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MECHANISMS

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Interleukin (IL)-33 immunobiology in asthma and airway inflammatory diseases

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ABSTRACT

Objective: Identify key features of IL-33 immunobiology important in allergic and nonallergic airway inflammatory diseases and potential therapeutic strategies to reduce disease burden.
Data Sources: PubMed, clinicaltrials.gov
Study Selections: A systematic and focused literature search was conducted of PubMed from March 2021 to December 2021 using keywords to either PubMed or BioMed Explorer including IL-33/ST2, genetic polymorphisms, transcription, translation, post-translation modification, nuclear protein, allergy, asthma, and lung disease. Clinical trial information on IL-33 was extracted from clinicaltrials.gov in August 2021.
Results: In total, 72 publications with relevance to IL-33 immunobiology and/or clinical lung disease were identified (allergic airway inflammation/allergic asthma $n=26$, non-allergic airway inflammation $n=9$, COPD $n=8$, lung fibrosis $n=10$). IL-33 levels were higher in serum, BALF and/or lungs across inflammatory lung diseases. Eight studies described viral infections and IL-33 and 4 studies related to COVID-19. Mechanistic studies ($n=39$) including transcript variants and post-translational modifications related to the immunobiology of IL-33. Single nucleotide polymorphism in IL-33 or ST2 were described in 9 studies (asthma $n=5$, inflammatory bowel disease $n=1$, mycosis fungoides $n=1$, ankylosing spondylitis $n=1$, coronary artery disease $n=1$). Clinicaltrials.gov search yielded 84 studies of which 17 were related to therapeutic or biomarker relevance in lung disease.
Conclusion: An integral role of IL-33 in the pathogenesis of allergic and nonallergic airway inflammatory disease is evident with several emerging clinical trials investigating therapeutic approaches. Current data support a critical role of IL-33 in damage signaling, repair and regeneration of lungs.

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IL-33; allergic asthma; non-allergic asthma; lung fibrosis; asthma-COPD overlap; repair; regeneration; COVID-19

Introduction

Interleukin-33 (IL-33) is an alarmin that senses damage/activation of epithelial or endothelial cells and responds immediately by its release into the cytoplasm and extracellular fluids from the nucleus (1). It was first identified in endothelial cells as a nuclear protein called NF-HEV (nuclear factor from high endothelial venules) (1), and in 2005, it was reidentified as a member of the IL-1 family that binds to its orphan receptor ST2 (2). Upon binding to ST2 as an extracellular cytokine, IL-33 stimulates type 2 innate lymphoid cells (ILC2), mast cells, basophils, and T-helper type 2 (Th2) cells to secrete high levels of IL-5, IL-9, and IL-13 (3,4). These Th2 cytokines are involved in the pathogenesis of multiple disease processes including allergy and asthma. Additionally, IL-33 expression has been implicated in environmental-induced nonallergic airway inflammation such as agricultural organic dust exposure (5). Emerging roles for IL-33 include repair, inflammation, homeostasis, and fibrosis. However, the precise mechanisms of IL-33 activation are not well understood and the downstream signaling pathways are complex. Understanding immunobiology of IL-33 is necessary to comprehend the clinical relevance and potential of this versatile cytokine. This review seeks to connect the relevance of IL-33 biology in allergic and nonallergic asthma and chronic inflammatory airway diseases to current and potential clinical interventions.

