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Biological mechanisms and therapeutic prospects of interleukin-33 in pathogenesis and treatment of allergic disease

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Abstract

Allergic diseases significantly impact the quality of life of people around the world. Cytokines play a crucial role in regulating the immune system. Due to their importance in pro-inflammatory mechanisms, cytokines are used to understand pathogenesis and serve as biomarkers in many diseases. One such cytokine is interleukin-33, a member of the IL-1 family, including IL- 1α, IL-1β, and IL-18. The IL-33 receptor is a heterodimer of IL-1 receptor-like 1 and IL-1 receptor accessory protein. IL-33 plays a critical role in regulating innate and adaptive immune responses. The primary targets of IL-33 in vivo are tissue-resident immune cells, including mast cells, group 2 innate lymphoid cells, regulatory T cells, T helper 2 cells, eosinophils, basophils, dendritic cells, Th1 cells, CD8+T cells, NK cells, iNKT cells, B cells, neutrophils, and macrophages. However, IL-33 appears to act as an alarm signal that is promptly released by producing cells under cellular damage or stress conditions. IL-33 regulates signaling and various biological functions, including induction of pro-inflammatory cytokines, regulation of cell proliferation, and involvement in tissue remodeling. IL-33 is fundamental in immune-related diseases and plays a critical role in the control of inflammation. Recently, IL-33 has been shown to significantly impact allergic diseases, primarily by inducing Th2 immune responses. IL-33 is a key regulator of mast cell function and a promising therapeutic target for treating allergic diseases. This review provides an overview of the current understanding of the role of IL-33 in allergy pathogenesis and potential clinical approaches.

Keywords Allergic diseases, Interleukin-33, IL-33 receptor, Immune system, MyD88

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Introduction

Allergic disorders are widespread in developed countries and have an essential socio-economic impact [1]. Allergic rhinitis (AR), asthma, and atopic dermatitis (AD) are examples of chronic allergic diseases that persist throughout life [2, 3]. Recent clinical and experimental studies have helped to understand the underlying mechanisms and to develop targeted therapies. Ultimately, allergen exposure triggers mast cell stimulation and degranulation, eosinophil employment and penetration, T helper (Th2) cell activation and differentiation, and antigen-specific immunoglobulin E (IgE) creation. There is now a bias towards a type 2 cytokine response, categorized by excessive manufacture of IL-4, IL-5, and IL-13 cytokines in the upper and lower airways [4, 5]. IL-4 initiates and encourages Th2 replies and also triggers these effector cells, whereas IL-13 donates to the advancement of allergic answers by stimulating mucus creation and eosinophilic penetration by making eotaxin [6, 7]. Upon FcεRI binding, basophils and mast cells manufacture numerous chemical intermediaries, including histamine and lipid metabolites [8]. The airway epithelium is the primary protection contour, defending the airway from pathogens and potential threats [9, 10]. Nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) and Toll-like receptors (TLRs) are taking place in the outside of epithelial cells and enable them to identify structurally preserved pathogen-associated molecular patterns (PAMPs). Upon encountering these external danger signs, epithelial cells initiate immunity replies [11, 12]. The primary epithelial response to PAMP-TLR/NLR communication is the creation of numerous cytokines that can stimulate specific immune responses, bias the type 2 immune response, and reduce inflammation [12, 13]. Cytokines perform a vital role in the instruction of adaptive and innate systems and have been used to comprehend pathogenesis and as biomarkers in different illnesses, including allergic disorders, autoimmune disorders, and cancer [14, 15]. Recent studies suggest that IL-33 plays a significant role in allergic disorders [16, 17]. This review focuses on the structure, biology, and currently reported role of the IL-33 cytokine and its potential clinical implications in allergic inflammatory disorders.

