Research Progress on the Role of the ST2/IL-33 Signaling Pathway in Chronic Airway Inflammatory Diseases (Postprint)

Authors: Guo Wanjin, Yahong Chen, Yahong Chen

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Abstract

Interleukin-33 (IL-33) is released during cell injury and activates innate and adaptive immune responses by binding to its receptor, the growth stimulation-expressed gene 2 (ST2) protein. The ST2/IL-33 pathway plays a crucial role in the occurrence and development of inflammation in chronic airway diseases, such as chronic obstructive pulmonary disease (COPD) and asthma, and has become a research hotspot; however, existing research findings still lack a systematic summary. This paper systematically reviews the physiological functions and pathological mechanisms of the ST2/IL-33 pathway and summarizes the clinical research progress of biologics targeting ST2/IL-33 in COPD and asthma. Studies indicate that the ST2/IL-33 pathway plays a key role in driving airway inflammation, mucus hypersecretion, tissue remodeling, and acute exacerbations by activating immune responses. Biologics targeting this pathway can improve patients' lung function and reduce the risk of acute exacerbations. In conclusion, the ST2/IL-33 pathway serves not only as an inflammatory regulatory mechanism for chronic airway diseases but also provides a direction for the development of novel targeted therapies. With the emergence of more clinical evidence, targeting the ST2/IL-33 pathway is expected to become a new therapeutic approach for chronic airway diseases, thereby improving patients' long-term prognosis and quality of life.

Full Text

Preamble

Research Progress on the Role of the ST2/IL-33 Signaling Pathway in Chronic Airway Inflammatory Diseases

Abstract

Chronic airway inflammatory diseases, including asthma and chronic obstructive pulmonary disease (COPD), are characterized by persistent inflammation and structural remodeling of the respiratory tract. Recent studies have highlighted the critical role of the interleukin-33 (IL-33) and its receptor, suppression of tumorigenicity 2 (ST2), in the pathogenesis of these conditions. As an "alarmin" released from damaged epithelial cells, IL-33 activates the ST2 signaling pathway, triggering a cascade of immune responses that involve both innate and adaptive immunity. This review summarizes the biological characteristics of the ST2/IL-33 axis and explores its specific mechanisms in driving airway inflammation, mucus hypersecretion, and tissue remodeling. Furthermore, we discuss the potential of targeting the ST2/IL-33 pathway as a novel therapeutic strategy for managing chronic airway inflammatory diseases.

1. Overview of the ST2/IL-33 Signaling Pathway

Interleukin-33 (IL-33) is a member of the IL-1 family of cytokines, primarily localized in the nuclei of endothelial and epithelial cells. Unlike traditional cytokines, IL-33 functions as an alarmin; it is released into the extracellular space upon cell injury or mechanical stress. The biological effects of IL-33 are mediated through its specific receptor, ST2. The ST2 gene encodes two main isoforms via alternative splicing: a transmembrane form (ST2L) and a soluble form (sST2).

The interaction between IL-33 and ST2L leads to the recruitment of the IL-1 receptor accessory protein (IL-1RAcP), forming a ternary complex. This complex activates intracellular signaling pathways, including the MyD88-dependent pathway, which subsequently triggers mitogen-activated protein kinases (MAPK) and nuclear factor-kappa B (NF-κB). These pathways promote the production of various pro-inflammatory cytokines and chemokines. Conversely, sST2 acts as a "decoy" receptor, sequestering free IL-33 and thereby inhibiting the activation of the ST2L signaling axis, serving as a negative regulator of the inflammatory response.

2. ST2/IL-33 in Bronchial Asthma

Bronchial asthma is a heterogeneous disease characterized by chronic airway inflammation. The ST2/IL-33 pathway plays a pivotal role

100191 北京，北京大学第三医院呼吸与危重症医学科

Interleukin-33 (IL-33) is released upon cellular damage and activates both innate and adaptive immune responses by binding to its receptor, Suppression of Tumorigenicity 2 (ST2). The ST2/IL-33 signaling pathway plays a critical role in the onset and progression of inflammation in chronic airway diseases, such as chronic obstructive pulmonary disease (COPD) and asthma. While this pathway has become a focal point of recent research, a systematic summary of existing findings is currently lacking. This paper provides a systematic review of the physiological functions and pathological mechanisms of the ST2/IL-33 pathway and summarizes the clinical research progress of biologics targeting this pathway in COPD and asthma. Research indicates that the ST2/IL-33 pathway plays a key role in driving airway inflammation, mucus hypersecretion, tissue remodeling, and acute exacerbations by activating immune responses. Biologics targeting this pathway have demonstrated the potential to improve lung function and reduce the risk of exacerbations in patients. In conclusion, the ST2/IL-33 pathway serves not only as a regulatory mechanism for inflammation in chronic airway diseases but also provides a promising direction for the development of novel targeted therapies.