IL-33 signal transduction

IL-33 is a member of the IL-1 family that consists of 11 members including IL-1α, IL-1β, and IL-18 (6). Like many of the family members (e.g. IL-1β and

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IL-18), IL-33 follows an unconventional secretion mechanism (7). Devoid of a hydrophobic signal peptide, it is synthesized with a propeptide at the N-terminus, upstream of the IL-1-like cytokine domain (1). The mature IL-33 has a single β-trefoil domain that is shared with fibroblast growth factors (FGFs) and binds to IL-1 signaling receptors on their target cells (1). This class of receptors typically possess three extracellular immunoglobulin (Ig)-like repeats and belong to the greater Toll-IL-1 receptor (TIR) superfamily by virtue of their intracellular signaling domain, a distinctive TIR module (8). IL-1RL1 (ST2) is flexible and, hence, changes its conformation on binding to IL-33 resulting in signal transduction (9). The IL-1 receptor accessory protein (IL-1RAP) is rigid and cannot bind to IL-33 directly, but assists the ST2 receptor in ligand binding and signal transduction (9). The heterodimer ternary signaling complex with paired TIR domains recruit myeloid differentiation factor 88 (MyD88), tumor necrosis factor receptor-associated factor 6 (TRAF6), interleukin-1 receptor-associated kinase (IRAK)1 and 4 to activate nuclear factor kappa B (NF-κB) (10) and activator protein 1 (AP-1) (via p38/ERK/JNK pathway) triggering transcription of proinflammatory genes (Figure 1). The MyD88 signaling pathway is also critical in environmental-associated airway diseases that activate immune responses through TLR recognition pathways (5). In complex agriculture-related organic dust extract exposures, IL-33 induction is dependent upon MyD88 signaling (5).

Role of functional genetic polymorphisms

Genome-wide association studies (GWAS) of asthma have led to identification of several genetic variants in the IL1RL1 (ST2) gene, but the molecular mechanisms are unclear. Two single nucleotide polymorphisms (SNPs) in IL1RL1—*rs1420101* and *rs11685480* have been indicated to regulate plasma sST2 levels in airway epithelial cells and distal lung parenchyma, respectively, resulting in an increased risk of classic, type 2, airway inflammation in asthmatics (11). In a Brazilian population, IL-33 SNP *rs12551256* has been