IL-33: sources, structure, functions

IL-33 (IL-1F11) was first recognized as high endothelial venule nuclear protein (NF-HEV) in endothelial cells of human lymphoid tissues [18, 19]. In 2005, IL-33 was reclassified as a participant in the IL-1 superfamily [19]. IL-33 has a double job as an extracellular cytokine of the IL-1 superfamily (pro-inflammatory) and intracellularly as a nuclear factor regulating gene appearance [19, 20]. Intracellularly, IL-33 has transcriptional repressive properties, while nuclear IL-33 attenuates pro-inflammatory signaling via appropriating nuclear NF-kB, reducing NF-kB-driven gene expression [21]. Conversely, IL-33 encourages inflammation in endothelial cells by upregulating the p65 subunit of the NF-kB compound in the nucleus. In the excite of cells, IL-33 functions as a pro-inflammatory cytokine, and its biological properties are initiated by connecting to their receptor [22]. The IL-33 gene is situated on chromosome 9 at 9p24.1 [23]. The human IL-33 gene contains eight exons and produces a 270 amino acid protein (30 kDa) with two evolutionarily conserved domains [24, 25]. The cytokine area is structured like IL-1 and has folding possessions analogous to IL-1α, IL-1β, and IL-18 [26, 27]. Under normal conditions, complete IL-33 is continuously present in numerous cell kinds throughout human tissues and is situated in their nuclei [19, 23].

The main foundations of activity in humans include human endothelial cells, epithelial cells in barrier tissues, and reticular fibroblast cells in lymphoid tissues. The nervous system comprises glial cells, neurons and astrocytes, smooth muscle cells, osteoblasts, adipocytes, and various immune cells such as macrophages, mast cells, monocytes, and dendritic cells (DCs). This suggests a significant character in defending the body against damage and contamination in standard and recurrently irritated tissues and tumor tissue [23, 28]. In the inactive situation, IL-33 is located in the nucleus and bound to chromatin via a chromatin-connecting domain, a critical component of cellular homeostasis that acts as a transcriptional repressor [29, 30]. IL-33 shares similarities with alarmins or damage-associated molecular patterns (DAMPs), pro-inflammatory factors released through injured cells [31, 32]. Alarmins perform as intercellular indications via binding to chemotactic and pattern recognition receptors (PRRs) to enhance immunity cell responses in host protection [18]. IL-33 has multiple effects on the immune response. It is a component of the host's immunity to pathogens or immune-related inflammatory disorders. The innate immune system can produce IL-33 to respond to infectious agents and irritants [33, 34]. PAMP-generated IL-33 is vital in encouraging local airway inflammation related to Th2-dependent antigens and augmenting innate immunity [35, 36]. It can straightly cause airway inflammation and is frequently not required to initiate and distinguish antigen-specific Th2 cells [37, 38]. The IL-33 receptor (IL-33R) is a heterodimer containing a flexible ST2 (T1, IL-1RL1, IL-1R4) and a familiar, generally stated coreceptor known as IL-1 receptor accessory protein (IL-1RAcP) (IL-1R3) [39, 40]. ST2, a toll-like receptor/interleukin-1 receptor (TIR) superfamily participant, constitutes the IL-33 receptor [41, 42].

ST2 is the sole receptor for IL-33, although it has four splice isoforms from a single transcript according to

promoter complicated [33, 43]. The two main products of ST2 genes, which result from substitute splicing, are transmembrane shape ST2 (ST2 or ST2L) and soluble shape ST2 (sST2) [44, 45]. ST2L is a functional element of IL-33R that is selectively and persistently stated on a diversity of immune cells such as eosinophils, mast cells, ILC2, basophils, DCs, NKs, Th2 cells, macrophages, Tregs, B cells, airway smooth muscle cells, also on endothelial cells, epithelial cells and fibroblasts [23, 46, 47]. Conversely, sST2 is considered to be an IL-33 decoy receptor [20, 48]. The heterodimer formed by the binding of IL-33, ST2, and IL-1RAP results in dimerization of the TIR domain, which stimulates downstream signaling through the heterodimeric complex. IARK-1, IARK-4, and mitogen-activated protein kinase (MAPK) kinases activate the TNF receptor-associated factor 6 (TRAF6) signaling pathway, which in turn activates activator protein 1 (AP-1) through c-Jun N-terminal kinases (JNKs). TRAF6 also activates the inhibitor of nuclear factor-κB (NF-κB) kinase (IKK) complex, releasing active NF-κB from the complex and activating nuclear transcription signals necessary for creating other inflammatory cytokines. Upon receptor stimulation, Jun kinase (JNK) and extracellular signal-regulated kinase (ERK) 1/2 promote IRF1 activation, resulting in the inhibition of Foxp3 and GATA3 expression [49], thereby inducing inflammatory cytokine production [50, 51](Fig. 1).

