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REVIEW

The IL-1 cytokine family and its role in inflammation and fibrosis in the lung

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Abstract The IL-1 cytokine family comprises 11 members (7 ligands with agonist activity, 3 receptor antagonists and 1 anti-inflammatory cytokine) and is recognised as a key mediator of inflammation and fibrosis in multiple tissues including the lung. IL-1 targeted therapies have been successfully employed to treat a range of inflammatory conditions such as rheumatoid arthritis and gouty arthritis. This review will introduce the members of the IL-1 cytokine family, briefly discuss the cellular origins and cellular targets and provide an overview of the role of these molecules in inflammation and fibrosis in the lung.

Keywords IL-1 · IL-18 · IL-33 · Fibroblast · Inflammation · Fibrosis · Lung

Introduction

Progressive loss of organ function due to fibrosis contributes significantly to the ever-growing burden of chronic disease in the world. In addition, because progression in these diseases occurs over several years, they account for enormous morbidity within society, major health resource utilisation and loss of working days and tax revenues. For example, the total cost of respiratory disease in the 28 countries of the EU alone amounts to more than €380 billion annually (European Lung White Book, Chapter 2). Improving our understanding of the processes that fail to orchestrate physiological repair in the injured organ and instead cause pathological repair as fibrosis will aid the identification of new therapeutic approaches that can impact in this area.

Fibrosis causes excessive collagen and extra-cellular matrix deposition in an organ or tissue as part of an attempted reparative process following injury. It may represent an aberrant response to a single large injury but more commonly is a response to a persistent or repetitive injury. The association of fibrosis with many chronic inflammatory conditions suggests that the beneficial reparative processes that restore tissue homeostasis in physiological healing continue unchecked and instead result in pathological damage and loss of organ function. Chronic lung disease is a very common cause of morbidity and mortality across Europe, with diseases such as idiopathic pulmonary fibrosis (IPF) accounting for >2500 deaths a year and chronic obstructive pulmonary disease (COPD) causing over 30,000 deaths/year in the UK with a rising incidence (predicted to become the third common cause of death by 2020) [1, 2]. Fibrosis causes significant dysfunction of the lung by remodelling the small airways in COPD contributing to airflow limitation [3] and by remodelling the parenchyma in IPF severely impairing gas exchange [4]. Both conditions are associated with significant inflammation, yet the mechanisms linking inflammation to fibrosis in the lung are poorly understood.

The IL-1 family consists of 11 members, 7 of which have been demonstrated to have broad pro-inflammatory activity (IL-1α, IL-1β, IL-18, IL-33, IL-36α, IL-36β and IL-36γ) while the remaining 4 have antagonistic (IL-1Ra, IL-36Ra, IL-38) or anti-inflammatory (IL-37) properties. The IL-1 receptor family comprises 10 members, namely, IL-1R1, IL-1R2, IL-1R accessory protein (IL-1RAcP), IL-18Rα, IL-

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18Rβ, ST2 (IL-33R), IL-36R (previously IL-1Rrp2), single Ig IL-1R-related molecule (SIGIRR or TIR8), three Ig domain-containing IL-1R related-2 (TIGIRR-2 or IL-1RAPLI) and TIGIRR-1 (IL-1RAPL2). A simplified nomenclature for IL-1 receptor family members (IL-1R1–IL-1R10) was recently proposed by Garlanda et al. in Immunity [5]. The known interactions between the IL-1 family members and the IL-1 receptor family are summarised in Fig. 1.

In this review, I will introduce the members of the IL-1 cytokine family, briefly discuss the cellular origins and cellular targets and provide an overview of the role of these molecules in inflammation and fibrosis in the lung. Where appropriate, readers will be directed to more substantial reviews that focus on specific topics in more detail. Additionally, although the IL-1 cytokine family has been shown to be important in inflammation and fibrosis in numerous organs, this review will primarily focus on the role of the IL-1 cytokine family in the lung.

IL-1 subfamily

IL-1 and IL-1Ra

In the 1940s, during the search for the endogenous mediator of fever, researchers identified a small soluble candidate protein released by activated white blood cells that was termed leukocytic pyrogen [6]. In 1977, leukocytic pyrogen was purified [7] and was demonstrated to be identical to lymphocyte activation factor [8], a factor released from stimulated mononuclear cells that augmented lymphocyte proliferation [9]. The term