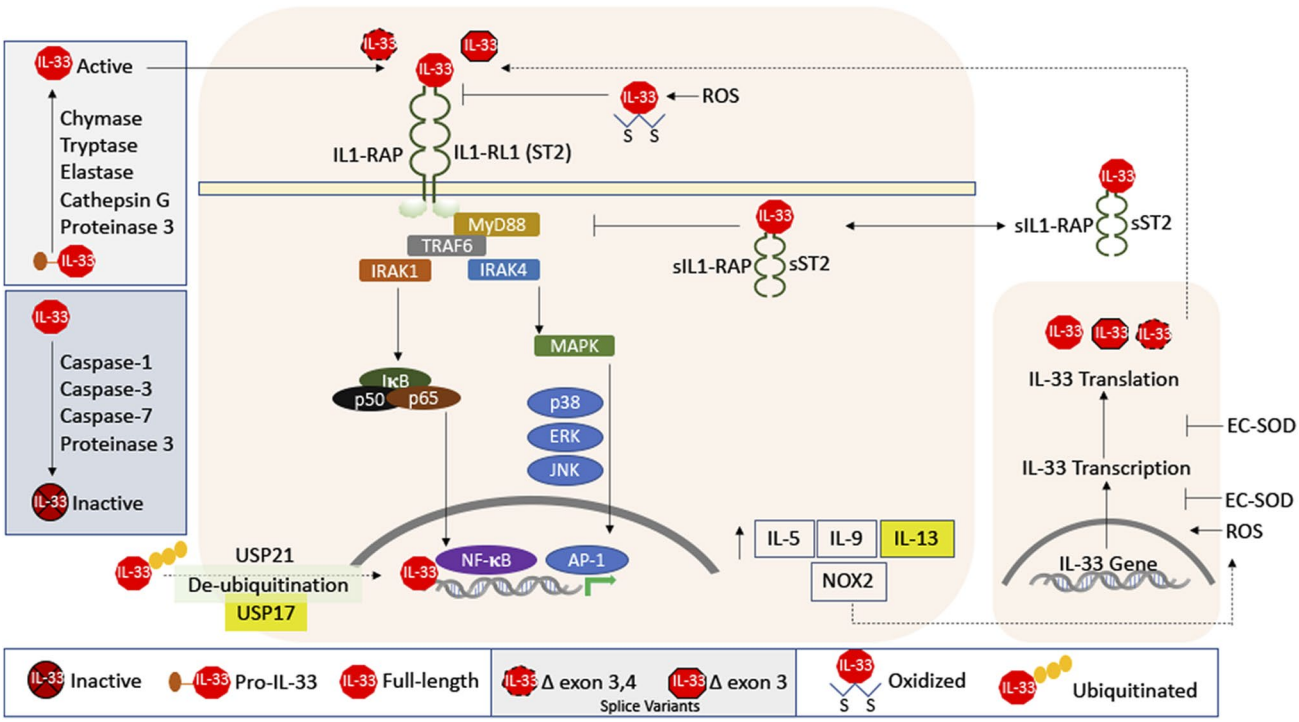

Figure 1. Schematic of IL-33 immunobiology. IL-33 transcription and translation is controlled by many factors including oxidative stress. Different transcript/splice variants of IL-33 result in a variety of IL-33 proteins with differential activity in health and disease. Pro-IL-33 is cleaved by chymase, tryptase, elastase, cathepsin G and proteinase 3 to give rise to an active full-length IL-33. The full-length IL-33 can be inactivated through cleavage by caspase-1, 3, and 7, and proteinase 3. IL-33 protein can also be inactivated by oxidization leading to formation of disulfide bridges. If not inactivated, the full-length IL-33 binds to the ST2-IL1-receptor accessory protein complex to induce signal transduction via MyD88-TRAF6-IRAK1/4 to induce NF-κB and/or AP-1 through MAPK pathway. Activation of these transcription factors result in an increase in transcription of Th2 cytokines such as IL-5, IL-9, and IL-13. Nuclear IL-33 is stabilized by de-ubiquitination through USP21 and USP17 to either stimulate IL-13 or to do repression or newly discovered functions.

shown to be protective in asthma, whereas IL1RL1 SNP *rs1041973* is positively correlated with increased IL-5 and sIgE levels (12). Another SNP in IL-33, *rs1888909*, is implicated in regulating IL-33 expression in human airway epithelial cells and plasma through differential binding of OCT-1 (octamer-binding protein-1) to the asthma-risk allele (13). IL-33 receptor SNPs *rs1041973* and *rs873022* are associated with decreased production of sST2 in atopic subjects and regulate expression of the IL1RL1 gene (12), whereas *rs13048661 (rs13431828)* increases asthma risk and is associated with post-bronchiolitis asthma in children (14). Several other SNPs in IL-33/ST2 are associated with either increased or decreased risk of developing diseases such as inflammatory bowel disease (15), mycosis fungoides (16), ankylosing spondylitis (17), obesity and coronary artery disease (18). Numerous SNPs are predicted in the IL-33 gene to be associated with functional or structural changes (19), leading to potential risk of developing respiratory diseases. Future studies understanding associations between IL-33 SNPs and their role in IL-33 expression and function in various lung diseases could inform future therapeutic approaches for asthmatics.

Significance of splice variants

Alternative splicing of exons results in several splice variants of IL-33, and some of these splice variants are more potent than the full-length IL-33. Deletion of exons 3 and 4 results in a splice variant (Δ exon 3,4) that prefers cytoplasmic localization and is also readily secreted extracellularly with intact signaling capacity (20). Unlike its full-length counterpart, Δ exon 3,4 has been strongly associated with type 2 allergic airway inflammation in non-exacerbating asthmatics (20). An isoform that lacks exon 3 (Δ exon 3) is relatively less potent than the full-length IL-33, but it is constitutively active and contributes to proinflammatory signaling (21). Namely, it lacks caspase-1 cleavage site to elude caspase-1-dependent inactivity during apoptosis making it resistant to cleavage-dependent inactivation (22).