Altering the subcellular localization of IL-33 may significantly impact immune homeostasis, suggesting that nuclear sequestration of IL-33 may limit its pro-inflammatory potential [52]. IL-33 may also perform as a link among non-specific and specific immune cells, promoting Th2-mediated inflammation [53, 54]. In reply to IL-33, ILC2 can multiply and secrete IL-5 and IL-13 in mouse models [55, 56]. Also, IL-33 can activate further non-specific immune cells such as basophils, macrophages, mast cells, and eosinophils, leading to a more significant contribution to airway inflammation [55, 56]. In addition, IL-33 can affect specific immunity by stimulating ILC2 and DCs and adaptive immune cells that express the ST2 receptor. Therefore, IL-33 induces DC to make a variety of cytokines and chemokines [57, 58].

Exposure to IL-33 can induce DCs to support the extension and specialization of CD4 + T cells by promoting the manufacture of IL-5 and IL-13 [59, 60]. IL-33 plays a critical character in the immune response associated with Th2 [63, 64], with ST2-expressing Th2 cell's ability to generate IL-5 and IL-13 in response to IL-33 [61]. When combined with an antigen, IL-33 can polarize human naive CD4 + T cells towards IL-5 manufacture. In addition, differentiation of IL-5 + T cells was induced by the classical IL-33 ways, including MyD88, MAPKs, and NF-κB only in the attendance of the IL-1R addition protein [62, 63]. IL-33 has been rolled into numerous non-allergic disorders such as infectious diseases, musculoskeletal diseases, inflammatory bowel disease, cancer, obesity, and diabetes [33, 51]. IL-33 strongly stimulates the manufacture of Th2 cytokines and thus

