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Published in:
Trends in Pharmacological Sciences

DOI:
[10.1016/j.tips.2021.01.007](https://doi.org/10.1016/j.tips.2021.01.007)

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Kortekaas, R. K., Burgess, J. K., van Orsoy, R., Lamb, D., Webster, M., & Gosens, R. (2021). Therapeutic Targeting of IL-11 for Chronic Lung Disease. *Trends in Pharmacological Sciences*, 42(5), 354-366. <https://doi.org/10.1016/j.tips.2021.01.007>

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Review

Therapeutic Targeting of IL-11 for Chronic Lung Disease

Rosa K. Kortekaas,^{1,2} Janette K. Burgess,^{2,3} Roël van Orsoy,^{1,2} David Lamb,⁴ Megan Webster,⁴ and Reinoud Gosens^{1,2,*}

Interleukin (IL)-11 was originally recognized as an immunomodulatory and hematopoiesis-inducing cytokine. However, although IL-11 is typically not found in healthy individuals, it is now becoming evident that IL-11 may play a role in diverse pulmonary conditions, including IPF, asthma, and lung cancer. Additionally, experimental strategies targeting IL-11, such as humanized antibodies, have recently been developed, revealing the therapeutic potential of IL-11. Thus, further insight into the underlying mechanisms of IL-11 in lung disease may lead to the ability to interfere with pathological conditions that have a clear need for disease-modifying treatments, such as IPF. In this review, we outline the effects, expression, signaling, and crosstalk of IL-11 and focus on its role in lung disease and its potential as a therapeutic target.

The Emerging Role of IL-11 in Disease

Interleukin (IL)-11 is a member of the IL-6 family of cytokines. The most well-known role of IL-11 is in **hematopoiesis** (see [Glossary](#)) because it promotes **megakaryocytopoiesis**, **erythropoiesis**, and **thrombopoiesis**. In recognition of these properties, human IL-11 **recombinant protein** (rhIL-11) is used clinically for treating chemotherapy-induced thrombocytopenia [1,2]. In addition, IL-11 has extensive immunomodulatory effects, both anti- and proinflammatory. It inhibits the release of proinflammatory cytokines by macrophages and monocytes and induces type 2 T-helper cell (**Th2**) **polarization** and the Th2 cytokines IL-4 and IL-10 while inhibiting Th1 polarization and the Th1 cytokines IL-12, IL-2, and interferon (IFN)- γ [3,4]. IL-11 exerts additional effects on the proliferation and survival of structural cells. In the intestine, IL-11 was shown to stimulate proliferation of epithelial cells and reduce apoptosis of mature epithelial cells and their progenitors [5,6]. In contrast, hepatocytes become apoptotic in response to IL-11 [7]. Previously, the literature concerning IL-11 was regarded as controversial. This aspect and other considerations of IL-11 biology are discussed in [Box 1](#).

Although IL-11 may play a role in fetal (lung) development [8–11], serum protein levels are frequently undetectable in healthy adults. Yet, in disease states such as viral infection, fibrosis, and various cancers, IL-11 overexpression is observed [12–15], suggesting a role for IL-11 in diverse pathological conditions. However, many aspects of IL-11, such as the main source *in vivo* and its role in homeostasis and disease, are still not completely clear. Although IL-11 was originally discovered as a hematopoietic and anti-inflammatory cytokine, it is now becoming evident that it is involved in various pathological processes, such as cancer and fibrosis [13,14,16]. It is therefore important to shed more light on IL-11, its role in disease, and its therapeutic potential. In this review, we focus on these roles of IL-11 in lung disease.

The Expression of IL-11 and Its Receptor

The IL-6 family is composed of nine members, which are reviewed in more detail elsewhere [17,18]. IL-6 family receptors are divided into signal-transducing receptors, including glycoprotein

Highlights

The pleiotropic cytokine interleukin (IL)-11 is emerging as a protein involved in various pathological conditions such as fibrosis and cancer.

It is becoming apparent that IL-11 also plays a role in lung diseases, which was most recently discovered in idiopathic pulmonary fibrosis, and its cellular effects in lung pathophysiology are starting to be revealed.

IL-11 can be targeted with inhibitors that can suppress pathological processes associated with lung diseases in animal models, suggesting IL-11 may have potential as a new therapeutic target.

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Box 1. Considerations for IL-11 Biology

Although the role of IL-11 in disease is now emerging, the literature on IL-11 has previously been regarded as conflicting because it can have both protective and harmful effects [13,45,69,94–96]. We propose that the effect of IL-11 is complex and actually depends on the cell type and the context. For example, IL-11 can activate fibroblasts and stimulate their collagen deposition, and overactivity of IL-11 leads to fibrosis in multiple organs [13,16,72]. It can have proinflammatory effects, such as the stimulation of Th2 formation [48], and anti-inflammatory effects by reducing macrophage and monocyte function [3]. IL-11 can protect endothelial cells from damage and may stimulate angiogenesis, which is protective in hyperoxia-induced lung injury [97–99]. Thus, because IL-11 can influence various different cell types, their specific responses may lead to different outcomes. In addition, it was recently shown that rhIL-11 is unable to strongly affect murine cardiac fibroblasts, whereas rmlIL-11 activates species-matched fibroblasts, although rhIL-11 can still activate murine cardiac fibroblasts moderately in higher concentrations. Interestingly, rhIL-11 was suggested to interact with the murine IL-11R α without inducing signal transduction. This should be read with caution, however, since this is shown in a manuscript that has not been peer reviewed yet [16,100]. Comparing the sequences of human and mouse IL-11 protein reveals 88% sequence homology overall, whereas the region that is essential for interaction with the receptor is 100% identical. Thus, it is very likely that rhIL-11 can indeed interact with the murine IL-11R α . The use of species-matched recombinant IL-11 protein is therefore essential for drawing the correct conclusions.