Soluble ST2 (sST2) acts as a decoy receptor for IL-33, and quenches IL-33 to thereby reduce IL-33-ST2-dependent inflammatory signaling (23,24). Similarly, a soluble IL-1 receptor accessory protein acts synergistically with sST2 to block IL-33 signaling (24,25). Targeting these soluble receptor proteins for IL-33 could be of therapeutic interest in allergic and non-allergic airway inflammatory diseases. Several lung diseases are associated with high levels of sST2 including asthma (26), idiopathic pulmonary fibrosis (IPF) (27), chronic obstructive pulmonary disease (COPD) (28), and acute respiratory distress syndrome (ARDS) (29). Although the significance of elevated sST2 expression in these diseases remains unknown and may represent a negative feedback system, sST2 could be considered a biomarker of airway inflammatory disease.

Role of nuclear localization of IL-33

Functional information available on IL-33 is based on the known interaction between IL-33 with its receptor ST2 and downstream MyD88-dependent signal transduction. IL-33, however, is a nuclear protein bound to the heterochromatin and mitotic chromosomes, and thus possesses potential transcriptional repressor properties like other nuclear alarmins including IL-1α and high mobility group box protein 1 (HMGB1) (30,31). A conserved consensus nuclear localization sequence in the N-terminal region of IL-33 determines its nuclear localization (31). Although a strong dual function is predicted for IL-33, future studies are warranted to understand the functional role of nuclear-bound IL-33 in regulating airway disease. A recent report suggests that the chromatin binding of IL-33 acts as a post-translational modification in esophageal epithelium to regulate its release, availability, and bioactivity (7). Another report, however, emphasizes a novel homeostatic role of the nuclear IL-33 in fibroblast differentiation in renal interstitial fibrosis (2). Nuclear IL-33 also has been shown to increase p65 transcript levels as it binds to the NF-κB promoter in endothelial cells (32). It is plausible that nuclear IL-33 has distinctive roles in different cell types. Specifically, utilizing ST2 and IL-33 knock out mice, nuclear IL-33 was proposed to serve as a checkpoint in epithelial stem cells including basal and type II alveolar epithelial cells for their growth and survival (8). Collectively, emerging evidence support an active role of nuclear IL-33 in maintaining homeostasis, growth, and repair; thereby, underpinning the importance of future studies to investigate the precise role of nuclear localization of IL-33 in airway disease.

Post-translational modification of IL-33

Reversible or irreversible post-translational modifications regulate protein function and expression levels (33). These modifications include phosphorylation, acetylation, ubiquitination, methylation, glutathionylation, citrullination, among others (33). Most known post-translational modifications in IL-33 are related to

its proteolytic cleavage leading to diverse functional outcomes. The full-length IL-33 is cleaved by mast cell chymase (34,35), tryptase (35), and neutrophil proteases such as elastase, and cathepsin G (35) to highly active forms. The active full-length form is inactivated by caspase-1, 3 and 7 during apoptosis to reduce or prevent the inflammatory cascade (22). Interestingly, neutrophil-derived proteinase 3 appears to have a dual role in IL-33 processing (36). It cleaves the full length IL-33 to promote bioactivity (35,36), but with prolonged exposure, proteinase 3 decreases IL-33 bioactivity (36) (Figure 1). Others report regulation of IL-33-ST2 axis by ubiquitination processes (37–39). For example, FBXL19 is an 'orphan' member of the Skp1-Cullin-F-box family of E3 ubiquitin ligases that selectively binds ST2 leading to its polyubiquitination and proteasomal degradation in a murine model of pneumonia (37), resulting in reduced inflammatory signals.