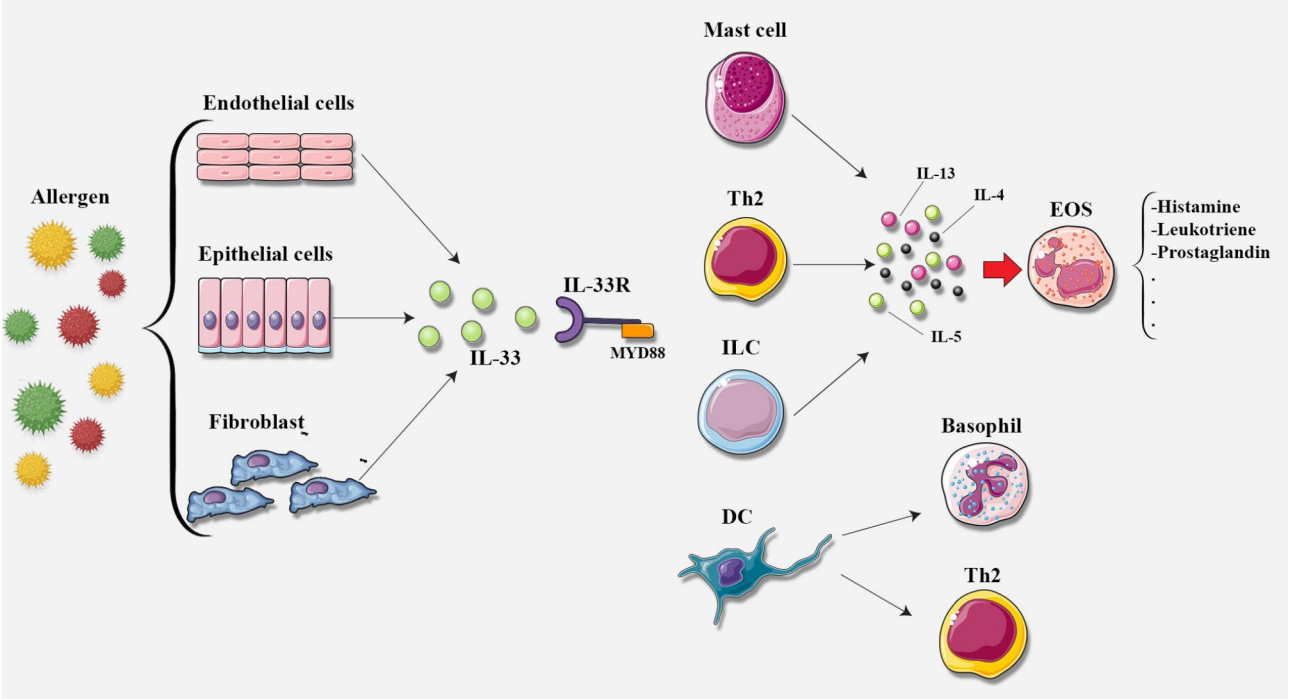

Fig. 1 IL-33 impact in different cells. IL-33 is primarily expressed by different types of structural cells. IL-33 through linking to ST2 + immune cells cause different effect on cells, such as Induce production of various cytokines and chemokines by mast cells or Induces eosinophilia. transmembrane shape (ST2)

exacerbates the progression of Th2-associated diseases such as asthma and allergic rhinitis [64]. In addition, IL-33 has been revealed to play an essential character in immune regulatory responses [65, 66]. The genes programming IL-33 and ST2/IL1RL1 have been recognized as significant vulnerability loci for human asthma in numerous genome-wide association educations [67, 68]. Manufacture of pro-inflammatory cytokines and activation of Th2-type immune cells can exacerbate allergic diseases [39, 69]. Several studies have shown that IL-33 is a potent activator of mast cells and basophils, inducing cell migration, maturation, adhesion, and survival while producing several pro-inflammatory cytokines [70, 71]. Examination of patient samples and mouse models supports the critical character of the IL-33/ILC2 axis in allergic inflammation in numerous tissues and disorders [69, 72]. The essential function of endogenous IL-33 in allergic inflammation was primarily established in IL-33-deficient mice [73]. In addition, IL-33 expression is increased in bronchial epithelial cells of samples with asthma and epidermal keratinocytes of patients with atopic dermatitis [74, 75]. Increased expression of IL-33 and ST2 has been reported in lung tissue from both asthmatic and allergic airways, with ST2 playing a critical character in antigen-induced airway inflammation [76].

IL-33 in different allergic diseases

Asthma

The incidence of allergic asthma has amplified significantly in industrialized countries over the last century (ranging from 5.2 to 16.8%) [77]. Asthma is highly heterogeneous, and all endotypes are typically characterized via airway hyperresponsiveness (AHR), tissue renovation, and extreme Th2 inflammation [78, 79]. Asthma is now understood to be a multifaceted disease with different entities and some variation in pathogenesis [45, 79]. Previous research has revealed that a principal Th2 lymphocyte answer may contribute to the development of asthma symptoms, primarily through the secretion of cytokines such as IL-4, IL-5, and IL-13 [45, 68].

In calculation, nonspecific immune cells such as mast cells, basophils, neutrophils, EOSs, DC, and ILC2s have been occupied in the beginning or development of the disorders [80, 81]. Recent studies have shown that the motivation of cells of the nonspecific immune system triggers the stimulation of NF-kB, which results in the creation of pro-Th2 cytokines such as IL-33 [59, 82]. Airway epithelial cells and APCs enhance allergic airway inflammation and thus the pathophysiological symbols of asthma through discharging cytokines such as IL-1β and IL-6. IL-33 derived from Epithelium encourages Th2 and ILC2 distinction, which straight allergic immune responses via the release of IL-4, IL-5, and IL-13 [6, 63, 82].