As more clinical evidence emerges, targeting the ST2/IL-33 pathway is expected to become a new therapeutic approach for chronic airway diseases, thereby improving long-term patient prognosis and quality of life.

Keywords: Chronic airway diseases; ST2; IL-33; Signaling pathway; Mechanism of action

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Research Progress of the ST2/IL-33 Signaling Pathway in Chronic Airway Inflammatory Diseases

Wanjin, Yahong Department of Pulmonary and Critical Care Medicine, Peking University Third Hospital, Beijing 100191, China

Abstract

Interleukin-33 (IL-33) is released in response to cellular damage and mediates its biological effects by binding to its specific receptor, growth stimulation expressed gene 2 (ST2), thereby activating both innate and adaptive immune responses. Accumulating evidence indicates that the ST2/IL-33 signaling pathway plays a critical role in the initiation and progression of chronic airway inflammatory diseases, including chronic obstructive pulmonary disease (COPD) and asthma, and has emerged as a major focus of current research.

However, the available findings have not yet been systematically integrated. This review comprehensively summarized the physiological functions and pathological mechanisms of the ST2/IL-33 pathway. And it further highlighted recent advances in clinical studies of biologics targeting this axis, such as anti-

IL-33 and anti-ST2 monoclonal antibodies, in COPD and asthma. Current data indicated that activation of the ST2/IL-33 pathway contributes to airway inflammation, mucus hypersecretion, airway remodeling, and acute exacerbations through immune-mediated mechanisms. Correspondingly, emerging clinical trial data demonstrated that biologics targeting this pathway could improve lung function and reduce the frequency of acute exacerbations. In summary, the ST2/IL-33 pathway represents a central inflammatory regulatory mechanism in chronic airway diseases and provides a promising therapeutic target. As the high-quality clinical evidence continues to accumulate, targeting the ST2/IL-33 pathway may offer a novel strategy for the treatment of chronic airway diseases, with the potential to improve long-term outcomes and quality of life for patients.

Key words Chronic airway diseases; ST2; IL-33; Signaling pathway; Mechanism of action

Chronic inflammatory airway diseases, such as chronic obstructive pulmonary disease (COPD) and asthma, are characterized by high prevalence and frequent exacerbations, posing a significant burden on global public health [**?**]. In recent years, a deeper understanding of the molecular mechanisms underlying airway inflammation has facilitated the development of targeted biological therapies, which have demonstrated remarkable clinical efficacy in severe asthma. In contrast, anti-inflammatory biological treatments for COPD remain in the exploratory stage, with emerging targets such as interleukin-33 (IL-33) and its receptor, growth stimulation expressed gene 2 (ST2), garnering significant attention [**?**].

The ST2/IL-33 pathway is not only involved in allergic airway inflammation but also plays a crucial role in non-atopic inflammation—such as that seen in COPD—and in the repair of lung tissue damage. This pathway is considered a bridge between innate and adaptive immunity, exerting a critical regulatory role in the progression of chronic airway diseases [**?**]. Developing interventions based on the mechanism of the ST2/IL-33 pathway holds promise for providing new biomarkers and therapeutic strategies for diseases like COPD and asthma. This article provides a comprehensive review of the biological characteristics of the ST2/IL-33 pathway and the recent research progress regarding its role in chronic airway diseases.

1 本文文献检索策略

A computer-based systematic search was conducted across databases including PubMed and Web of Science, with the search period spanning from the inception of each database through September 2025. The English search terms utilized were "IL-33,""ST2,""IL1RL1,""chronic airway inflammation,""asthma,""chronic obstructive pulmonary disease," "COPD," "airway remodeling," "inflammation," "immune regulation," and "signaling pathway."

The inclusion criteria for the literature were defined as studies involving the expression characteristics, molecular mechanisms, immunomodulatory roles, or

basic and clinical research and reviews concerning the ST2/IL-33 signaling pathway in chronic inflammatory airway diseases. Conversely, the exclusion criteria included literature that was irrelevant to the core topic, lacked mechanistic exploration, demonstrated low research quality, or for which the full text was unavailable. Following this screening process, a total of 41 articles were ultimately included in this study.

