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Review article

Adding pieces to the puzzle: IL-33 contribution to fibrogenesis in chronic lung allograft dysfunction

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ABSTRACT

Interleukin-33 (IL-33) is a pleiotropic, chromatin-binding cytokine primarily expressed by non-hematopoietic cells, including endothelial cells, fibroblasts and bronchial epithelial cells. It participates in various respiratory diseases, such as acute and chronic inflammatory diseases, viral infections, lung cancer and COPD, and is known to mediate asthma and allergic conditions. IL-33 plays a dual and context-dependent role, contributing to tissue homeostasis and immune regulation under physiological conditions, while promoting inflammation and fibrosis in pathological contexts. Its signalling is mediated by the ST2 receptor, which exists in two forms: the membrane-bound ST2L that activates immune responses, and the soluble decoy receptor sST2 that negatively regulates IL-33 activity. Over the past decade, medical research has cast a spotlight on the widespread contribution of IL-33 biology not only to inflammation but also to the development of fibrosis and lung transplant rejection. A comprehensive overview of the interactions between rejection following lung transplant and IL-33 signalling is lacking. In this review, we summarize the most recent literature regarding the IL-33 in relation to chronic lung allograft dysfunction (CLAD) and acute rejection. We also discuss the potential contribution of microbial and environmental stimuli in shaping IL-33-driven type 2 and autophagic responses in the lung transplant micro-environment. Recent findings regarding therapeutic implications of IL-33 were also reported.

1. IL-33 cytokine biology

Interleukin-33 (IL-33) is a pleiotropic chromatin-binding cytokine that influences both innate and adaptive (Th-2) immune responses [1,2]. This protein consists of 270 amino acids with two essential domains: the first domain (amino acids 1–65) facilitates nuclear localization and chromatin association; the second domain (amino acids 112–270) acts as the IL-1-like cytokine domain responsible for cytokine activities [3]. These domains are separated by a central linker region (amino acids 66–111) [4]. Full-length IL-33 (fIL-33) is the active form of the protein that can be cleaved proteolytically to generate "mature" bioactive fragments; alternatively, it can be inactivated through apoptotic caspase-mediated cleavage at the cytokine domain. Once in the extracellular space, IL-33 is rapidly inactivated by oxidation or neutralised by soluble decoy receptor ST2 [5].

In the past, IL-33 was believed to be secreted extracellularly only in relation to cell necrosis or injury [6]. A mechanism by which IL-33 is co-secreted from cells via exosomes and the nSMase2-regulated endosome pathway was recently described [7].

The functions of IL-33 in the lung have been reported in several conditions, including acute and chronic inflammatory diseases, viral infections [8,9] and other lung diseases such as lung cancer and COPD [10–14]. The best known mechanism of IL-33 is as mediator of asthma and allergic conditions [9,15]. It has been associated with inducing airway hyperresponsiveness (AHR) in allergic patients and after viral infections [16].

Although it is well analysed the role of IL-33 in allergy and asthma pathobiology, its

function is subject to an intriguing level of host and context-dependent modifications [17]. These aspects make difficult to define the exact role of IL-33 in diseases.

Nuclear localization of IL-33 has been described for cell types such as

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human high endothelial venule cells, lung airway epithelium, keratinocytes and fibroblastic reticular cells [18].

In lung epithelial cells, IL-33 results in constitutive expression and serves as an "alarmin" in response to infection or injury. The presence of an N-terminal domain nuclear-localization sequence and a homeodomain-like helix-turn-helix motif enables IL-33 to bind to heterochromatin, potentially granting it transcriptional regulatory capacities [19]. IL-33 acts as a pleiotropic protein: it stimulates the release of proinflammatory mediators from mast cells and enhances Th-2 cytokine responses, including those from ILC2s. IL-33 can also upregulate FOXP3+ CD4 regulatory T cells to promote tolerance and reduce inflammation. At the same time, it promotes differentiation of "unconventional" $CD4^{+}$T-cells into the Th2 phenotype, characterised by expression of IL-5 and IL-13 but not IL-4. IL-33 also enhances differentiation of "alternatively activated" macrophages and stimulates responses in mast cells, basophils and eosinophils [20]. A mechanism related to autophagy pathways involving IL-33 was recently described [21,22].

The aim of this review of the recent scientific literature was to analyse reports regarding IL-33 in lung diseases, with a focus on the latest data on lung injury and fibrosis and their role in acute and chronic rejection after lung transplant. Very little is known about its role in lung injury, hence the need to understand its ambivalent role of being simultaneously protective and harmful for lung tissue.

2. IL-33 Lung inflammation

2.1. The IL-33/ST2 axis and its role in adaptive and innate immunity

IL-33 is expressed mainly by non-hematopoietic cells, including endothelial cells, fibroblasts and bronchial epithelial cells [23,24]. ST2 exerts its biological effects by acting as receptor for IL-33. It consists of two main splice variants due to differential promoter binding: a membrane-bound form (ST2), which promotes NF-κB signalling, and a soluble form (sST2), which acts as a decoy receptor to sequester free IL-33 and prevent ST2/IL-33 signalling.

ST2 is expressed in a large variety of immune cells such as conventional T cells, regulatory T cells (Tregs), type 2 innate lymphoid cells (ILC2), mast cells, eosinophils, natural killers (NK) and invariant-NKT cells (iNKT). In the context of asthma patients, signalling through ST2 in immune cells induces type 2 and Treg immune responses, IgE production and eosinophilia [24,25]. Studies on Treg-depleted mice observed increased lung levels of IL-33.

IL-33 has been demonstrated to promote tissue repair through activation of ST2-Treg cells, which in turn induces amphiregulin (AREG) and suppresses the innate immune responses to allergens. IL-33 is of critical importance in preventing mortality after acute lung injury (ALI) through control of the early inflammatory response to tissue injury by regulation of the actions of Tregs.

The mechanism by which IL-33 exerts control over the local inflammatory immune response after ALI depends on induction of interleukin-13 (IL-13) production by ST2+ Tregs, which serves to limit local inflammatory cytokines and the presence of inflammatory myeloid cells [26,27]. This mechanism is considered a potential target for the development of therapies for ALI [26].

IL-33 also activates ILC2s (that express ST2), and this can contribute to enhanced production of interleukin-4 (IL-4) after Treg depletion [28]. Intranasal administration of IL-33 in mice resulted in activation of ILC2s and subsequent induction of lung inflammation. This caused severe lung pathology, including goblet cell hyperplasia, increased numbers of eosinophils and ILC2s in lung tissue and bronchoalveolar lavage fluid (BALF) of mice.

In particular, the neuropeptide neuromedin U (NMU) and related receptor (NMU receptor 1 (NMUR1) expressed by ILC2s act as a robust activator of ILC2 proliferation during helminth infection, cooperatively activating gene expression of IL-33 and enhancing proinflammatory cytokines. In contrast, CGRP (a-calcitonin gene-related peptide) – a product of the calcitonin (Calca) gene secreted by pulmonary neuroendocrine cells (PNECs) in the lung – counteracts NMU by suppressing cell proliferation and gene expression of inflammatory cytokines, including IL-33 [29].

IL-33 has been demonstrated to play a role in induction of ILC2-mediated airway inflammation through activation of the mammalian target of the rapamycin (mTOR) pathway via p110δ phosphoinositide 3-kinase. Blockade of the mTOR pathway has been shown to inhibit IL-33-induced IL-5 and IL-13 production by Th2 cells and ILCs. Specifically, inhibition of the mTOR pathway with rapamycin has been demonstrated to suppress Th2 cell and ILC cytokine production in vitro. In vivo, it has been shown to attenuate IL-33-induced airway inflammation by reducing ILC accumulation, cytokine secretion, eosinophilia and mucus deposition in the airways. Additionally, modulation of the mTOR pathway may represent a potential therapeutic target for the management of airway inflammation in human disease [30]. iNKT cells have also been investigated in relation to IL-33, due to expression of ST2 on the cell surface. In a recent paper, the transfer of iNKT cells to Jα18 KO mice resulted in a reduction of lung inflammation, thereby confirming the regulatory role of iNKT cells during IL-33-mediated lung inflammation [31,32]. Recently, IL-33 has been shown to have a protective role. In particular, it expands ILC2s with subsequent release of IL-13 and directs macrophages toward an M2 phenotype that cooperate for airway dysfunction and inflammation following inhalation of Irritant-owned airway inflammation and dysfunction [33].

2.2. IL-33 and lung inflammatory disease

IL-33 inflammatory pathways work with others (e.g. TSLP) to change the non-immune parts of the lung microenvironment (such as smooth muscle contraction/hyperreactivity, goblet cell mucus production, fibroblast activation and sensory neurons), leading to symptoms and traits of asthma and COPD [34].

IL-33 is a 270-amino acid protein, but shorter isoforms have been shown to have different effects. Furthermore, cleavage of IL-33 by proteases from different cell types can also lead to differing effects within microenvironments, dependent on the cell types present or recruited to an inflammatory insult. A spliced variant of IL-33 has been associated with elevated T2 cytokine activity in airway epithelial cells from individuals with asthma. Conversely, another isoform has been detected to be augmented in airway cells from COPD patients [34].

Loss-of-function mutations in IL33 have been associated with reduced risk of developing asthma and COPD, while gain-of-function have been associated with increased risk of both diseases. Many single-nucleotide polymorphisms (SNPs) increase susceptibility to asthma. Beyond the IL33 gene, IL1RL1 variants also regulate IL-33 signalling. A protective IL1RL1 variant in asthma reduces IL-33 signalling via sST2. The genetics of the IL-33/ST2 axis could determine disease progression [34]. Understanding IL-33 SNPs' role in IL-33 expression and function in various lung diseases could inform therapeutic approaches for asthmatics [9].

IL-33 concentrations were found higher in nasal than in bronchoalveolar-lavage fluid (BALF), indicating that the interleukin may play a more significant role in the upper than the lower airways [35].

Signalling via ST2/IL-33 in mast cells, ILC2, eosinophils, basophils, Th2 and Th9 cells is a key driver of allergic asthma. This is achieved through production of IL-4, IL-5 and IL-13 in the lungs, which subsequently induces airway hyperresponsiveness and goblet cell hyperplasia [24].

The homeostatic levels and protein stability of IL-33 are regulated by phosphate-pyridoxal (PLP), the active form of vitamin B6 [36]. Patients with asthma show reduced blood levels of PLP, which correlates with impaired lung function and elevated circulating eosinophil levels [37,38]. Systemic or local administration of PLP reduced lung

inflammation and eosinophil density in several mouse models of acute lung inflammation, confirming a direct role of PLP in the control of immune or allergic airway disease [37]. Intranasal administration of PLP can also reduce local IL-33 levels in the lung, which may have significant therapeutic implications [39].

Recently, it was also reported the association of IL-33 with neutrophil activation. In particular, IL-33 promotes the release of NETs, facilitating dendritic cell (DC) activation and Th2/Th17 immune response [40]. These results highlighted the role of IL-33 also in non T2 immune responses. In addition, mast cells that have been activated by IL-33 may be a contributing factor to the effects of IL-33. Transcriptomic analysis of sputum cells from patients with severe asthma has revealed the presence of an IL-33-activating mast cell signature, which was enriched in patients exhibiting a mixed granulocytic and neutrophilic phenotype. Conversely, IgE-activated mast cell signatures were found to be enriched in patients with a predominantly eosinophilic phenotype. Collectively, these data suggest the hypothesis that IL-33 activation of mast cells could represent a pivotal mechanism in determining a mixed inflammatory response phenotype of T1 and T2 [34].