IL-33, an important allergy cytokine, participates in nonspecific and specific immunity in asthmatic immune stimulation [79, 83]. This cytokine directly stimulates macrophages, osteoclasts, Th2 cells, mast cells, DCs, and other subsets that express T1/ST2, the IL-33 receptor [84]. Downstream IL-33 provokes high levels of IL-5 and IL-13 manufactured by IL-33-irritated ILC2s, resulting in a strong pro-allergic response [85]. A genetic polymorphism in IL-33 or ST2 has been recognized in patients with asthma [86]. Two single nucleotide polymorphisms (SNPs) in ST2 - rs1420101 and rs11685480 - have been suggested to control plasma sST2 levels in airway epithelial cells and the distal lung parenchyma, correspondingly, subsequent in an amplified risk of classical airway inflammation in asthmatics [87]. Significant correlations were found between the plasma parts of the IL-33/ST2 axis in patients with allergic rhinitis and those with associated allergic asthma [88]. Remarkably, IL-33 appearance is upregulated in the bronchial mucosa of asthmatic patients. This is associated with disease harshness [89]. In a mouse model, airway inflammation and AHR were decreased by knocking out ILC2s or blocking IL-33-ST2 signaling [90]. in asthma, When basophils stimulated by IL-33, basophils express ST2 and create Th2 cytokines [91]. Another study showed that in vitro motivation with IL-33 amplified ST2L mRNA expression in eosinophils, leading to improved eosinophil adhesiveness and CD11b expression, also feasibility, which was reduced by a deactivating antibody to ST2 [44](Fig. 2).

Given the significance of IL-33 signaling in allergic asthma, numerous biologics have been advanced and tried as potential treatments. Inhibition of the AHR reduced IL-5 levels in BALF, and reduced eosinophil numbers were observed in an OVA challenge mouse model preserved with anti-IL-33 or sST2 [92]. Monoclonal antibodies such as RG6149 [93], and CNTO7160 [94], either against ST2 or IL-33, such as ANB020 [93], REGN3500 [93], and MEDI3506, have undergone or completed clinical trials. A high-affinity monoclonal antibody against dokimab (LY3375880) is in preclinical development to inhibit IL-33-dependent inflammatory signaling [95].

Allergic rhinitis

Allergic rhinitis (AR) is a public allergic inflammatory disease in 10–40% of the population [96, 97]. AR is an IgE-mediated type 1 allergic disorder of the nasal mucosa triggered via exposure to nasal allergens. Nasal responses in AR consist of IgE-related early-stage responses and Th2 cytokine-related late-stage responses [98]. Due to early-stage responses, medical signs, including sneezing and rhinorrhea, happen within 5–30 min. Late-stage responses occur 6–24 h after allergen exposure, and Eosinophilic accumulation in the nasal mucosa is the