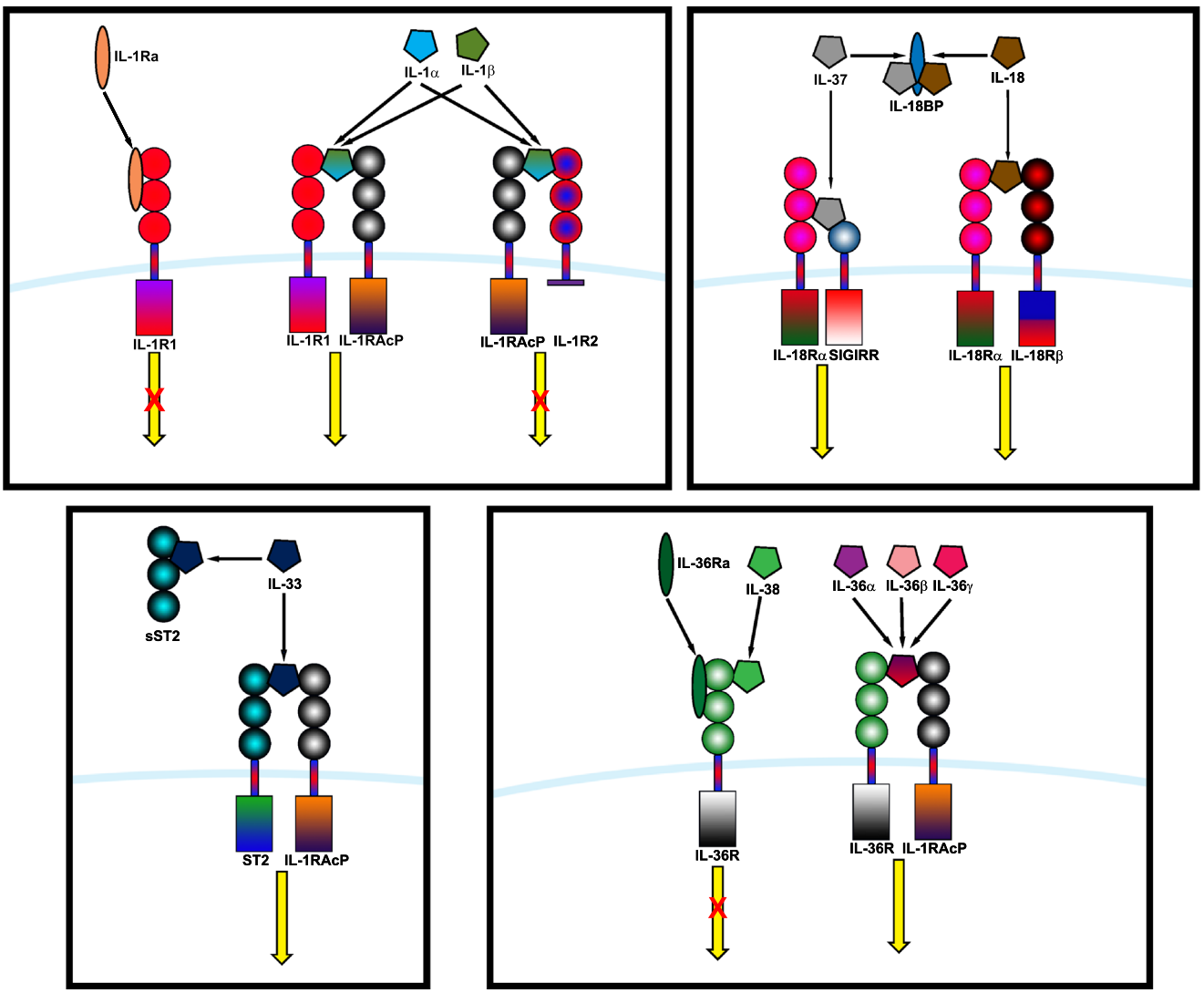

Fig. 1 IL-1 family cytokines and their known receptors. The IL-1 cytokine family consists of seven agonists (IL-1α, IL-1β, IL-18, IL-33, IL-36α, IL-36β and IL-36γ), three antagonists (IL-1Ra, IL-36Ra and IL-38) and one anti-inflammatory cytokine (IL-37). The known interactions of the IL-1 cytokines with the IL-1 receptor family are summarised above

interleukin was introduced in 1979 to consolidate the nomenclature for factors with the ability to act as communication signals between different populations of leukocytes, and the term IL-1 was assigned to leukocytic pyrogen/lymphocyte activation factor [10]. Several years' later, two sequences for IL-1 cDNA were cloned in mice and humans and were subsequently named IL-1α and IL-1β [11, 12]. The genes for IL-1α and IL-1β are located adjacent to one another on the long arm of chromosome 2 and encode proteins of 271aa and 268aa (~31 kDa) respectively [13]. Although both proteins bind to the same receptor (IL-1R1), triggering the recruitment of IL-1RAcP to form a signal transducing complex [14], there are several differences in their expression and proteolytic processing that impact on their respective roles in vivo.

IL-1α is a dual-function cytokine, meaning that in addition to functioning as a classical cytokine via cell surface receptor ligation, full-length IL-1α can also directly regulate gene expression. For example, full-length IL-1α contains a nuclear localisation site within its N-terminal amino acid sequence [15] and has been shown to facilitate pro-inflammatory gene transcription independent of IL-1R1 binding [16]. Full-length IL-1α is constitutively expressed in the cytoplasm and nuclei of a range of non-haematopoietic cells such as epithelial cells in a range of tissues including the lung, liver and kidney [17]. Damage to the epithelium of the lung as a result of infection with bacteria or virus [18, 19] or by non-infective insults such as air pollution, oxidative stress, aspiration injury or cigarette smoke results in the release of IL-1α from stressed/necrotic cells into the extracellular space [20–24]. The release of IL-1α from necrotic cells is unique as cells directed to the apoptotic pathway concentrate IL-1α in dense nuclear foci and therefore it is not released along with the cytoplasmic contents during apoptosis [25, 26]. Full-length IL-1α, unlike full-length IL-1β, is biologically active and functions as a damage-associated molecular pattern (DAMP) or an 'alarmin' by binding to IL-1R1 and rapidly initiating the production of chemokines and inflammatory cytokines, driving 'sterile inflammation' [27, 28]. Therefore, nuclear retention of IL-1α is likely a mechanism to distinguish between apoptotic and necrotic cell death and to limit sterile inflammation in response to programmed cell death. As well as being constitutively expressed in epithelial cells, numerous other cell types have been shown to upregulate and release IL-1α in response to a range of different stimuli including macrophages [29, 30], monocytes [31, 32] and endothelial cells [33] among others [34].

IL-1β is an inducible cytokine and is not generally expressed in healthy cells or tissue; however, full-length IL-1β is rapidly induced in cells by activation of pattern recognition receptors (PRRs) such as TLRs by pathogen products or factors released by damaged cells, leading to intracellular accumulation of the protein [35]. Processing of the full-length precursor to the biologically active mature form of the protein requires caspase-1 which cleaves the N-terminal 116 amino acids from the precursor to generate a mature active cytokine [36]. In the majority of cell types, caspase-1 is maintained in an inactive state and therefore the secretion of active IL-1β is tightly regulated. The inflammasome is a multi-protein intracellular complex that is required for the conversion of pro-caspase-1 to active caspase-1, and has been shown to be required for the cleavage and release of mature IL-1β [37]. However, inflammasome-independent processing of IL-1β has also been demonstrated in caspase-1-deficient mice with neutrophil proteases including elastase, proteinase-3, granzyme A, and cathepsin G able to convert the IL-1β precursor to the active mature protein extracellularly [38, 39]. Pro-IL-1β lacks an N-terminal secretory signal or leader sequence and therefore is not secreted via the classical endoplasmic reticulum–Golgi pathway [40]. Despite over two decades of research, the mechanism by which the active IL-1β protein is secreted from cells remains elusive although several potential mechanisms have been proposed including exocytosis of secretory lysosomes [41, 42], microvesicle shedding from the plasma membrane [43, 44], shedding of multivesicular bodies containing exosomes [45] and direct efflux across hyperpermeable plasma membranes during pyroptotic cell death [46].

Once extracellular, IL-1α and mature IL-1β bind to the IL-1R1 to initiate downstream signalling in a range of cell types [14]. However, additional control on the actions of IL-1α and IL-1β at the level of receptor interactions is provided by IL-1Ra and IL-1R2. The gene for IL-1Ra, like those encoding IL-1α and IL-1β, is located on chromosome 2 in humans, and the similarities in the intron–exon organisation suggests that the IL-1Ra gene originated as a consequence of gene duplication [47, 48]. IL-1Ra binds to IL-1R1 with comparable affinity to IL-1α and IL-1β but fails to induce the conformational change in the receptor that is required for the recruitment of the IL-1RAcP co-receptor and signal transduction [49, 50]. Consequently, IL-1Ra acts as a competitive inhibitor for IL-1R1 and completely inhibits the activity of IL-1α and IL-1β. IL-1R2 is expressed in numerous cell types in a range of tissue in both humans and mice [48]. Also located on chromosome 2, the gene encodes a 68-kDa (compared to the 80-kDa IL-1R1) membrane-bound protein with a truncated (29 amino acids) cytoplasmic tail that is lacking the TIR domain and is therefore incapable of intracellular signalling [51]. IL-1R2 can also be proteolytically cleaved in the proximal extracellular region to generate a soluble receptor (sIL-1R2) [52]. Although IL-1R2 binds to IL-1α, IL-1β and IL-1Ra, the binding affinity for IL-1Ra is ~100-fold less than for IL-1α and IL-1β [53] and therefore IL-1R2 is likely to further enhance the inhibitory action of IL-1Ra. For example, reducing IL-1R2 expression in keratinocyte by RNA interference increased IL-1-mediated CCL2 and CCL5 mRNA and protein expression confirming the inhibitory effect of IL-1R2 [54].