Several clinical trials are currently investigating therapeutic strategies targeting the IL-33/ST2 pathway for the treatment of asthma and COPD, highlighting growing interest in this axis as a promising target in chronic airway inflammation. These trials explore both anti–IL-33 and anti-ST2 monoclonal antibodies in diverse patient populations and disease stages. Table 1 summarizes key ongoing and complete trials, focusing on design, endpoints, and targeted mechanisms (see Figs. 1–3 and Tables 2 and 3).

3. IL-33 in the interstitium and in the development of lung fibrosis

During the last years, the research about the role of IL-33 in lung fibrosis increase, and recently this an antifibrotic therapeutic approach is proposed and preclinically tested in mice and in vivo based on targeting the full-length IL-33 precursor protein [48].

IL-33 has also been investigated in relation to recruitment of monocytes to the lung interstitium during T2 inflammatory responses, via upregulation of chemokines CCL2, CCL7 and CCL22. By inhibiting IL-33 or its downstream chemokines, a comprehensive strategy may be devised to mitigate early monocyte-driven inflammation [49].

The extensive molecular interactions of IL-33 in the lung microenvironment have prompted study of its role in promoting fibrosis after injury to lung alveolar epithelial cells. Several studies have demonstrated that IL-33- and IL-33-positive cells are elevated during the inflammatory and pro-fibrotic stages [50].

Pulmonary fibroblasts from the lungs of patients with IPF and systemic sclerosis show increased IL-33 mRNA expression, suggesting that fibroblasts could be a significant source of IL-33 [51,52]. Notably, human BAL samples and lung tissue of patients with IPF showed increased IL-33 mRNA and protein levels, markers associated with response to damage [52].

The potential role of IL-33 in the pathogenesis of pulmonary fibrosis has been thoroughly explored in the bleomycin-mice model of fibrosis. Through interaction with its receptor ST2, IL-33 promotes recruitment of ILC2s which leads to eosinophil recruitment. On the other hand, IL-33 induces macrophages to move toward the M2 cell phenotype. These cells in turn enhance release of IL-13 and TGF-β1, thereby amplifying the fibrotic response [53].

After exposure to IL-33, mice with the genes Akt1 and Akt2 knocked out in macrophages showed reduced IL-13 and TGF-β production and impaired fibrinogenesis, indicating that these genes are essential for IPF progression in response to IL-33 [54].

A second mechanism of IL-33 is ST2-independent. It consists in the "immature" form of IL-3 (full-length IL-33 (flIL-33)), which has lower affinity for the ST2 receptor and is an important intracellular gene regulator, promoting production of pro-inflammatory mediators, such as TGF-β, IL-6, MCP-1 and TNF-α [53,55]. Once released in response to inflammatory stimuli, flIL-33 can be processed by neutrophil-derived

Table 1
Summary of selected clinical trials targeting the IL-33/ST2 axis in asthma and COPD.

Drug (study)	Target	Phase	Target population	Study design	End points
Asthma					
Itepekimab (NCT03387852) [41]	IL-33	II	Moderate-to-severe asthma	Randomized, double-blind, placebo-controlled, parallel-group (alone or in combination with dupilumab)	• Event indicating a loss of asthma control • Lung function, asthma control, quality of life, type 2 biomarkers, and safety
GSK3772847 (NCT03207243) [42]	IL-33	IIa	Moderate-to-severe asthma	Randomized, multicenter, double-blind	• Change from baseline to Week 12 in blood eosinophils and fractional exhaled nitric oxide
Tozorakimab (NCT04570657) [43]	IL-33	II	Moderate-to-severe asthma	Randomized, double-blind, placebo-controlled	• Efficacy (FEV1, asthma control, exacerbation rate) • Safety and tolerability
Astegolimab (ZENYATTA) [44]	ST2	IIb	Uncontrolled severe asthma	Randomized, double-blind, placebo-controlled, dose-ranging proof-of-concept study	• Reduction of exacerbations • Time to first asthma exacerbation • Prebronchodilator FEV1 • Patient-reported outcomes
COPD					
Itepekimab (AERIFY-1/2) [45]	IL-33	II/III	Moderate-to-severe COPD	Randomized, double-blind, placebo-controlled trials	• Reduction of exacerbations • Change of pre-BD-FEV1 at week 24 • Symptom control and safety and tolerability of treatment
Tozorakimab (NCT04631016) [46]	IL-33	IIb	Moderate-to-severe COPD	Randomized, double-blind, placebo-controlled	• Change in pre-BD FEV_1 from baseline to week 12 • Post-BD FEV_1 • Time-to-first COPDCompEx event • Safety
Astegolimab (NCT03615040) [47]	ST2	IIb	Moderate-to-very severe COPD	Single-center, randomized, double-blinded, placebo-controlled	• Reductions of exacerbations • Saint George's Respiratory Questionnaire for COPD (SGRQ-C) • FEV_1 • Blood and sputum cell counts

The table reports phase II and III studies investigating monoclonal antibodies directed against IL-33 or its receptor ST2. Trials are stratified by disease indication (asthma or COPD) and include information on target molecule, study phase, population, design, and key primary and secondary endpoints. BD = bronchodilator; FEV1 = forced expiratory volume in 1 s; COPDCompEx = composite COPD exacerbation endpoint; SGRQ-C = Saint George's Respiratory Questionnaire for COPD.

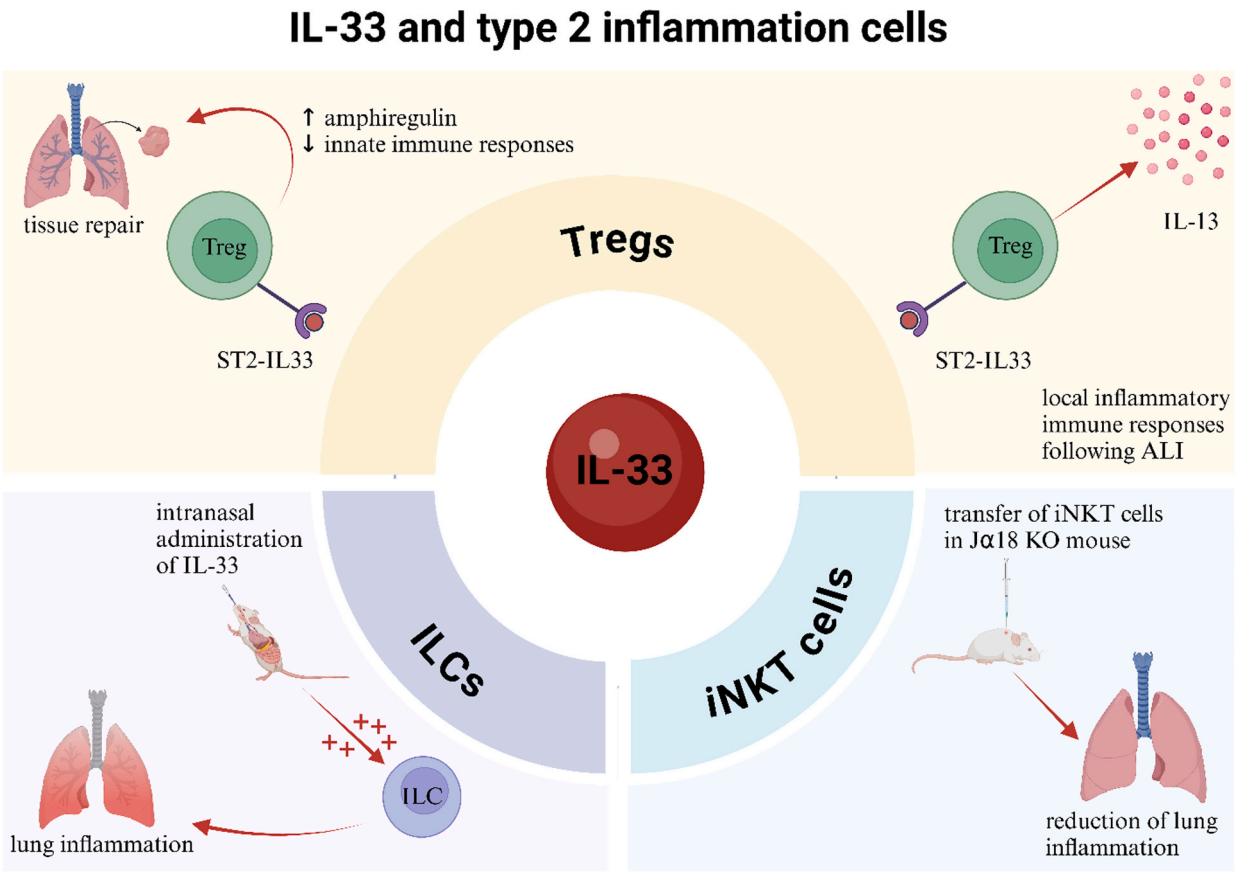

Fig. 1. IL-33 interaction with type-2 inflammatory cells. IL-33 promotes tissue repair through the activation of ST2-Treg cells, which in turn induces amphiregulin (AREG) and suppresses the innate immune responses to allergens; IL-33 exerts control over the local inflammatory immune responses following ALI upon the induction IL-13 production by ST2+ Tregs; intranasal administration of IL-33 in mice resultes in the activation of ILC2s and the subsequent induction of lung inflammation; iNKT cells have a regulatory role during IL-33-mediated lung inflammation, as demonstrated by the transfer of iNKT cells to Jα18 KO mice.

proteases into its mature form, mIL-33, which acts as an extracellular cytokine, binding to specific receptors, including ST2 [53].

Bleomycin-induced lung injury has been shown to be exacerbated by flIL-33, independently of ST2. This effect may be linked to release of pro-inflammatory and fibrotic cytokines, particularly TGF-β, IL-6, MCP-1 and TNF-α, triggered by flIL-33 [55].

The combination of flIL-33 and bleomycin-induced fibrosis in the knockout mouse model had a synergistic effect on pulmonary lymphocyte and collagen accumulation. By contrast, no increase in levels of Th2 cytokines IL-4, IL-5 or IL-13 was evident [55].

flIL-33 was found to significantly increase expression of several heat shock proteins (HSPs), in particular HSP70, which is known to be associated with ILD [56–58]. HSPs play an important role in a wider range of fibrotic diseases, including lung fibrosis, liver fibrosis and idiopathic pulmonary fibrosis via modulation of cytokine induction and inflammatory response [58].

In IPF patients was recently demonstrated that *MIR205HG,* a prognostic factor in these diseases, is involved in the regulation of IL-33 expression. The interaction between *AluJb* element of *MIR205HG* and the *Alu* element of *IL33* was important for these regulatory mechanisms. Furthermore, *MIR205HG* expression was positively correlated with IL-33 expression and the number of ILC2s in tissue samples from patients with IPF [59].

The pleiotropic effects of IL-33 were also recently investigated. The ST2 receptor is reported to be expressed in T regulatory cells as well. Due to its impact on ST2+ Tregs, IL-33 deficiency proved to shorten survival during BLM-induced acute lung injury. IL-33-induced Treg IL-13 production limited the inflammatory response [26], making the timing and context of IL-33 blockade critical in pulmonary fibrosis; indeed, in the early inflammatory phase, IL-33 may be tissue-protective [50]. IL-33 may contribute to the pathogenesis of lung fibrogenesis through the IL-33/ST2 axis, and by modulating the pulmonary inflammatory milieu.