2 ST2/IL-33

Physiological Functions and Pathological Mechanisms of the Pathway

The biological pathway serves as a fundamental regulatory network within the cellular environment, orchestrating a wide array of physiological processes essential for maintaining homeostasis. Under normal physiological conditions, this pathway is responsible for mediating signal transduction, metabolic flux, and gene expression patterns that govern cell growth, differentiation, and survival. By integrating extracellular stimuli—such as growth factors, hormones, and environmental stressors—the pathway ensures that cellular responses are precisely tuned to the organism' s requirements. This intricate balance is maintained through a series of highly coordinated protein-protein interactions, phosphorylation cascades, and feedback inhibition loops that prevent overactivation and ensure metabolic efficiency.

However, the dysregulation of this pathway is a hallmark of various pathological states. When the regulatory checkpoints of the pathway are compromised —whether through genetic mutations, epigenetic modifications, or chronic environmental insults—the resulting aberrant signaling can lead to severe cellular dysfunction. In the context of oncology, constitutive activation of the pathway often drives uncontrolled cell proliferation, evasion of apoptosis, and metabolic reprogramming, all of which contribute to tumorigenesis and metastasis. Conversely, a pathological reduction in pathway activity is frequently associated with degenerative conditions, where insufficient signaling leads to impaired tissue repair and premature cell death.

Beyond cancer, the pathological mechanisms of this pathway are deeply implicated in inflammatory and metabolic disorders. Chronic overstimulation can trigger a persistent inflammatory response, leading to tissue damage and the development of autoimmune diseases. In metabolic contexts, disruptions in the pathway' s feedback mechanisms can result in insulin resistance or lipid imbalances, contributing to the pathogenesis of type 2 diabetes and cardiovascular diseases. Understanding the transition from precise physiological regulation to pathological disruption is therefore critical for the identification of novel biomarkers and the development of targeted therapeutic interventions. By characterizing the specific molecular nodes that become dysfunctional, researchers can design small-molecule inhibitors or biological agents aimed at restoring the pathway' s homeostatic balance.

2.1 IL-33

Sources and Release Mechanisms of IL-33

IL-33 is a member of the interleukin-1 (IL-1) cytokine family and is constitutively expressed in the nuclei of various tissue cells, including airway epithelial cells, endothelial cells, and fibroblasts [**?**, **?**]. Under physiological conditions, IL-33 may function as a transcriptional regulator. However, when cells undergo damage, stress, or necrosis, the IL-33 stored within the nucleus is passively released into the extracellular space, where it acts as an "alarmin" to rapidly signal tissue injury or infection to the immune system [**?**]. During cell necrosis, the rupture of the cell membrane leads to the passive release of full-length IL-33 protein. This precursor is subsequently cleaved into its mature form by proteases such as neutrophil elastase, basophil proteases, or mast cell proteases, which can enhance its biological activity by 10 to 30 times [**?**, **?**]. Recent studies have classified IL-33 into reduced IL-33 ($IL-33_{red}$) and oxidized IL-33 ($IL-33_{ox}$). $IL-33_{red}$ activates downstream inflammatory signaling pathways by binding to the ST2 receptor, playing a critical role in the regulation of airway inflammation. In contrast, $IL-33_{ox}$ primarily functions in an ST2-independent manner; it forms complexes with the receptor for advanced glycation end products (RAGE) and the epidermal growth factor receptor (EGFR) in the airway epithelium, thereby promoting goblet cell hyperplasia and increasing mucus secretion.

IL-33 Signaling and Transduction

IL-33 exerts its biological effects primarily by binding to its receptor, ST2. ST2 is the product of the interleukin 1 receptor-like 1 ($IL1RL1$) gene and belongs to the IL-1 receptor/Toll-like receptor superfamily [**?**, **?**]. The expression of ST2 is cell-type specific, being predominantly distributed on type 2 T helper (Th2) cells, type 2 innate lymphoid cells (ILC2s), mast cells, basophils, eosinophils (EOS), and regulatory T cells [**?**, **?**]. Additionally, natural killer (NK) cells and neutrophils can upregulate ST2 expression upon stimulation. Based on structural and functional differences, the ST2 receptor exists in two primary isoforms: membrane-bound ST2 (growth stimulation expressed gene 2 ligand, ST2L) and soluble ST2 (soluble growth stimulation expressed gene 2, sST2) [**?**, **?**]. When $IL-33$ binds to ST2L, it forms a complex with the interleukin-1 receptor accessory protein (IL-1RAcP). This complex recruits myeloid differentiation primary response 88 (MyD88)-dependent signaling molecules, thereby activating signaling pathways such as nuclear factor kappa-B (NF-κB) and inducing the expression of inflammation-related genes. Conversely, sST2 binds to IL-33 and neutralizes its activity, thereby acting as a decoy receptor that negatively regulates IL-33 signaling.

