels were increased in SSc patients compared to controls and were significantly associated with each other. Interestingly, IL-13 and IL-33 exhibit an inverse correlation with pulmonary function measurements (including diffusing capacity of the lung for carbon monoxide, forced vital capacity and total lung capacity). The subgroup of SSc patients with lung function impairment showed a significant increase in IL-33 and IL-13; accordingly, the extent of interstitial fibrosis, topographically evaluated using the Warrick score on computed tomography imaging, was significantly related to IL-33 and IL-13 levels [42], supporting the potential as severity biomarkers of SSc lung involvement.

Clinical implications of IL-33 in RA-ILD

Similarly, various scientific inquiries have investigated IL-33 contribution to pulmonary fibrosis secondary to RA. Abdel-Wahab *et al*. [43] examined serum IL-33 levels in RA patients and explored their association with disease activity and clinical features, including lung involvement. Serum IL-33 levels were notably higher in RA patients compared to healthy controls and a significant correlation was observed between IL-33 levels and the presence of ILD, as well as bone erosion.

To further characterise IL-33's role in disease activity and lung fibrosis, Xiangyang *et al*. [44] measured serum levels of IL-33 and matrix metalloproteinase (MMP)-3, a crucial factor in lung fibrogenesis, which is also produced by fibroblast-like synoviocytes involved in bone erosion in RA patients. Again, serum IL-33 was elevated in patients with RA and was associated with bone erosion and ILD complication. A significant positive correlation between IL-33 and MMP-3 levels was detected suggesting that IL-33 may trigger fibroblastic activation both in lung and in synovial compartments leading to pulmonary fibrosis and bone erosion.

Further evidence of the potential pathogenic role of IL-33 in RA-ILD comes from the work of Poole *et al*. [45] that assessed the association between serum alarmins and the risk of RA-ILD by measuring IL-33, TSLP, and IL-25 in a prospective multicentre cohort of RA patients. No significant associations were found between TSLP or IL-25 levels (at baseline) and the risk of developing RA-ILD during follow-up. In contrast, a significant inverse association was identified between IL-33 levels and the development of ILD during follow-up. This association remained significant even after adjusting for other ILD risk factors in the studied population.

This unexpected finding is challenging to interpret, as the data only reflect systemic IL-33 levels without comparison to lung compartment-specific data. However, IL-33 is the only epithelial alarmin that has shown correlations with incidental ILD, suggesting that disruptions in the IL-33 axis could trigger a complex, compartmentalised response in the lung microenvironment, ultimately driving fibrogenesis.

Limitations of clinical studies

Despite the growing interest in the role of epithelial alarmins in the pathogenesis of pulmonary fibrosis, clinical studies conducted to date have several limitations. The samples considered are limited in scope and frequently exhibit heterogeneity, rendering them difficult to compare across studies with respect to demographic, clinical, laboratory and functional characteristics. The temporal gaps between follow-up appointments are often inadequate for the evaluation of clinical and laboratory trends over time. Concomitant immunosuppressive or antifibrotic therapies are frequently not taken into account, thus representing a confounding factor. Furthermore, the evaluation of alarmins is frequently conducted in diverse sample types, including blood, bronchoalveolar lavage and EBC. The limitations described above have a detrimental effect on the reproducibility of the results (table 3).

In addition, patients with IPF and CTD-ILD display significant heterogeneity in terms of age, sex, smoking status, comorbidities (such as COPD, diabetes or cardiovascular disease) and underlying genetic factors [13, 46].

These differences are not only relevant for disease risk and progression, but can also influence the biological environment of the lung, including immune activation and fibrotic processes [13, 47]. Alarmin expression is shaped by clinical and demographic heterogeneity, which likely impacts therapeutic

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TABLE 3 Summary of key clinical studies investigating alarmins in interstitial lung disease (ILD)