These findings highlight the significant role of IL-33/ST2 signalling and the intracellular regulation of cell expression by flIL-33 in lung fibrogenesis. However, the exact contribution of the IL-33/ST2 pathway and fIL-33 gene regulation to key events in lung fibrosis is still not completely clear.

4. IL-33 in other organ: similarities and differences with lung

Several cellular and molecular mechanisms were described between lung and other organ transplantion, such as kidney and liver transplantation. IL-33 is a key player in kidney and liver ischemia–reperfusion injury, acting as an alarmin in these settings [6]. In the liver, IL-33 is primarily released by hepatic stellate cells (HSCs) or hepatocytes. During acute injury, IL-33 released by damaged hepatocytes promotes tissue healing, while in the case of chronic injury, IL-33 is a critical fibrotic player. As in acute lung injury, in the liver, IL-33 triggers the secretion of IL-13 from ILC2s, thereby enhancing the differentiation and activation of HSCs through direct actions on the HSCs or by amplifying IL-6 and TGF-β signalling, leading to HSC-secreted fibrillar collagen and subsequent fibrogenesis.

As in inflammatory diseases of the lung, such as Asthma, IL-33 has been shown to act as an alarmin in the context of liver ischemia/reperfusion (I/R) injury. Furthermore, IL-33 has been shown to have a deleterious effect on hepatic I/R injury. In the context of liver transplantation, elevated serum levels of IL-33 immediately following reperfusion have been observed to be associated with the development

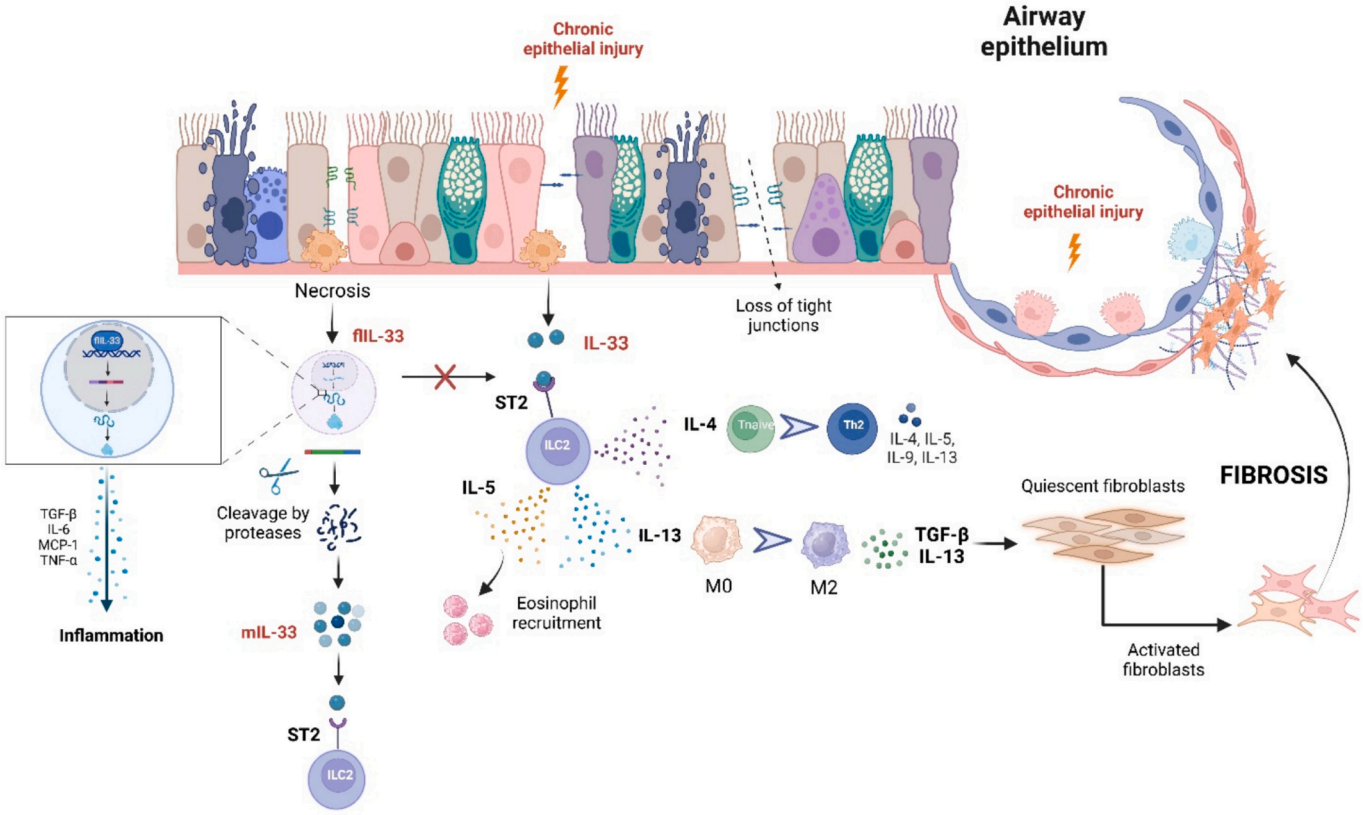

Fig. 2. The role of IL-33 in lung fibrosis through both ST2-dependent and ST2-independent mechanisms. In the ST2-dependent pathway, IL-33 binds to its receptor ST2, leading to the activation of type 2 innate lymphoid cells (ILC2s), which promote eosinophil recruitment and drive naïve T cell (TN) differentiation into a TH2 phenotype, enhancing the release of cytokines such as IL-5 and IL-13. Additionally, IL-33 drives macrophage polarization toward the M2 phenotype, inducing the release of IL-13 and TGF-β1 (key mediators of fibrinogenesis). The ST2-independent mechanism involves the full-length form of IL-33 (flIL-33), which functions as an intracellular regulator of gene expression, promoting the production of pro-inflammatory mediators. Neutrophil-derived proteases can process flIL-33 into its mature form (mIL-33), which acts as an extracellular cytokine, binding to ST2 to modulate the inflammatory and fibrotic response.

of postreperfusion syndrome, acute renal failure, and impaired graft function.

Moreover, the IL-33/ST2 pathway plays a pivotal role in the progression of renal fibrosis, impacting two distinct aspects of this process. On the one hand, this pathway promotes the secretion of pro-inflammatory and pro-fibrotic factors, such as IL-4, IL-13, and TGF-β by certain immune cells. Notably, TGF-β is a central mediator of renal fibrosis. Conversely, the IL-33/ST2 pathway promotes fibrogenesis by inducing EMT of renal tubular epithelial cells and activating myeloid fibroblasts. It has been demonstrated that these changes contribute to the secretion of collagen and fibronectin to facilitate fibrogenesis [60].

As in chronic pathologies of the lung, during chronic kidney injury, IL-33 is released by endothelial cells, epithelial cells and fibroblasts. This activates ST2-expressing cells, such as M2 macrophages, ILC2s, CD4+ T cells and iNKTs, triggering inflammation and tissue repair. Macrophages play an important role in obstructive kidney injury. IL-33 and other cytokines promote the transformation of M0 macrophages into M2 macrophages, with M2 macrophages contributing to fibrosis [60].

IL-33 levels are increased in cases of chronic kidney transplant rejection. Furthermore, immunohistochemical analysis of renal tubules in patients with chronic allograft dysfunction has revealed the presence of IL-33+ cells. In a similar manner, in patients with renal allograft rejection, IL-33 has been detected in the renal tubules and interstitium [60].

Similar findings have also emerged in heart transplantation. Several preclinical studies have shown that IL-33 exerts immunoregulatory functions in cardiac allografts [61–64]. Administration of exogenous IL-33 prolongs graft survival in both acute and chronic rejection models by inducing a Th2-skewed immune response [63] and promoting the expansion of $ST2^{+}Foxp3^{+}$ regulatory T cells and myeloid-derived suppressor cells [61]. Moreover, stromal-derived IL-33 plays a protective role by attenuating early macrophage-driven inflammation and supporting long-term allograft tolerance [64]. In murine models, genetic deficiency of IL-33 exacerbated chronic rejection, underscoring its role in restraining pathogenic inflammation and preserving heart graft function [64].

5. IL-33 context-specific activity and mechanisms of regulation

Although IL-33 is frequently associated with pro-inflammatory and fibrotic responses, its function is highly context-dependent and shaped by a variety of regulatory layers [65]. IL-33 can act as an alarmin cytokine following cell damage, but it is also constitutively expressed in the nucleus of epithelial and endothelial cells, where it may exert transcriptional modulation or structural chromatin roles [66]. Upon release, IL-33 binds to the membrane-bound ST2L receptor to activate canonical MyD88/NF-κB signalling, yet its bioactivity is tightly modulated by several common variables: dose, duration of exposure, redox state, subcellular localization (nuclear vs extracellular), and the balance between ST2L and its decoy receptor sST2 [65,67].

The regulation of these modulatory factors is context-dependent, shaped by elements such as tissue type, severity and duration of epithelial injury, the presence of oxidative stress, and the balance of pro- and anti-inflammatory signals in the microenvironment [65].

These factors jointly determine whether IL-33 promotes type 2 immunity, tissue repair, or fibrosis. Importantly, IL-33 is not exclusively a