2.3 IL-33

Immune Effects and Regulation

IL-33 plays a dual regulatory role in the body' s immune response; it not only drives Type 2 inflammatory responses but can also regulate Type 1 and Type 3 inflammatory responses under specific conditions [**?**]. Classically, IL-33 serves as a key upstream factor inducing Type 2 inflammation. It stimulates ILC2s and Th2 cells to produce large quantities of interleukin-5 (IL-5) and interleukin-13 (IL-13), leading to the proliferation and activation of eosinophils (EOS) and airway hyperresponsiveness. Additionally, it can activate mast cells and basophils to release histamine and leukotrienes, thereby promoting allergic inflammation. However, in the context of infection and non-allergic inflammation, IL-33 stimulates alveolar macrophages and endothelial/epithelial cells to release interleukin-6 (IL-6) and interleukin-8 (IL-8), which drives neutrophil chemotaxis and causes tissue damage. High levels of IL-33 accompanied by increased neutrophil infiltration have been detected in the lung tissues of patients with Chronic Obstructive Pulmonary Disease (COPD), leading to neutrophil-dominant Type 1 and Type 3 immunity. Beyond the classical inflammatory responses mediated by the ST2/IL-33 pathway, clinical studies in COPD have also found that oxidized IL-33 ($IL-33_{ox}$) can induce a mucus hypersecretion phenotype by activating the RAGE/EGFR pathway. Exploring this mechanism contributes to our understanding of the pathogenesis of the hypersecretory phenotype of COPD.

The Role of ST2/IL-33 in Airway Remodeling and Fibrosis

Chronic airway diseases are often accompanied by structural changes such as tissue remodeling and fibrosis, and the role of IL-33 in these processes has received increasing attention. In asthma, which is primarily characterized by Type 2 inflammation, IL-33 is thought to participate in processes such as epithelial hyperplasia, mucus hypersecretion, and basement membrane thickening [**?**]. In COPD, characterized predominantly by neutrophilic inflammation, IL-33 not only participates in airway remodeling and fibrosis but also mediates inflammatory responses that lead to small airway mucus plugging and irreversible decline in lung function. Furthermore, IL-33 can promote the infiltration of inflammatory cells into airway tissues and cause interstitial edema by increasing vascular endothelial permeability [**?**]. Over the long term, this promotes fibrous tissue proliferation and thickening of the airway walls.

3 ST2/IL-33

Research Progress of Signaling Pathways in Chronic Inflammatory Airway Diseases

Chronic inflammatory airway diseases, primarily represented by asthma and chronic obstructive pulmonary disease (COPD), are characterized by persistent airway inflammation, structural remodeling, and hyperresponsiveness. These

conditions involve complex interactions between various immune cells (such as eosinophils, neutrophils, and T lymphocytes) and structural cells (such as airway epithelial cells and smooth muscle cells). Recent advances in molecular biology have highlighted the critical role of specific signaling pathways in orchestrating these inflammatory responses. Understanding these pathways is essential for developing targeted therapeutic interventions.

1. The JAK-STAT Signaling Pathway

The Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway is a central regulator of cytokine signaling in chronic airway inflammation. Upon cytokine binding to cell surface receptors, JAKs undergo phosphorylation and subsequently activate STAT proteins. Once activated, STAT dimers translocate to the nucleus to regulate the transcription of genes involved in cell proliferation and inflammation. In asthma, the IL-4/IL-13-mediated JAK1/STAT6 pathway is pivotal for Th2 cell differentiation and IgE production. Conversely, in COPD, the JAK2/STAT3 pathway is often upregulated in response to oxidative stress and cigarette smoke, contributing to persistent neutrophilic inflammation and mucus hypersecretion.

2. The NF-κB Signaling Pathway

Nuclear factor-kappa B (NF-κB) serves as a master regulator of the inflammatory response. In its inactive state, NF-κB is sequestered in the cytoplasm by IκB inhibitory proteins. Activation by stimuli such as pro-inflammatory cytokines (TNF-α, IL-1β) or Toll-like receptor (TLR) ligands leads to the degradation of IκB, allowing NF-κB to enter the nucleus. In chronic airway diseases, NF-κB activation induces the expression of a wide array of inflammatory mediators, including chemokines and adhesion molecules. Research indicates that the persistent activation of NF-κB in airway epithelial cells is a hallmark of both asthma and COPD, driving the recruitment of inflammatory cells to the lungs.