IL-33 and oxidative stress

Although oxidative stress can trigger inflammatory processes, it is counterintuitive that IL-33 would be inactivated in the presence of oxidative radicals. However, oxidation of cysteine residues in IL-33 results in conformational change (i.e. formation of two disulfide bonds) in the high-affinity ST2 binding site region (40). Because of this conformational change, oxidized IL-33 is unable to bind to ST2, and therefore, oxidative stress inhibits inflammatory signal transduction (40). The kinetics of this process remains unknown, but likely plays an important role in modulating allergic and non-allergic airway disease processes.

Glutathione (GSH)-protein adducts are also oxidative post-translational modifications that modulate IL-33 protein levels and function (41). Glutaredoxins are enzymes that catalyze removal of protein bound GSH to keep protein thiols in a reduced state without direct antioxidant effects (41). Lipopolysaccharide (LPS) increases glutaredoxin-1 in macrophages resulting in activation of NF-κB by de-gluathionylation (i.e. removal of GSH adducts) via TRAF6 to result in an increase in IL-33 transcription and translation (42).

An imbalance between reactive oxygen species (ROS) and antioxidants can result in oxidative stress in chronic lung diseases including allergic asthma (3). A recent report suggests that oxidative stress-induced activation of type 2 immune response is dependent on ATP-bound Ca^{2+} uptake resulting in IL-33 secretion from bronchial epithelial cells in humans and mice (43). High oxidative stress, particularly related to superoxide radicals, increase IL-33 transcripts and protein levels and release to BALF in allergic airway inflammation (3). Additionally, IL-33 stimulates NOX2 (nicotinamide adenine dinucleotide phosphate (NADPH) oxidase) transcript levels in human peripheral blood eosinophils (44). In summary, an important relationship exists with IL-33 and oxidative stress at the level of transcription, translation, and post-translational processes that could be further explored and exploited to regulated airway disease.

IL-33 in allergic asthma

As a potent promoter of type 2 immune response, IL-33 has been studied most extensively in allergic asthma. After engaging the ST2 receptor, IL-33 stimulates production of Th2 cytokines including IL-5, IL-9, and IL-13 from a variety of immune cells including ILC2, Th2, mast cells and macrophages.

Respiratory viral infections can increase the risk of developing allergic asthma and/or asthma exacerbation. Of these, respiratory syncytial virus (RSV) has been demonstrated to augment IL-33-dependent allergic airway inflammation in an ovalbumin model of mice (45). Considering the importance of IL-33 signaling in allergic asthma, several biologics are being developed and tested as therapies. Monoclonal antibodies against ST2, RG6149 (46), and CNTO7160 (47), or against IL-33, ANB020 (46), REGN3500 (46), and MEDI3506 are already in or have completed clinical trials. An overview of current clinical trials investigating IL-33 are summarized (Table 1). A high-affinity monoclonal antibody against dokimab (LY3375880), is currently in preclinical stages to block IL-33-dependent inflammatory signaling (48). Because of inherent immunogenicity with monoclonal antibodies, a new direction of biologics has also emerged that includes natural peptide sequences to block IL-33 signaling. IL-33trap is an IL-33 antagonist that has a fusion protein containing extracellular domains of ST2 and IL-1 receptor accessory protein (49,50). It has been suggested that this IL-33trap is more efficient in blocking the IL-33 signaling than the natural decoy receptor sST2 with less immunogenicity (49,50). As insights into the complexities of IL-33/ST2 signaling mechanisms continue to rapidly evolve, it is anticipated that several novel therapeutic options will emerge to target and reduce airway disease burden.

IL-33 in chronic obstructive pulmonary disease

Chronic bronchitis and emphysema are hallmarks of COPD marked by destruction of alveoli and loss of type II alveolar epithelial cells, peribronchiolar

Table 1. Clinical trials related to therapeutic or biomarker relevance of IL-33 in lung disease.