130 (gp130), and non-signaling receptors [18]. All members of the IL-6 family, except IL-31, form a receptor complex that includes gp130, which is ubiquitously expressed. It is found in tissues such as the heart, liver, brain, lungs, stomach, ovaries, adipose tissue, intestines, spleen, and muscle [19]. Some family members also interact with a more restrictively expressed non-signaling receptor that provides signaling specificity, including the IL-11 receptor α (IL-11R α) for IL-11. IL-11 can induce gp130 signaling transduction only when in a complex with both IL-11R α and gp130 [18]. Interestingly, IL-11R α -deficient individuals are almost completely healthy with no serious afflictions apart from the skull disorder craniosynostosis [20], suggesting redundancy of IL-11 signaling in homeostasis in adulthood.

Various cell types, including fibroblasts, osteoblasts, neurons, and endothelial cells, produce IL-11 *in vitro* [21]. The pulmonary cell types that produce IL-11 *in vitro* are fibroblasts, airway smooth muscle cells, epithelial cells, and eosinophils in response to stimulation with factors such as transforming growth factor β (TGF β). When unstimulated, these cells produce low or no detectable levels of IL-11, indicating a limited level of basal production [22–25]. The main source of IL-11 production *in vivo* is less clear, but (damaged) epithelial cells and fibroblasts have been suggested as important producers in the lungs [13,26–28].

IL-11R α is expressed at a low level in a wide variety of organs, including brain, heart, lung, kidney, intestines, and liver [29]. Expression is particularly high in stromal cells, including fibroblasts and smooth muscle cells [16,26]. Other cells, such as adipocytes, T cells, endothelial cells, mesenchymal stem cells, osteoblasts, osteoclasts, and epithelial cells such as hepatocytes and intestinal and pulmonary epithelial cells also express the receptor [4,7,30,31]. Using ‘IL-11RA’ as a search term in the Lung Cell Atlas¹ reveals that, in the lungs, most cells show no basal expression of IL-11R α , although various cell types of epithelial, immunological, and stromal origin express the receptor. Fibroblasts, macrophages, basal cells, and alveolar type 2 cells (AT2 cells) appear to express IL-11R α to a greater extent than other cell types. However, although the Lung Cell Atlas is very useful for comparing the expression levels of genes between cell types, single-cell RNA sequencing has its limitations. Lowly expressed genes are more affected by measurement noise and are therefore more difficult to reliably determine, and mRNA expression is well known to sometimes differ from protein levels [32,33]. Thus, clear, robust additional research into the expression of IL-11 and IL-11R α *in vivo*, including the protein level, is warranted.

IL-11 Signaling Pathway

IL-11 was previously proposed to signal via classic or *cis* signaling via membrane-bound IL-11R α . However, recent evidence suggests potential for *trans* signaling via a soluble form of

Glossary

Autocrine loop: a cell produces a cytokine or other factor that binds to receptors on its own cell membrane, allowing the cell to stimulate itself.

Cell senescence: a state of irreversible cell cycle arrest. The cell does remain metabolically active, but is morphologically and functionally different from non-senescent cells.

EMT: epithelial–mesenchymal transition. An epithelial cell loses its polarity and converts to a mesenchymal cell–like phenotype with migratory properties.

Erythropoiesis: the production of red blood cells.

Hematopoiesis: the formation of all types of blood cells and thrombocytes.

Megakaryocytopoiesis: the formation of megakaryocytes, which are responsible for producing thrombocytes.

Mutein: a protein that has a changed amino acid sequence compared with the wild type.

Recombinant protein: an artificially produced wild-type or modified human or animal protein, usually by micro-organisms.

Remodeling: the process of altering biological structures such as the airways or the extracellular matrix. Remodeling is generally a normal process in homeostasis, but excessive remodeling can significantly change the morphology and functionality of tissues.

SASP: senescence-associated secretory phenotype. This secretome is different from non-senescent cells.

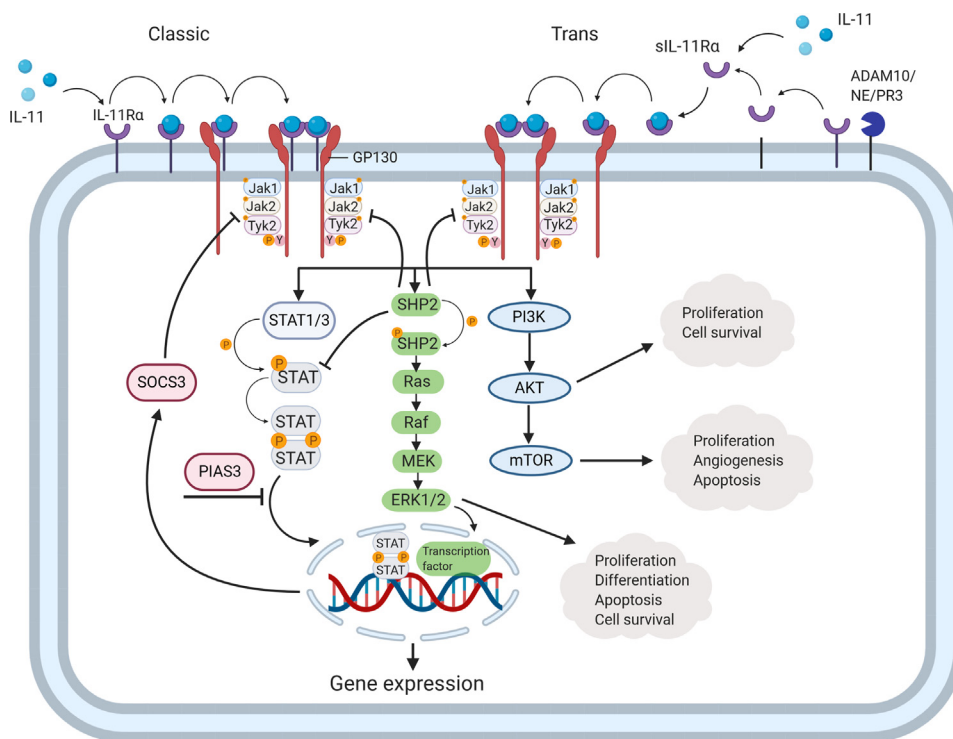
Although the SASP is variable between cell types, the SASP is generally proinflammatory and/or profibrotic.