3. The MAPK Signaling Pathway

The mitogen-activated protein kinase (MAPK) pathways, including the ERK, JNK, and p38 MAPK subfamilies, play significant roles in translating extracellular signals into cellular responses. In the context of chronic airway inflammation, the p38 MAPK pathway is particularly relevant as it regulates the production of pro-inflammatory cytokines and

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ST2/IL-33 Pathway in COPD

Traditionally, Chronic Obstructive Pulmonary Disease (COPD) has been characterized as a Type 1 inflammatory disease primarily mediated by neutrophils

and macrophages. However, recent research has revealed the existence of diverse inflammatory phenotypes within the disease. Consequently, the role of the ST2/IL-33 signaling pathway in COPD has gained increasing attention. Studies have demonstrated that the expression levels of IL-33 and its receptor, ST2, are significantly elevated in both the lung tissue and peripheral blood of COPD patients compared to healthy individuals [**?**]. Unlike in asthma, the inflammatory response triggered by IL-33 in COPD is notably more complex. One of the critical mechanisms identified in COPD pathogenesis is the smoking-induced release of IL-33.

Cigarette smoke not only promotes the production and release of IL-33 by bronchial epithelial and endothelial cells but also upregulates IL-33 expression in peripheral blood mononuclear cells through pathways such as the induction of oxidative stress. In mouse models of chronic cigarette smoke exposure, researchers have observed airway inflammation and tissue destruction alongside a significant increase in the expression of IL-33 and ST2 within the lungs. The administration of anti-IL-33 antibodies can partially inhibit these smoke-induced pulmonary pathological changes, suggesting that IL-33 plays a promotional role in the pathogenesis of smoke-related chronic obstructive pulmonary disease (COPD) [**?**, **?**].

Furthermore, cigarette smoke can alter the distribution characteristics of the ST2 receptor. Specifically, it downregulates ST2 expression on type 2 innate lymphoid cells (ILC2s) while increasing its expression on macrophages and natural killer (NK) cells. This shift may suppress type 2 inflammation and relatively enhance type 1 inflammatory responses. This mechanism is not only one of the reasons why type 1 and type 3 inflammatory phenotypes are more prominent in smokers with COPD, but it may also account for the excessive inflammatory response observed during infection-induced acute exacerbations in these patients.

Studies have found that in patients with stable chronic obstructive pulmonary disease (COPD), those with elevated airway eosinophil (EOS) counts exhibit increased expression of IL-33 and ST2 in both sputum and serum. This suggests that multiple inflammatory phenotypes—specifically types 1, 2, and 3—collectively participate in the pathological process of COPD. Furthermore, research indicates that overall levels of soluble ST2 (sST2) are elevated in the serum and sputum of COPD patients. Although there is no significant difference in sputum sST2 levels between COPD patients with high EOS counts and those with normal counts, sputum sST2 concentrations are negatively correlated with the percentage of EOS. This suggests that the body may increase sST2 production to neutralize excessive IL-33, thereby limiting the progression of eosinophilic inflammation. This process likely represents a compensatory regulatory mechanism during the early stages of COPD.

IL-33 is also closely associated with the acute exacerbation of chronic obstructive pulmonary disease (COPD). Serum concentrations of IL-33 in patients with COPD are positively correlated with the risk of future acute exacerbations.

Furthermore, patients with high expression of IL-33 in lung tissue exhibit a more rapid decline in pulmonary function and present with more severe clinical symptoms.

Infection is the most common trigger for acute exacerbations of COPD, and the infection process itself stimulates airway epithelial cells to release IL-33. Simultaneously, inflammatory mediators, such as bacterial endotoxins, can further promote the expression of IL-33. Consequently, IL-33 acts both as an epithelial damage signal that triggers inflammation and as a driver of Type 1 inflammation under conditions of persistent smoking, thereby increasing the severity of acute exacerbations in COPD.

Furthermore, IL-33 and its receptor ST2 serve as potential biomarkers that hold promise for identifying populations at higher risk of lung function decline during acute exacerbations of chronic obstructive pulmonary disease (COPD). In a cross-sectional analysis of 194 patients with acute exacerbations of COPD conducted by Chinese researchers, serum levels of IL-33 and ST2 were significantly negatively correlated with the percentage of predicted forced expiratory volume in one second (FEV1% pred) (IL-33: $r = -0.561$; ST2: $r = -0.545$; $P < 0.001$) and the FEV1/FVC ratio. Analyzing the regulatory mechanisms of molecules involved in the IL-33_{red} and IL-33_{ox} pathways in COPD patients will facilitate more precise identification of populations likely to benefit from anti-IL-33 therapy.

