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Interleukin-33 and its Receptor in Pulmonary Inflammatory Diseases

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Abstract

Interleukin-33 (IL-33) is a member of the IL-1 cytokine family. It modulates immune responses and biological functions through binding to its membrane receptor, ST2L. ST2L is a member of the Toll-like/IL-1 (TIR)–receptor superfamily, and its isoform, soluble ST2 (sST2), functions as an inhibitor of the IL-33/ST2L pathway. Levels of IL-33 and sST2 in serum and bronchoalveolar lavage fluid (BAL) are known biomarkers for a variety of disorders such as heart failure, non-small-cell lung cancer, and pulmonary inflammatory diseases. IL-33 also exists in the nuclei, and nuclear IL-33 seems to regulate cytokine gene expression. In this review, we focus on the role of IL-33/ST2 in the pathogenesis of pulmonary inflammatory diseases including asthma, chronic obstructive pulmonary disease (COPD), and lung injury.

Keywords

Interleukin-33; ST2; Asthma; COPD; ALI; Signal transduction

I. INTRODUCTION

Pulmonary inflammatory diseases, including asthma, COPD, and acute lung injury (ALI), are major lung disorders that cause breathing problems. Infections, inhaled environmental toxins, and genetics are responsible for most lung diseases. Excessive inflammation plays a central role in the pathogenesis of pulmonary inflammatory diseases. In response to insults, the inflammatory response defends against pathogens and protects lungs from infections, allergens, or pollutants, whereas imbalanced inflammation leads to tissue damage and respiratory failure.

Cytokines are polypeptides produced by most kinds of cells including T cells, macrophages, epithelial cells, and endothelial cells. Cytokines regulate cellular responses through binding to specific membrane receptors. Based on their functions, cytokines can be categorized as pro-inflammatory or anti-inflammatory. Major pro-inflammatory cytokines (e.g., TNF-α, IL-8, IL-6, and IL-1β) are involved in innate immune responses. IL-10 and TGF-β are considered anti-inflammatory cytokines and promote tissue repair and remodeling in the

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injured lungs. IL-4, IL-5, and IL-13 play critical roles in the adaptive immune response and promote allergic responses; they exhibit anti-inflammatory properties in acute inflammation. Loss of the delicate balance between pro-inflammatory and anti-inflammatory activity leads to respiratory dysfunction. IL-33 is a newly characterized cytokine that amplifies both innate and adaptive immune responses. In this review, we discuss the role of IL-33 and its receptor ST2 in the pathogenesis of pulmonary inflammatory diseases. The IL-33/ST2 pathway is a potential therapeutic target in the treatment of lung diseases.

II.IL-33

IL-33 is a cytokine that is constitutively expressed in the nuclei of endothelial and epithelial cells.[1–3] The full-length form of IL-33, pro-IL-33, serves as a gene regulator that is localized in the nuclei,[4] whereas mature IL-33 serves as a cytokine after release into the extracellular space at the onset of tissue injury.[5–7] Mature IL-33 is a relatively new member of the IL-1 family.[5] Unlike IL-1α and IL-1β, IL-33 processing does not involve the activity of the NLRP3 inflammasome.[8] In contrast, cleavage of pro-IL-33 by caspase-1[9] or apoptotic caspases (e.g., caspase 3 and caspase 7) leads to its inactivation.[9,10] Once pro-IL-33 (30 kDa) is released into the extracellular space, it is cleaved by proteases, such as calpain, cathepsin G, or neutrophil elastase, to become the pro-inflammatory, mature IL-33 (18 kDa).[11] Similar to other alarmin members of the IL-1 family, such as HMGB1 and IL-1α, IL-33 can signal and activate immune cells such as macrophages, mast cells, eosinophils, basophils, natural killer cells, T cells, circulating CD34(+) stem cells, epithelial cells, and endothelial cells to produce cytokines such as IL-5, IL-13, IL-6, and IL-8.[12–16] IL-33 has been implicated in both Th1- and Th2- cell–mediated immunity responses; it exhibits both pro-inflammatory and anti-inflammatory effects.[5] As a pro-inflammatory cytokine, IL-33 plays a crucial role in innate immunity, allergic inflammation, and tissue injury.[17–21] Increased IL-33 release can be detected in the serum or tissue of patients with asthma, COPD, idiopathic pulmonary fibrosis (IPF), or rheumatoid arthritis (RA).[22–27] Inhibition of IL-33 via administration of neutralizing IL-33 antibody or IL-33 decoy receptor attenuates lung inflammation in murine models of asthma, COPD, and lung injury.[28–31] Conversely, IL-33–deficient mice exhibit reduced cytokine release and mortality in the LPS-induced sepsis model, suggesting that IL-33 plays a critical role in innate immunity responses.[32] A recent study has revealed a new IL-33 function of promoting antiviral Th1 cell responses. IL-33 acts directly on and enhances the expansion of antiviral CD4+ Th1 effector T cells and cytokine production during viral infection.[33]