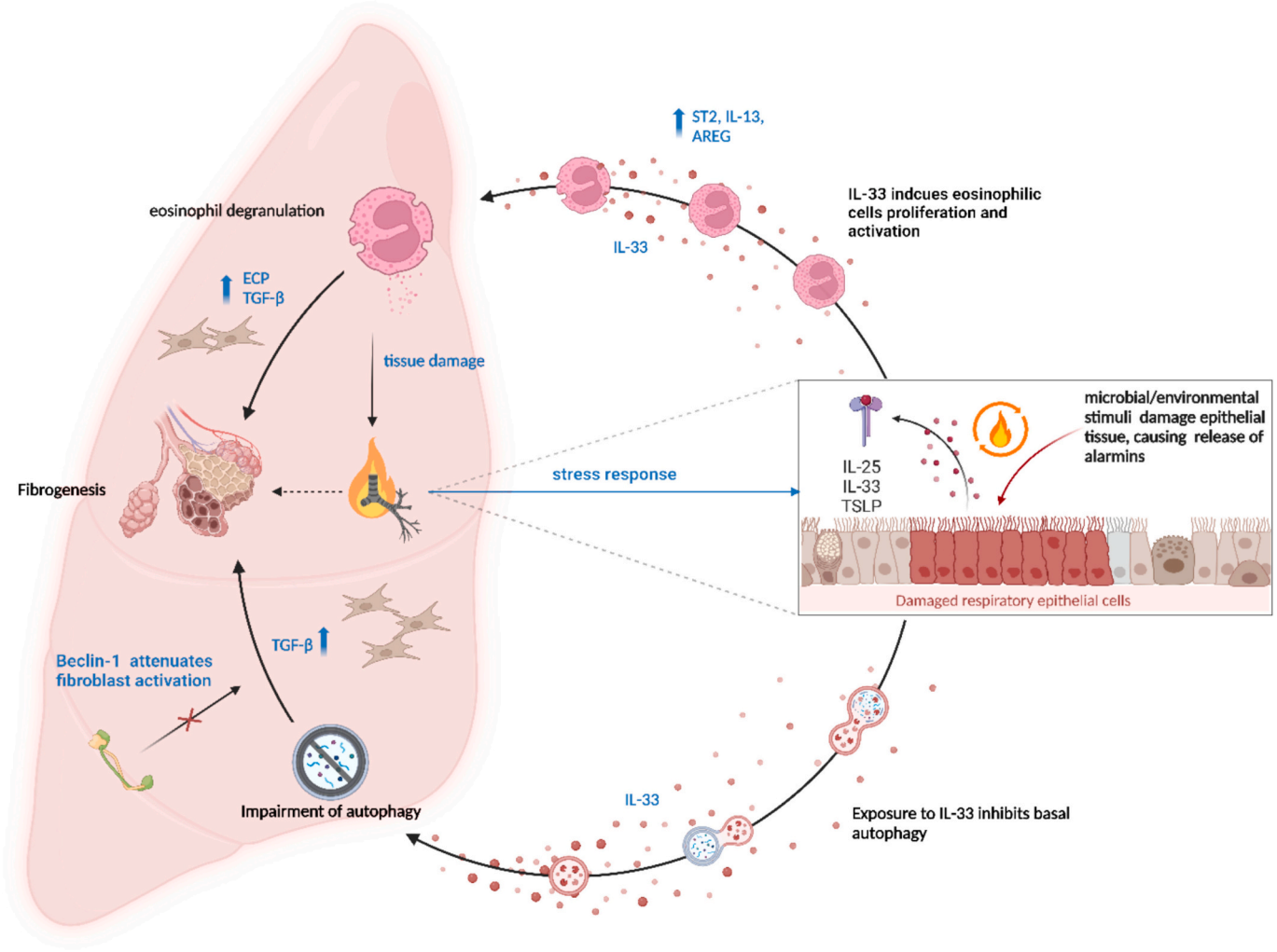

Fig. 3. Proposed model of involvement of IL-33 in the fibrogenesis of CLAD: noxious stimuli damage the respiratory epithelium, triggering secretion of alarmin. IL-33 release inhibits autophagy and promotes eosinophilic cell maturation and proliferation. Impaired autophagy contributes to the differentiation of myofibroblasts and the release of TGF-β, driving a pro-fibrotic response. Activated eosinophils release toxic mediators, such as eosinophilic cationic protein, which attracts fibroblasts and stimulates TGF-β secretion. The mediators released by eosinophils cause tissue damage, which in turn prompts further release of IL-33. IL-33: Interleukin 33; ECP: Eosinophil cationic protein; TGF-β: transforming growth factor-β; AREG: Amphiregulin; IL-33: Interleukin 33.

Table 2
Selected experimental and clinical models investigating IL-33 in lung transplantation. The table summarizes key studies that have elucidated IL-33 signalling across diverse contexts, including ex vivo lung perfusion, in vitro co-culture systems, and clinical bronchoalveolar lavage fluid (BALF) analyses. These models collectively demonstrate how IL-33 contributes to epithelial stress responses, immune cell activation, and fibrotic remodelling in the pathogenesis of CLAD and BOS.

Model type	Experimental insight	Study/ reference
Ex vivo lung perfusion (EVLP)	IL-33 release correlates with cold ischemia and graft dysfunction	[91]
In vitro epithelial–fibroblast co-culture	IL-33 suppresses autophagy, promotes fibroblast activation; reversed by ST2 blockade	[103]
Clinical BALF analysis	BAL eosinophilia linked to CLAD; IL-33/ST2/TSLP/eotaxin upregulation	[87]
BOS patient BALF analysis	$ST2^{+}CD64^{+}$ macrophages suggest IL-33-driven fibrotic activation in BOS	[88]

pro-inflammatory mediator; it can also play critical roles in maintaining tissue homeostasis and promoting repair [65,68]. For example, acute IL-33 signalling can enhance epithelial regeneration via amphiregulin-producing Tregs or ILC2s [69,70], whereas chronic or excessive IL-33 may skew macrophage polarization toward M2 phenotypes and amplify fibrogenic cascades [71,72]. Notably, increased IL-33 expression in disease does not necessarily reflect a causative pathogenic driver; it may instead represent a compensatory, regulatory, or protective response to ongoing tissue stress [68].

6. IL-33 and lung transplant rejection

Various experimental approaches have been used to investigate IL-33 signalling in the lung transplant setting, including in vitro epithelial–fibroblast co-cultures, ex vivo lung perfusion systems, and murine models of ischemia–reperfusion injury. Building on these experimental findings, recent studies have demonstrated that IL-33 contributes to both acute rejection and chronic lung allograft dysfunction (CLAD) following lung transplantation.

Acute cellular rejection was also triggered by Failure recruitment of Foxp3+ cells from the thymus. Continuous replenishment of these cells could be done by IL-33 administration. Local administration of IL-33 could expand and activate allograft-resident $Foxp3^{+}$ cells [73].

CLAD is a broad term for a variety of pathological processes leading to progressive irreversible failure of lung transplants [74]. CLAD is

Table 3
Summary of key IL-33–related pathogenic mechanisms implicated in CLAD. Each row outlines a distinct pathological aspect involving IL-33 signalling, including the cellular context, key effector cells, and main molecular pathways. The references cited correspond to the main studies supporting each mechanism.

Pathogenic aspects	Mechanistic description	Key cellular players	Molecular mediators/ pathways	Main references
IL-33 release as alarmin	Released by stressed or damaged epithelial cells post-transplant; triggers innate and adaptive immune activation via ST2 receptor.	Epithelial cells, stromal cells	IL-33/ST2 signalling axis	[56]
Activation of the IL-33/ ST2 axis	IL-33 binds to ST2 on immune cells, promoting pro-fibrotic cytokine production.	Tregs, ILC2s, macrophages, eosinophils	IL-13, TGF-β	[48–50]
Eosinophil hyperactivation	IL-33 induces eosinophil activation independent of IL-5; sustained epithelial injury amplifies IL-33 release.	Eosinophils, epithelial cells	IL-33, AREG, IL-13	[79]
Autophagy dysregulation	IL-33 suppresses autophagy pathways in epithelial cells and fibroblasts, impairing tissue homeostasis.	Epithelial cells, fibroblasts	Beclin-1, TGF-β, IL-33/ST2	[102,103]
Beclin-1 regulatory loop	IL-33-mediated inhibition of Beclin-1 disrupts autophagosome formation.	Fibroblasts	Beclin-1	[103]
Therapeutic potential	Blocking IL-33/ST2 restores autophagy and reduces fibrogenesis in preclinical models.	–	Anti-IL-33, Anti-ST2 therapies	[50]

classified into four phenotypes based on respiratory function and radiological findings, each with distinct underlying mechanisms and prognostic implications [75]. Being the most common fatal complication in lung transplant recipients, CLAD has become the focus of extensive research to unravel the molecular mechanisms that drive its various phenotypes [76]. In recent decades, some studies have investigated the multifaceted contribution of IL-33 to the pathogenesis of CLAD.

The intricate network of interactions between IL-33 and the innate and adaptive immune systems [2] has sparked increasing interest in understanding its role in CLAD.

Contrary to the protective role of eosinophilic cells in initial graft acceptance, increased BAL and/or blood eosinophilia is associated with increased risk of CLAD and poor outcome [77–81]. Although the pathogenetic link between eosinophilia and CLAD is not yet entirely clear, eosinophilic activation has been found to have toxic effects on airway epithelial cells, leading to tissue damage [76,78–80,82].

Additionally, eosinophil cationic protein (ECP) attracts fibroblasts and stimulates release of transforming growth factor-β (TGF-β), resulting in a pro-fibrotic response [80,82–86].

In the lung (as in other organ such as the liver), IL-33 release activates pro-fibrotic TGF-β, playing a clear pro-fibrotic role. The balance between resolving and pro-fibrotic capabilities of IL-33 is delicate, with a central role in the modulation of type 2 inflammation and fibrosis in response to tissue injury [50]. A better characterization of the T2 inflammatory signals driving eosinophilic activation and consequent CLAD-related lung fibrosis could enhance our understanding of the pathogenesis of CLAD and facilitate the development of new therapeutic approaches [76]. The widespread contribution of IL-33 in type-2 inflammation indicates that it may play a relevant mechanistic role. Todd and colleagues analysed biopsy data from a multicentre cohort of lung recipients and assessed eosinophil-related T2 immune activation in CLAD lung tissues. In line with previous reports, the degree of BAL eosinophilia in the first year after transplant was related to CLAD severity [87].

Surprisingly, eosinophil gene expression in CLAD has not shown upregulation of the IL-4 and IL-5 signalling pathways, which are the key regulators of eosinophilic proliferation and activation. This finding suggests that pulmonary eosinophil infiltration and degranulation are regulated by an IL-5-independent pathway. In this regard, the genes encoding epithelial-derived cytokines have shown intriguing results: IL-33 is overexpressed, alongside increased expression of the gene for its receptors, ST2, IL-13 and AREG, which are produced by immune cells in response to IL-33 signalling [87]. Based on this evidence, IL-33 release in response to post-transplant clinical events may lead to IL5-independent pulmonary eosinophil activation, subsequently driving fibrotic progression to CLAD.

Moreover, in BOS patients there was a significantly increased proportion of $ST2^{+}CD64^{+}$ macrophages in the BALF. Continuous epithelial damage stimulates these $ST2^{+}$ macrophages to produce excessive growth factors and extracellular matrix, resulting in airway remodelling and obstruction [88].

6.1. *From ischemia-reperfusion injury to CLAD*

Ischemia-reperfusion injury is the main reason for primary graft dysfunction and has emerged as a major risk factor for CLAD after lung transplant [89]. The inflammation that occurs during ischemia-reperfusion has been linked to danger-associated molecular patterns, molecules released by injured cells that activate pro-inflammatory signalling [90]. IL-33 has been evaluated during ischemia/reperfusion injury in experimental models, revealing a cell mechanism similar to danger-associated molecular patterns in the regulation of immune responses [91]. A rat transplant model showed that during ischemia-reperfusion injury, the IL-33-driven pathway promotes lung allograft acceptance by inducing eosinophil-mediated tolerance, [92] demonstrating that eosinophilic cells may promote lung allograft acceptance through downregulation of lung allo-immunity and activation of NO-dependent pathways [93,94]. IL-33 production by donor-derived stromal cells unlocked ischemia-reperfusion injury, leading to activation of ILC2s, the dominant producers of IL-5 in the lung graft. IL-5 production by recipient-derived ILC2s resulted in eosinophil migration into the transplanted lung, promoting graft acceptance. The increase in graft rejection observed in IL-33-deficient mice confirms the intriguing role of the IL-33/ILC2/IL-5 axis in safeguarding lung allografts during ischemia-reperfusion injury [92].