Th2 polarization: the direction of naive CD4⁺ T cells to subsets of T cells, such as Th1 and Th2 cells. Particular factors, including IL-12 or IL-4, drive polarization to the Th1 or Th2 phenotype, respectively. These T cell subsets have a particular secretome and are associated with different responses. The Th1 phenotype is believed to play a role in phagocyte-mediated immunity and diseases such as Crohn’s disease and rheumatoid arthritis, whereas the Th2 phenotype is associated with the humoral immune response and allergic conditions, including asthma and hay fever.

Thrombopoiesis: the process of forming blood platelets.

Transdifferentiation: the switch of a fully differentiated cell type to another cell.

IL-11R α . Indeed, a disintegrin and metalloproteinase 10 (ADAM10) and the neutrophil-derived serine proteases neutrophil elastase (NE) and proteinase 3 (PR3) have been shown to cleave membrane-bound IL-11R α , generating soluble IL-11R α (sIL-11R α), supporting such mechanisms (Figure 1) [34,35]. sIL-11R α has been detected in human serum, although not all healthy adults had measurable quantities in their blood. This suggests *trans* signaling may occur *in vivo* [35]. It is not yet clear whether IL-11 *trans* signaling has distinct functions from classic IL-11 signaling, as reported for IL-6 *trans* signaling [26,36,37]. Recent studies have suggested IL-11 may engage in cluster signaling, whereby IL-11R α -IL-11 complexes on cell membranes activate gp130 receptors on surrounding cells [38]; however, further studies are required to confirm such signaling. Early literature suggested the IL-11 signaling complex to be a tetramer composed of IL-11, IL-11R α , and gp130 at a ratio of 1:1:2, respectively; however, the complex was later proposed to be hexameric at a ratio of 2:2:2 [39,40]. Formation of the IL-11 signaling complex activates several downstream signaling cascades, which are discussed in detail in Box 2.



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Figure 1. Schematic Overview of the Interleukin (IL)-11 Signaling Pathway. The membrane-bound IL-11 receptor α (IL-11R α) can be cleaved by a disintegrin and metalloproteinase 10 (ADAM10), neutrophil elastase (NE), and proteinase 3 (PR3), resulting in a soluble form of the receptor (sIL-11R α). IL-11 binds to the membrane-bound (classic signaling) or soluble (trans signaling) form of IL-11R α , after which glycoprotein 130 (gp130) is recruited to the complex. It is believed that two of these receptor complexes dimerize, forming a hexamer consisting of two molecules each of IL-11, IL-11R α , and gp130. The gp130 dimer will then initiate intracellular signaling by activation of Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling, mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinase 1/2 (ERK1/2) signaling, and the phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway. Suppressor of cytokine signaling 3 (SOCS3), Src homology 2 domain-containing tyrosine phosphatase (SHP2), and protein inhibitor of activated STAT3 (PIAS3) are inhibitors of IL-11 signaling. Figure created by using BioRender (www.biorender.com).

Box 2. The IL-11 Signaling Pathway

Following the formation of the IL-11–IL-11R α –gp130 complex, dimerization of gp130 occurs, which causes transphosphorylation and activation of JAK1, JAK2, and tyrosine kinase 2 (TYK2). These JAKs then phosphorylate specific tyrosine residues on the stalk region of gp130, serving as a docking site for Src homology 2 (SH2) domain-containing proteins, including STAT1 and STAT3. STAT3 and, to a lesser extent, STAT1 are then phosphorylated by the JAKs [30,34]. The phosphorylated STATs (pSTATs) form homo- and heterodimers, which translocate to the nucleus, where they bind to a gamma-activated sequence in promoter or enhancer sequences of target genes to mediate gene transcription [34,101]. STAT3 induces the transcription of a wide variety of target genes, including but not limited to cyclin D1, survivin, VEGF, TGF β , vimentin, MMP9, and suppressor of cytokine signaling 3 (SOCS3) [46,47].

The phosphorylated gp130 receptor is also a docking site for SH2 domain-containing tyrosine phosphatase (SHP2), which is phosphorylated by JAKs. This leads to the activation of the Ras/Raf/MEK/ERK1/2 pathway [34]. ERK1/2 has a broad range of targets, including downstream MAPK-activated protein kinases and transcription factors including ETS like-1 protein, c-Fos, and c-Jun. ERK1/2 regulates cellular processes including differentiation, proliferation, survival, and apoptosis [102].

The final identified intracellular signaling pathway that can be activated by IL-11 signaling is the PI3K/Akt/mammalian target of rapamycin (mTOR) pathway. The kinase Akt targets proteins including forkhead box protein O1 and BCL2-associated agonist of cell death, and their phosphorylation is associated with increased cell survival and proliferation [34]. Akt is additionally thought to activate mTOR following IL-11 stimulation, which is a kinase that regulates proliferation, angiogenesis, and apoptosis [103,104].

Signal termination can be initiated by SOCS3, which inhibits the activity of the JAKs and thereby suppresses the phosphorylation of gp130, JAKs, and STATs. Because SOCS3 is a target gene of STAT3, this may function as an autoinhibitory feedback mechanism for IL-11 signaling. In addition, SHP2, which is also involved in the IL-11/MEK/ERK pathway, inhibits IL-11-induced signaling by dephosphorylating the different STATs and JAKs. Finally, protein inhibitor of activated STAT3 binds to STAT3, thereby preventing the interaction of STAT3 with transcription factors and thus impeding STAT3-mediated gene expression [34].