First author, reference, year	Type	Study population	Median or mean±SD age, years	Specimen type	Main outcomes	Key findings
Lee [39] 2017	Observational prospective	100 IPF patients	63.8	BAL	Measurement of alarmins in ILD patients	IL-33 and TSLP were significantly increased in the lungs of IPF patients compared to the other groups
Majewski [40] 2019	Observational prospective	52 IPF patients	68.21	EBC	Evaluation of alarmins in IPF *versus* healthy controls patients Study alarmin's kinetics after 1 year of antifibrotic therapy	TSLP was significantly increased in IPF patients *versus* healthy controls IL-25 decreased over time in both stable and progressive IPF patients TSLP decreased only in stable IPF patients
Majewski [41] 2019	Observational prospective	15 IPF patients	69.7±1.8	EBC	Measurement of alarmins in healthy controls, asthma, ILD and COPD patients	IL-25 levels were lowest in IPF IL-33 levels were significantly higher in IPF *versus* healthy controls IL-33 levels were similar in IPF, asthma and COPD
Versace [42] 2022	Observational prospective	30 SSc patients	58.5±12.4	Serum	Evaluate IL-33 and IL-13 levels in diffuse SSc-ILD patients *versus* SSc without ILD and healthy controls, using pulmonary function tests to identify ILD	IL-13 and IL-33 levels were significantly higher in SSc patients *versus* controls IL-13 and IL-33 levels showed a positive correlation Both IL-13 and IL-33 showed inverse correlations with lung function parameters (D_{LCO}, FVC, TLC) Both IL-13 and IL-33 positively correlated with radiological severity (Warrick score)
Abdel-Wahab [43] 2016	Observational prospective	50 RA patients	51.1±9.6	Serum	Analyse IL-33 levels in RA patients Investigate IL-33 relationship with clinical features and disease activity	Serum IL-33 levels were significantly elevated in RA patients *versus* healthy controls IL-33 correlated with the presence of ILD and bone erosion
Xiangyang [44] 2012	Observational prospective	132 RA patients	51±17	Serum	Analyse serum IL-33 levels in RA patients Investigate IL-33 potential pathogenic role alongside MMP-3	Serum IL-33 and MMP-3 levels were significantly higher in RA patients *versus* healthy controls IL-33 was significantly elevated in RA patients with ILD compared to those without MMP-3 and IL-33 levels showed a positive correlation
Poole [45] 2024	Observational prospective	2835 RA patients	65	Serum	Quantify baseline alarmin levels and their association with future RA-ILD risk	Inverse association between IL-33 levels and risk of developing RA-ILD during follow-up period

Main study characteristics, evaluated outcomes and principal findings are reported to provide an overview of current clinical evidence on the role of alarmins in ILDs. BAL: bronchoalveolar lavage; EBC: exhaled breath condensate; D_{LCO}: diffusing capacity of the lung for carbon monoxide; FVC: forced vital capacity; IL: interleukin; IPF: idiopathic pulmonary fibrosis; MMP-3: matrix metalloproteinase-3; RA: rheumatoid arthritis; SSc: systemic sclerosis; TLC: total lung capacity; TSLP: thymic stromal lymphopoietin

responses. Such variability may contribute to distinct alarmin profiles in CTD-ILDs compared to IPF, highlighting the need for larger cohort studies to better characterise their pathogenic and prognostic roles across ILD subtypes.

Conclusion and future directions

In recent decades, the immune landscape of the human lung has expanded to include new players in respiratory physiology and pathology. Notably, progress in the understanding of alarmin biology has led to new therapeutic approaches for severe asthma, paving the way for more personalised treatment options.

Pre-clinical studies have shown epithelial alarmins are also deeply involved in the development of lung fibrosis. Alarmins contribute to an imbalance in immune activation by promoting a shift towards type2-cytokine dominated milieu. In addition, they play a dynamic role in regulating fibroblast–macrophage interactions during lung injury. This process influences macrophage polarisation and drives the EMT.

However, the exceptional complexity of the crosstalk between innate and adaptive immune responses in pulmonary fibrosis complicates the task of providing a thorough overview of the interactions between fibrogenesis and alarmin signalling. Unravelling the signalling network driving the various fibrotic ILDs is critical for the development targeted therapeutic strategies and improve patient outcomes. In this regard, several important questions remain to be addressed regarding the physiopathological and clinical significance of epithelial alarmins both in IPF and CTD-ILD.