6.2. *IL-33 and regulation of autophagy in the pathogenesis of CLAD*

CLAD develops as a consequence of complex overlapping immune-mediated mechanisms, resulting in repeated lung injury, tissue remodelling/repair and irreversible fibrosis [95]. The blockade of fibrotic remodelling is a key to improving clinical outcomes in CLAD patients and has led to unsuccessful experimentation with antifibrotic therapeutic approaches [96]. Autophagy is an adaptive cell response to stress which plays a crucial role in maintaining cellular, tissue and organism homeostasis [97]. Over recent decades, the dysfunctional autophagy response has emerged as a key player in lung fibrogenesis [98]. Inhibition of autophagy induces myofibroblast differentiation of lung fibroblasts and promotes the epithelial–mesenchymal transition of alveolar epithelial cells via aberrant epithelial–fibroblast crosstalk [99–101]. Pre-clinical studies have analysed the role of IL-33 in the promotion of lung fibrosis by regulating expression of profibrotic genes in the lungs [53,55]. Autophagy and IL-33 share similar signalling pathways triggered by environmental stimuli. CLAD tissue shows a marked increase in IL-33 expression associated with impairment of basal autophagy [102].

Exposure to *Pseudomonas aeruginosa* has also been shown to compromise epithelial cell autophagy, leading to increased TGFβ1 expression and myofibroblast differentiation. IL-33/ST2 blockade rescues cellular autophagy and reduces myofibroblast differentiation on

exposure to *Pseudomonas aeruginosa*.

Exposure to IL-33 also inhibits autophagy, like exposure to infective triggers, confirming the pivotal role of IL-33 in inducing autophagy dysfunction and fibrogenesis downstream. The IL-33/autophagy axis is regulated by Beclin-1, a key regulator of autophagosome formation. Overexpression of Beclin-1 attenuates fibroblast activation, suggesting the existence of a negative feedback loop [103].

7. Conclusive remarks

Over the past decade, medical research has cast a spotlight on the widespread contribution of IL-33 biology not only to inflammation but also to the development of fibrosis and lung transplant rejection. IL-33 plays a central role in transplant rejection across multiple organs – lung, kidney, heart and liver – primarily through its dual function as an alarmin and pro-fibrotic cytokine. While its early release supports tissue repair in acute injury, persistent IL-33/ST2 activation contributes to chronic inflammation, immune dysregulation, and fibrosis across the kidney, heart, liver, and lung. Throughout these organs, IL-33 presents shared mechanisms including activation of type 2 immunity, stimulation of TGF-β signalling, induction of EMT and release of ECM components. A comparative analysis of IL-33 signalling across organs may help delineate common versus tissue-specific pathways of alloimmune injury and fibrosis, informing organ-adapted therapeutic approaches. In this context, the lung appears to present unique IL-33–related features—particularly involving autophagy regulation and eosinophil biology—not fully shared by other transplanted organs such as the kidney, liver, or heart.

These unique lung-specific characteristics are especially relevant in the context of CLAD.

Several interesting issues remain to be solved regarding eosinophil biology and type 2 immunity in lung recipients. The biphasic behaviour of the eosinophilic allo-responses reported in the murine orthotopic lung transplant model and in human CLAD lung tissues complicates our incomplete understanding of the graft microenvironment, which may influence and regulate type 2 immunity [104]. IL-33 appears to be a master regulator of type 2 responses and modulator of autophagy. In CLAD, IL-33 downstream pathways may bridge eosinophil-mediated tissue damage and autophagy dysfunction-related fibrogenesis. The toxic effects of eosinophilic degranulation on airway epithelial cells could trigger the release of IL-33, inducing the IL-33/autophagy axis and additional eosinophilic recruitment. A deeper exploration of the microbial and environmental stimuli that activate IL-33 downstream type 2 and/or autophagic responses may improve our understanding of the behaviour of IL-33. The role of type 2 responses in CLAD suggests that therapeutic strategies focused on targeting type 2 inflammatory pathways and particularly those involving anti-epithelial-derived cytokines could be effective. Moreover, involvement of IL-33 in the impairment of autophagy and subsequent fibrogenesis underscores the potential therapeutic benefit of targeting the IL-33/autophagy axis to prevent and/or treat CLAD. In this regard, several biologics targeting the IL-33/ST2 axis have been developed and tested in asthma and COPD, including the anti–IL-33 antibody itepekimab and the anti-ST2 agents astegolimab and tozorakimab. Although these therapies have not yet been tested in CLAD, they have shown promising safety and efficacy profiles in selected subgroups of airway diseases, supporting the rationale for their future evaluation in lung transplant recipients.

In parallel, emerging high-dimensional approaches, including omics technologies and functional screening platforms, may offer powerful tools to dissect IL-33–driven mechanisms in CLAD, aiding both mechanistic insight and therapeutic development. To advance the field, future research would benefit from standardized and integrated experimental models—including in vitro co-cultures, ex vivo perfusion systems, and in vivo genetic tools such as IL-33- or ST2-deficient mice and bone marrow chimeras. Future translational studies, grounded in rigorous target validation, will be essential for deepening our understanding of CLAD pathogenesis and for informing the rational development of targeted therapeutic strategies.

CRediT authorship contribution statement

B. Perea: Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **C. Gambini:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Investigation, Conceptualization. **I. Paggi:** Writing – original draft, Visualization, Resources, Project administration, Methodology, Investigation, Conceptualization. **S. Biancucci:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Conceptualization. **S. Cattelan:** Writing – original draft, Visualization, Conceptualization. **M. Genovese:** Writing – original draft, Visualization, Conceptualization. **M. d'Alessandro:** Writing – review & editing, Writing – original draft, Conceptualization. **P. Cameli:** Writing – review & editing, Visualization, Validation, Supervision. **E. Bargagli:** Writing – review & editing, Writing – original draft, Supervision. **A. Dilroba:** Writing – review & editing, Writing – original draft, Visualization, Project administration, Conceptualization. **T. Pianigiani:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Conceptualization. **L. Bergantini:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data presented in this study are available on request from the corresponding author.

References

[1] E. Di Salvo, M. Casciaro, S. Gangemi, IL-33 genetics and epigenetics in immune-related diseases, Clin. Mol. Allergy 19 (2021) 18, https://doi.org/10.1186/s12948-021-00157-6.
[2] X.-M. Yi, H. Lian, S. Li, Signaling and functions of interleukin-33 in immune regulation and diseases, Cell Insight 1 (2022) 100042, https://doi.org/10.1016/j.cellin.2022.100042.
[3] C.A. Dinarello, Overview of the IL-1 family in innate inflammation and acquired immunity, Immunol. Rev. 281 (2018) 8–27, https://doi.org/10.1111/imr.12621.
[4] G.K. Dwyer, L.M. D'Cruz, H.R. Turnquist, Emerging functions of IL-33 in homeostasis and immunity, Annu. Rev. Immunol. 40 (2022) 15–43, https://doi.org/10.1146/annurev-immunol-101320-124243.
[5] M.-R. Choi, J.A. Sosman, B. Zhang, The Janus face of IL-33 Signaling in tumor development and immune escape, Cancers (Basel) 13 (2021) 3281, https://doi.org/10.3390/cancers13133281.
[6] C. Cayrol, J.-P. Girard, Interleukin-33 (IL-33): a nuclear cytokine from the IL-1 family, Immunol. Rev. 281 (2018) 154–168, https://doi.org/10.1111/imr.12619.
[7] E. Katz-Kiriakos, D.F. Steinberg, C.E. Kluender, O.A. Osorio, C. Newsom-Stewart, A. Baronia, D.E. Byers, M.J. Holtzman, D. Katafiasz, K.L. Bailey, S.L. Brody, M. J. Miller, J. Alexander-Brett, Epithelial IL-33 appropriates exosome trafficking for secretion in chronic airway disease, JCI Insight 6 (2021) e136166, https://doi.org/10.1172/jci.insight.136166.
[8] G. Murdaca, F. Paladin, A. Tonacci, M. Borro, M. Greco, A. Gerosa, S. Isola, A. Allegra, S. Gangemi, Involvement of il-33 in the pathogenesis and prognosis of major respiratory viral infections: future perspectives for personalized therapy, Biomedicines 10 (2022) 715, https://doi.org/10.3390/biomedicines10030715.
[9] R. Gaurav, J.A. Poole, Interleukin (IL)-33 immunobiology in asthma and airway inflammatory diseases, J. Asthma 59 (2022) 2530–2538, https://doi.org/10.1080/02770903.2021.2020815.

