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Hiding in Plain Sight: Interleukin-11 Emerges as a Master Regulator of Fibrosis, Tissue Integrity, and Stromal Inflammation

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Abstract

Interleukin (IL)-11 is upregulated in a wide variety of fibro-inflammatory diseases such as systemic sclerosis, rheumatoid arthritis, pulmonary fibrosis, inflammatory bowel disease, kidney disease, drug-induced liver injury, and nonalcoholic steatohepatitis. IL-11 is a member of the IL-6 cytokine family and has several distinct properties that define its unique and nonredundant roles in disease. The IL-11 receptor is highly expressed on stromal, epithelial and polarized cells, where noncanonical IL-11 signaling drives the three pathologies common to all fibro-inflammatory diseases—myofibroblast activation, parenchymal cell dysfunction, and inflammation—while also inhibiting tissue regeneration. This cytokine has been little studied, and publications on IL-11 peaked in the early 1990s, when it was largely misunderstood.

Here we describe recent advances in our understanding of IL-11 biology, outline how misconceptions as to its function came about, and highlight the large potential of therapies targeting IL-11 signaling for treating human disease.

INTRODUCTION TO INTERLEUKIN-11: AN INTERLEUKIN-6 FAMILY MEMBER

Interleukin (IL)-11 is a member of the IL-6 family of cytokines (1) that includes IL-6, leukemia inhibitory factor (LIF), oncostatin M (OSM), ciliary neurotrophic factor (CNTF), and cardiotrophin-1, among others (2). All family members require the ubiquitously expressed gp130 receptor to activate downstream signaling pathways, which has fueled the popular belief that these cytokines may have redundant and overlapping functions. However, unique receptor subunits provide specificity and define the very different biological activities of cytokines in this family. This diversity of effect is clearly apparent from genetics: Rare mutations in the LIF receptor cause Stüve-Wiedemann syndrome, a severe form of bent-bone dysplasia that typically causes death in the first months of life (3). Mutations affecting the function of OSM-specific receptor β (OSMRβ) lead to familial primary localized cutaneous amyloidosis with chronic skin itching. Mice lacking OSMRβ develop insulin resistance and mature-onset obesity (4). Null mutations in CNTF cause motor neuron degeneration in mice (5) but do not cause disease in humans (6). While IL-6 itself has been extensively characterized and its biology translated to the clinic, the other IL-6 family members remain less well understood.

IL-11 AND IL-6: SIMILAR BUT DIFFERENT

IL-11 is often compared to IL-6, as both cytokines form a similarly arranged gp130 heterodimer complex to initiate downstream signaling. However, it is notable and somewhat fascinating that the IL-6 receptor (IL-6R) and IL-11 receptor subunit α (IL-11RA) are expressed in almost mutually exclusive cell types (7). Therefore, IL-6 and IL-11 control distinct cellular compartments and have core functions for different biological processes (**Figure 1**).

IL-6R is expressed mostly on cells of the immune system, and IL-6 signaling has become a prominent therapeutic target for several immune-mediated diseases. Fueled by the clinical success of the IL-6R antibody tocilizumab for arthritis and arteritis, multiple clinical trials are investigating the therapeutic benefits of IL-6- or IL-6R-neutralizing antibodies and of STAT3 and JAK inhibitors in inflammatory and autoimmune diseases as well as cancer and other indications (8). IL-6 is expressed at high levels in healthy individuals and has important functions required for human immunity. Humans with homozygous loss-of-function mutations in IL-6R suffer from severe immunodeficiency (9), and predicted loss-of-function mutations are selected against in the general population. In keeping with this, one of the most frequent on-target side effects of anti-IL-6 therapy is infection (10).