At present, no clinical trials are investigating TSLP as a therapeutic target for any form of pulmonary fibrosis. Nevertheless, pre-clinical studies, particularly in murine models of IPF, suggest that TSLP plays a significant role in fibrotic pathogenesis, making it a promising candidate for future therapeutic development. Currently, anti-TSLP therapies such as tezepelumab are approved for asthma and are under investigation for other inflammatory airway diseases, including COPD. Further research is warranted to explore the potential of TSLP inhibition in pulmonary fibrosis.

The role of IL-33 in the pathogenesis of pulmonary fibrosis remains a subject of debate. Research conducted on the BLM models suggests that mIL-33/ST2 may induce the activation of type 2 inflammatory cells, the polarisation of M2 macrophages and the secretion of TGF-β, ultimately contributing to the development of pulmonary fibrosis. As demonstrated by the findings of the aforementioned studies, IL-33 may play a pivotal role in the early inflammatory phase that precedes fibrotic remodelling. Conversely, studies on human pulmonary fibroblasts suggest that IL-33 likely has no substantial profibrotic role. However, in cases of CTD-ILD, serum IL-33 levels have been observed to be elevated in patients with SSc-ILD and RA-ILD compared to those without pulmonary involvement of CTD. Currently, there are no clinical trials testing IL-33 for the treatment of pulmonary fibrosis, with the exception of those for the treatment of obstructive pulmonary diseases. The potential value of anti-IL33 therapies in the early stages of fibrotic diseases is worthy of exploration, with the aim of determining whether these therapies can be used to slow or block the fibrotic process.

Although IL-25 has been investigated in a limited number of pre-clinical studies, primarily in murine models, current evidence suggests that it promotes type 2 immune responses and contributes to ECM remodelling through increased collagen deposition. To date, no clinical trials have targeted IL-25 in the context of pulmonary fibrosis. Nonetheless, these preliminary findings indicate that the IL-25 pathway represents a potentially promising target for future therapeutic investigation.

In addition, recent studies conducted on patients undergoing antifibrotic therapies suggest the use of alarmins as potential biomarkers for assessing treatment response. Notably, it was observed that serum and EBC levels of TSLP and IL-25 in patients with IPF were reduced after 1 year of treatment, while in patients with disease progression, a significant reduction was observed only in EBC levels of IL-25. In the case of IL-33, however, no evidence was found to support its use in the clinical monitoring of patients with IPF.

These findings highlight the need for further investigation into the pathogenic role of alarmins in pulmonary fibrosis. In particular, their potential utility as biomarkers of treatment response or disease progression should be rigorously evaluated. Future clinical trials specifically targeting alarmins could contribute to the development of novel therapeutic strategies. Given the emerging role of IL-33 in CTD-ILD, it would be especially important to determine whether IL-33 may serve as a selective therapeutic target within this subgroup of patients. These considerations raise the possibility that, in the future, more tailored therapeutic strategies could be developed for specific subtypes of pulmonary fibrosis.