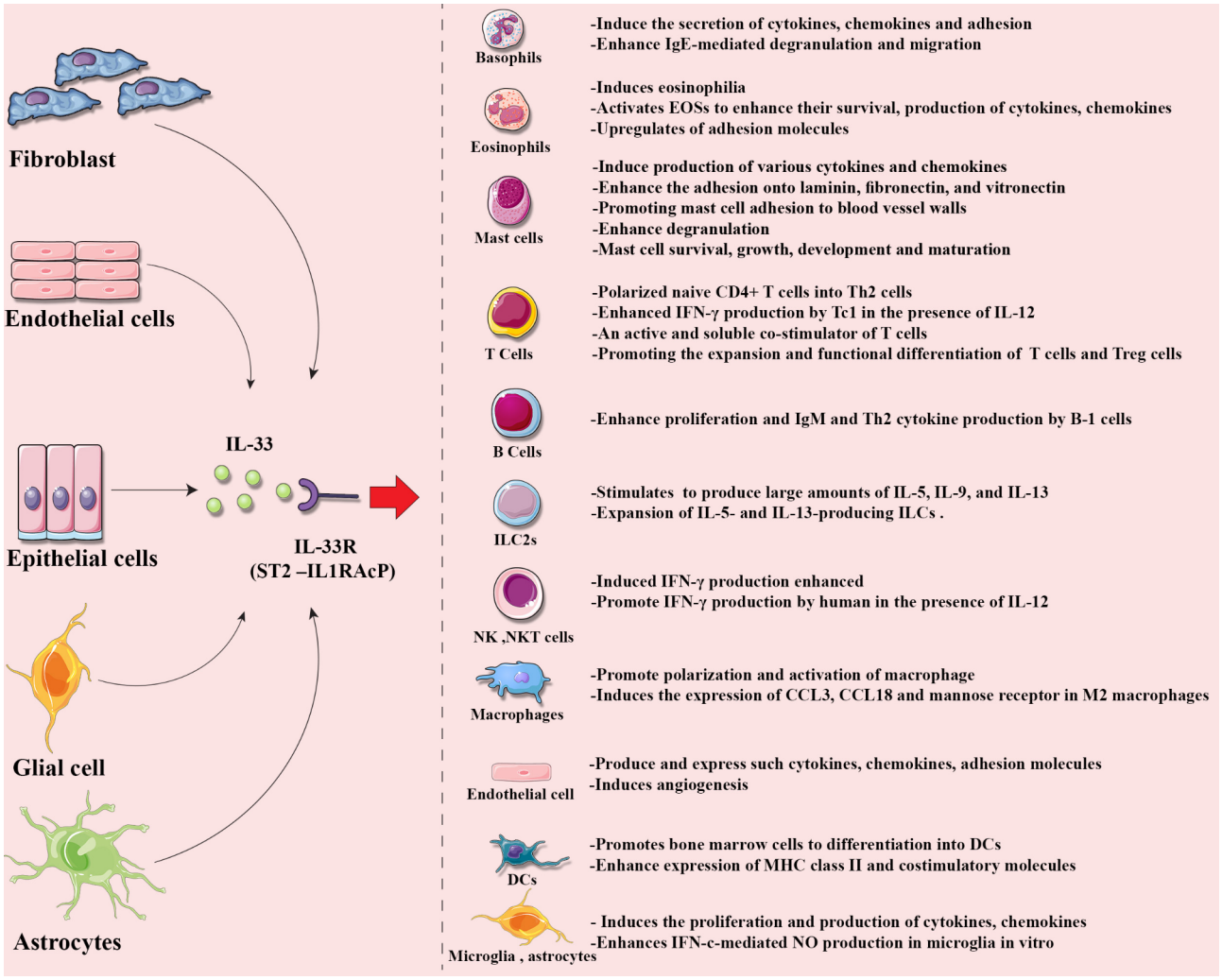

Fig. 2 IL-33 in allergic diseases pathology. IL-33 produce by different cell such as epithelial cells and bind to its receptor, then activates various ST2 + immune cell types implicated in the allergic responses for example, Th2, ILC, Mast cell. These cells produce cytokine such as IL-4, IL-5 and IL-13, that impact on EOS for mediator releases. Innate lymphoid cells (ILC2s); Eosinophil (EOS)

primary pathological change associated with the late-stage response [98, 99]. A previous study established an essential rise in serum IL-33 levels in Japanese patients suffering from seasonal AR and also found a significant correlation between vulnerability to AR and polymorphisms in the IL-33 gene [100]. Notably, the amount of IL-33-responsive ILCs was also found to be amplified in nasal polyps from patients with rhinosinusitis [101]. After exposure to ragweed, mice show exacerbated symptoms of AR, activation of nasal Th2, increased serum levels of ragweed-specific IgE, and penetration of the nasal mucosa by eosinophils and basophils, which are not detected in IL-33- and ST2-deficient mice [102]. IL-33 protein is consistently stated in the nucleus of nasal epithelial cells and is rapidly released into the nasal fluid in response to ragweed pollen exposure [103]. Collected with the involvement of IL-33 in activating eosinophils, basophils, and mast cells to manufacture allergic inflammatory mediators, this mechanism may result in the persistent attacks and permanent mucosal hypertrophy seen in AR [104, 105]. However, during the pollen season, IL-33 mRNA appearance is significantly upregulated in nasal epithelial cells of AR patients, and this increased extracellular statement is related to decreased IL-33 protein appearance in inflamed nasal epithelial cells [103]. Furthermore, the IL-33 receptor ST2 is significantly stated in the nasal mucosa of AR patients, proposing that IL-33/ST2 may be critical in developing allergic nasal disease [52, 106]. In addition, the IL-33-ST2 encouraged the Th2 response to cooperate with the Th17 immune response, demonstrating numerous T cell responses in developing allergic nasal disease [103, 107]. Targeting IL-33 and its receptor represents a new therapeutic method for handling allergic rhinitis [108]. Anti-IL-33 treatment decreases nasal scratching, improves skin stripping, and decreases eosinophilic infiltration and