IL-11RA is highly expressed on stromal cells, including fibroblasts, smooth muscle cells, adipocytes, and hepatic/pancreatic stellate cells or pericytes, and also on epithelial/polarized cells such as hepatocytes, alveolar epithelial cells, and kidney tubular epithelial cells, among others (7, 11). In addition to activating different cell types, the molecular structures of IL-11 and IL-6 suggest that gp130 molecules are assembled in different conformations by these molecules (12). Thus, even if a cell were to express both IL-6R and IL-11RA, the downstream signaling events triggered via gp130 may be different. IL-6 family cytokines signal predominantly via JAK/STAT (2), whereas IL-11 has been shown to activate ERK in fibroblasts without a detectable transcriptional

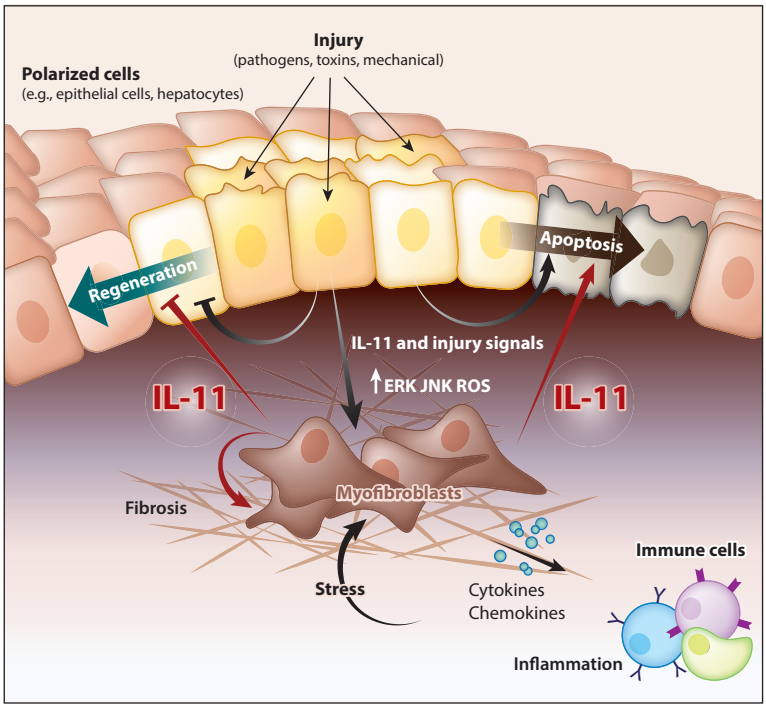

Figure 1

IL-11 is secreted from polarized cells or fibroblasts in response to injury and has autocrine and paracrine action. In polarized cells, IL-11 causes cellular dysfunction and can initiate apoptotic cell death, while at the same time blocking regeneration. In stromal cells, IL-11 triggers extracellular matrix production, invasion, and migration of myofibroblasts. IL-11-activated fibroblasts and myofibroblasts secrete cytokines and chemokines and are strongly proinflammatory. Inhibition of IL-11 protects the parenchyma, is antifibrotic, and reduces stromal-driven inflammation. In tissues with regenerative capacity, inhibition of IL-11 is permissive for the proliferation and repopulation of damaged cells (e.g., hepatocytes) and organ regeneration. Abbreviations: ERK, extracellular regulated kinase; IL, interleukin; JNK, c-Jun N-terminal kinase; ROS, reactive oxygen species.

(STAT-mediated) response (7). Soluble forms of both IL-6R and IL-11RA have been described, although the relevance/occurrence of *trans*-signaling for IL-11 is unclear (13, 14).

In stark contrast to *IL6* or *IL6R*, predicted loss-of-function mutations in *IL11* or *IL11RA* are as common in the general population as expected by chance (15), and several individuals and families with biallelic null mutations in *IL11RA* have been identified (**Table 1**). Lifelong loss of IL-11 signaling causes delayed tooth eruption and mild craniosynostosis, but null individuals are otherwise well, with no reported cancer, cardiovascular, wound healing, or infection issues (16–19). A more recent study of *IL11RA*-null humans suggests that IL11-dependent developmental phenotypes are somewhat milder than first reported due to earlier ascertainment bias, and that joint laxity can also sometimes be encountered (20). *Il11ra1* knockout mice phenocopy human nulls: They have slight developmental abnormalities of the skull/teeth and are otherwise healthy with a normal lifespan, although female mice are infertile (21).