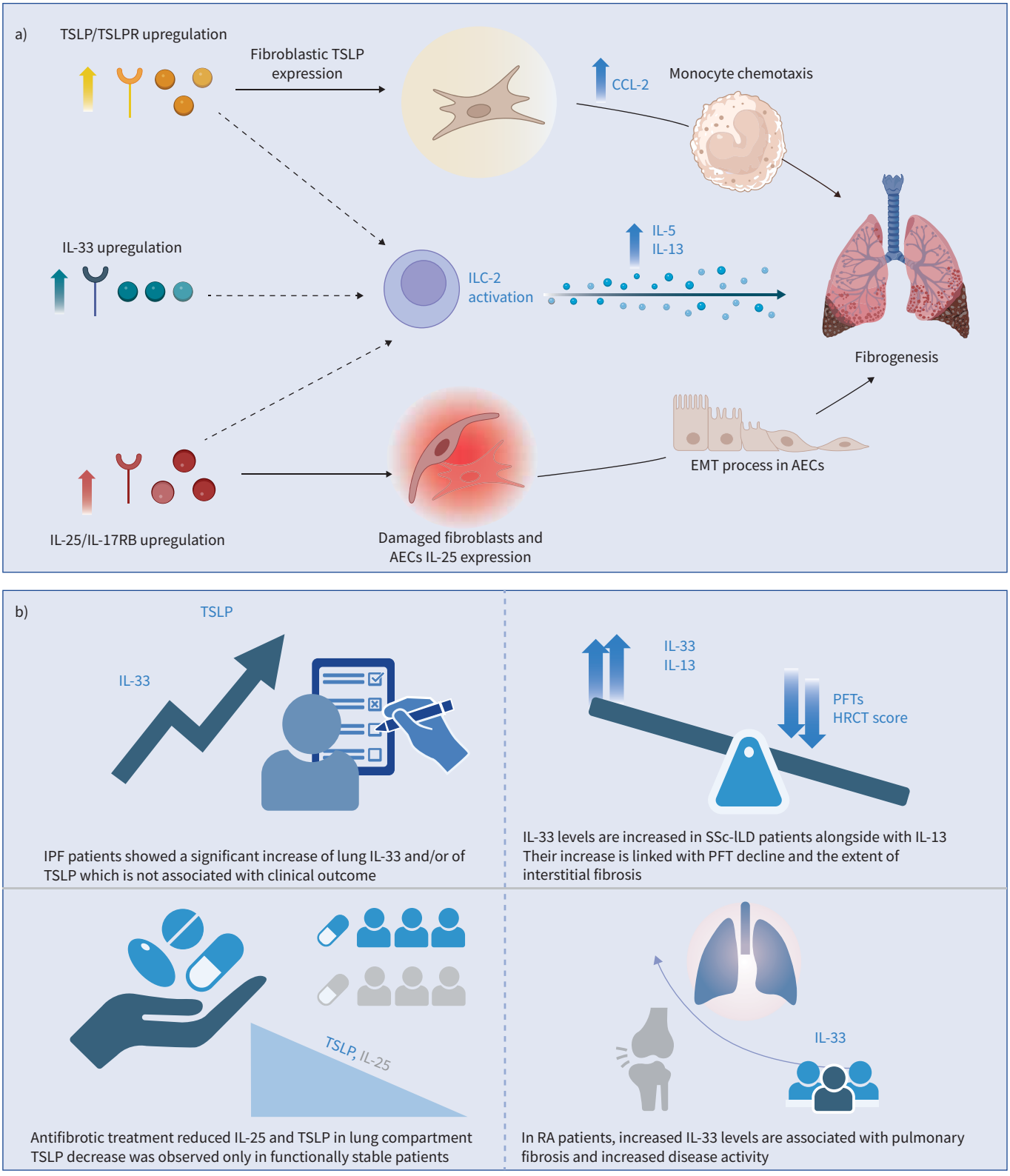

FIGURE 2 The main findings of clinical and pre-clinical studies on epithelial alarmins in pulmonary fibrosis. a) Proposed model of immunological mechanisms underlying the establishment of a pro-fibrotic microenvironment based on pre-clinical evidence. Activation of the thymic stromal lymphopoietin (TSLP)/TSLP receptor (TSLPR) axis enhances TSLP production by fibroblasts and promotes monocyte recruitment *via* C-C motif chemokine ligand 2 (CCL-2), while interleukin (IL)-25 released by damaged fibroblasts and alveolar epithelial cells (AECs) drives epithelial-to-mesenchymal transition (EMT). These pathways converge to sustain a type 2 cytokine-rich environment that promotes progression of

pulmonary fibrosis. b) Clinical significance of epithelial-derived alarmins in fibrotic interstitial lung diseases (ILDs). TSLP and IL-33 are elevated in idiopathic pulmonary fibrosis (IPF), although their levels do not consistently correlate with clinical outcomes. Antifibrotic treatment decreases IL-25 and TSLP, with a significant reduction in TSLP observed only in patients with stable lung function. In systemic sclerosis (SSc)-ILD, elevated IL-33 and IL-13 are associated with lung function decline and greater fibrosis extent. Similarly, in rheumatoid arthritis (RA), IL-33 correlates with both fibrotic lung involvement and overall disease activity. HRCT: high-resolution computed tomography; ILC: innate lymphoid cell; PFT: pulmonary function test. Created with BioRender.com.

The advancement of our understanding of alarmin biology through translational research will be crucial to the confirmation of pre-clinical findings in human models and to the acceleration of the development of effective, targeted therapies for the various subtypes of pulmonary fibrosis (figure 2).

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