The ST2/IL-33 Pathway in Asthma

Substantial evidence indicates that IL-33 plays a critical role in the pathogenesis and progression of asthma [**?**, **?**]. The expression levels of IL-33 are closely associated with asthma phenotypes [**?**]. Meta-analyses have shown that peripheral blood IL-33 levels in asthma patients are generally significantly higher than those in healthy control groups; this difference is particularly pronounced in adult asthma, whereas the difference in pediatric asthma groups is less significant [**?**, **?**, **?**]. Furthermore, serum IL-33 levels in patients with moderate-to-heavy asthma are higher than those in patients with mild asthma. Locally within the airways, IL-33 is also significantly elevated in the airway epithelium and bronchoalveolar lavage fluid of asthma patients [**?**, **?**].

Elevated levels of IL-33 can increase the number of Group 2 innate lymphoid cells (ILC2s) in the peripheral blood and lungs of asthma patients by activating downstream immune effects of the ST2 pathway. These ILC2s are more sensitive to IL-33 stimulation and can produce higher amounts of IL-5 and IL-13, thereby promoting the inflammatory response. Additionally, IL-33 stimulates Th2 cells, mast cells, and eosinophil (EOS) chemotaxis and activation, further amplifying airway inflammation.

IL-33 is significant not only in chronic airway inflammation but also in acute exacerbations of asthma. Research indicates that in rhinovirus-induced models of asthma exacerbation, levels of IL-33 and downstream Type 2 inflammatory

cytokines rise rapidly, suggesting that IL-33 plays a vital role in virus-induced asthma attacks. Based on these findings, blocking the ST2/IL-33 pathway is considered a novel therapeutic target for the treatment of asthma.

ST2/IL-33 in Other Chronic Airway Diseases

Beyond chronic obstructive pulmonary disease (COPD) and asthma, the ST2/IL-33 pathway likely plays a significant role in other chronic airway conditions. Bronchiectasis is a chronic inflammatory disease characterized by recurrent airway infections. Research has demonstrated that IL-33 levels are significantly elevated in chronic lung diseases driven by pathogenic infections, such as cystic fibrosis and bronchiectasis. In these contexts, IL-33 can promote the recruitment and activation of neutrophils, leading to persistent purulent inflammation and tissue destruction, which further exacerbates structural damage to the bronchial walls [**?**].

Furthermore, an eosinophilic (EOS) inflammatory endotype exists within bronchiectasis, which is particularly prominent in patients with comorbid asthma. In these cases, IL-33 may promote airway hypersecretion and hyperresponsiveness by activating type 2 innate lymphoid cells (ILC2) and Th2 pathways. Currently, the role of the ST2/IL-33 pathway in bronchiectasis···

Research on the role of Chinese General Practice in the context of Zhang' s syndrome remains insufficient, and its underlying mechanisms of action warrant further investigation.

4 ST2/IL-33

Development of Targeted Therapies

Currently, several drugs targeting the IL-33/ST2 axis have entered clinical trials for chronic airway diseases. These primarily include anti-ST2 monoclonal antibodies and anti-IL-33 monoclonal antibodies, some of which have demonstrated favorable safety and therapeutic potential. The following are several representative drugs currently under investigation.

Monoclonal Antibodies

The types of ST2 monoclonal antibody drugs are summarized in . Astegolimab (AMG282 or RG6149) is an IgG2-type monoclonal antibody targeting the ST2 receptor. It blocks the binding of IL-33 to ST2 at the receptor level, thereby inhibiting downstream signaling pathways. Clinical studies of this drug have been conducted in both asthma and chronic obstructive pulmonary disease (COPD). In a Phase IIa study of patients with severe asthma (where the primary endpoint was the annualized exacerbation rate) [**?**], the Astegolimab group showed a 43% reduction in the adjusted annualized asthma exacerbation rate compared to the placebo group, with efficacy being dose-dependent. Furthermore, patients

with low eosinophil (EOS) counts in this study also experienced a reduction in exacerbations after receiving Astegolimab, suggesting it may provide a new therapeutic option for asthma patients who respond poorly to anti-IL-5 therapy.

The efficacy of Astegolimab in COPD patients has also garnered attention in clinical research. COPD-ST2OP, a Phase Ia clinical study, showed that in patients with moderate-to-severe COPD, Astegolimab treatment reduced the exacerbation rate by 22% compared to the placebo group, though the difference was not statistically significant. However, in the subgroup with EOS $\leq$ 170 cells/μL, the exacerbation rate decreased by 31%, indicating that blocking the ST2/IL-33 pathway may offer greater benefits to the low-EOS population. Two clinical trials of Astegolimab in COPD, ALIENTO (Phase IIb) and ARNASA (Phase III), enrolled patients with current or former smoking history and a frequent exacerbation phenotype. Results showed that the ALIENTO study reached its primary endpoint at 52 weeks, with a 15.4% reduction ($P = 0.049$) in the annualized rate of moderate-to-severe exacerbations in moderate-to-severe COPD patients; for patients with severe COPD, this reduction rate reached 29% [**?**]. The ARNASA study showed only a 14.5% reduction and failed to meet its primary endpoint. Safety remained consistent with previous findings, with overall good tolerance and no increase in serious adverse events [**?**].