Recombinant IL-1α and IL-1β has been shown to have potent effects on a range of cell types in vitro, and therefore

any unique effects attributed to IL-1α and IL-1β are likely due to differences in the expression and/or release of the biologically active proteins rather than receptor binding or downstream signalling events. For example, work from our group and others has demonstrated that fibroblasts are induced to secrete a range of inflammatory cytokines in response to challenge with both recombinants IL-1α and IL-1β. However, damaged lung epithelial cells release large quantities of biologically active IL-1α, but little to no mature IL-1β, and therefore it is IL-1α that acts as the primary fibroblast stimulatory factor in this setting [55, 56]. In contrast, peritoneal and alveolar macrophages have been demonstrated to regulate fibroblasts through the release of IL-1β, with little to no requirement for IL-1α [57, 58]. Both IL-1α and IL-1β have also been shown to directly stimulate collagen synthesis and proliferation in fibroblasts [59, 60]. However, this function is controversial as there is a large body of literature demonstrating an inhibition of collagen synthesis [61, 62], and therefore further research is required to clarify this contradiction. IL-1β has also been shown to enhance TGF-β1-driven epithelial-to-mesenchymal transition in vitro highlighting another potential mode of action for the cytokine [63, 64]. However, the in vivo relevance of epithelial to mesenchymal transition has been challenged by a number of lineage tracing studies showing that mesenchymal cells in fibrotic tissue do not have an epithelial origin [65, 66], and therefore further research is required to establish the potential in vivo relevance of EMT-derived mesenchymal cells in fibrosis.

Despite the aforementioned differences, both IL-1α and IL-1β have been demonstrated to play important roles in fibrosis in vivo. In 2001, Kolb et al. used adenoviral gene transfer to transiently overexpress IL-1β in rat lungs which led to an acute inflammatory response with severe progressive tissue fibrosis [67]. Subsequently, numerous studies have shown that administration of IL-1β can drive a fibrotic response in the lung and that the degree of fibrosis is of a similar magnitude to that induced by bleomycin challenge [68, 69]. Intratracheal challenge of wild-type mice with human recombinant IL-1α induced neutrophilia, myeloperoxidase activity and inflammation, all of which were abrogated in mice overexpressing IL-1Ra [70]. Similar effects of intratracheal IL-1α challenge were also seen in ventilated preterm lambs [71] and in rats where IL-1α intratracheally causes an acute, neutrophil-dependent, oxidative lung leak that closely resembles human acute lung injury [72]. Furthermore, both IL-1α and IL-1β have been shown to be increased in mice following bleomycin challenge and IL-1α-, IL-1β- and IL-1R1-deficient mice are protected from bleomycin-induced pulmonary fibrosis [55, 68]. Neutralisation of IL-1β has also been shown to attenuate silica-induced inflammation and fibrosis by inhibiting other inflammatory and fibrogenic mediators and modulating the Th1/Th2 balance [73].

Mice overexpressing IL-1Ra have a reduction in the incidence and severity of collagen-induced arthritis whereas mice lacking IL-1Ra have an earlier onset of collagen-induced arthritis [74]. Administration of IL-1Ra by an osmotic minipump in mice exposed to intra-tracheal instillation of bleomycin or silica completely prevented lung damage and the increase in collagen deposition seen in control mice [75]. A similar inhibition of bleomycin-induced lung pathology was seen with Anakinra [68], an IL-1 receptor antagonist used to treat patients with rheumatoid arthritis [76]. Using both IL-1α- and IL-1β-deficient mice and neutralising antibodies, Botelho et al. demonstrated a novel role for IL-1α in murine models of COPD. The authors conclusively demonstrate that neutrophilic inflammation induced by cigarette smoke exposure is IL-1α dependent, but IL-1β and caspase-1 independent. Furthermore, the authors used bone marrow chimeric mice to demonstrate that IL-1R1 expression on non-hematopoietic cells is required to induce inflammation following cigarette smoke exposure [77].

The inflammasome has also been demonstrated to be important in the pathogenesis of lung fibrosis. For example, Gasse et al. demonstrated that mice deficient in apoptosis-associated speck-like protein containing a CARD (ASC), an important component of the inflammasome, have attenuated IL-1β production and are protected from bleomycin-induced lung fibrosis suggesting that one of the mechanisms of action of bleomycin is via the activation of the inflammasome [68]. In a subsequent study, the authors found that uric acid was released into the lung parenchyma following bleomycin challenge and that a reduction in uric acid levels lead to a decrease in IL-1β production, inflammation and fibrosis [78]. The authors postulated that precipitation of uric acid and the resultant formation of monosodium urate crystals could cause membrane damage to cells leading to inflammasome activation and downstream release of IL-1β. Subsequently, the authors demonstrated that administration of exogenous uric acid crystals recapitulates lung inflammation and repair via an inflammasome and IL-1R1-dependent pathway [78].

Asbestos and silica are sensed by the NLRP3 inflammasome leading to the subsequent activation and secretion of active IL-1β [79, 80]. NLRP3-deficient mice demonstrate a reduction in immune cell recruitment to the lungs and a lower inflammatory cytokine burden in a model of asbestosis inhalation [80]. Significantly, both NLRP3- and ASC-deficient mice are protected from silica-induced collagen deposition confirming an important role for the inflammasome in silica-induced lung fibrosis. A recent study by dos Santos et al. employing vimentin-deficient mice has highlighted a novel role for vimentin in Lipopolysaccharides (LPS)-induced caspase-1 activation and IL-1β maturation via interactions with the NLRP3 inflammasome. The authors demonstrate that vimentin-deficient mice are protected from asbestos- and bleomycin-induced lung injury and fibrosis and that

vimentin-expressing bone-marrow-derived cells are important for bleomycin-induced activation of the NLRP3 inflammasome and pulmonary fibrosis [81].

The potential therapeutic value of targeting IL-1α and/or IL-1β in a range of lung diseases becomes clear when reviewing the literature.

Development of the chronic inflammatory airway pathology characteristic of COPD is thought to be triggered by inhalation of noxious particles, primarily cigarette smoke which accounts for ~80–90 % of cases in the USA [82]. Healthy smokers have significantly elevated levels of IL-1β in their bronchoalveolar lavage (BAL) compared to healthy non-smokers, with IL-1β levels correlating in a cigarette-dose-dependent manner [83]. Increased levels of IL-1β in induced sputum from patients with stable COPD have also been reported [84], and in a subsequent study, the number of IL-1α- and IL-1β-positive cells was shown to be increased in biopsy samples taken from GOLD I/II COPD patients compared to non-COPD controls. In addition, levels of IL-1α and IL-1β in sputum and lung tissue of COPD patients are increased [22], while levels of IL-1α and IL-1β correlated during stable disease, at the onset of exacerbation and post-exacerbation [77]. Uric acid, which has been demonstrated to play an important role in lung fibrosis in mice via an inflammasome- and IL-1R1-dependent pathway, has also been reported to be elevated in BAL of healthy smokers compared to healthy non-smokers as well as COPD patients who smoke compared to healthy smokers [85, 86]. Furthermore, serum uric acid has been shown to be associated with increased 30-day mortality and risk for acute exacerbations and hospitalisation in COPD patients [87].