Given the similarities of the human and mouse *IL11RA*-null phenotype, IL-11 function appears conserved across mammalian species. Thus, murine proof-of-concept studies in disease should yield relevant insights into IL-11 biology in humans. Craniosynostosis is also caused by mutations

Table 1 Comparison between IL-6 and IL-11

Feature	IL-6	IL-11
Specific receptor subunit	IL-6R	IL-11RA
Major cell types with specific receptor subunit expression	Immune cells (e.g., mononcytes, B cells, or neutrophils)	Fibroblasts, hepatocytes, hepatic stellate cells, epithelial cells, smooth muscle cells, endothelial cells
Functional downstream signaling pathway	JAK-STAT3	ERK in stromal cells, ERK and JNK in hepatocytes
Dominant regulatory effect	RNA transcription of immune genes	Post-transcriptional regulation of extracellular matrix genes/mesenchymal genes
Mendelian loss-of-function variants	IL6R: autosomal, recessive immunodeficiency and abnormal inflammatory responses	IL11RA: autosomal recessive craniosynostosis, joint laxity, lack of tooth eruption
Prevalence of predicted loss-of-function variants in the general population	IL6R and IL6: strongly constrained	IL11RA and IL-11: no evidence of constraint
Indications with approved therapeutics against cytokine or receptor	Castleman disease, rheumatoid arthritis, arteritis	None
Expression in health	Highly expressed across tissues. Detectable in human serum in health and disease	Very low/no expression in healthy adults. Not readily detectable in human serum
Trans-signaling and other "non-*cis*" signaling modes	Established role	Functional relevance not established
Publications listed on PubMed	21,421 (title contains IL-6, IL6, or interleukin 6)	862 (title contains IL-11, IL11, or interleukin 11)

Abbreviations: ERK, extracellular regulated kinase; IL, interleukin; JNK, c-Jun N-terminal kinase.

in the fibroblast growth factor receptor family (22, 23), which implies that IL-11 signaling may be important for fibroblast biology. However, these genetic loss-of-function data give only limited insight into IL-11 biology. This may be related to its low expression in healthy adults, where IL-11 likely plays a very limited role.

IL-11 FROM AN EVOLUTIONARY PERSPECTIVE

The role of IL-11 throughout evolution may provide insights into IL-11 biology beyond effects in mammalian skull development and tooth eruption. IL-11 arose ~450 million years ago in bony fish and is constitutively expressed in their intestine and gills, which are in constant contact with pathogens. Following bacterial or viral infection or after lipopolysaccharide injection, IL-11 expression is elevated in systemic and mucosal immune systems of fish, comprising the liver, kidney, spleen, skin, and gills (24–26). Along with very ancient acute phase proteins, IL-11 is one of the most highly upregulated factors across tissues following injection of fish with synthetic flagellin pathogen-associated molecular pattern (PAMP). The large and acute upregulation of IL-11 through toll-like receptor activation strongly suggests that IL-11 is an important component of the innate immune response in fish (25). Interestingly, in vitro experiments showed that the cellular source of IL-11 in the fish liver is not immune cells but that IL-11 may be upregulated in cells of the parenchyma or stroma after infection (25).

Thus, in fish, IL-11 likely plays an important role in innate immunity at the mucosal barrier (e.g., gills and intestine), and pathogens breaching this barrier induce further IL-11 upregulation

across tissues. This ancient immune activity does not appear to be of equal relevance in humans, where loss of IL-11 signaling is not associated with infection risk. However, innate immune system activation is an established cause of pathobiology in human disease, and IL-11 is upregulated in many human fibro-inflammatory diseases.

DISCOVERY OF IL-11 AND USE OF RECOMBINANT HUMAN IL-11 AS A DRUG TO INCREASE PLATELETS

IL-11 was discovered in bone-marrow-derived stromal cell lines and found to support the growth of hematopoietic cells (27) and adipocytes of the bone marrow niche (28). In these experiments, IL-11 was expressed in the fibroblast-like COS-1 cell line, and the supernatant was found to stimulate cell growth. The initial characterization of IL-11 as a hematopoietic cytokine inspired studies of IL-11 and platelet production, which it was found to increase in vivo. This chance finding led to the development of recombinant human IL-11 (rhIL-11) for the treatment of thrombocytopenia in chemotherapy patients (29). It was later shown that *Il11ra1* knockout mice and human nulls for *IL11RA* display normal blood cell counts at baseline and in response to varied hemodynamic stressors (20, 21), which shows that IL-11 is, in fact, redundant for normal hematopoiesis. IL-11 alone was found not to directly stimulate megakaryocytes (30), and long-term anti-IL-11 therapy in mice has no effect on platelet counts (11). Human knockouts for *IL11RA* have normal platelet counts and no reported issues with hemostasis after surgeries.