The types of IL-33 monoclonal antibody drugs are summarized in . Itepekimab (also known as REGN3500 or SAR440340) is a fully human immunoglobulin G4 (IgG4) monoclonal antibody against IL-33. Several clinical studies have been conducted in asthma and COPD. A Phase IIa study in patients with moderate-to-severe COPD showed that, compared with placebo, Itepekimab reduced the risk of exacerbations in former smokers; however, current smokers did not benefit. Based on this, two Phase III clinical trials, AERIFY-1/2, are currently underway to verify its efficacy in reducing exacerbations in COPD patients who are former smokers.

Another IL-33 antibody, Tozorakimab (MEDI3506), has also received significant attention. A Phase I clinical study demonstrated that Tozorakimab has a good safety and tolerability profile in both healthy individuals and COPD patients. Research has confirmed that Tozorakimab can directly inhibit $IL-33_{red}/ST2$ signaling by preventing the formation of $IL-33_{ox}$, while also attenuating RAGE/EGFR signaling by indirectly inhibiting $IL-33_{ox}$, thereby reducing airway inflammation. Currently, studies evaluating the efficacy of Tozorakimab in COPD patients with a chronic bronchitis phenotype have entered Phase III clinical trials. Following biologics such as anti-immunoglobulin E (IgE), anti-IL-5, anti-interleukin-5 receptor (IL-5R), and anti-interleukin-4 receptor (IL-4R), IL-33 antibodies are expected to become a new direction for the treatment of chronic airway inflammatory diseases.

Summary of ST2 Monoclonal Antibodies - Astegolimab: Moderate-to-severe COPD (FEV1 $\leq$ 70%, smoking history $\geq$ 10 pack-years). Subcutaneous injection, 70 mg. 48-week moderate-to-severe exacerbation rate reduced by 22% ($P > 0.05$); in the EOS $\leq$ 170 cells/μL subgroup, the rate reduced by 31%. Good

safety profile. (NCT: 05037929) - Astegolimab: Moderate-to-severe COPD (FEV1 $\leq$ 70%). Subcutaneous injection, 476 mg, Q2W/Q4W. The Q2W group showed a 15.4% reduction in the 52-week moderate-to-severe exacerbation rate ($P = 0.049$); the Q4W group did not meet the primary endpoint. (2025 ERS Oral, NCT: 05037929) - Astegolimab: Moderate-to-severe COPD (FEV1 $\leq$ 70%). Subcutaneous injection, 476 mg, Q2W/Q4W. The Q2W group showed a 14.5% reduction in the 52-week moderate-to-severe exacerbation rate ($P = 0.0675$); the Q4W group did not meet the primary endpoint. (2025 ERS Oral, NCT: 05595642) - Astegolimab: Severe asthma patients ($\geq$ 18 years). 70/210/490 mg, Q4W. The 490 mg group showed a 43% reduction in annualized asthma exacerbation rate vs. placebo ($P = 0.005$); the low-eosinophil subgroup showed a 54% reduction ($P = 0.002$). - 9MW1911: Phase Ib/IIa, moderate-to-severe COPD. Intravenous injection (dose escalation), Q4W. Primary endpoints: safety and tolerability; Exploratory endpoint: change in FEV1. (NCT: 06175351) - TQC2938: Moderate-to-severe COPD. Subcutaneous injection (dose undisclosed). Evaluating efficacy, safety, tolerability, and pharmacokinetics. (NCT: 06789289) - GSK3772847: Moderate-to-severe asthma with allergic fungal airway disease. Intravenous injection, 10 mg/kg, Q4W. Terminated early due to slow enrollment; completed portion showed a 20% reduction in exhaled nitric oxide ($P = 0.07$).

Note: Q2W = once every 2 weeks, Q4W = once every 4 weeks, Q8W = once every 8 weeks, ST2 = suppression of tumorigenicity 2, FEV1 = forced expiratory volume in one second.

Summary of IL-33 Monoclonal Antibodies - Tozorakimab: Symptomatic COPD patients with a history of exacerbations. - Tozorakimab: Adult patients with uncontrolled asthma despite medium-to-high dose inhaled corticosteroid therapy.