The Interaction of IL-11 with Other Signaling Pathways

The expression of IL-11 is regulated by transcription factors such as signal transducer and activator of transcription 3 (STAT3), STAT1, c-Jun, and activator protein 1 (AP-1), and accordingly multiple factors that activate these pathways can induce IL-11 in various cell types [41,42]. In pulmonary epithelial cells, fibroblasts, and airway smooth muscle cells, IL-11 production is induced by TGF- β 1, IL-1 α , histamine, and respiratory viruses, including respiratory syncytial virus, parainfluenza virus type 3, rhinovirus 14, cytomegalovirus, and adenovirus [12,22,43]. In primary lung fibroblasts, various profibrotic stimuli, including platelet-derived growth factor (PDGF), IL-13, oncostatin M (OSM), fibroblast growth factor 2 (FGF2), and endothelin 1 (ET-1), induce IL-11 expression [13].

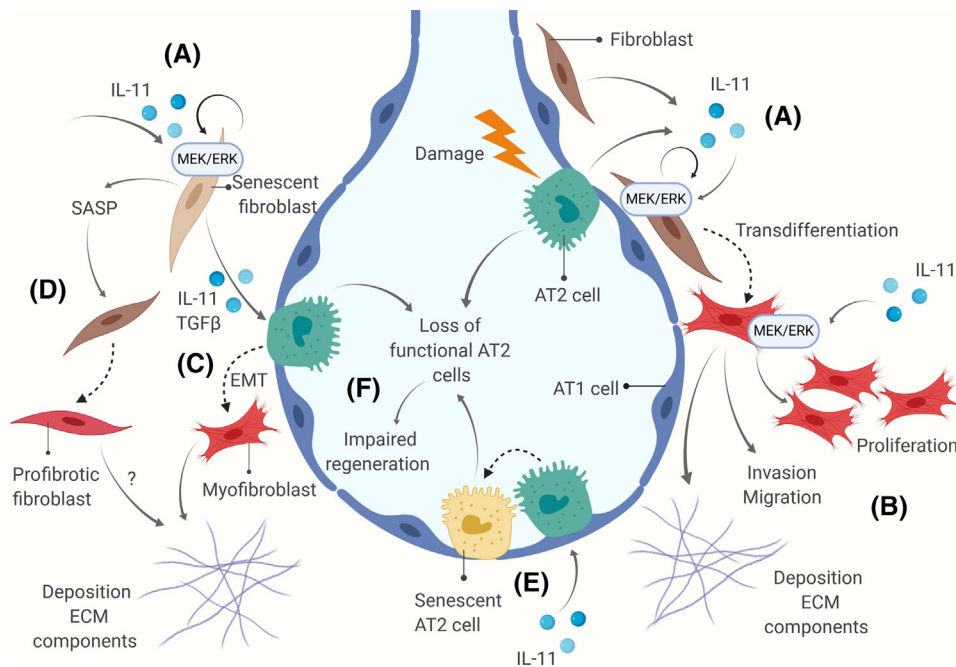
The induction of IL-11 production by TGF β is mediated by the mitogen-activated protein kinase (MAPK) pathway [22,44]. IL-11 is among the most upregulated genes induced by TGF β and is likely to play an essential role in TGF β -induced profibrotic responses, since stimulation of IL-11R α -deficient pulmonary fibroblasts with TGF β inhibited their differentiation toward myofibroblasts and extracellular matrix (ECM) production [13,22]. Interestingly, IL-11R α -null mice show a reduced production of matrix metalloproteinase 9 (MMP9) and TGF β , suggesting that IL-11 signaling itself is able to directly influence TGF β as well, possibly through regulation of MMP9 expression, which is reported to activate latent TGF β [45]. In addition, TGF β is a known target gene of STAT3, which is one of the downstream effectors activated by IL-11 signaling [46,47]. In addition to TGF β , IL-13 stimulates the expression of IL-11 and IL-11R α in the murine lung. Furthermore, IL-13-induced pulmonary inflammation and fibrosis is alleviated in IL-11R α -deficient mice and in the presence of an antagonistic IL-11 **mutein** in wild-type mice [45,48]. The profibrotic effects of IL-13 are thought to be the consequence of increased TGF β levels, partially mediated by the induction of MMP9 [45]. Since TGF β is a known inducer of IL-11 expression, it is plausible that IL-13 causes the increased expression of IL-11 through TGF β . The regulation of IL-11R α is largely unexplored [49].

IL-11 in Lung Disease

Idiopathic Pulmonary Fibrosis (IPF)

In healthy individuals, the IL-11 serum protein level is frequently undetectable. However, in pathological conditions such as infection, cancer, and fibrosis, it can be upregulated, and in many conditions, its expression is correlated with disease severity [13,25,50,51]. Recently, IL-11 was proposed to be imperative in IPF. IPF is thought to be caused by repeated epithelial microinjuries, leading to the induction of myofibroblasts, accumulation of ECM, and destruction of the physiological alveolar structure [52]. The possible effects of IL-11 in IPF are summarized in Figure 2.

IL-11 mRNA is upregulated in the lung tissue of patients with IPF, and fibroblasts isolated from patients with IPF have been shown to secrete more IL-11 than control fibroblasts, both at baseline and in response to TGF β . IL-11 activates primary human lung fibroblasts *in vitro* via activation of extracellular signal-regulated kinase (ERK) signaling, causing their **transdifferentiation** into myofibroblasts. The proliferation, migration, invasion, actin alpha 2 (ACTA2) expression, and collagen secretion of activated myofibroblasts are stimulated by IL-11 as well [13,53].