It was reported in 1996 that rhIL-11 induces bone marrow fibrosis (myelofibrosis) in ~60% of patients within two weeks of treatment (31). This observation of IL-11 gain of function in humans is intriguing, as one of the recognized clinical features of early myelofibrosis is an increased/reactive platelet count. Further studies are required to better understand how rhIL-11 affects platelet counts and if the therapeutic benefits observed in patients are secondary and depend on cell types outside of the hematopoietic niche. Following its development as a therapeutic, rhIL-11 became readily available as a molecular tool in the 1990s and was extensively used by the scientific community to study rhIL-11 effects in murine preclinical models.

REDEFINING THE ROLE OF IL-11 IN THE LIVER

A role for IL-11 in acute liver disease is consistent with the marked IL-11 upregulation seen in hepatocytes in response to reactive oxygen species (32) as well as in murine liver ischemia (33) and in acute liver disease induced by acetyl-para-aminophenol (APAP, commonly known as acetaminophen or paracetamol) (32, 34, 35). To better understand IL-11 signaling in the pathogenesis of hepatic disease, investigators have administered rhIL-11 in various preclinical mouse models. rhIL-11 was shown to protect the liver from Concanavalin A-induced T cell–mediated hepatotoxicity (36), APAP-induced hepatotoxicity (32, 37), acute endotoxemia (38), and ischemia-reperfusion injury (33, 39). In several of these studies, rhIL-11 had a beneficial effect on survival. This body of work documenting the protective effects of rhIL-11 in the mouse liver triggered a clinical trial where rhIL-11 was administered to patients suffering from hepatitis C, which was not progressed beyond a single study (40).

More recent studies by our group have revisited IL-11 biology in the context of APAP overdose (35). IL-11 was confirmed to be highly upregulated in mouse liver and also detectable in the periphery following APAP. In these experiments, recombinant mouse IL-11 (rmIL-11, not used in earlier studies), rhIL-11 (used in all previous studies), or IL-11-neutralizing antibodies binding to IL-11RA (anti-IL-11RA) were administered following APAP-induced liver injury. This study confirmed previous observations that rhIL-11 is protective in the murine model of APAP overdose. On the contrary, and of absolutely central importance, Widjaja et al. (35) showed that the

species-matched rmIL-11 was not protective—indeed rmIL-11 caused liver damage and directly induced hepatocyte death in mice. Furthermore, IL-11-neutralizing antibodies had profound therapeutic benefits when given 10 h after APAP overdose, protecting the liver and markedly improving survival. The authors showed that APAP triggers a vicious cycle in which IL-11 upregulation in hepatocytes amplifies oxidative stress and activates extracellular signal-regulated kinase (ERK) and c-JUN N-terminal kinase (JNK). Neutralization of IL-11 broke this cycle and substantially lowered oxidative stress in the liver, which had strong protective effects on hepatocytes and promoted liver regeneration (35).

Follow-up work revealed the cause of the disparity between the recent results (endogenous IL-11 and rmIL-11 drives liver disease in mice) (11) and those of previous studies (rhIL-11 protects from liver disease in mice) (32–34, 36–39). It turns out that in the mouse, rhIL-1 binds to the mouse IL-11ra1 but does not activate it, acting instead as an inhibitor that blocks and antagonizes the effects of endogenous mouse IL-11. Thus, in murine diseases, when endogenous IL-11 is upregulated in diseased tissues, its effect on target cells (e.g., hepatocytes) is blocked by the administration of exogenous and foreign rhIL-11, which does not stimulate IL-11 signaling in the mouse. This unanticipated and overlooked effect led the field to erroneously believe that IL-11 generically has antifibrotic, anti-inflammatory, and cytoprotective properties. This, it now appears, is the exact opposite of the true biological role of endogenous IL-11, which drives organ fibrosis and dysfunction. Experiments with rhIL-11 on human cells show this pathogenic role is conserved from mouse to human (7, 11, 41), and rhIL-11 is expected to have mostly negative effects in humans. This insight has large implications for the understanding of IL-11 biology.