Several studies have presented evidence of activation of the inflammasome in COPD. For example, increased caspase-1 activation was observed in lung samples from smokers and emphysema patients, compared with non-smokers [88]. Inhibition of caspase-1 significantly reduces inflammation in response to challenge with cigarette smoke in animal models [89]. Various molecules that activate the inflammasome have also been shown to be elevated in COPD patients. For example, extracellular ATP activates the NLRP3 inflammasome by engaging the purinergic $P2X_7$ receptor [90], and the $P2X_7$ receptor is upregulated on alveolar macrophages and blood neutrophils from patients with COPD [91]. In addition, extracellular ATP is elevated in BAL fluid from patients with COPD as compared with normal control subjects and ATP concentrations correlate with an increase in airway infiltration and is associated with a decline in lung function [91, 92]. Together, these data suggest a role for the inflammasome in contributing to the airway inflammation seen in COPD.

IL-1β has also been shown to be elevated in BAL and lung biopsies from IPF patients compared to normal volunteers [69]. Furthermore, in both serum and BAL, a decreased IL-1Ra/IL-1β ratio was found in IPF patients compared to healthy controls, and this imbalance might contribute to a proinflammatory environment in IPF lungs [93]. Autoantibodies against IL-1α were detected in the sera of 11/11 rapidly progressive IPF patients on the 21st hospital day following admission for severe symptoms (compared to 5/11 on the first hospital day) suggesting that extracellular IL-1α may be an undesirable factor in fibrotic lung diseases [94]. Alveolar macrophages isolated from patients with asbestosis, sarcoidosis and IPF have higher levels of IL-1β mRNA and spontaneous IL-1β secretion compared to control subject [95, 96]. In contrast IL-1Ra release from ILD alveolar macrophages was reduced compared to healthy controls, further increasing the IL-1β/IL-1Ra ratio. Importantly, a high IL-1β/IL-1Ra ratio was shown to correlate with BAL cellularity and was associated with advanced or active disease [96]. Similar to COPD, there is data indicating an important role for the inflammasome in the development of IPF. For example, the expression of both NLRP3 and caspase-1 are elevated in unstimulated macrophages isolated from the BAL of IPF patients compared to controls [97]. Additionally, exogenous ATP is elevated in the BAL of stable IPF patients compared to controls and was further elevated in patients with exacerbated IPF [98].

Recently, the US FDA approved the first two drugs proven to slow progression of IPF: pirfenidone (Esbriet by Roche) and nintedanib (Ofev by Boehringer Ingelheim). Nintedanib is a small molecule tyrosine kinase inhibitor while the precise mechanism of action of pirfenidone is incompletely understood. Both nintedanib and pirfenidone have been shown to inhibit lung fibrosis in murine models, and these effects were associated with a reduction in IL-1β levels in lung tissue [99, 100]. This inhibition of IL-1β may help to dampen the profibrotic milieu in the lung, and improving our understanding of whether this reduction in IL-1β is important for the inhibitory action of nintedanib and pirfenidone will be extremely informative.

The primary limitation to survival after lung transplantation is the development of bronchiolitis obliterative syndrome (BOS), a chronic inflammatory process characterised by fibroproliferation, deposition of extracellular matrix and obliteration of the airways. Levels of IL-1Ra were elevated in patients with BOS compared to healthy lung transplant recipients and patients with acute rejection [101]. Furthermore, work in my laboratory has demonstrated that IL-1α and IL-1β concentrations are elevated in BAL samples acquired immediately prior to BOS diagnosis compared to patient-matched BAL samples acquired at other times following transplant or in BAL samples acquired from stable transplant controls [102, 103]. Further investigation of whether these markers contribute to disease pathology or are simply markers of disease progression is required.

IL-33 and ST2

Unlike most IL-1 family cytokines which are located on chromosome 2, the gene for IL-33 is found on chromosome 9 (or

chromosome 19 in mice) where it encodes a peptide of 270aa corresponding to a full-length protein of ~30 kDa [104]. The full-length IL-33 protein contains a non-classical nuclear localisation sequence (aa1-75 in human IL-33) and a non-classical homeodomain-like helix-turn-helix DNA binding domain in the same region with a chromatin binding domain (aa40-58 in human IL-33) [105–107]. Consequently, the full-length protein translocates to the nucleus where it has intracrine gene regulatory functions by interacting with and modulating the function of a number of proteins [108]. For example, full-length IL-33 can function as a transcriptional repressor by binding to the N-terminus of the p65 NF-kappaB subunit, inhibiting binding of p65 to its promoter sequence and therefore impairing transactivation of NF-kappaB-regulated genes including IL-1 and TNF [109]. This function is exclusive to the full-length IL-33 protein as the mature IL-33 protein (aa110-266 in human) losses the nuclear localisation and DNA/chromatin binding domains during proteolytic processing.

Although full-length IL-33 is biologically active, cleavage generates mature forms of IL-33 with up to 10-fold more biologically active compared to the full-length protein [110]. It was originally proposed that, like other members of the IL-1 cytokine family, caspase-1 was responsible for cleavage of the full-length protein to active mature forms [104]. However, the predicted cleavage site for caspase-1 is not conserved in IL-33, and further studies have suggested inactivation of IL-33 following maturation by caspase-1 [111]. Indeed cleavage sites in IL-33 more closely resemble those for caspase-3 and caspase-7, proteins activated during apoptosis, and cleavage of full-length IL-33 by caspase-3 and caspase-7 generates biologically inactive breakdown products suggesting that IL-33 is destroyed in apoptotic cells [108, 112, 113]. However, extracellular full-length IL-33 can be matured by calpain, neutrophil elastase and cathepsin G to generate biologically active forms of the protein (aa95-270, aa99-270, aa109-270) with greater activity than the full-length IL-33 [110, 114, 115].

ST2, previously known as an orphan receptor of the IL-1 receptor family, was identified as the IL-33 receptor in 2005 [104]. Binding of IL-33 to ST2 drives a conformational change in ST2 leading to the binding of the IL-33-ST2 dimer to IL-1RAcP and downstream signalling via MyD88 [116, 117]. In addition to membrane-bound ST2, the ST2 gene in humans encodes at least two additional spliced isoforms, sST2 and ST2V. Characterised by the lack of both a transmembrane domain and an intracellular TIR domains, sST2 is released from the cells to act as a soluble decoy receptor by sequestering IL-33 and preventing its binding to membrane-bound ST2 [118]. While ST2 and sST2 are widely expressed throughout tissues, the expression of ST2V is limited primarily to stomach, small intestine and colon [119]. The exact role for ST2V in vivo requires further investigation; however, it can be found integrated into the plasma membrane when transfected into COS7 cells suggesting a possible role in modifying the IL-33-ST2 signalling complex [119].