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Figure 2. Interleukin (IL)-11 May Contribute to the Pathophysiology of Idiopathic Pulmonary Fibrosis (IPF) by Inducing the Formation of Profibrotic Myofibroblasts and by Impairing the Regeneration of the Alveolar Epithelium. (A) IL-11 is possibly secreted by fibroblasts or (damaged) epithelial cells, whereas (senescent) fibroblasts may engage in an autocrine loop of IL-11 signaling. (B) IL-11 is thought to activate fibroblasts through mitogen-activated protein kinase (MEK)/extracellular signal-regulated kinase (ERK) signaling; stimulation of fibroblast-to-myofibroblast transdifferentiation; and inducing their proliferation, invasion, migration, and deposition of extracellular-matrix (ECM) components. IL-11 may also induce senescence in fibroblasts through MEK/ERK signaling. (C) Senescent fibroblasts are thought to secrete increased amounts of IL-11 and transforming growth factor β (TGF β), which may induce epithelial-mesenchymal transition (EMT) of alveolar type 2 cells (AT2 cells), resulting in the formation of ECM-secreting myofibroblasts. (D) In addition, the senescence-associated secretory phenotype (SASP) of senescent fibroblasts may induce a fibrotic phenotype in healthy fibroblasts, which may contribute to the formation of ECM. (E) Finally, IL-11 may induce the senescence of AT2 cells. (F) Due to epithelial damage, EMT, and senescence of AT2 cells, a loss of functional AT2 cells occurs, resulting in impaired regeneration of the alveolar epithelium. This unresolved alveolar damage, in combination with myofibroblast infiltration and excessive ECM deposition, may contribute to the pathophysiology of IPF. Figure created by using BioRender (www.biorender.com).

Although multiple cytokines stimulate a profibrotic response in mouse fibroblasts as discussed earlier, such responses, including the induced expression of ACTA2 and collagen, type I, alpha 1 (COL1A1), were not evident in mouse fibroblasts null for IL-11R α [13]. This suggests that reported profibrotic responses may result from a direct upregulation of IL-11 by these cytokines and that IL-11 is a key profibrotic cytokine. Furthermore, subcutaneous administration of recombinant mouse IL-11 (rmlL-11) in mice was sufficient to cause lung fibrosis, leading to elevated lung weights, collagen content, expression of profibrotic genes, and the infiltration of COL1A1-positive fibroblasts [13]. Fibroblast-specific overexpression of IL-11 also leads to the development of pulmonary fibrosis in mice, and the fibroblast-specific conditional knockout of IL-11R α was sufficient to suppress the fibrotic response to bleomycin [13,54], indicating IL-11 fibroblast biology to be a key driver of IPF. The deletion of IL-11R α in fibroblasts was associated with a reduction of ERK, but not STAT3 activation, in these specific cells [54], providing further evidence for the importance of ERK signaling with regard to IL-11 biology and fibrosis.

Fibroblasts obtained from patients with IPF show characteristics of **cell senescence**, such as increased expression of senescence-associated secretory phenotype (**SASP**)-related cytokines, including IL-6, IL-1 β , FGF2, TGF β , and COL1A1 [55,56]. A recent publication showed induced expression of fibrotic genes *ACTA2*, *COL1A1*, *COL1A2*, and fibronectin 1 following treatment of healthy human cell line fibroblasts with conditioned medium from senescent human cell line fibroblasts, suggesting SASP to be a key contributor to the disease phenotype [56]. Interestingly, senescence of both fibroblasts and epithelial cells is associated with increased TGF β /IL-11/mitogen-activated protein kinase kinase (MEK)/ERK signaling, and senescent primary murine fibroblasts produce increased amounts of TGF β and IL-11, pointing to the existence of an IL-11 **autocrine loop**. Likewise, murine wild-type fibroblasts treated with IL-11 or TGF β have increased expression of the senescence marker p16. Furthermore, senescence-associated increases in TGF β and IL-11 release were suggested to promote epithelial–mesenchymal transition (**EMT**) of AT2 cells as shown by a reduction of surfactant protein C (SFTPC)-positive areas and an increase in α -SMA–positive areas [57]. However, although EMT of AT2 cells in IPF has been reported previously, this is still a disputed process in IPF [58].

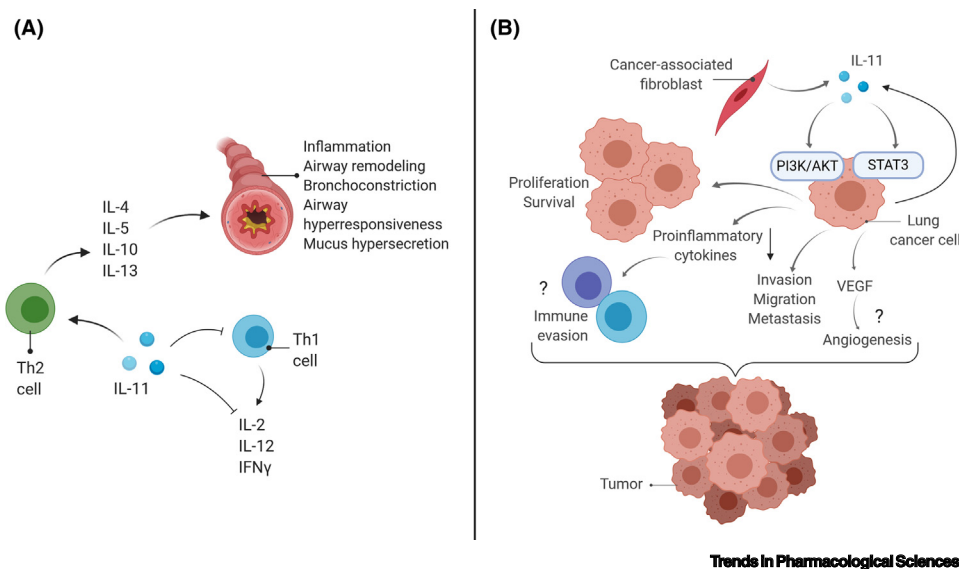
Although (myo)fibroblasts are key to IPF pathology, there is a growing body of evidence suggesting high importance of epithelial–fibroblast crosstalk in IPF, where injured or senescent epithelial cells, particularly AT2 cells, are thought to regulate and activate fibroblasts, thereby associating with the initiation of fibrosis [59,60]. Additionally, AT2 cells are thought to function as progenitor cells in the adult lung, which can give rise to AT1 cells [61]. The regenerative capacity of this population may be impaired in IPF due to injury and senescence [60]. In a human embryonic stem cell–derived organoid model of Hermansky-Pudlak syndrome–associated interstitial pneumonia (HPSIP), which recapitulates features of IPF, a significant upregulation of IL-11 mRNA was found in the epithelial fraction by transcriptomic analysis. The knockout of IL-11 in these HPSIP organoids inhibited fibrosis, as shown by a reverse of the fibrotic phenotype and a decrease in fibrotic markers on mRNA and protein levels, including fibronectin, vimentin, collagen I, collagen III, and PDGF receptor compared with HPSIP organoids. Furthermore, lung sections of patients with IPF suggest that mainly SFTPC-positive cells express IL-11 [28], although we believe this proposition needs more evidence. Lung tissue with a normal appearance from patients with IPF also shows IL-11 overexpression, as observed with transcriptomics, suggesting IL-11 plays a role in the early pathogenesis of IPF [28]. Therefore, it has been suggested that IL-11 produced by injured or dysfunctional epithelial cells contributes to the initiation of fibrosis [28].