#	Identifier	Title	Site	Status	Sponsor
1	NCT03984383	IL-33, Endocan and Endothelial Cells (IL-33)	France	Not recruiting yet	Univ Hospital, Lille
2	NCT00707811	Evaluation of ST2 and IL-33 in Patients Presenting to the Emergency Department With Trouble Breathing	USA	Unknown	The Cleveland Clinic
3	NCT02492204	The Role of IL33/ST2 Axis in ARDS Patients	Spain	Completed	Hospital Univ Vall d'Hebron Research Institute
4	NCT03546907	Proof-of-Concept Study to Assess the Efficacy, Safety and Tolerability of SAR440340 (Anti-IL-33 mAb) in Patients with Moderate-to-severe Chronic Obstructive Pulmonary Disease (COPD)	USA	Completed	Sanofi & Regeneron
5	NCT04701983	Study to Assess the Efficacy, Safety, and Tolerability of SAR440340/ REGN3500/Itepekimab in Chronic Obstructive Pulmonary Disease (COPD) (AERIFY-1)	USA	Recruiting phase 3	Sanofi & Regeneron
6	NCT04751487	Study to Assess the Efficacy, Safety, and Tolerability of SAR440340/ REGN3500/Itepekimab in Chronic Obstructive Pulmonary Disease (COPD) (AERIFY-2)	USA	Recruiting phase 3	Sanofi & Regeneron
7	NCT04256044	Analysis of Peripheral Blood ILC2s and Th2 Cells in Response to ANB020	UK	Completed	University of Leicester
8	NCT03615040	Anti-ST2 (MSTT1041A) in COPD (COPD-ST2OP)	UK	Completed	University of Leicester
9	NCT02289391	Effect of Dexmedetomidine on Levels of Plasma Inflammatory Factor in Asthma Patients Undergoing General Anesthesia	China	Unknown	Second Affiliated Hospital of Xi'an Jiaotong University
10	NCT01973751	Asthma Biomarkers for Predicting Response to Therapy	China	Unknown	Tongji Hospital
11	NCT03423693	Small Airway Obstruction in Asthma, COPD, ACOS	Thailand	Recruiting	Mahidol University
12	NCT03960359	Inflammatory and Immune Profiles During a Severe Exacerbation in Preschool Asthmatic Children (<5 Years) (VIRASTHMA2)	France	Active, not recruiting	University Hospital, Lille
13	NCT03563521	Identifying Serum Cytokine Profiles of Distinct Inflammatory Phenotypes in Severe Asthma	Turkey	Completed	TC Erciyes University
14	NCT04570657	Study to Assess the Efficacy and Safety of MEDI3506 in Adults with Uncontrolled Moderate-to-severe Asthma (FRONTIER-3)	81 global sites	Recruiting	AstraZeneca
15	NCT04319705	Anti-viral Effects of Azithromycin in Patients with Asthma and COPD (AZIMUNE)	Denmark	Recruiting	Bispebjerg Hospital
16	NCT04631016	A Phase II, Randomized, Double-blind, Placebo-controlled Study to Assess MEDI3506 in Participants with COPD and Chronic Bronchitis (FRONTIER-4)	126 global sites	Recruiting	AstraZeneca
17	NCT03112577	Study of REGN3500 and Dupilumab in Patients with Asthma	USA & UK	Completed	Regeneron & Sanofi

fibrosis and typically driven by Th1/Th17 processes (51,52). Asthma-COPD overlap (ACO) is also recognized as a disease entity representing an admixture of asthma and COPD-like inflammatory profiles (53). Serum IL-33 levels are positively correlated with COPD exacerbation and poor lung function (54,55). Additionally, plasma IL-33 correlates with eosinophilia and chronic bronchitis in stable COPD patients (56). However, no difference in IL-33 levels have been observed between asthma and COPD patients in serum, bronchial mucosa, and induced sputum (57). In humans with COPD, IL-33 expression is associated with mucin expression and airway basal epithelial cells with early progenitor phenotype (58). Lung tissue expression of IL-33 is increased in COPD patients (52) and is related to the disease severity (58). Lung IL-33 is also selectively increased in murine models of COPD following viral infections (58), suggesting a role in disease exacerbations. Considering the heterogeneity among COPD patients, additional studies are warranted to understand the role IL-33 plays at different stages and phenotypes of disease.