In separate experiments, our group investigated the role of IL-11 in chronic liver diseases, and IL-11 was found to be upregulated in the liver of patients suffering from nonalcoholic steatohepatitis (NASH), alcoholic liver disease, or primary biliary cholangitis (11). Across several preclinical models of NASH, anti-IL-11 treatments had notable beneficial effects on the three pillars of NASH pathology: fibrosis, inflammation, and steatosis. IL-11 was found to directly drive fibrosis via the activation of hepatic stellate cells, the precursors of myofibroblasts in the liver (42). Experiments in cirrhotic livers showed that anti-IL-11 treatment can reverse established fibrosis, which was accompanied by a shift of TIMP/MMP (tissue inhibitor of metalloproteinase/matrix metalloproteinase) ratios that trigger beneficial remodeling of the extracellular matrix. This second study underlines further the pathological—and not beneficial—effect of IL-11 in the liver in chronic disease. Interestingly, anti-IL-11 treatments in NASH models resulted not only in lower triglycerides in the liver but also in reduced serum triglycerides, cholesterol, and fasting blood glucose. This overall improved metabolic profile seen in response to anti-IL-11 treatment may, at least in part, arise from improved hepatocyte metabolic function, which requires further study. IL-11 inhibition also reversed inflammatory gene expression signatures in the liver, reduced immune cell invasion, and lowered circulating levels of transforming growth factor β1 (TGFB1), suggesting that the treatment is disease modifying. It is notable that the inhibition of IL-11 (or IL-6) *trans*-signaling with soluble gp130 does not protect from NASH in mouse models (43), suggesting *cis*-IL-11 signaling is dominant in liver disease.

REDEFINING THE ROLE OF IL-11 IN THE CARDIOVASCULAR SYSTEM

IL-11 was first reported as a cardioprotective cytokine that activates STAT3 (signal transducer and activator of transcription 3) signaling in cardiomyocytes by Kimura et al. in 2007 (44). Follow-up studies showed that rhIL-11 induces protective and antifibrotic effects in the mouse heart in the context of ischemia-reperfusion injury (44, 45), myocardial infarction (46), and cold ischemia (47). Studies in the kidney came to similar conclusions and showed that rhIL-11 suppresses extracellular

matrix deposition in experimental glomerulonephritis (48) and protects from renal ischemia-reperfusion injury (49). In all these studies, rhIL-11 was injected into rodents at high doses.

We studied IL-11 in cardiovascular fibrosis because *IL11* is the most upregulated gene (8.4-fold) when human atrial fibroblasts are stimulated with TGFB1, and IL-11 expression was highly correlated with the fibrotic response (7). By way of comparison, IL-6 was upregulated only 1.3-fold. Schafer et al. (7) then demonstrated that rmIL-11 is profibrotic and required for mouse fibroblast activation and that germline deletion of *Il11ra1* protects mice from cardiac and renal fibrosis while preserving organ function. On the other hand, rhIL-11 did not activate mouse fibroblasts at physiologically relevant concentrations, consistent with the effect in mice as observed in studies of the liver (11).

It is notable that paroxysmal atrial fibrillation is seen in up to 15% of patients receiving the rhIL-11 drug Neumega. This suggests that rhIL-11 in humans may induce atrial fibrosis, which is known to underlie atrial fibrillation. It should also be noted that elevated IL-11 has been associated with cardiac events in patients with chronic heart failure (50). Furthermore, brain natriuretic peptide increases by an average of tenfold after rhIL-11 administration to patients, and up to 80% of patients present with brain natriuretic peptide levels consistent with a diagnosis of heart failure (51). These and other features suggest that rhIL-11 induces a cardio-renal syndrome when given to humans. These clinical observations mirror the effects of rmIL-11 administration in mice, at the same dose and for the same duration as used in patients, where it also causes cardiac and renal dysfunction (7).