III. ST2

IL-33 exerts its function through the heterodimeric IL-33 receptor, which consists of one ST2[34] and one IL-1R accessory protein (IL-1RAcP) molecule.[35–37] (IL-1RAcP is a common component of receptors for the IL-1 cytokine family.) ST2 exists in both a secreted form (sST2) and a transmembrane, long form (ST2L).[38] Pro-inflammatory stimuli (e.g., LPS, TNFα, LPA, and IL-6) upregulate ST2 mRNA expression.[39–41] sST2 and ST2L exhibit diametric effects with regard to inflammatory responses.[42] ST2L is highly expressed on immune effector cells, including lung epithelia, and it plays a critical role in triggering inflammation.[43–45] In contrast, secreted sST2 acts as a decoy receptor for IL-33 and

functions as an inhibitor of IL-33 signals, exerting an anti-inflammatory effect.[5] ST2L is a classic type I membrane receptor that contains three extracellular IgG-like domains, a transmembrane domain and an intracellular Toll/IL-1 receptor (TIR) domain.[34,46] IL-33 binding to extracellular domain of ST2L results in the recruitment of MYD88 to the TIR domain of ST2L, inducing inflammatory mediators by activating transcription factor AP-1 or IRAK-mediated TRAF6, subsequent mitogen-activated protein kinase (MAPK), and IKK/NF-κB.[34] Efforts to elucidate the specific role of ST2L in inflammatory diseases have been confounded by data showing that *st2* knockout or overexpressing mice exhibit changes in both sST2 and ST2L expression.[47–50] Direct targeting of ST2L is more specific for the IL-33/ST2L pathway. ST2L stability is regulated by a ubiquitin E3 ligase SCF FBXL19 that induces ST2L ubiquitination and proteasome degradation, and thus blocks IL-33 signaling.[31] Glycogen synthase kinase 3β (GSK3β), a serine/threonine kinase, regulates ST2L internalization.[51] It has been shown that inhibition of GSK3β attenuated IL-33–induced cytokine release.[31] As a negative regulator of the IL-33/ST2 signaling pathway, TIR8 (also known as SIGIRR) dimerizes with ST2L and ultimately dampens the bioactivity of IL-33.[52] SIGIRR-deficient Th2 cells show increased production of Th2 cytokines in response to IL-33 treatment.[53] All evidence suggests that modulation of ST2 expression impacts IL-33–induced biological functions.

IV. IL-33/ST2 IN ALLERGIC DISEASES

Allergic inflammation is driven by an imbalance of cytokine production between Th1 and Th2 lymphocytes.[54] Th1 lymphocytes normally initiate immune response by producing IL-2 and INF-γ in response to allergens.[55] In contrast, Th2 lymphocytes produce pro-inflammatory cytokines including IL-4, IL-5, IL-6, IL-9, and IL-13.[55] IL-4 and IL-13 are required for Th2-cell development and regulation of B-lymphocyte IgE production.[34,56–58] Furthermore, IgE and Th2 cytokines stimulate mast cells, basophils, and eosinophils that produce histamine and prostaglandins; thus, they mediate the subsequent inflammation-driven immunity response.[59] Hyper-reactive type-2 immune responses are the primary contributor to the development of allergic disorders such as asthma, atopic dermatitis, allergic rhinitis, and anaphylaxis.[24,60–63] ST2L is mainly expressed on the surfaces of Th2 cells, mast cells, and NKT cells and is only transiently expressed on Th1 cells under certain states of cellular activation.[33,34,64]