Recent evidence shows that bleomycin injury leads to an increased infiltration of monocytes, macrophages, and neutrophils, an induction of proinflammatory genes, and activation of nuclear

factor- κ B (NF- κ B), an essential mediator of the immune system. These inflammatory effects were inhibited by the fibroblast-specific conditional knockout of IL-11R α in mice, particularly during the late fibrogenic stage (day 14 or 21 after bleomycin injury). This suggests that fibroblasts affected by IL-11 mediate the immune response, mostly during the fibrogenic phase and not the acute inflammatory stage of bleomycin injury [54]. Although it was suggested that immune cells may contribute to the pathology of fibrosis mainly through paracrine effects, the role of inflammation in IPF is increasingly debated [52,54], partly as a consequence of the lack of clinical efficacy demonstrated by a number of anti-inflammation concepts [62–64]. In contrast, single-cell RNA-sequencing analysis suggests that inflammatory cells, particularly macrophages, may contribute to aberrant epithelial repair and profibrotic processes [65–67]. This apparent mismatch between the presence of inflammatory drivers in pulmonary fibrosis and the lack of clinical efficacy of anti-inflammatory principles remains to be resolved.

Asthma

IL-11 is also upregulated in moderate and severe asthma and is associated with disease severity [25]. It is compelling to hypothesize that IL-11 contributes to the pathology of asthma, since it is an immunomodulatory cytokine that quenches Th1 polarization while promoting Th2 polarization and stimulating the production of Th2 cytokines such as IL-4 and IL-10, whereas asthma is typically related to such Th2 responses (Figure 3A) [4,68]. Th2 responses are related to airway



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Figure 3. Interleukin (IL)-11 Is Associated with the Type 2 T-Helper Cell (Th2 cell) Responses in Allergic Asthma, and IL-11 May Be a Tumorigenic Cytokine in Lung Cancer by Stimulating Proliferation, Survival, Immune Evasion, Invasion, Migration, Metastasis, and Angiogenesis. (A) IL-11 induces Th2 cell polarization and inhibits Th1 polarization. Th2 cells play a central role in the pathology of allergic asthma and are thought to contribute to the inflammation, airway remodeling, bronchoconstriction, airway hyper-responsiveness, and mucus hypersecretion commonly seen in patients with asthma. (B) In lung cancer, cancer-associated fibroblasts (CAFs) may secrete IL-11, which possibly activates phosphatidylinositol 3-kinase (PI3K)/Akt and/or signal transducer and activator of transcription 3 (STAT3) signaling in lung cancer cells. Additionally, lung cancer cells may induce autocrine IL-11 signaling. IL-11 is thought to stimulate proliferation and survival of lung cancer cells. STAT3 activation may reduce the secretion of proinflammatory cytokines, thereby inhibiting the activation of inflammatory cells and thus contributing to immune evasion. IL-11 is also implicated in the increased migration, invasion, and metastasis of lung cancer. Finally, STAT3 activation stimulates the release of vascular endothelial growth factor (VEGF), leading to increased angiogenesis. These processes can contribute to the formation of a tumor. Immune evasion and angiogenesis are established effects of STAT3 activation in lung cancer but should be confirmed in the context of IL-11 signaling. Figure created by using BioRender (www.biorender.com).

hyper-responsiveness, inflammation, airway **remodeling**, mucus hypersecretion, and bronchoconstriction, which are hallmarks of asthma [68]. In addition, the overexpression of IL-11 in murine airways led to the development of multiple features also seen in asthma, including bronchiolar inflammation with infiltration of B and T cells, airway hyper-responsiveness, increased thickness of the airway smooth muscle layer, and characteristics of subepithelial fibrosis such as increased collagen types I and III and accumulation of fibroblasts and myofibroblasts, as shown by electron microscopy and immunohistochemistry for ACTA2 and desmin [12,69]. Furthermore, ovalbumin challenge led to the production of immunoglobulin E (IgE) and Th2 cytokines (including IL-13, IL-4, and IL-5), the infiltration of eosinophils and macrophages, and increased mucus production, which were all markedly reduced in IL-11R α -deficient mice. A similar effect was found in wild-type ovalbumin-challenged mice treated with an IL-11 antagonist, mutein [48]. In contrast, another study showed that IL-11 overexpression in the murine lung by using the club cell 10 kD protein (CC10) promoter reduced ovalbumin-induced inflammation, Th2 cell accumulation, and release of Th2-associated cytokines [70]. It was speculated that this difference may be because of the effects of endogenous versus transgenic overexpression of IL-11 [48].