[10] K. Yang, C. Tian, C. Zhang, M. Xiang, The controversial role of IL-33 in lung cancer, Front. Immunol. 13 (2022) 897356, https://doi.org/10.3389/fimmu.2022.897356.
[11] L. Riera-Martínez, L. Cànaves-Gómez, A. Iglesias, A. Martin-Medina, B.G. Cosío, The role of IL-33/ST2 in COPD and its future as an antibody therapy, Int. J. Mol. Sci. 24 (2023) 8702, https://doi.org/10.3390/ijms24108702.
[12] J. Chang, Y.-F. Xia, M.-Z. Zhang, L.-M. Zhang, IL-33 Signaling in Lung Injury, Transl Perioper, Pain Med. 1 (2016) 24–32.
[13] X. Ding, S. Jin, Z. Shao, L. Xu, Z. Yu, Y. Tong, Z. Chen, H. Turnquist, B.R. Pitt, T. R. Billiar, L.-M. Zhang, Q. Li, The IL-33-ST2 pathway contributes to ventilator-induced lung injury in septic mice in a tidal volume-dependent manner, Shock 52 (2019) e1–e11, https://doi.org/10.1097/SHK.0000000000001260.
[14] S.-H. Yang, J.-C. Lin, S.-Y. Wu, K.-L. Huang, F. Jung, M.-C. Ma, G.-S. Wang Hsu, G.-M. Jow, Membrane translocation of IL-33 receptor in ventilator induced lung injury, PLoS ONE 10 (2015) e0121391, https://doi.org/10.1371/journal.pone.0121391.
[15] Y. Sun, H. Pavey, I. Wilkinson, M. Fisk, Role of the IL-33/ST2 axis in cardiovascular disease: a systematic review and meta-analysis, PLoS ONE 16 (2021) e0259026, https://doi.org/10.1371/journal.pone.0259026.
[16] B.C.L. Chan, C.W.K. Lam, L.-S. Tam, C.K. Wong, IL33: roles in allergic inflammation and therapeutic perspectives, Front. Immunol. 10 (2019) 364, https://doi.org/10.3389/fimmu.2019.00364.
[17] A.H. Bowles, K.J. Warren, Regulating neutrophilic asthma with IL-33: maybe we shouldn't block IL-33 after all? Am. J. Respir. Cell Mol. Biol. (2025) https://doi.org/10.1165/rcmb.2025-0230ED.
[18] C. Moussion, N. Ortega, J.-P. Girard, The IL-1-like cytokine IL-33 is constitutively expressed in the nucleus of endothelial cells and epithelial cells in vivo: a novel "alarmin"? PLoS ONE 3 (2008) e3331 https://doi.org/10.1371/journal.pone.0003331.
[19] H. Guo, E.A. Bossila, X. Ma, C. Zhao, Y. Zhao, Dual immune regulatory roles of Interleukin-33 in pathological conditions, Cells 11 (2022) 3237, https://doi.org/10.3390/cells11203237.
[20] C. Afferni, C. Buccione, S. Andreone, M.R. Galdiero, G. Varricchi, G. Marone, F. Mattei, G. Schiavoni, The pleiotropic immunomodulatory functions of IL-33 and its implications in tumor immunity, Front. Immunol. 9 (2018) 2601, https://doi.org/10.3389/fimmu.2018.02601.
[21] L.Y. Drake, H. Kita, IL-33: biological properties, functions, and roles in airway disease, Immunol. Rev. 278 (2017) 173–184, https://doi.org/10.1111/imr.12552.
[22] Y. Zhou, Z. Xu, Z. Liu, Role of IL-33-ST2 pathway in regulating inflammation: current evidence and future perspectives, J. Transl. Med. 21 (2023) 902, https://doi.org/10.1186/s12967-023-04782-4.
[23] L.Y. Drake, Y.S. Prakash, Contributions of IL-33 in non-hematopoietic lung cells to obstructive lung disease, Front. Immunol. 11 (2020) 1798, https://doi.org/10.3389/fimmu.2020.01798.
[24] B. Griesenauer, S. Paczesny, The ST2/IL-33 Axis in immune cells during inflammatory diseases, Front. Immunol. 8 (2017) 475, https://doi.org/10.3389/fimmu.2017.00475.
[25] S.M. Pinto, Y. Subbannayya, D.A.B. Rex, R. Raju, O. Chatterjee, J. Advani, A. Radhakrishnan, T.S. Keshava Prasad, M.R. Wani, A. Pandey, A network map of IL-33 signaling pathway, J. Cell Commun. Signal. 12 (2018) 615–624, https://doi.org/10.1007/s12079-018-0464-4.
[26] Q. Liu, G.K. Dwyer, Y. Zhao, H. Li, L.R. Mathews, A.B. Chakka, U.R. Chandran, J. A. Demetris, J.F. Alcorn, K.M. Robinson, L.A. Ortiz, B.R. Pitt, A.W. Thomson, M. H. Fan, T.R. Billiar, H.R. Turnquist, IL-33–mediated IL-13 secretion by ST2+ Tregs controls inflammation after lung injury, JCI Insight 4 (2019), https://doi.org/10.1172/jci.insight.123919.
[27] I. Martínez-González, O. Roca, J.R. Masclans, R. Moreno, M.T. Salcedo, V. Baekelandt, M.J. Cruz, J. Rello, J.M. Aran, Human mesenchymal stem cells overexpressing the IL-33 antagonist soluble IL-1 receptor-like-1 attenuate endotoxin-induced acute lung injury, Am. J. Respir. Cell Mol. Biol. 49 (2013) 552–562, https://doi.org/10.1165/rcmb.2012-0406OC.
[28] A.-C. Jonckheere, B. Steelant, S.F. Seys, J. Cremer, E. Dilissen, L. Boon, A. Liston, R. Schrijvers, C. Breynaert, J.A.J. Vanoirbeek, J.L. Ceuppens, D.M.A. Bullens, Peribronchial inflammation resulting from regulatory T cell deficiency damages the respiratory epithelium and disturbs barrier function, J. Immunol. 209 (2022) 1595–1605, https://doi.org/10.4049/jimmunol.2200416.
[29] H. Nagashima, T. Mahlakõiv, H.-Y. Shih, F.P. Davis, F. Meylan, Y. Huang, O. J. Harrison, C. Yao, Y. Mikami, J.F. Urban, K.M. Caron, Y. Belkaid, Y. Kanno, D. Artis, J.J. O'Shea, Neuropeptide CGRP limits group 2 innate lymphoid cell responses and constrains type 2 inflammation, Immunity 51 (2019) 682–695.e6, https://doi.org/10.1016/j.immuni.2019.06.009.
[30] R.J. Salmond, A.S. Mirchandani, A.-G. Besnard, C.C. Bain, N.C. Thomson, F. Y. Liew, IL-33 induces innate lymphoid cell-mediated airway inflammation by activating mammalian target of rapamycin, J. Allergy Clin. Immunol. 130 (2012) 1159–1166.e6, https://doi.org/10.1016/j.jaci.2012.05.018.
[31] S.H. Krovi, L. Gapin, Invariant natural killer T cell subsets-more than just developmental intermediates, Front. Immunol. 9 (2018) 1393, https://doi.org/10.3389/fimmu.2018.01393.
[32] E.A. Bourgeois, A. Levescot, S. Diem, A. Chauvineau, H. Bergès, P. Milpied, A. Lehuen, D. Damotte, J.-M. Gombert, E. Schneider, J.-P. Girard, P. Gourdy, A. Herbelin, A natural protective function of invariant NKT cells in a mouse model of innate-cell-driven lung inflammation, Eur. J. Immunol. 41 (2011) 299–305, https://doi.org/10.1002/eji.201040647.
[33] U. Fujii, T. Nishizawa, Y. Ishii, E. Nakada, K. Makita, R. Sun, T. McGovern, A. Morozan, R. Chakraborty, J.G. Martin, Interleukin-33 induces a protective response against irritant-induced airway inflammation and dysfunction, Am. J. Respir. Cell Mol. Biol. (2025), https://doi.org/10.1165/rcmb.2024-0395OC.
[34] A.A. Calderon, C. Dimond, D.F. Choy, R. Pappu, M.A. Grimbaldeston, D. Mohan, K.F. Chung, Targeting interleukin-33 and thymic stromal lymphopoietin pathways for novel pulmonary therapeutics in asthma and COPD, Eur. Respir. Rev. 32 (2023) 220144, https://doi.org/10.1183/16000617.0144-2022.
[35] S.-Y. Ma, N. Zhao, L. Cui, Y. Li, H. Zhang, J. Wang, J. Pang, M. Wang, C. Wang, S. Ying, Z.-B. Jin, L. Zhang, Therapeutic effects of human pluripotent stem cell-derived mesenchymal stem cells on a murine model of acute Type-2-dominated airway inflammation, Stem Cell Rev. Rep. 18 (2022) 2939–2951, https://doi.org/10.1007/s12015-022-10389-x.
[36] S. Zhu, S. Zhong, K. Cheng, L.-S. Zhang, J.-W. Bai, Z. Cao, S. Wang, W. Chen, S. Cheng, L. Ma, Z. Ling, Y. Huang, W. Gu, X. Sun, C. Yi, M. Zhao, S. Liang, J.-F. Xu, B. Sun, Y. Zhang, Vitamin B6 regulates IL-33 homeostasis to alleviate type 2 inflammation, Cell. Mol. Immunol. 20 (2023) 794–807, https://doi.org/10.1038/s41423-023-01029-6.
[37] W.E. LeSuer, M. Kienzl, S.I. Ochkur, R. Schicho, A.D. Doyle, B.L. Wright, M. A. Rank, A.S. Krupnick, H. Kita, E.A. Jacobsen, Eosinophils promote effector functions of lung group 2 innate lymphoid cells in allergic airway inflammation in mice, J. Allergy Clin. Immunol. 152 (2023) 469–485.e10, https://doi.org/10.1016/j.jaci.2023.03.023.
[38] Y. Solomon, B. Malkamu, A. Berhan, T. Eyayu, A. Almaw, B. Legese, B. Woldu, Peripheral blood eosinophilia in adult asthmatic patients and its association with the severity of asthma, BMC Pulm. Med. 23 (2023) 96, https://doi.org/10.1186/s12890-023-02383-x.
[39] H.R. Turnquist, Vitamin B-reath easier: vitamin B6 derivatives reduce IL-33 to limit lung inflammation, Cell. Mol. Immunol. 20 (2023) 1527–1529, https://doi.org/10.1038/s41423-023-01076-z.
[40] J. Liu, P. Tao, B. Su, L. Zheng, Y. Lin, X. Zou, H. Yang, W. Wu, T. Zhang, H. Li, Interleukin-33 modulates NET formation via an autophagy-dependent manner to promote neutrophilic inflammation in cigarette smoke-exposure asthma, J. Hazard. Mater. 487 (2025) 137257, https://doi.org/10.1016/j.jhazmat.2025.137257.
[41] M.E. Wechsler, M.K. Ruddy, I.D. Pavord, E. Israel, K.F. Rabe, L.B. Ford, J. F. Maspero, R.M. Abdulai, C.-C. Hu, R. Martincova, A. Jessel, M.C. Nivens, N. Amin, D.M. Weinreich, G.D. Yancopoulos, H. Goulaouic, Efficacy and safety of Itepekimab in patients with moderate-to-severe asthma, N. Engl. J. Med. 385 (2021) 1656–1668, https://doi.org/10.1056/NEJMoa2024257.
[42] C. Akinseye, C. Crim, A. Newlands, D. Fairman, Efficacy and safety of GSK3772847 in participants with moderate-to-severe asthma with allergic fungal airway disease: a phase IIa randomized, multicenter, double-blind, sponsor-open, comparative trial, PLoS ONE 18 (2023) e0281205, https://doi.org/10.1371/journal.pone.0281205.
[43] J. Corren, F. Reid, R. Moate, E. Jimenez, M.W. Sadiq, A. Williams, M. Rytelewski, S. Cameron-Christie, D. Muthas, B. Georgi, D. Brooks, E. Lindqvist, C. Kell, A. Platt, M.G. Belvisi, H. Pandya, FRONTIER-3: a randomised phase 2a study to investigate tozorakimab (an anti-IL-33 mAb) in early onset asthma, ERJ Open Res. (2025), https://doi.org/10.1183/23120541.00183-2025.
[44] S.G. Kelsen, I.O. Agache, W. Soong, E. Israel, G.L. Chupp, D.S. Cheung, W. Theess, X. Yang, T.L. Staton, D.F. Choy, A. Fong, A. Dash, M. Dolton, R. Pappu, C. E. Brightling, Astegolimab (anti-ST2) efficacy and safety in adults with severe asthma: a randomized clinical trial, J. Allergy Clin. Immunol. 148 (2021) 790–798, https://doi.org/10.1016/j.jaci.2021.03.044.
[45] K.F. Rabe, F.J. Martinez, S.P. Bhatt, T. Kawayama, B.G. Cosio, R.M. Mroz, M. M. Boomsma, H. Goulaouic, M.C. Nivens, M. Djandji, X. Soler, Y. Liu, M. P. Kosloski, C.R. Xu, N. Amin, H. Staudinger, D.J. Lederer, R.M. Abdulai, AERIFY-1/2: two phase 3, randomised, controlled trials of itepekimab in former smokers with moderate-to-severe COPD, ERJ Open Res. 10 (2024) 00718–02023, https://doi.org/10.1183/23120541.00718-2023.
[46] D. Singh, P. Guller, F. Reid, S. Doffman, U. Seppälä, I. Psallidas, R. Moate, R. Smith, J. Kiraga, E. Jimenez, D. Brooks, A. Kelly, L.H. Nordenmark, M. W. Sadiq, L.M. Caballero, C. Kell, M.G. Belvisi, H. Pandya, A phase 2a trial of the IL-33 monoclonal antibody tozorakimab in patients with COPD: FRONTIER-4, Eur. Respir. J. 66 (2025) 2402231, https://doi.org/10.1183/13993003.02231-2024.
[47] A.J. Yousuf, S. Mohammed, L. Carr, M.Y. Ramsheh, C. Micieli, V. Mistry, K. Haldar, A. Wright, P. Novotny, S. Parker, S. Glover, J. Finch, N. Quann, C. L. Brookes, R. Hobson, W. Ibrahim, R.J. Russell, C. John, M.A. Grimbaldeston, D. F. Choy, D. Cheung, M. Steiner, N.J. Greening, C.E. Brightling, Astegolimab, an anti-ST2, in chronic obstructive pulmonary disease (COPD-ST2OP): a phase 2a, placebo-controlled trial, the lancet, Respir. Med. 10 (2022) 469–477, https://doi.org/10.1016/S2213-2600(21)00556-7.
[48] S.P. Atamas, V. Lockatell, N.W. Todd, J.C. Papadimitriou, V. Rus, K.N. Lugkey, S. N. Vogel, V.Y. Toshchakov, I.G. Luzina, Therapeutic targeting of full-length interleukin-33 protein levels with cell-permeable decoy peptides attenuates fibrosis in the bleomycin model in vivo, J. Pharmacol. Exp. Ther. 392 (2025) 100008, https://doi.org/10.1124/jpet.123.002050.
[49] M.Y. Tjota, D.F. Camacho, H.R. Turnquist, A.I. Sperling, IL-33 drives monocyte recruitment to lung Interstitium through chemokine upregulation, Immunohorizons 1 (2017) 101–108, https://doi.org/10.4049/immunohorizons.1700024.
[50] S. Di Carmine, M.M. Scott, M.H. McLean, H.J. McSorley, The role of interleukin-33 in organ fibrosis, Discov. Immunol. 1 (2022) kyac006, https://doi.org/10.1093/discim/kyac006.
[51] M. Manetti, L. Ibba-Manneschi, V. Liakouli, S. Guiducci, A.F. Milia, G. Benelli, A. Marrelli, M.L. Conforti, E. Romano, R. Giacomelli, M. Matucci-Cerinic,