IL-33/ST2L contributes to the pathogenesis of allergic inflammatory disorders by activating mast cells and Th2 cells.[6,24,56,65,66] IL-33 levels and ST2L expression are upregulated in patients with asthma and atopic dermatitis.[28,39,67] Serving as a chemotactic factor for Th2 cells, IL-33 induces Th2 immune responses by producing pro-inflammatory cytokines, chemokines, and lipid mediators, including IL-4, IL-5, IL-13, tumor necrosis factor-α, GM-CSF, CCL2 (monocyte chemoattractant protein-1), and prostaglandin D_2.[6,66,68] Tjota et al. discovered that immune complex (IC) increased IL-33 levels from dendritic cells sufficiently to induce the development of a Th2 response.[69] Administration of an antibody against IL-33 or blockade of IL-33/ST2L by sST2 attenuates allergic airway inflammation by inhibiting Th2 cytokine production and reducing eosinophil infiltration and IgE.[1,2]

Asthma is a complex and chronic inflammatory airway disease that is influenced by genetic and environmental factors. Several genome-wide association studies (GWAS) have revealed that the gene coding IL-33 and ST2 is a major susceptibility loci for human asthma.[70–73] Genetic polymorphisms in *Il-33/St2* are found in relation to asthma and specific wheezing phenotypes, especially intermediate-onset wheeze (a phenotype closely associated with sensitization).[74] A GWA study identified single-nucleotide polymorphisms (SNPs) in *St2* (*e.g.*, rs1420101 for Icelandic population and rs950880 for non-Icelanders) associated with blood eosinophils and all three asthma phenotypes: asthma, atopic asthma, and nonatopic asthma.[75] These SNPs also correlated positively with serum IgE.[75] The SNP located 32-kbp proximal to the start codon of *Il33* (rs3939286) has been significantly associated with both eosinophil counts and asthma, except in the nonatopic phenotype.[75] These findings indicate that *Il33/St2* SNPs are one of the significant genetic factors for asthma. The TIR domain is the intracellular domain of ST2L that interacts with MYD88, which plays a crucial role in signal transduction. A recent study has shown that missense SNPs in the TIR domain of ST2, such as rs10204137, enhance the IL33/ST2L pathway.[76] These SNPs also enhance the proximal and distal promoter activity of *St2*.[76] All of these genetic studies support the hypothesis that IL-33/St2 contributes to the pathogenesis of asthma.

V. IL-33/ST2 IN COPD

COPD is a progressive inflammatory disorder of the lung. Levels of serum IL-33 and ST2 in COPD patients have been examined by several investigators.[23,77] Tang et al. discovered that IL-33 levels in COPD patients were lower than those in healthy controls.[77] Interestingly, IL-33 levels were higher in COPD patients in the stable phase than in COPD patients with chronic *cor pulmonale* during the acute episode stage. In contrast to this study, Xia et al. showed that serum levels of both of IL-33 and ST2 were higher in COPD patients than in control subjects.[23] Consistent with the study, Byer et al. revealed that levels of both IL-33 mRNA and protein were higher in the lungs of COPD patients that in those of non-COPD subjects.[78] Although the cause of the data disagreement is unknown, more data from clinical and translational research studies, especially studies related to cigarette smoking, suggest that IL-33 contributes to the pathogenesis and progression of COPD. Cigarette smoking is a major cause of COPD. Both IL-33 and ST2 expression was increased in the lungs of mice with cigarette-smoke–induced COPD.[30,78,79] Anti-IL-33 antibody delivered intranasally inhibited cigarette-smoke–induced pathogenic changes in murine lungs.[30] Taken together, these studies suggest that IL-33 plays a critical role in the pathogenesis of COPD. Airway epithelial cells,[23,80,81] including epithelial progenitor cells,[78,82] have been considered a major source of IL-33, whereas cigarette smoke also induces IL-33 expression in PBMC[79] and peripheral blood lymphocytes (PBLs).[23]

COPD is characterized by chronic inflammation and alveolar structure disruption.[83] Higher levels of interleukins (IL-6 and IL-8) have been detected in BAL and lungs in COPD patients than in normal subjects.[84–87] The induced cytokine storm leads to a neutrophil influx into the lungs, resulting in tissue damage.[87–89] IL-33 increased IL-6 and IL-8 release in lung epithelial and endothelial cells and promoted cigarette-smoke–induced cytokine release via activation of p38 MAPK.[79,80] As discussed earlier, IL-33 promotes adaptive immune responses and contributes to mucus generation,[78] which is common in COPD. Zhao

et al. showed that IL-33 also triggers apoptosis in alveolar epithelial cells, suggesting that elevated IL-33 levels may directly induce tissue damage in COPD.[31] Although Qiu et al. showed that inhibition of IL-33 signaling may be beneficial in airway inflammation induced by cigarette smoke, the development of potential therapeutic strategies for treating COPD with anti-IL-33 antibody or sST2 administration requires more preclinical studies.[30]