IL-33 in interstitial lung disease

Interstitial lung disease, particularly idiopathic pulmonary fibrosis (IPF), is a progressive fibroproliferative disease associated with the deposition of extracellular matrix proteins and classical Th2 cytokines such as IL-4, IL-5, IL-9, and IL-13 (59). An increase in IL-33 lung expression and serum levels are demonstrated in IPF (52,60), albeit one report did not find any difference in the serum IL-33 levels between control and IPF patients (61). Others demonstrate increased serum soluble ST2 of IPF patients with acute exacerbation (27). Lung IL-33 expression in IPF occurs in the nucleus and cytoplasm of endothelial cells, macrophages, type II alveolar epithelial cells, other mesenchymal and/or progenitor-like cells (52). In the bleomycin model of murine pulmonary fibrosis, serum IL-33 levels are elevated and strongly correlated with lung fibrosis (62,63). Consistent with IPF, persons with rheumatoid arthritis-associated interstitial lung disease also had increased serum IL-33 levels (64) and lung tissue IL-33 expression (65). Correspondingly, mouse models of RA-associated lung

disease demonstrate increased expression of lung IL-33 in disease pathogenesis (65).

IL-33 in COVID-19

Infection with SARS-CoV-2 virus results in the release of IL-33, and elevated serum IL-33 levels have been strongly associated to the severity and adverse outcomes in COVID-19 (66). Conversely, lung IL-33 expression is exhausted (depleted) in postmortem lungs of COVID-19 patients, and in one case of post-COVID lung fibrosis, IL-33 lung expression is markedly elevated (52). Collectively, these observations support a time-dependent role for IL-33 with disproportionately increased levels at an early-stage infection, followed by depletion, and potential increase with lung remodeling events.

The mechanistic role of IL-33 in COVID-19 and/or other viral infections may be related to interferon (IFN) regulation (67,68). It is well-recognized that viral infections result in increased release of IFN as well as IL-33 levels, and IFNγ inhibits activation and proliferation of type II innate lymphoid cells through an IL-33-dependent pathway and promotes Th1 immune response (69). Conversely, IL-33 supplementation increases IFNγ levels by promoting γδ T cells and NK cells in a murine model of sepsis and improves survival rate (70). In turn, IFNγ downregulates IL-33 mRNA and protein levels in lung fibroblasts (71). This complex relationship between IFNs and IL-33 necessitates further studies to understand the relationship in context to cell phenotype, time course, and/or microenvironment. A strong and early interferon host response is beneficial to reduce viral infectivity (72); however, it is possible that a corresponding and robust early IL-33 response could mitigate anti-viral responses and/or could lead to an unchecked adverse systemic inflammatory response. Additional studies are needed to understand the precise relationship of IL-33 in viral lung infections as a potential biomarker of disease severity and whether therapeutics aimed at IL-33 are warranted.

Conclusion/future directions

The multiple layers in the regulation and function of IL-33 underscore its complexity in allergic and non-allergic airway inflammatory diseases. IL-33 splice variants as compared to full-length IL-33 play strong roles in modulating airway disease. Transcript variants of the IL-33 receptor ST2 impact function noting that the soluble ST2 inhibits IL-33 signaling by quenching free IL-33. Oxidation of IL-33 inactivates IL-33, while de-glutathionylation can activate IL-33 expression and signaling. Although receptor signaling through ST2 has been relatively well-studied, the functional role of nuclear IL-33 remains unclear. Understanding the immunobiology of IL-33 regulation and signaling is important considering the pivotal role it plays in allergic and nonallergic airway diseases. IL-33 may be an important biomarker of airway disease, and moreover, clinical therapeutic strategies targeting IL-33/ST2 are currently underway in asthma and COPD.

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