Although the expression of IL-33 was originally thought to be restricted to constitutive expression in a small number of cell types including endothelial cells [120], it is now clear that IL-33 is much more abundant (fibroblasts, epithelial cell, macrophages, among others) and that its expression can be regulated in much the same way as other members of the IL-1 family. For example, treatment with various microbial components (for example, PolyIC–TLR3 and flagellin–TLR5) increased IL-33 expression in human corneal epithelial cells [121] and murine macrophages [122], and pro-inflammatory cytokines including IL-3 and IL-4, and IFN-γ and TNF-α have been shown to upregulate IL-33 in a range of murine cell types [123] and human epidermal keratinocytes [114]. However, while it is clear that IL-33 can be upregulated and serves many important functions in vivo, the mechanism by which IL-33 is actively secreted from the cells is subject to ongoing debate. What is clear is that in addition to functioning as a classical cytokine, IL-33 can also function as an alarmin or danger signal that is released into the extracellular space in response to necrotic cell death or mechanical injury. For example, full-length biologically active IL-33 can be released from mechanically injured or damaged endothelial cells [111]. Given that IL-33 is constitutively expressed intracellularly in epithelial cells and endothelial cells in uninjured tissue, it is likely to function as a very efficient alarmin in vivo.

Regardless of the mechanism leading to its release/secretion, once in the extracellular environment, IL-33 has been demonstrated to have an effect on a wide range of cell types in a range of different organs [124]. IL-33 plays a role in type-2 immunity in response to helminth infection by driving the proliferation and activation (IL-13 secretion) of innate lymphoid cells (ILC2) leading to goblet cell hyperplasia and expulsion of the parasite [125–127]. The IL-33-ST2 axis has also been shown to be important in physiological remodelling of the lung following infection with influenza virus, with blockade of IL-33-ST2 resulting in severely decreased lung function, loss of airway epithelial integrity and impaired tissue remodelling [128]. IL-33-deficient mice have impaired IL-5/IL-13 secretion from ILC2, reduced eosinophil and Th2 cell recruitment in response to intranasal challenge with papain, a protease allergen [129]. Dendritic cells exposed to IL-33 secrete high levels of IL-6, TNF and IL-1β and prime naïve lymphocytes to produce Th2 cytokines in vitro while adoptive transfer of IL-33-activated dendritic cells exacerbates lung inflammation in an allergy airway inflammation model [130]. Alveolar macrophages are polarised towards an alternatively activated phenotype in response to IL-33- and ST2-deficient mice have attenuated ovalbumin-induced airway inflammation associated with a decrease in AAM differentiation [131]. Several recent publications have thoroughly reviewed the role of IL-33 in tissue injury and inflammation [124, 132, 133].

The potential of IL-33 to have a direct effect on fibroblasts has generated conflicting data. For example, IL-33 increases expression of both IL-6 and TNF-α expression in human keratinocytes [134] and has been demonstrated to induced eotaxin/CCL11 production in murine lung fibroblasts [135] and IL-6 and MCP-1 expression in murine cardiac fibroblasts [136]. However, in another study, human lung epithelial cells and endothelial cells, but not fibroblasts, were shown to express ST2 and secrete IL-8 in response to IL-33 stimulation [137]. Further work to investigate the IL-33-ST2 axis on fibroblasts is required.

IL-33 and ST2 have been demonstrated to play a role in pulmonary fibrosis in vivo [138]. In response to bleomycin challenge, mice show a substantial accumulation of IL-33-positive cells in the lung and full-length IL-33 can potentiate bleomycin-induced inflammation and fibrosis, potentially by upregulating expression of TGF-β and other non-Th2 cytokines [139]. A subsequent study demonstrated that intratracheal instillation of lentivirus expressing soluble ST2 significantly attenuated pulmonary inflammatory cell infiltration and fibrotic changes and markedly reduced the levels of inflammatory cytokines and TGF-β1 in BAL in mice challenged with bleomycin [140]. Li et al. demonstrated that ST2-deficient mice have attenuated bleomycin-induced lung fibrosis, and this phenomenon could be recreated by IL-33 neutralising antibody treatment [141]. Mechanistically, the authors demonstrate that although IL-33 is constitutively expressed in epithelial cells, it is induced in macrophages in response to bleomycin challenge and that depletion of alveolar macrophages using clodronate liposomes abolished both bleomycin-induced lung fibrosis and IL-33-exacerbated lung fibrosis. IL-33 was shown to polarise M2 macrophages to produce IL-13 and TGF-β1 and induced the expansion of type 2 ILC2s to produce IL-13 in vitro and in vivo. Furthermore, ILC2s were almost completely absent in ST2-deficient mice, and adoptive transfer of ILC2s led to exacerbation of lung inflammation and fibrosis compared to bleomycin challenge alone [141]. Patients with idiopathic pulmonary fibrosis have also been reported to have elevated levels of IL-33 in BAL and lung tissue compared to healthy controls. Significantly, Western blotting was used to determine the relative quantities of full-length and mature IL-33, and higher levels of the mature, more biologically isoform of IL-33 was seen in IPF patients [142]. In addition, serum IL-33 levels are elevated in patients with systemic sclerosis and correlated with the extent of skin sclerosis and the severity of pulmonary fibrosis [143].

Expression of IL-33 and ST2 were markedly enhanced in the lung tissue of mice challenged with cigarette smoke and were accompanied by increased neutrophil and macrophage infiltration and expression of inflammatory cytokines and chemokines. Importantly, all pathological changes were attenuated by a neutralising anti-IL-33 antibody suggesting that IL-33 plays a critical role in cigarette-smoke-mediated airway inflammation [144]. A subsequent study identified that IL-33 is expressed in bronchial endothelial cells and peripheral blood mononuclear cells in response to cigarette smoke challenge in mice and that challenge of peripheral blood mononuclear cells with IL-33 enhanced cigarette-smoke-induced inflammatory cytokine release [145]. Kearley et al. used a combination of cigarette smoke and infection to model exacerbations of COPD in mice and shown that on the background of smoke exposure, exaggerated inflammation to infection is completely attenuated in the absence of IL-33 signalling. Mechanistically, the authors demonstrate that cigarette smoke upregulates epithelial-derived IL-33 and decreases ST2 expression on ILC2s while elevating ST2 expression on macrophages and NK cells. Consequently, upon viral infection, IL-33 significantly amplified type I proinflammatory responses via synergistic modulation of macrophage and NK cell function. The authors conclude that in COPD, smoke alters the lung microenvironment to facilitate an alternative IL-33-dependent exaggerated proinflammatory response to infection, exacerbating disease [146].

IL-33 and soluble ST2 are higher in plasma samples from COPD patients compared to controls, and the frequency of IL-33 expressing peripheral blood lymphocytes and neutrophils as well as the expression of IL-33 in bronchial epithelial cells is increased in COPD patients [147]. In another study, IL-33 expression was demonstrated to be restricted to a subset of airway basal cells with increased capacities for pluripotency [148]. Smoking is the leading cause of COPD or COPD-related inflammation, and cigarette smoke extract has been shown to accentuate the IL-33-induced expression of IL-6 and IL-8 in human bronchial epithelial cells and PBMCs [149]. In mice, cigarette-smoke-induced airway inflammation is characterised by neutrophil and macrophage infiltration and increased expression of inflammatory cytokines and mucin in the airways. Significantly, expression of IL-33 and ST2 was also increased in response to cigarette smoke, and neutralising IL-33 inhibited all pathogenic changes [144]. The potential of targeting IL-33 as a therapeutic option in COPD has recently been discussed [150].