VI. IL-33/ST2 IN ALI

ALI is a life-threatening inflammatory lung disorder that causes difficulty breathing and organ failure. According to the Berlin definition, ALI is a slightly less severe form of acute respiratory distress syndrome (ARDS) that is caused by direct insults, such as pneumonia, or indirect insults, such as sepsis. ALI is characterized by increased cytokine release, neutrophil influx into the lungs, and pulmonary endothelial barrier disruption. The serum and BAL levels of IL-33 were significantly higher in patients with acute eosinophilic pneumonia than in chronic eosinophilic pneumonia.[90] Consistent with this study, Ampawong et al. recently demonstrated that bronchial IL-33 levels were increased in severe malaria patients with lung injury.[91] Acute *Plasmodium falciparum* infection increased eosinophil activity,[92] suggesting that IL-33 may play a role in lung injury with eosinophilic lung inflammation. However, the serum and BAL IL-33 levels in patients with ARDS were not eleveated.[90] Unlike IL-33 expression in ARDS patients, serum sST2 concentrations were higher in ARDS patients,[93, 94] and these higher sST2 levels were associated with worse outcomes in these patients.[94]

The changes in IL-33/ST2 expression in the lungs have been documented in preclinical animal models of ALI. In a mechanical-ventilation–induced lung injury model, IL-33 levels were increased in rat lungs. Interestingly, ST2L accumulation in the membrane fraction was found in the ventilation group.[95] In an LPS-induced murine model of ALI, BAL IL-33 and ST2 levels in the lungs were significantly elevated.[16,31,32,96] Several studies have shown that modulation of IL-33 or ST2 expression affects lung injury. Overexpression of IL-33 by adenovirus-mediated gene delivery promotes bleomycin-induced lung injury.[22] Overexpression of sST2 by administration of human adipose tissue-derived mesenchymal stem cells overexpressing sST2, adenovirus-mediated sST2 transfer, hydrodynamic gene transfer, or administration of sST2 protein significantly reduced LPS- or bleomycin-induced lung injury.[16,96–98] Zhao et al. showed that reduction of ST2L stability by a ubiquitin E3 ligase attenuated LPS-induced lung injury.[31] Downregulation of IL-33 by heme oxygenase-1 ameliorated LPS-induced ALI.[96] Taken together, these preclinical studies suggest that inhibition of the IL-33/ST2L pathway may be a potential therapeutic strategy for treating ALI or ARDS.

Elevated cytokine release and endothelial or epithelial barrier dysfunction are major pathological changes in lung injury. IL-33 triggers IL-8 and IL-6 release from PBMCs, pulmonary endothelial cells, and epithelial cells,[31,51,80,99] thus inducing neutrophil influx into alveolar spaces. The effect of IL-33 on cytokine production might be partly blocked by sST2[80] or downregulation of ST2L.[31] In addition to modulating cytokine expression, IL-33 has been known to increase pulmonary endothelial barrier permeability and alveolar

epithelial cell death. All of these effects by IL-33 directly contribute to the pathogenesis of lung injury.

VII. CONCLUSIONS

IL-33 and ST2 are considered biomarkers for a variety of human disorders, including pulmonary inflammatory diseases, which supports the hypothesis that IL-33 is closely associated with the pathogenesis of lung inflammatory diseases. Early preclinical models have shown significant preventative effects with delivery of sST2, an anti-IL-33 antibody, or increases in FBXL19 levels (Fig. 1). Targeting the IL-33/ST2 pathway could be a therapeutic strategy for treating pulmonary inflammatory diseases; however, this approach requires more preclinical studies with post-treatment in animal models. Additionally, the role of IL-33 in the nuclei has not been well studied. Its binding partners in the nuclei need to be identified. The association of IL-33 polymorphisms with asthma, COPD, and lung injury also need to be explored.

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ABBREVIATIONS

IL-33	interleukin-33
BAL	bronchoalveolar lavage fluid
COPD	chronic obstructive pulmonary disease
TIR	Toll-like/IL-1
IPF	idiopathic pulmonary fibrosis
RA	rheumatoid arthritis
IL-1RAcP	IL-1R accessory protein
ARDS	acute respiratory distress syndrome
GWAS	several genome-wide association studies
MAPK	mitogen-activated protein kinase
GSK3β	glycogen synthase kinase 3β
SNP	single-nucleotide polymorphism.