P. Cipriani, The IL1-like cytokine IL33 and its receptor ST2 are abnormally expressed in the affected skin and visceral organs of patients with systemic sclerosis, Ann. Rheum. Dis. 69 (2010) 598–605, https://doi.org/10.1136/ard.2009.119321.
[52] J.-U. Lee, H.S. Chang, H.J. Lee, C.A. Jung, D.J. Bae, H.J. Song, J.S. Park, S.-T. Uh, Y.H. Kim, K.-H. Seo, C.-S. Park, Upregulation of interleukin-33 and thymic stromal lymphopoietin levels in the lungs of idiopathic pulmonary fibrosis, BMC Pulm. Med. 17 (2017) 39, https://doi.org/10.1186/s12890-017-0380-z.
[53] D. Li, R. Guabiraba, A.-G. Besnard, M. Komai-Koma, M.S. Jabir, L. Zhang, G. J. Graham, M. Kurowska-Stolarska, F.Y. Liew, C. McSharry, D. Xu, IL-33 promotes ST2-dependent lung fibrosis by the induction of alternatively activated macrophages and innate lymphoid cells in mice, J. Allergy Clin. Immunol. 134 (2014) 1422–1432.e11, https://doi.org/10.1016/j.jaci.2014.05.011.
[54] Y. Nie, Y. Hu, K. Yu, D. Zhang, Y. Shi, Y. Li, L. Sun, F. Qian, Akt1 regulates pulmonary fibrosis via modulating IL-13 expression in macrophages, Innate Immun. 25 (2019) 451–461, https://doi.org/10.1177/1753425919861774.
[55] I.G. Luzina, P. Kopach, V. Lockatell, P.H. Kang, A. Nagarsekar, A.P. Burke, J. D. Hasday, N.W. Todd, S.P. Atamas, Interleukin-33 potentiates bleomycin-induced lung injury, Am. J. Respir. Cell Mol. Biol. 49 (2013) 999–1008, https://doi.org/10.1165/rcmb.2013-0093OC.
[56] I. Peters, S. Müller, C. Küchler, U. Jäger, S. Drube, The heat shock protein 90 (HSP90) is required for the IL-33-induced cytokine production in mast cells (MCs), Int. J. Mol. Sci. 23 (2022) 10855, https://doi.org/10.3390/ijms231810855.
[57] J. Sellares, K.L. Veraldi, K.J. Thiel, N. Cárdenes, D. Alvarez, F. Schneider, J. M. Pilewski, M. Rojas, C.A. Feghali-Bostwick, Intracellular heat shock protein 70 deficiency in pulmonary fibrosis, Am. J. Respir. Cell Mol. Biol. 60 (2019) 629–636, https://doi.org/10.1165/rcmb.2017-0268OC.
[58] X. Zhang, X. Zhang, W. Huang, X. Ge, The role of heat shock proteins in the regulation of fibrotic diseases, Biomed. Pharmacother. 135 (2021) 111067, https://doi.org/10.1016/j.biopha.2020.111067.
[59] T. Takashima, C. Zeng, E. Murakami, N. Fujiwara, M. Kohara, H. Nagata, Z. Feng, A. Sugai, Y. Harada, R. Ichijo, D. Okuzaki, S. Nojima, T. Matsui, Y. Shintani, G. Kawai, M. Hamada, T. Hirose, K. Nakatani, E. Morii, Involvement of lncRNA MIR205HG in idiopathic pulmonary fibrosis and IL-33 regulation via Alu elements, JCI Insight 10 (2025) e187172, https://doi.org/10.1172/jci.insight.187172.
[60] X.-Y. Tan, H.-Y. Jing, Y.-R. Ma, Interleukin-33/suppression of tumorigenicity 2 in renal fibrosis: emerging roles in prognosis and treatment, Front. Physiol. 12 (2021) 792897, https://doi.org/10.3389/fphys.2021.792897.
[61] H.R. Turnquist, Z. Zhao, B.R. Rosborough, Q. Liu, A. Castellaneta, K. Isse, Z. Wang, M. Lang, D. Beer Stolz, X.X. Zheng, A.J. Demetris, F.Y. Liew, K.J. Wood, A.W. Thomson, IL-33 expands suppressive CD11b+ Gr-1int and regulatory T cells, including ST2L+ Foxp3+ cells, and mediates regulatory T cell-dependent promotion of cardiac allograft survival, J. Immunol. 187 (2011) 4598–4610, https://doi.org/10.4049/jimmunol.1100519.
[62] S.M. Brunner, G. Schiechl, W. Falk, H.J. Schlitt, E.K. Geissler, S. Fichtner-Feigl, Interleukin-33 prolongs allograft survival during chronic cardiac rejection, Transpl. Int. 24 (2011) 1027–1039, https://doi.org/10.1111/j.1432-2277.2011.01306.x.
[63] H. Yin, X.-Y. Li, X.-B. Jin, B.-B. Zhang, Q. Gong, H. Yang, F. Zheng, F.-L. Gong, J.-Y. Zhu, IL-33 prolongs murine cardiac allograft survival through induction of TH2-type immune deviation, Transplantation 89 (2010) 1189, https://doi.org/10.1097/TP.0b013e3181d720af.
[64] T. Li, Z. Zhang, J.G. Bartolacci, G.K. Dwyer, Q. Liu, L.R. Mathews, M. Velayutham, A.S. Roessing, Y.C. Lee, H. Dai, S. Shiva, M.H. Oberbarnscheidt, J.L. Dziki, S.J. Mullet, S.G. Wendell, J.D. Wilkinson, S.A. Webber, M. Wood-Trageser, S.C. Watkins, A.J. Demetris, G.S. Hussey, S.F. Badylak, H.R. Turnquist, Graft IL-33 regulates infiltrating macrophages to protect against chronic rejection, J. Clin. Invest. 130 (2020) 5397–5412, https://doi.org/10.1172/JCI133008.
[65] F.Y. Liew, J.-P. Girard, H.R. Turnquist, Interleukin-33 in health and disease, Nat. Rev. Immunol. 16 (2016) 676–689, https://doi.org/10.1038/nri.2016.95.
[66] V. Carriere, L. Roussel, N. Ortega, D.-A. Lacorre, L. Americh, L. Aguilar, G. Bouche, J.-P. Girard, IL-33, the IL-1-like cytokine ligand for ST2 receptor, is a chromatin-associated nuclear factor in vivo, Proc. Natl. Acad. Sci. USA 104 (2007) 282–287, https://doi.org/10.1073/pnas.0606854104.
[67] E.S. Cohen, I.C. Scott, J.B. Majithiya, L. Rapley, B.P. Kemp, E. England, D.G. Rees, C.L. Overed-Sayer, J. Woods, N.J. Bond, C.S. Veyssier, K.J. Embrey, D.A. Sims, M. R. Snaith, K.A. Vousden, M.D. Strain, D.T.Y. Chan, S. Carmen, C.E. Huntington, L. Flavell, J. Xu, B. Popovic, C.E. Brightling, T.J. Vaughan, R. Butler, D.C. Lowe, D.R. Higazi, D.J. Corkill, R.D. May, M.A. Sleeman, T. Mustelin, Oxidation of the alarmin IL-33 regulates ST2-dependent inflammation, Nat. Commun. 6 (2015) 8327, https://doi.org/10.1038/ncomms9327.
[68] A.B. Molofsky, A.K. Savage, R.M. Locksley, Interleukin-33 in tissue homeostasis, injury, and inflammation, Immunity 42 (2015) 1005–1019, https://doi.org/10.1016/j.immuni.2015.06.006.
[69] L.A. Monticelli, L.C. Osborne, M. Noti, S.V. Tran, D.M.W. Zaiss, D. Artis, IL-33 promotes an innate immune pathway of intestinal tissue protection dependent on amphiregulin-EGFR interactions, Proc. Natl. Acad. Sci. USA 112 (2015) 10762–10767, https://doi.org/10.1073/pnas.1509070112.
[70] N. Arpaia, J.A. Green, B. Moltedo, A. Arvey, S. Hemmers, S. Yuan, P.M. Treuting, A.Y. Rudensky, A distinct function of regulatory T cells in tissue protection, Cell 162 (2015) 1078–1089, https://doi.org/10.1016/j.cell.2015.08.021.
[71] M. Kurowska-Stolarska, B. Stolarski, P. Kewin, G. Murphy, C.J. Corrigan, S. Ying, N. Pitman, A. Mirchandani, B. Rana, N. van Rooijen, M. Shepherd, C. McSharry, I. B. McInnes, D. Xu, F.Y. Liew, IL-33 amplifies the polarization of alternatively activated macrophages that contribute to airway inflammation, J. Immunol. 183 (2009) 6469–6477, https://doi.org/10.4049/jimmunol.0901575.
[72] T. Pianigiani, A. Dilroba, C. Gambini, F. Hernandez-Gonzalez, M. d'Alessandro, L. Bergantini, J. Sellares, E. Bargagli, P. Cameli, Beyond inflammation: alarmins as critical drivers of pulmonary fibrosis, ERJ Open Res. (2025), https://doi.org/10.1183/23120541.00747-2025.
[73] W. Li, Y. Terada, Y.Z. Bai, Y. Yokoyama, H.M. Shepherd, J.M. Amrute, A.I. Bery, Z. Liu, J.M. Gauthier, M. Terekhova, A. Bharat, J.H. Ritter, V. Puri, R.R. Hachem, H.R. Turnquist, P.T. Sage, A. Alessandrini, M.N. Artyomov, K.J. Lavine, R. G. Nava, A.S. Krupnick, A.E. Gelman, D. Kreisel, Maintenance of graft tissue-resident Foxp3+ cells is necessary for lung transplant tolerance in mice, J. Clin. Invest. 135 (2025) e178975, https://doi.org/10.1172/JCI178975.
[74] J.M. Gauthier, R.R. Hachem, D. Kreisel, Update on chronic lung allograft dysfunction, Curr. Transplant. Rep. 3 (2016) 185–191, https://doi.org/10.1007/s40472-016-0112-y.
[75] S.E. Verleden, R. Vos, B.M. Vanaudenaerde, G.M. Verleden, Chronic lung allograft dysfunction phenotypes and treatment, J. Thorac. Dis. 9 (2017) 2650–2659, https://doi.org/10.21037/jtd.2017.07.81.
[76] S. Bos, L. Milross, A.J. Filby, R. Vos, A.J. Fisher, Immune processes in the pathogenesis of chronic lung allograft dysfunction: identifying the missing pieces of the puzzle, Eur. Respir. Rev. 31 (2022), https://doi.org/10.1183/16000617.0060-2022.
[77] S. Aguado Ibáñez, M. Pérez Aguilar, A. Royuela Vicente, C. López García-Gallo, G. Díaz Nuevo, C. Salas Antón, M.P. Ussetti Gil, Peripheral blood eosinophilia as a marker of acute cellular rejection in lung transplant recipients, J. Heart Lung Transplant. 41 (2022) 501–507, https://doi.org/10.1016/j.healun.2021.12.007.
[78] D.R. Darley, J. Ma, E. Huszti, P. Fiset, L. Levy, D.M. Hwang, P. Pal, W. Klement, R. Zamel, S. Keshavjee, G. Tomlinson, L.G. Singer, J.M. Tikkanen, T. Martinu, Eosinophils in transbronchial biopsies: a predictor of chronic lung allograft dysfunction and reduced survival after lung transplantation - a retrospective single-center cohort study, Transpl. Int. 34 (2021) 62–75, https://doi.org/10.1111/tri.13760.
[79] J. Kaes, E. Van der Borght, A. Vanstapel, A. Van Herck, A. Sacreas, T. Heigl, B. M. Vanaudenaerde, L. Godinas, D.E. Van Raemdonck, L.J. Ceulemans, A. P. Neyrinck, R. Vos, G.M. Verleden, S.E. Verleden, Null group the Leuven lung transplant, peripheral blood eosinophilia is associated with poor outcome post-lung transplantation, Cells 9 (2020) 2516, https://doi.org/10.3390/cells9112516.
[80] S.E. Verleden, D. Ruttens, E. Vandermeulen, D.E. van Raemdonck, B. M. Vanaudenaerde, G.M. Verleden, R. Vos, Elevated bronchoalveolar lavage eosinophilia correlates with poor outcome after lung transplantation, Transplantation 97 (2014) 83–89, https://doi.org/10.1097/TP.0b013e3182a6bae2.
[81] A.K. Dosanjh, T.E. Robinson, J. Strauss, G. Berry, Eosinophil activation in cardiac and pulmonary acute allograft rejection, J. Heart Lung Transplant. 17 (1998) 1038.
[82] S. Bos, A.J. Filby, R. Vos, A.J. Fisher, Effector immune cells in chronic lung allograft dysfunction: a systematic review, Immunology 166 (2022) 17–37, https://doi.org/10.1111/imm.13458.
[83] U. Zagai, E. Dadfar, J. Lundahl, P. Venge, C.M. Sköld, Eosinophil cationic protein stimulates TGF-beta1 release by human lung fibroblasts in vitro, Inflammation 30 (2007) 153–160, https://doi.org/10.1007/s10753-007-9032-4.
[84] J. Bystrom, K. Amin, D. Bishop-Bailey, Analysing the eosinophil cationic protein - a clue to the function of the eosinophil granulocyte, Respir. Res. 12 (2011) 10, https://doi.org/10.1186/1465-9921-12-10.
[85] M. Goldman, A. Le Moine, M. Braun, V. Flamand, D. Abramowicz, A role for eosinophils in transplant rejection, Trends Immunol. 22 (2001) 247–251, https://doi.org/10.1016/s1471-4906(01)01893-2.
[86] U. Zagai, J. Lundahl, J. Klominek, P. Venge, C.M. Sköld, Eosinophil cationic protein stimulates migration of human lung fibroblasts in vitro, Scand. J. Immunol. 69 (2009) 381–386, https://doi.org/10.1111/j.1365-3083.2009.02233.x.
[87] J.L. Todd, J.M. Weber, F.L. Kelly, M.L. Neely, H. Mulder, C.W. Frankel, A. Nagler, C. McCrae, P. Newbold, J. Kreindler, S.M. Palmer, BAL fluid eosinophilia associates with chronic lung allograft dysfunction risk: a Multicenter study, Chest 164 (2023) 670–681, https://doi.org/10.1016/j.chest.2023.03.033.
[88] T. Yanagihara, K. Hata, K. Suzuki, K. Matsubara, K. Kunimura, K. Tsubouchi, D. Eto, H. Ando, M. Uehara, S. Ikegame, Y. Fukui, I. Okamoto, Expansion of ST2-expressing macrophages in a patient with bronchiolitis obliterans syndrome, ERJ Open Res. 9 (2023) 00033–02023, https://doi.org/10.1183/23120541.00033-2023.
[89] G.I. Snell, R.D. Yusen, D. Weill, M. Strueber, E. Garrity, A. Reed, A. Pelaez, T.P. Whelan, M. Perch, R. Bag, M. Budev, P.A. Corris, M.M. Crespo, C. Witt, E. Cantu, J.D. Christie, Report of the ISHLT Working Group on Primary Lung Graft Dysfunction, part I: Definition and grading-A, Consensus group statement of the International Society for Heart and Lung Transplantation, J. Heart Lung Transplant. 36 (2017) (2016) 1097–1103, https://doi.org/10.1016/j.healun.2017.07.021.
[90] C.C. Frye, A.I. Bery, D. Kreisel, H.S. Kulkarni, Sterile inflammation in thoracic transplantation, Cell. Mol. Life Sci. 78 (2021) 581–601, https://doi.org/10.1007/s00018-020-03615-7.
[91] A. Hasenauer, B. Bédat, R. Parapanov, J. Lugrin, A. Debonneville, E. Abdelnour-Berchtold, M. Gonzalez, J.Y. Perentes, L. Piquilloud, C. Szabo, T. Krueger, L. Liaudet, Effects of cold or warm ischemia and ex-vivo lung perfusion on the release of damage associated molecular patterns and inflammatory cytokines in