Exposure of mice to multi-walled carbon nanotubes increased BAL total cell counts, macrophage, and neutrophil recruitment, and increased inflammation and fibrosis located proximal to the airways. In contrast, IL-33-deficient mice were protected from all pathologies suggesting that IL-33 is critical for the pulmonary toxicity induced by multi-walled carbon nanotubes [151]. IL-33 has also recently been shown to be elevated in the BAL and lung tissue of CF patients where it has been hypothesised to be involved in neutrophil recruitment [152, 153].

IL-18 subfamily

IL-18 and IL-18BP

Although originally identified in 1989 as 'IFN-γ-inducing factor', IL-18 was reclassified as a member of the IL-1

cytokine family in 1995 following purification and molecular cloning [154]. The gene, the only member of the IL-1 cytokine family to be located on chromosome 11 in humans (chromosome 9 in mice), encodes a full-length protein of ~24 kDa that is biologically inactive. Within the IL-1 cytokine family, IL-18 is most closely related to IL-1β and shares many common traits including cleavage by caspase-1 to a biologically active mature protein of ~17 kDa that is actively secreted from cells [155, 156]. Extracellular mature IL-18 binds to the alpha chain of the IL-18 receptor (IL-18Rα) with low affinity. Binding to a co-receptor, the beta chain of the IL-18 receptor (IL-18Rβ), forms a high-affinity heterodimer complex with signalling activity [157]. However, unlike IL-1α and β which are active on cells in the pg/ml range, IL-18 is required in high levels of >10 ng/ml to activate responsive cells [158–160]. In addition to the high levels of IL-18 required to elicit a response, there are other levels of regulation within the IL-18 signalling pathway. For example, while IL-18Rα is expressed on numerous cell types, the expression of the IL-18Rβ co-receptor is more limited, being expressed on T cells and dendritic cells but not commonly mesenchymal cells [157]. In addition, the IL-18 binding protein (IL-18BP) is a constitutively secreted protein with very high affinity for mature IL-18 that functions by sequestering IL-18 and therefore preventing the formation of IL-18-IL-18R interactions [161, 162]. IL-18BP levels in the serum of healthy individuals are in a 20-fold molar excess [163], likely acting as a very effective regulatory mechanism.

Despite this, a role for IL-18 in many biological processes has been reported [160, 164]. IL-18 is involved in regulation of the Th1 response by modulating production of IFN-γ. For example, in synergy with either IL-12 or IL-15, which upregulates the expression of the IL-18Rβ co-receptor, IL-18 induces the production of IFN-γ from T cells [165] and treatment of NK cells with IL-18 induced a CD83+CCR7+ helper phenotype characterised by high ability to produce IFN-γ [166]. Reducing IL-18 activity using IL-18 vaccination, IL-18 neutralising antibodies, IL-18BP, or performing experiments in IL-18 deficient mice has been shown to reduce disease severity in a number of animal models including dextran sulphate sodium (DSS)-induced colitis [167, 168], collagen-induced arthritis [169, 170] and allergic airway hyperresponsiveness [171]. Readers are directed to the excellent review by Novick et al. that further highlights the many disease processes IL-18 and IL-18BP contribute to [160].

The role of the IL-18-IL-18R signalling pathway in fibrosis is unclear with both pro- and anti-fibrotic effects suggested in the literature. For example, IL-18 deficient mice were shown to have increased mortality, lung injury, and leukocyte infiltration in the BAL in response to bleomycin challenge compared to wild-type mice, and prophylactic treatment of wild-type mice with IL-18 prior to bleomycin challenge reduced lung injury and fibrosis suggesting that IL-18 plays a protective role against bleomycin-induced lung fibrosis [172]. However, a subsequent study by Hoshino et al. demonstrated that IL-18 and IL-18Rα are elevated in the lungs of patients with bleomycin-induced lethal lung injury and in the lungs of mice following bleomycin challenge and that IL-18- and IL-18Rα-deficient mice are protected from bleomycin-induced lung fibrosis, suggesting a pro-fibrotic role for IL-18 [173]. Furthermore, overexpression of IL-18 in mice drives inflammatory cell accumulation (primarily $CD8^+$ T cells, macrophages, neutrophils and eosinophils) resulting in severe emphysema and airway fibrosis [174, 175]. In summary, IL-18 has been reported to have pro-fibrotic actions in vivo in the majority of studies. In agreement with this, several studies have demonstrated a direct effect for IL-18 on mesenchymal cells. IL-18 enhanced the production of angiogenic factors and key regulators of osteoclastogenesis in synovial tissue fibroblasts [176, 177]. Stimulation of cardiac fibroblasts with IL-18 promotes a pro-fibrotic response characterised by increased expression of collagen I/III and periostin, increased proliferation and increased migration [178]. IL-18 levels in serum and BAL of patients with IPF were higher than those in control subjects, and while IL-18Rα was expressed in bronchial epithelium and alveolar macrophages in control subjects, it was found to be strongly expressed in interstitial cells, especially the fibroblastic foci, in patients with IPF [179]. Conversely, a recent study by Lasithiotaki et al. failed to demonstrate a difference in IL-18 levels in BAL of patients with IPF compared to a control group but did show a significant increase in IL-18 levels in BAL of patients with rheumatoid arthritis–usual interstitial pneumonia [97].

Cigarette-smoke-induced inflammation and emphysema in the lung of wild-type mice were also associated with an increase in IL-18 expression. Importantly, IL-18Rα-deficient mice are protected from cigarette-smoke-induced inflammation and emphysema [180]. Clinically, IL-18 was shown to be elevated in pulmonary macrophages from patients with COPD, and levels of serum and circulating IL-18 have also been shown to be increased in patients with COPD [180–183]. Furthermore, there is a negative correlation between serum IL-18 level and the predicted forced expiratory volume in 1 s in patients with COPD suggesting that overproduction of IL-18 in the lungs may be involved in disease pathogenesis [184].