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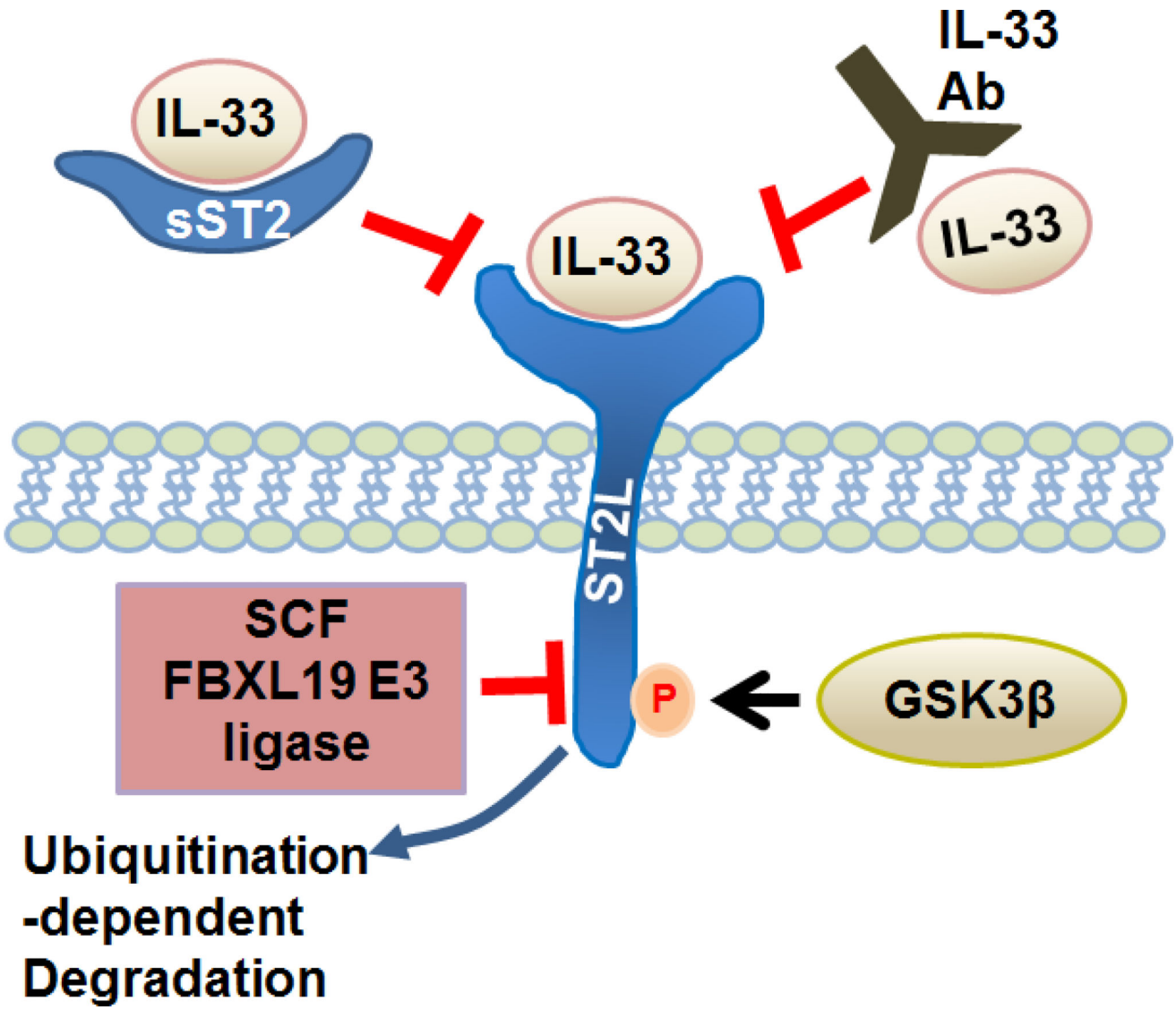

FIG. 1.

Regulation of IL-33/ST2 pathway by sST2, IL-33 neutralizing antibodies, and GSK3β-regulated ubiquitin-proteasome system. Administration of sST2 or IL-33 antibody (Ab) targets extracellular IL-33 to prevent IL-33/ST2L interaction. FBXL19 and GSK3β regulate ST2L stability and internalization, thus reducing IL-33/ST2L downstream signaling. Targeting IL-33/ST2 pathway is a potential therapeutic strategy for treating pulmonary inflammatory diseases.