IL-11 is also relevant in the pathological responses induced by IL-13, a key cytokine in the pathophysiology of asthma [48,71]. IL-13 overexpression caused eosinophilic inflammation, fibrosis, and increased sputum production, which was ameliorated in IL-11R α -deficient mice and in wild-type mice treated with the IL-11 antagonist mutein [45,48]. In summary, IL-11 is important in the IL-13- and Th2-associated pathological responses, which are relevant in asthma, although the molecular mechanisms behind this remain to be elucidated.

Although IL-11 possibly contributes to airway remodeling in asthma through Th2-mediated inflammation, it should be considered that IL-11 may also promote subepithelial fibrosis directly, since it has been implicated in various fibrotic diseases, including IPF [13,16,72], in which it activates fibroblasts and stimulates their deposition of collagen directly [13].

Lung Cancer

The two main subtypes of lung cancer are small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), the latter of which can be subdivided into adenocarcinoma (ADC), squamous cell carcinoma (SCC), and large cell lung carcinoma [73]. In several of these types, IL-11 is likely to play a role (summarized in Figure 3B). The expression of IL-11R α is elevated in ADC, SCC, and SCLC tissue compared with non-malignant lung tissue of the same patient [50]. In addition, IL-11 is hypothesized to be involved in the progression of NSCLC and the ability of extrapulmonary cancer cells to metastasize to the lungs [51,74]. The release of IL-11 by cancer-associated fibroblasts (CAFs) can protect tumor cells derived from an ADC cell line from apoptosis induced by cisplatin [75]. In an NSCLC cell line, a carcinogenic effect of IL-11 was shown, which was associated with Akt and STAT3 activation and the induction of several processes involved in tumorigenesis, including proliferation, migration, invasion, EMT, and metastasis, whereas IL-11/Janus kinase (JAK)/STAT3 signaling leads to the expression of the antiapoptotic proteins Bcl-2 and survivin in an ADC cell line [51,75].

Although the phosphatidylinositol 3-kinase (PI3K)/Akt pathway may contribute to tumorigenesis, possibly by stimulating proliferation, inhibiting apoptosis, and driving metastasis, the IL-11-PI3K-Akt axis in oncogenesis is not well understood. The tumorigenic effects of IL-11 are mainly associated with STAT3 [76]. Persistent activation of STAT3 is associated with growth, survival, invasion, and metastasis in lung cancer [49] and processes important for carcinogenesis such as proliferation, resistance to apoptosis, and cancer stem cell renewal, which are discussed in detail elsewhere [77]. STAT3 is also associated with angiogenesis by inducing the release of

proangiogenic factors such as vascular endothelial growth factor (VEGF) and with immune evasion by the inhibition of proinflammatory cytokine release [77]. It is worth noting that aberrant activation of STAT3 by other factors such as IL-6 and epidermal growth factor receptor (EGFR) is also correlated with lung carcinogenesis [78–80]. Thus, although it is tempting to link the aforementioned effects of STAT3 to IL-11, it would be useful to confirm this. Interestingly, IL-11 is suggested to engage in an autocrine loop in a cancer cell line, which would lead to sustained STAT3 activation and thus contribute to the development of cancer [51].

Because IL-11 likely plays a role in lung cancer and IL-11R α is overexpressed in lung cancer cells, colleagues have explored its value as a drug target. Specifically targeting IL-11R α -expressing cells with a proapoptotic protein was found to induce tumor cell apoptosis and delayed tumor growth in ADC, SCC, and large cell lung carcinoma [50]. In addition, inhibiting IL-11 reduced the tumor burden and increased the survival time of mice with NSCLC [51]. Finally, lung metastases of osteosarcoma cell lines overexpressed IL-11R α , which could be specifically targeted by T cells expressing a chimeric antigen receptor (CAR) directed against IL-11R α . These IL-11R α CAR T cells induced cancer cell apoptosis and reduced osteosarcoma metastasis to the lung [81].

Chronic Obstructive Pulmonary Disease (COPD)

IL-11R α is downregulated in patients with COPD compared with healthy individuals, and a polymorphism in the promoter region of the IL-11 gene is correlated with COPD, especially in non-smokers [82,83]. Additionally, in an elastase-induced mouse model of emphysema, an increased IL-11 protein level was found in lung tissue compared with controls [84]. Although these studies indicate an association between IL-11 and COPD, literature on this topic is scarce, and the role of IL-11 in COPD is still unclear.

Therapeutic Perspective

Although agonistic potentiation of IL-11 signaling has proved beneficial in the treatment of thrombocytopenia [2], the discovery of increased activation of IL-11 signaling associated with lung diseases has led to the exploration of antagonistic interventions that may reduce IL-11 signaling activity. As discussed earlier in this review, the activation of IL-11 signaling leads to the activation of intracellular proteins, including JAK, ERK, and STAT1/3. Indeed, several recent publications suggest the potential for the use of JAK and/or STAT1/3 inhibitors for the treatment of lung diseases [85–87]; however, such mechanisms are not specific to IL-11 signaling, owing to the involvement of these proteins in a large variety of signaling pathways. As such, one should carefully consider the potential for off-target effects of JAK and STAT1/3 inhibitors. In addition, the role of IL-11 in IPF pathology appears to be mostly related to the activation of ERK signaling [13,53,54,57]. Thus, STAT inhibitors may not only induce more off-target effects but may also be less effective than inhibitors targeting IL-11 and all its downstream effects. Indeed, despite a number of JAK inhibitors already approved for clinical use in inflammatory diseases [88], to our knowledge, there are no JAK inhibitors currently in clinical trials to treat lung disease.