serum total and OVA-specific IgE levels [109, 110] (Table 1).

Food allergy (FA)

A food allergy is an abnormal immune response to an antigen ingested through food [111]. The medical features of FA are varied and random, influenced by many factors—symptoms of FA vary from oral allergy syndrome to life-threatening anaphylaxis [111, 112]. The prevalence of food allergy is growing worldwide, affecting both industrialized and developing countries, with about 8% of children and 11% of adults in the United States affected [113]. Symptoms of food allergy can differ from somebody to somebody, with some experiencing mild abdominal discomfort and others experiencing severe, dangerous anaphylaxis [114, 115]. Consequently, food allergy has public health and economic implications [116]. In the sensitivity stages, food allergens first come into contact with protective surfaces on the skin, gastrointestinal tract, or respiratory tract. Skin barrier surfaces with defects and a decrease in their honesty increase the permeability of allergens, producing proinflammatory cytokines derived from epithelial tissue, particularly IL-33 and IL-25 [46, 117]. Together, these cytokines begin an allergic inflammatory process that leads to allergic responses in individuals with food allergies [8, 115]. Cytokines activate ILC2s, induce distinction of naive CD4 + T cells into Th2 cells, create proinflammatory cytokines such as IL-4, IL-5, IL-9, and IL-13, induce isotype switching from IgG to IgE in B cells, trigger linking of IgE to FcεRI receptors on mast cells or basophils followed by degranulation, and result in the liberate of histamine and other proinflammatory allergic mediators [8, 81, 111, 115]. Animal surveys found that epithelial cell-derived IL-33 is vital in advancing food allergy [118]. Also, another study showed that skin exposure to peanut induced cytokine appearance in T cells and dendritic cells that was reliant on IL-33-ST2 signaling, signifying that IL-33 may perform a role in mediating food allergy through skin exposure early in life [118, 119]. At the sensitization stage, IL-33 induced intestinal anaphylaxis through cross-linking of IgE and degranulation of mast cells [118, 120]. In calculation to mast cells, IL-33 can stimulate ILCs and overwhelm the Treg role, which promotes FA immunity [121]. The study proposes that IL-33 plays a significant role in the association between barrier defects and FA [120, 121]. Recently, a study reported that injection of an mAb against the IL-33 receptor effectively prevents the advancement of FA [122]. Thus, IL-33 and its receptor ST2 may serve as potential therapeutic goals to attenuate the mast cell-associated pathogenesis of FA [119]. Some suggest that IL-33 inhibitors may be of healing worth in FA patients (Table 2) [123].

Atopic dermatitis

Atopic dermatitis (AD) is a primary inflammatory skin condition branded by long-lasting or recurrent pruritus and may be associated with other atopic situations such as asthma and food allergy [124]. AD has a higher occurrence in children but can also disturb adults [125]. It is more likely to occur in people with allergies [126, 127]. AD is associated with over-reactivity of the skin, disruption of the epidermal barrier role, dry skin, and increased vulnerability to skin contaminations. The cause of inflammation has been ascribed to the stimulation of various immune cells. Mast cells are critical in initiating the disease, while Tregs performance is essential in controlling the inflammatory response [128]. AD is characterized by Th2 cytokines in the acute phase and raised levels of Th1 cytokines in the lasting phase [126, 128]. A dysfunction in the nonspecific and specific immune response could initiate skin injury, provoking an elevated Th2 response that exacerbates and progresses AD [129]. However, CD4 + T lymphocytes respond to IL-33 and stimulate interferon-gamma production. This promotes chronic skin inflammation [130]. In addition, IL-33, as tissue-derived cytokines, has recently been implicated in atopic dermatitis [131, 132]. Based on current explanations, IL-33 is identified as a prominent threat signal and pathogenic driving force in atopic dermatitis [131].