IL-11 AND LUNG INFLAMMATION AND FIBROSIS

One of the most upregulated genes in pulmonary fibroblasts of patients suffering from scleroderma-associated interstitial lung disease is *IL11* (52). It is also consistently upregulated in the airways of asthma patients (53) and the lung tissue of idiopathic pulmonary fibrosis patients (54). The expression of IL-11 correlates with the extent of fibrosis and negatively correlates with lung function in disease (41). While these observations suggested IL-11 plays a role in lung diseases, until recently it was not clear whether IL-11 upregulation is pathogenic or protective due to the conflicting literature. When rhIL-11 was overexpressed in mouse lung cells, animals were strongly protected from hyperoxia-induced lung injury and death (55). In conflict with this finding, the very same mouse model was found to have aspects of lung inflammation and bronchial remodeling (56). Furthermore, injection of rhIL-11 reduced lung inflammation and improved mortality after lipopolysaccharide challenge of the lung (57), but in contrast, Chen et al. (58) showed that IL-13-driven airway inflammation or remodeling is dependent on IL-11 signaling. In short, the literature to date on IL-11 in the lung has been confusing, and studies of IL-11 in lung pathology were not pursued.

Recently, the role of IL-11 as a central driver of fibrotic lung disease has become apparent in contemporaneous and orthogonal studies to our own. One study focused on the rare human genetic condition Hermansky-Pudlak syndrome (HPS), which is associated with early-onset, aggressive, and untreatable pulmonary fibrosis and, less commonly, colitis. Epithelial cells from human lung organoids with pulmonary fibrosis–associated HPS mutations had highly elevated levels of IL-11 in genome-wide analyses. This is interesting as it points to the damaged lung epithelium as a source for IL-11 production. Consistent with this, previous studies have shown that viral infection of the lung epithelium can stimulate IL-11 secretion (59), which can be inhibited by dexamethasone (60). In the recent HPS study, genetic deletion of IL-11RA was sufficient to block fibrosis in HPS organoids (54), and it was inferred that IL-11 signaling may represent a therapeutic target in HPS-associated lung fibrosis.

In studies by our group, Ng et al. (41) used therapeutic antibodies that bind to IL-11 and neutralize IL-11 signaling in the bleomycin model of mouse lung fibrosis. With both early and late intervention, anti-IL-11 therapy significantly reduced/reversed collagen levels in the lung and had anti-inflammatory effects. Confirming the central importance of ERK signaling downstream of IL-11, antibody treatment reduced ERK activation in vivo. Follow-up studies determined the specific importance of fibroblast activation by IL-11 in lung fibrosis and examined the temporal relationship between fibroblast activation and lung inflammation (61). In this study, animals with conditional and fibroblast-specific deletion of *Il11ra1* were strongly protected from lung fibrosis and inflammation after bleomycin treatment. Notably, inflammatory markers in the knockouts were comparable to healthy controls, suggesting that fibroblast activation precedes inflammation. This new study highlights the central importance of the stroma for the inflammatory response in lung fibrosis and warrants further investigation.

IL-11 AND DERMAL FIBROSIS

Dermal fibrosis and inflammation are hallmarks of connective tissue diseases, atopic dermatitis, psoriasis, and systemic sclerosis (SSc). In atopic dermatitis patients, IL-11 expression is elevated in chronic, but not acute, skin lesions and also correlates with collagen deposition (62). Justified by incorrectly interpreted properties of rhIL-11 in mouse experiments, clinical trials of rhIL-11 in psoriasis patients were initiated. As we would now expect, clinical data were inconclusive and did not warrant further study (63, 64).