experimental lung transplantation, J. Heart Lung Transplant. 40 (2021) 905–916, https://doi.org/10.1016/j.healun.2021.05.015.
[92] Y. Guo, Z. Mei, D. Li, A. Banerjee, M.A. Khalil, A. Burke, J. Ritter, C. Lau, D. Kreisel, A.E. Gelman, E. Jacobsen, I.G. Luzina, S.P. Atamas, A.S. Krupnick, Ischemia reperfusion injury facilitates lung allograft acceptance through IL-33-mediated activation of donor-derived IL-5 producing group 2 innate lymphoid cells, Am. J. Transplant. 22 (2022) 1963–1975, https://doi.org/10.1111/ajt.17084.
[93] O.O. Onyema, Y. Guo, B. Mahgoub, Q. Wang, A. Manafi, Z. Mei, A. Banerjee, D. Li, M.H. Stoler, M.T. Zaidi, A.G. Schrum, D. Kreisel, A.E. Gelman, E. A. Jacobsen, A.S. Krupnick, Eosinophils downregulate lung alloimmunity by decreasing TCR signal transduction, JCI Insight 4 (2019) e128241, https://doi.org/10.1172/jci.insight.128241.
[94] O.O. Onyema, Y. Guo, Q. Wang, M.H. Stoler, C. Lau, K. Li, C.D. Nazaroff, X. Wang, W. Li, D. Kreisel, A.E. Gelman, J.J. Lee, E.A. Jacobsen, A.S. Krupnick, Eosinophils promote inducible NOS-mediated lung allograft acceptance, JCI Insight 2 (2017) e96455, https://doi.org/10.1172/jci.insight.96455.
[95] I.E. Fernandez, K. Heinzelmann, S. Verleden, O. Eickelberg, Characteristic patterns in the fibrotic lung, comparing idiopathic pulmonary fibrosis with chronic lung allograft dysfunction, Ann. Am. Thorac. Soc. 12 (Suppl. 1) (2015) S34–S41, https://doi.org/10.1513/AnnalsATS.201410-476MG.
[96] M.P. Combs, E.A. Belloli, N. Gargurevich, K.R. Flaherty, S. Murray, C.J. Galbán, V.N. Lama, Results from randomized trial of pirfenidone in patients with chronic rejection (STOP-CLAD study), J. Heart Lung Transplant. 43 (2024) 1468–1477, https://doi.org/10.1016/j.healun.2024.05.013.
[97] A.M.K. Choi, S.W. Ryter, B. Levine, Autophagy in human health and disease, N. Engl. J. Med. 368 (2013) 651–662, https://doi.org/10.1056/NEJMra1205406.
[98] C. Hill, Y. Wang, Autophagy in pulmonary fibrosis: friend or foe? Genes Dis. 9 (2022) 1594–1607, https://doi.org/10.1016/j.gendis.2021.09.008.
[99] C. Hill, J. Li, D. Liu, F. Conforti, C.J. Brereton, L. Yao, Y. Zhou, A. Alzetani, S. J. Chee, B.G. Marshall, S.V. Fletcher, D. Hancock, C.H. Ottensmeier, A.J. Steele, J. Downward, L. Richeldi, X. Lu, D.E. Davies, M.G. Jones, Y. Wang, Autophagy inhibition-mediated epithelial-mesenchymal transition augments local myofibroblast differentiation in pulmonary fibrosis, Cell Death Dis. 10 (2019) 591, https://doi.org/10.1038/s41419-019-1820-x.
[100] A.S. Patel, L. Lin, A. Geyer, J.A. Haspel, C.H. An, J. Cao, I.O. Rosas, D. Morse, Autophagy in idiopathic pulmonary fibrosis, PLoS ONE 7 (2012) e41394, https://doi.org/10.1371/journal.pone.0041394.
[101] S. Rangarajan, A. Kurundkar, D. Kurundkar, K. Bernard, Y.Y. Sanders, Q. Ding, V. B. Antony, J. Zhang, J. Zmijewski, V.J. Thannickal, Novel mechanisms for the antifibrotic action of Nintedanib, Am. J. Respir. Cell Mol. Biol. 54 (2016) 51–59, https://doi.org/10.1165/rcmb.2014-0445OC.
[102] J.A. Belperio, K. Lake, H. Tazelaar, M.P. Keane, R.M. Strieter, J.P. Lynch, Bronchiolitis obliterans syndrome complicating lung or heart-lung transplantation, Semin. Respir. Crit. Care Med. 24 (2003) 499–530, https://doi.org/10.1055/s-2004-815601.
[103] M.M. Banday, S.B. Rao, S. Shankar, M.A. Khanday, J. Finan, E. O'Neill, A. Coppolino, A. Seyfang, A. Kumar, D.E. Rinewalt, H.J. Goldberg, A. Woolley, H. R. Mallidi, G. Visner, A. Gaggar, K.N. Patel, N.S. Sharma, IL-33 mediates Pseudomonas induced airway fibrogenesis and is associated with CLAD, J. Heart Lung Transplant. 42 (2023) 53–63, https://doi.org/10.1016/j.healun.2022.09.018.
[104] O.O. Onyema, Y. Guo, A. Hata, D. Kreisel, A.E. Gelman, E.A. Jacobsen, A. S. Krupnick, Deciphering the role of eosinophils in solid organ transplantation, Am. J. Transplant. 20 (2020) 924–930, https://doi.org/10.1111/ajt.15660.