IL-37

In 2000, several independent groups described IL-37 following expression sequence tag (EST) database screening and sequencing of the IL-1 gene cluster on human (no mouse homologues have been described) chromosome 2 [185–188]. There are five spliced variants and isoforms of IL-37, termed IL-37a-e, although isoform IL-37b has the most complete set of exons and is the best characterised. IL-37 has been shown to bind to IL-18Rα, although the affinity for the receptor is lower than IL-18 and without any effect on IFN-γ

production induced by IL-18 [189–191]. More recently, SIGIRR has been shown to be indispensable for IL-37 to carry out its anti-inflammatory effect [192]. IL-37 has also been demonstrated to bind to the natural inhibitor of IL-18 activity, the IL-18 binding protein (IL-18BP), leading to an enhancement of IL-18BPs ability to inhibit IFN-γ production in response to IL-18 stimulation [162, 191]. Intracellular modes of action for IL-37 have also been demonstrated. For example, when overexpressed in epithelial cells or macrophages, IL-37 almost completely suppressed the production of pro-inflammatory cytokines whereas the silencing of the IL-37 gene increased the abundance of these cytokines in human blood cells suggesting that IL-37 may possess anti-inflammatory properties [193]. Generation of an IL-37 over-expressing transgenic mouse has allowed the investigation of the role of IL-37 in vivo. For example, IL-37 transgenic mice have decreased levels of circulating cytokines, are protected from lipopolysaccharide-induced shock and show improved lung and kidney function as well as reduced liver damage in response to lipopolysaccharide [193].

Mechanistically, caspase-1-mediated cleavage to the mature form of IL-37 is required for translocation to the nucleus. In RAW macrophages, stable transfection with IL-37 substantially reduced (72–98 %) LPS-stimulated TNF-α, IL-1α and IL-6 [194]. This inhibitory effect of IL-37 is linked to binding to the Smad3 transcription factor as inhibition of Smad3 reversed the inhibition of IL-6 expression in RAW macrophages [195, 196]. The contribution of the IL-37-Smad3 interaction was confirmed in vivo using IL-37 transgenic mice that had been pretreated intranasally with siRNA specific to Smad3 prior to intranasal challenge with LPS. The reduction in cytokines in the lungs in IL-37 transgenic mice was reversed following Smad3 knockdown [193]. IL-37 transgenic mice also exhibited reduced clinical disease scores and histological evidence of colitis in the DSS model of induced colitis [197], suppressed contact hypersensitivity in response to hapten antigen 2,4-dinitrofluorobenzene by inducing tolerogenic dendritic cells [198] and are protected from myocardial and hepatic ischemic damage [199, 200]. Furthermore, recombinant human IL-37 injected intraperitoneally into mice markedly reduced NLRP3-dependent neutrophil recruitment and IL-1β production and mitigated lung inflammation and damage in response to intranasal infection with live *Aspergillus fumigatus* conidia suggesting that IL-37 functions as a broad spectrum inhibitor of the innate response to infection-mediated inflammation [201]. Excellent recent reviews further describe the anti-inflammatory action of IL-37 [185, 202].

The CLARA childhood asthma study revealed reduced mRNA expression of IL-37 in children with allergic asthma and, thus, pointed toward an implication of this cytokine for human asthma pathogenesis [203]. In addition, IL-37 levels in serum and induced sputum were lower in asthma patients compared to healthy controls and levels of IL-37 correlated with disease severity suggesting a potential protective effect [204]. A subsequent study demonstrated that IL-37 production from PBMCs was lower in allergic asthmatic compared to healthy children. The authors go on to demonstrate that intranasal IL-37 ablated airway inflammation, mucus hyperproduction and airway hyperresponsiveness in response to ovalbumin challenge via an IL-18Rα/GIGIRR-dependent pathway [205]. In contrast, level of plasma and serum IL-37 in patients with active pulmonary tuberculosis was significantly higher than that in healthy controls but recovered after treatment [206, 207]. Mechanistically, the authors demonstrate that IL-37 inhibited the production of pro-inflammatory cytokines and induced macrophages toward an M2-like phenotype [207]. IL-37 has been shown to be increased in the bronchial mucosa in COPD patients compared to control healthy smokers and non-smokers [208].

Although the exact role played by IL-37 in fibrosis is yet to be fully elucidated, it is clear that IL-37 functions as a broad-spectrum inhibitor of the innate response to infection-mediated inflammation and could be considered to be therapeutic in reducing the pulmonary damage due to non-resolving infection and disease.

IL-36 subfamily

IL-36 and IL-36Ra

The IL-36 cytokine subfamily consists of three agonists, IL-36α, IL-36β and IL-36γ, which bind to IL-36R (IL-1Rrp2) and employ IL-1RAcP as a co-receptor, and a receptor antagonist, IL-36Ra, which binds to IL-36R to inhibit IL-1RAcP recruitment and the formation of a functional signalling complex [36, 188, 209, 210]. Although IL-1RAcP is shared with IL-1α, IL-1β and IL-33, the IL-36R is exclusively employed by IL-36 cytokines. Similar to other IL-1 cytokines, IL-36 cytokines require N-terminal cleavage to achieve full bioactivity (~1000–10,000-fold increase compared to non-truncated form). Interestingly, although IL-36Ra shares 52 % homology with IL-1Ra, the antagonistic activity of IL-36Ra is uniquely dependent on post translational modification, specifically the removal of its N-terminal methionine [211]. The amino acid sequence at the truncation sites for IL-36 cytokines share little homology and do not resemble classical caspase-1 cleavage sites. Moreover, no cleavage of IL-36α is observed in bone-marrow-derived macrophages with confirmed LPS/ATP-induced caspase-1 activation suggesting that the protease(s) responsible for cleavage of IL-36 cytokines are still to be determined [211–213].

IL-36α, IL-36β and IL-36γ have been shown to have a restricted expression pattern with keratinocytes, bronchial epithelial cells, brain tissue and monocytes/macrophages as the primary sites of expression although T lymphocytes,

peripheral blood lymphocytes and γδ T cells can also express IL-36 cytokines in response to a range of stimuli [213–217]. Studies in Jurkat cells transfected to express IL-36R or in a mammary epithelial cell line that naturally expresses IL-36R (NCI/ADR-RES) demonstrated that IL-36α, IL-36β and IL-36γ directly activate NF-kappaB [218] as well as MAPKs, JNK and ERK1/2 leading to the downstream activation of an IL-8 promoter reporter and the secretion of IL-6 [219]. For all molecules, blocking the IL-36R or the IL-1RAcP co-receptor inhibited the downstream effects confirming the importance of the IL-36R-IL-1RAcP complex [219].

IL-36 cytokines have also been shown to exert effects on immune cells, particularly dendritic cells. For example, mouse bone-marrow-derived dendritic cells upregulate key markers of activation (CD80, CD86 and MHCII) and produce IL-6, IL-12 and IL-23 upon stimulation with IL-36 agonists via an IL-36R-dependent pathway [215]. IL-36 has also been demonstrated to play a role in T cell polarisation by synergising with IL-12 to drive the in vitro differentiation of Th0 cells into IFN-γ + Th1 cells and to induce the production of IL-17 from murine CD4+ cells [215, 220]. Human bronchial epithelial cells stimulated with TNF, IL-17, IL-1β or double-stranded (ds)-RNA upregulated the intracellular expression of IL-36α and promoted the release of IL-36γ. Furthermore, lung fibroblasts were demonstrated to express IL-36R and IL-36RAcP and stimulation of lung fibroblasts with IL-36γ leads to the activation of MAPKs and NF-kappaB and the downstream expression of neutrophil chemokines (IL-8, CXCL3) and Th17 chemokines (CCL20). The data suggests that viral infection and/or selected cytokines from Th17 cells or inflammatory cells may drive neutrophil recruitment via IL-36γ-dependent activation of lung fibroblasts [221]. Furthermore, challenge of human bronchial epithelial cells with infectious agents such as *Pseudomonas aeruginosa* or rhinovirus has been shown to induce the expression of IL-36γ in vitro [222, 223], and intranasal challenge of mice with either IL-36α or IL-36γ induces a rapid neutrophilia [224, 225]. This data has led to the suggestion that IL-36γ released from epithelial cells may contribute to neutrophil recruitment during rhinovirus-induced exacerbation of asthma [226]. Similarly, challenge of human bronchial epithelial cells with cigarette smoke extract induced expression of IL-36α, IL-36β and IL-36γ [227]. Cigarette smoke is a causative agent for COPD, and the disease is characterised by neutrophilic accumulation in the airways. It is therefore possible that IL-36 released from epithelial cells in response to cigarette smoke challenge could contribute to the recruitment/accumulation of neutrophils seen in patients with COPD [226, 227].