IL-11 is highly upregulated in SSc skin fibroblasts (65) as well as in pulmonary fibroblasts of patients who suffer from SSc-associated interstitial lung disease (52). Upregulation of IL-11 in this context may be expected because TGFB signaling is important in SSc (66) and IL-11 secretion is the dominant response of human fibroblasts to TGFB family members (7). TGFB blockage has been discussed extensively in the context of SSc, but on-target toxicities associated with TGFB inhibition have prevented therapeutic development. One possible strategy to try to overcome safety concerns is the inhibition of integrin-mediated activation of latent TGFB isoforms in the context of fibrotic disorders (67). However, attempts to more safely block TGFB activation by inhibiting integrins have not gone well: A recent phase II trial of a monoclonal antibody targeting integrin αvβ6 was stopped due to safety concerns. It is important to point out that targeting integrins is likely not viable in SSc, as it has recently been shown that TGFB2, and not TGFB1 or TGFB3, is elevated in the skin of SSc patients (68), which is consistent with unbiased RNA-seq studies of SSc fibroblasts (65). A lack of RGD sequence in the latency-associated peptide leads to human TGFB2 activation being largely independent of integrin activation. The inhibition of IL-11 in SSc may hold promise given IL-11's dominant upregulation in both SSc skin and lung fibroblasts and considering that TGFB-driven activation of fibroblasts is IL-11 dependent.

IL-11 AND INFLAMMATION

Historically, IL-11 has been described as both anti- and proinflammatory. This interpretation shifts in a major way when we take into account that foreign rhIL-11 is an inhibitor of endogenous murine IL-11 in the context of IL-11-driven diseases in mice (35). rhIL-11 has been shown to reduce inflammation in rodent models of rheumatoid arthritis (RA) (69), Lyme disease (70), graft-versus-host disease (71), lung inflammation (57), hepatitis (36), ulcerative mucositis (72, 73), and colitis (74, 75). We believe it is likely that in most of these instances, endogenous mouse IL-11 was upregulated in the diseased tissue and then inhibited by rhIL-11, which resulted in the observed therapeutic effect. These varied studies led to the notion that IL-11 is anti-inflammatory and stimulated clinical trials of rhIL-11 in RA (76) and Crohn's disease (77, 78).

We review here in more depth the studies of IL-11 in arthritis. Experiments by Feldmann and colleagues showed in 1998 that IL-11 is elevated in the synovial fluid and membrane of RA patients (79) and that rhIL-11 (unbeknownst to them, likely acting as an inhibitor of endogenous IL-11) can effectively reduce established arthritis in the mouse (69). It is quite telling that, some years later, the opposite effect was observed when endogenous mouse IL-11 was inhibited using gene- or antibody-mediated loss of function (80). More recently, a study of human RA patients shed some light on the role of IL-11 in RA (81). IL-11 was found upregulated in RA and IL-11RA was located on synovial fibroblasts and endothelial cells but not macrophages, which did not react to IL-11. Activated fibroblasts also secreted other angiogenic factors such as vascular endothelial growth factor (VEGF), which, together with IL-11, drive angiogenesis in the RA joint (81). *IL11* was also found to be the most highly upregulated gene genome-wide in macrophage-activated synovial fibroblasts in RA (82). Taken together, these data suggest IL-11 as a potential drug target in RA.

Up to 40% of ulcerative colitis (UC) patients do not respond to anti–tumor necrosis factor (anti-TNF) therapy. In 2009, global expression profiling of the colonic mucosa of UC patients using DNA microarray technology identified five genes that were highly upregulated in nonresponders compared to responders (83). These included the genes encoding IL-11 and the receptor for IL-13, which depends on IL-11 to activate fibroblasts (7, 58). Ten years later, single-cell RNA sequencing of the colonic mucosa of similar patient groups replicated these results and defined the cellular source and mode of action of IL-11 in UC. IL-11 is expressed in a cell type the authors termed "inflammatory fibroblasts," which are defined by IL-11 and IL-13RA expression and drive anti-TNF resistance in UC patients (84). Remarkably, in a separate study in 2010, *IL11*, along with *S100A8/9*, was one of five genes that predicted anti-TNFα failure in Crohn's disease (85). These patient data, together with previous studies showing a protective (inhibitory) effect of rhIL-11 in rodent models of colitis (74, 75) and a study showing that species-matched mouse IL-11 causes inflammatory bowel disease (86), make a strong case for IL-11 as a drug target in UC and Crohn's more generally, and anti-TNF therapy-resistant UC, specifically.