A series of recent publications highlighted the potential of anti-IL-11 and anti-IL-11R α humanized antibodies in directly inhibiting the association between IL-11 and IL-11R α [7,13,16,26]. Since inhibiting this interaction is more specific than the broad JAK and STAT inhibitors, and since IL-11 signaling seems to be redundant in adulthood, off-target effects are likely more limited, making it a more appealing alternative. The binding affinity of IL-11 to IL-11R α has been calculated to be within the range of 14–35 nM (65% confidence interval, K_d of 22 nM) [89], which is considered weak enough to permit blockade with antibodies of moderate or strong affinity toward IL-11. Therefore, the use of anti-IL-11 and/or anti-IL-11R α humanized antibodies to block the low-nanomolar affinity between IL-11 and IL-11R α is therapeutically attractive.

Of specific interest here is the proposed use of anti-IL-11 antibodies for the treatment of IPF. Generation of this antibody, termed 'X203', following immunization of mice with rhIL-11 was able to prevent a TGF β 1-induced increase in ACTA2 and COL1A1 staining in fibroblasts, a key cell type involved in the pathophysiology of IPF. Furthermore, intraperitoneal injection of mice with X203 following treatment with bleomycin to induce an IPF-like phenotype caused a significant decrease in lung hydroxyproline content and the fibrosis-associated Ashcroft score, although there was no effect on survival. In addition, COL3A1 and fibronectin expression were also reduced with efficacy attributed to a substantial reduction in ERK1/2 phosphorylation [13]. Similar data have been reported for cardiac and liver fibrosis [7,16]. These findings strongly support the use of IL-11 as a therapeutic target in IPF.

Concluding Remarks and Future Perspectives

IL-11 may contribute to the pathology of chronic lung diseases, as we have discussed extensively. The development of therapeutics targeting IL-11, such as humanized antibodies, show promising results in preventing and reversing pulmonary fibrosis [13]. Although this review focuses on IL-11 in pulmonary diseases, its role in pathological conditions is not limited to the lung, because the fibrogenic and carcinogenic potential of IL-11 was shown in a number of other organs as well [14,16,72].

Recent studies have certainly advanced our knowledge of IL-11 and its role in disease, but there remains much to be uncovered (see Outstanding Questions). For example, some evidence suggests that IL-11 is able to engage in *trans* signaling, but it is so far not firmly established whether this is a relevant process *in vivo* and whether this leads to different effects from classic signaling [26,36,37]. Researching this further could lead to opportunities to specifically target only classic or *trans* signaling, thereby possibly limiting off-target effects even further, as has been proposed for IL-6 with olamkicept. Olamkicept is a dimer of the soluble form of gp130 (sgp130) fused with the fragment crystallizable region (Fc region) of human IgG, which is proposed to selectively inhibit IL-6 *trans* signaling and is currently in phase II clinical trials^{i,iii} (trial numbers DRKS00010101 and NCT03235752) [90]. However, it should be mentioned that *trans* signaling of the entire IL-6 family is not yet well understood. IL-6 appears to have the ability to interact with gp130 without the presence of IL-6R [91,92], albeit with lower affinity, suggesting olamkicept may affect not only *trans* signaling but also classic and cluster signaling. Furthermore, the potential of multiple IL-6 family members, including IL-6, IL-11, and ciliary neurotrophic factor to elicit *trans* signaling is now emerging [93], indicating olamkicept may not be specific for IL-6 *trans* signaling. Thus, more research into *trans* signaling and olamkicept is needed to gain more knowledge of their effects. Another aspect of IL-11 and the IL-6 family to be assessed concerns the occurrence of ligand competition, which will contribute to a better understanding of IL-6 family biology. Furthermore, we discussed various proteins that modulate IL-11 expression, but there is no data available on the strength of these effects. Establishing this would allow evaluation of the relative importance of the various interactions. In addition, we have outlined the possible role of IL-11 in chronic lung disease, but in many instances, the underlying molecular mechanisms are to be studied further. Besides, in many studies concerning IPF, the focus is placed on (myo)fibroblasts, which are important effector cells in the pathology, but it is becoming increasingly clear that the epithelium is severely affected in IPF as well, because it is unable to regenerate properly and may contribute to the pathology through paracrine effects. Because IL-11 can affect both cell types and is possibly involved with their crosstalk related to IPF, the effect of IL-11 on the epithelium and its role in epithelial–fibroblast crosstalk deserves more attention in the future. There is also little information on the role of IL-11 in COPD. Considering the clear need for disease-altering therapeutic options for this disease, it may be valuable to study the possible role of IL-11 in COPD pathology. Finally, several aspects of therapeutic strategies targeting IL-11, such as the ability to improve clinical outcomes and the possible off-

Outstanding Questions

Do cluster and *trans* signaling occur *in vivo*, and what are their particular effects?

Does competition for interaction with gp130 occur between IL-6 family members and between membrane-bound and soluble forms of IL-11R α ?

Do modulators of IL-11 regulate its expression to the same extent?

What are the underlying molecular mechanisms by which IL-11 affects various (pulmonary) pathological processes?

What is the role of IL-11 in COPD?

Are IL-11 inhibitors able to improve therapeutic outcomes in chronic lung diseases?

What are the off-target effects of therapeutic strategies targeting IL-11?

target effects, have not been explored extensively yet; this is essential information when considering IL-11 as a therapeutic target. To conclude, current progress in the understanding of IL-11 signaling in lung disease, and the ability to inhibit such mechanisms using humanized antibodies, may allow significant steps forward in correcting pathophysiologies associated not only with IPF and other interstitial lung diseases but also lung diseases such as asthma and lung cancer.

Declaration of Interests

D.L. and M.W. are employees of Boehringer Ingelheim Pharma GmbH & Co. KG at the time of writing the manuscript. J.K.B. and R.G. received research funding from Boehringer Ingelheim Pharma GmbH & Co. KG.

Resources

ⁱ asthma.cellgeni.sanger.ac.uk

ⁱⁱ www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00010101

ⁱⁱⁱ www.clinicaltrials.gov/ct2/show/NCT03235752

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