Human synovial fibroblasts express IL-36R and produce pro-inflammatory mediators in response to stimulation with recombinant IL-36β, albeit to a lower magnitude than other IL-1 cytokines. In contrast, although IL-36β gene expression was elevated in response to challenge with TNF-α and IL-1β, the IL-36β protein was undetectable suggesting that fibroblasts are unlikely to be a source of IL-36β but may instead act as responsive cells. However, similar levels of IL-36β protein were detected in serum and synovial fluid isolated from healthy donors and patients with rheumatoid arthritis, osteoarthritis or septic shock, and levels of IL-36β failed to correlate with inflammation [228]. Additionally, blocking IL-36R or IL-36α, both found to be elevated in inflamed knee joints of TNF-induced arthritic mice compared to wild-type controls, had no effect on clinical onset, pattern of disease or histological evidence of arthritis suggesting that IL-36 cytokines do not affect the development of inflammatory arthritis in vivo [229], potentially due to redundancy with other members of the IL-1 family such as IL-1, a dominant cytokine in rodent arthritis models [226]. Excellent reviews further describing the biology of IL-36 cytokines have recently been published [213, 226].

There has been very little research looking at the expression of IL-36 cytokines in human disease. IL-36γ mRNA is increased in biopsies from patients with recurrent respiratory papillomas, and expression levels correlate with disease severity [230], and systemic IL-36α levels are decreased during acute exacerbation episodes in patients with COPD [231]. Further investigation is required to determine the disease relevance of these proteins and to identify a potential role in fibrosis.

IL-38

IL-38 was cloned and identified as a member of the IL-1 family in 2001 [232, 233]. The IL-38 gene is located on chromosome 2, between the genes encoding IL-1Ra and IL-36Ra [234], and shares 41 and 43 % homology with IL-1Ra and IL-36Ra respectively [233]. IL-38 is a 152-amino-acid protein without either a signal peptide or a caspase-1 cleavage site and is expressed in a wide range of tissues including foetal liver, salivary glands, spleen, thymus, tonsil and skin [48, 232, 233, 235]. An initial study reported that IL-38 was able to bind to IL-1R1, albeit with lower affinity than IL-1α, IL-1β or IL-1Ra [232]. However, a subsequent study has identified that IL-38 binds exclusively to IL-36R and has an antagonistic effect similar to IL-36Ra. Specifically, the authors demonstrated that *Candida albicans*-induced production of IL-22 and IL-17 in peripheral blood mononuclear cells could be reduced by IL-38 and that the level of reduction was similar to that achieved with IL-36Ra [236]. IL-38 has been shown to be elevated in the salivary glands of patients with primary Sjögren's syndrome, and IL-38 polymorphisms are associated with psoriatic arthritis and ankylosing spondylitis [235, 237, 238]. However, to date, there is no literature regarding a role for IL-38 in fibrosis, and further work is required to determine its relevance in vivo. A recent review by Yuan et al. nicely summarises the known roles of IL-38 [239].

Future perspective

The complexity of the IL-1 cytokine family and the body of literature relating to it continue to grow. In this review, I have attempted to provide a brief overview of the current understanding of the IL-1 cytokine family in inflammation and fibrosis in the lung while highlighting some recent key observations and review articles. However, there are still numerous outstanding questions that need to be answered. For example, although the role of some members of the IL-1 cytokine family in fibrosis is well established (IL-1α, IL-1β, IL-33), leading to compelling arguments for these molecules as potential therapeutic targets, the role of others (IL-36, IL-37, IL-38) remains to be elucidated. As we begin to understand more about the more recently described members of the IL-1 cytokine family, we are likely to identify potential new targets for consideration as innovative therapies. Furthermore, the same receptors can be employed by several members of the IL-1 cytokine family (for example, IL-1RAcP is shared by IL-1α, IL-1β, IL33 and IL-36), highlighting likely redundancy. Given the clear importance of IL-1α, IL-1β and IL-33 in lung fibrosis and the likely compensatory action provided by members of the IL-1 cytokine family in vivo, targeting the shared receptors (for example, IL-1RAcP) may be more effective. Further research to establish the potential benefits of targeting these shared receptors or simultaneously blocking multiple member of the IL-1 cytokine family in vivo is required.

Despite these outstanding questions, there is already a compelling body of preclinical evidence to support the potential of targeting IL-1 family cytokines in inflammatory and fibrotic diseases, and this has resulted in a number of compounds being evaluated as therapeutic options in a range of inflammatory and fibrotic diseases. Notable success has been achieved with Anakinra in the treatment of rheumatoid arthritis and other chronic inflammatory diseases such as gouty arthritis [240] and cryopyrin-associated periodic syndrome (CAPS) [241]. In addition, there are several compounds with mechanism of action against IL-1 family cytokines and the inflammasome currently under investigation in a range of diseases such as $P2X_7$ receptor antagonists (AZD9056 - 2005-004110-32) and an anti-IL-1RI monoclonal antibody (MEDI8968 - NCT01448850). Furthermore, there are other IL-1α and IL-1β targeting agents such as Xilonix, canakinumab, rilonacept, gevokizumab and AMG108 currently under investigation for other inflammatory diseases that could also be worthwhile exploring for the treatment of chronic respiratory inflammatory disorders [241, 242].

However, the slow progression of many fibrotic diseases and the lack of early quantifiable clinical endpoints make clinical trials expensive and prohibitive; therefore, the vast majority of compounds described above will not be tested in patients with fibrotic lung disease. Therefore, research to identify bio-markers (sputum, serum, plasma, BAL, urine) and imaging technologies that can accurately measure the rate of disease progression are urgently needed. Furthermore, the majority of preclinical data described in this review has been generated in 2D submerged single cell culture systems or animal models. To build preclinical confidence, more advance culture systems (ALI, 3D culture models) and ex vivo tissue culture technique such as precision cut slices should be considered [243, 244]. Similarly, the use of primary human cells isolated from diseased tissue is preferential when interrogating mechanism of inflammation and fibrosis as there is a large body of evidence to suggest that fibroblasts isolated from normal and fibrotic tissue behave differently in culture [245–248].

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