IL-11 AND CANCER

The role of IL-11 in cancer has been reviewed elsewhere (87) and is discussed only briefly here. While IL-11 may have cancer cell–autonomous effects, we believe the report of its effects in cancer-associated fibroblasts (CAFs) may be of particular relevance. In 2014, a paper in *Nature* (88) showed convincingly that neoplastic subclones drive tumor growth in an IL-11-dependent manner and that this effect is non–cell autonomous and stroma dependent. In the absence of IL-11 subclones, the stroma can no longer support the tumor. More recent studies identified an effect of tumor-derived IL-11 on mesenchymal stromal cells that promote neutrophil-related tumorigenesis and metastasis, again highlighting an indirect effect of IL-11 in cancer (89). Other studies have shown a role for IL-11 in CAF-driven chemotherapy resistance (90). It is notable that some cancers secrete large amounts of IL-11; indeed, TGFB-stimulated IL-11 release from the A549 lung epithelial cancer cell line was developed to specifically test TGFB bioactivity (91). Whether IL-11 is a useful target in the tumor stroma is not yet known. This could be investigated further in the context of Peutz-Jeghers syndrome–associated polyposis/cancer, where polyp formation is driven by IL-11 from the stroma (92).

CONCLUSIONS AND THE FUTURE

There are far fewer studies of IL-11 than of IL-6. This likely reflects the conflicting nature of the published literature, due, in part, to the misinterpretation of the effect of rhIL-11 in the mouse,

where—as recognized only recently—it acts as an inhibitor of endogenous murine IL-11. The earlier studies thus led us away from the true IL-11 biology: What was thought of as a gain-of-function result paradoxically reflected loss of function. The consequent erroneous interpretations, especially from early studies, were sufficient to trigger several clinical trials where rhIL-11 was administered to humans (40, 77, 78, 93). Ironically, for these indications, IL-11 inhibition may prove to be a successful intervention. The systemic administration of IL-11 cannot be expected to recapitulate the pathophysiology of IL-11-driven disease—no more than injecting TNF causes RA. Nevertheless, the side effect profile of rhIL-11 in humans suggests that patients receiving IL-11 commonly develop a cardio-renal syndrome (50, 51) and that the increased platelet counts may be indirect and relate to bone marrow stromal activation, which remains to be proven (31).

It appears that IL-11 signaling drives a number of cellular mechanisms that have different outcomes depending on the cell type affected. Epithelial cells and polarized cells of the parenchyma, such as hepatocytes (11), are adversely affected and indeed die from apoptosis and lose their regenerative capacity when exposed to IL-11. In contrast, stromal cells such as fibroblasts or smooth muscle cells become activated, invasive, resistant to stress, and matrix secreting (7, 11). At the molecular level, these cellular transitions have intriguing similarities such as ACTA2 expression and reactive oxygen species production, which occurs in both activated fibroblasts and injured parenchymal cells that can undergo a partial epithelial-to-mesenchymal transition, exemplified in both liver and kidney injury (94, 95). IL-11-driven effects, initiated in either the epithelium or the stroma, shift the balance away from tissue function and integrity to tissue dysfunction and scarring, which are accompanied by an immune response that is of a secondary nature but likely centrally important for disease. IL-11-neutralizing therapies may provide a means to target disease at the site of tissue injury and not mute the immune system at the organismal level, a possibility that needs to be examined in future studies. We end by observing that *IL11* has been hiding in plain sight for the last few decades and now—with its emergence as a disease gene—we suggest a new era of IL-11 biology presents itself.

DISCLOSURE STATEMENT

S.A.C. and S.S. are coinventors on the following patent applications: WO/2017/103108: TREATMENT OF FIBROSIS, WO/2018/109174: IL-11 ANTIBODIES, WO/2018/109170: IL-11RA ANTIBODIES, WO/2019/073057: TREATMENT OF SMC MEDIATED DISEASE. S.A.C. and S.S. are cofounders and shareholders of Enleofen Bio PTE LTD, a company that develops anti-IL-11 therapeutics.

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