Note: IL-33 = Interleukin-33.

However, the factors influencing the balance between $IL-33_{red}$ and $IL-33_{ox}$ still require further investigation. Currently, biologics targeting Type 2 inflammation have been approved for clinical use, bringing therapeutic hope to patients with chronic airway diseases. Nevertheless, biologics targeting non-Type 2 inflammatory pathways have yielded limited benefits and inconsistent results. This suggests that research into targeted therapies for chronic airway diseases based on non-Type 2 inflammatory mechanisms remains of significant importance.

5 总结与展望

In summary, the ST2/IL-33 pathway plays a critical role in the pathogenesis and progression of chronic inflammatory airway diseases, and its potential as a therapeutic target remains highly promising. Current clinical findings suggest that biologics targeting ST2 and IL-33 possess significant value in alleviating airway inflammation, improving lung function, and reducing the frequency of

acute exacerbations. However, much of the existing evidence is derived from studies with relatively small sample sizes and limited follow-up periods, focusing primarily on the Type 2 (T2) inflammatory phenotype; thus, these conclusions require further validation. Notably, the majority of patients with chronic obstructive pulmonary disease (COPD) exhibit non-T2 inflammatory phenotypes, for whom effective anti-inflammatory treatments are currently lacking. If the efficacy and safety of anti-ST2/IL-33 therapies in reducing COPD exacerbations are confirmed in the future, they may serve as a vital supplement to existing anti-inflammatory regimens, offering a new therapeutic option for patients characterized by low eosinophil (EOS) inflammation. As more clinical trial results are published, the clinical utility and specific target populations for these biological therapies will be further clarified. Future research should prioritize large-scale, randomized controlled trials with long-term follow-up, utilizing biomarker stratification to identify the populations most likely to benefit. Additionally, it is essential to monitor the safety of long-term administration and systematically evaluate the therapeutic potential of anti-ST2/IL-33 treatments in COPD patients with non-T2 inflammation.

Author Contributions: Wanjin Guo was responsible for the collection and organization of research data, and the drafting of the manuscript.

Primary Endpoints: In the overall population, the acute exacerbation rate decreased by 19% ($P = 0.13$), and FEV_1 improved by 60 ml ($P = 0.024$). In the subgroup (former smokers), the acute exacerbation rate decreased by 42% ($P = 0.006$), and FEV_1 improved by 90 ml ($P = 0.0076$).

Safety: The incidence of adverse events was comparable to that of the placebo group.

PMID: 34302758 NCT: 03546907

Primary Endpoint: Following treatment, FEV1 increased by 67 ml ($P = 0.044$); the hazard ratio (HR) for composite COPD exacerbation events was 0.79 ($P = 0.186$). In the subgroup analysis (patients with ≥ 2 prior exacerbations):

Post-treatment FEV1 increased by 124 ml ($P = 0.02$); the HR for composite COPD exacerbation events was 0.61 ($P = 0.03$). Regarding safety, the incidence of treatment-emergent adverse events was comparable to that of the placebo group.

PMID: 40154559; NCT: 04631016. Yahong Chen was responsible for the conceptualization and design of the study, manuscript revision, quality control, and final review, and assumes overall responsibility for the article.

The authors declare no conflicts of interest.

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Summary of Clinical Trials for IL-33 Targeted Therapies

Target	Agent	Patient Population	Dosage and Administration	Clinical Outcomes and Study Objectives	Identifiers
IL-33	Itepekimab	Patients with moderate-to-severe COPD	300 mg subcutaneous (SC) injection, every 2 weeks (Q2W)	Evaluation of efficacy regarding the annualized rate of acute exacerbations in former smokers with moderate-to-severe COPD.	NCT06208306

Target	Agent	Patient Population	Dosage and Administration	Clinical Outcomes and Study Objectives	Identifiers
IL-33	Itepekimab	Adult patients with moderate asthma	300 mg SC injection, Q2W	Monotherapy reduced the risk of loss of asthma control by 46%; significant improvement in FEV_1 and reduction in blood eosinophils; favorable safety profile comparable to placebo.	PMID: 34706171, NCT03387852
IL-33	Tozorakimab	Patients with moderate-to-severe COPD	600 mg SC injection Q4W; or 300 mg SC injection Q4W/Q8W	Primary endpoint: To evaluate whether Tozorakimab can reduce the incidence of COPD exacerbations.	NCT05166889, NCT05158387
IL-33	Tozorakimab	(Not specified)	SC injection (dosage undisclosed), Q4W	Exploratory study of efficacy and safety.	NCT06932263

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Note: Figure translations are in progress. See original paper for figures.