Imai et al. established that a transgenic mouse expressing IL-33 impulsively advances AD by stimulating ILC2s and basophils [132]. Additionally, IL-33 was found to be a significant regulator of eosinophil role [132]. Shimizu et al. investigated the correlation between AD and a polymorphism of the ST2 gene and proposed that the IL-33-ST2 axis plays a crucial character in AD [133]. Other studies showed the upregulation of IL-33 in the epidermis and the penetration of ST2-positive cells in the dermis of skin lesions in AD patients [75, 134]. An SNP located in the distal promoter of the ST2 gene on chromosome 2q12 shows a significant association with AD, and there is a robust association between tall soluble ST2 and total IgE stages in the sera of AD patients [135].

Still, mRNA levels of IL-33 and ST2 were significantly higher in AD patients' affected skin than in non-affected skin and healthy people [75]. Various treatments have been advanced to heal AD, including topical steroids, calcineurin inhibitors, and immunosuppressive agents [133]. Blocking IL-33/ST2 signaling may be a potential healing goal for alleviating the pruritus and skin inflammation of dermatitis related to IL-33/ST2 signaling [75, 136].

Allergic conjunctivitis

Th2 responses on the ocular surface are responsible for causing inflammation to various allergens, which can lead to tissue damage and infection, ultimately resulting in the

Table 1 Animal model and in vitro surveys of IL-33 allergic diseases

Model of study	Result	Ref
OVA-sensitized mice received ovalbumin solution and were fed with capsaicin	-Not reduce production of IgE and weight loss -Reduced macrophage infiltration and IL-33 in the proximal jejunum -Reduced hepatic triglycerides and intestinal hydroperoxides	[150]
intra-lymphatic injection of OVA-flagellin (FlaB) mixture in the murine AR	-Reduce the production of IL-33 -Ameliorate allergic inflammation	[151]
ST2 and IL-33 in OVA-induced airway inflammation in mice	-Increased of sST2 and IL-33 are in the serum -Increased of sST2 and IL-33 are in the lung -Expressed of IL-33 in alveolar macrophages, CD11c + cells, and epithelial cells in the lungs	[140, 152]
transgenic overexpression or fed of IL-33 In mouse models	-Generates airway eosinophilia -Upregulates Th2 cytokine expression -Elevates serum IgE, AHR, and mucus secretion	[69, 153]
preventative use of an mIL-33 during OVA-induced asthma	-Modulated pulmonary inflammation -Decrease Th2 cytokine production	[154]
anti-ST2 antibody (clone E310), anti- IL-33 Ab, or soluble ST2-Fc fusion protein investigate role of the ST2/ IL-33 in asthma models	- Inhibits airway inflammation - Inhibits the Th2-associated responses - Reduced IgE level in serum - Reduced the numbers of eosinophils in BALF	[155, 156]
role of anti-IL-33 and sST2 in the blockade of airway inflammation in a murine model of asthma	- Reducing the total cell count - Serve as therapeutic agents for allergic asthma	[44]
experimental murine of severe airway inflammation and administered IL-33 neutralizing Ab	- Improved both airway remodeling - Improved inflammation improved, - IL-33 blockade decreases asthmatic exacerbations	[157]
Anti-mouse IL-33 antibody treatment in AD	- Improvement of AD symptoms - Reduction of cells (EOS and mast cells) - Reduction of serum IgE levels	[136, 158]
Anti–IL-33 treatments in a mouse model of allergic rhinitis	-Reduced nose-scratching events -Ameliorated skin denudation -Decreased eosinophilic infiltration -Decreased levels of serum total and IgE	[109]
Topical tacrolimus treatment of mouse AD	-Decreases expression of IL-33 -Decrease expression of ST2 in	[75]
IL-33 in a model of acute allergic airway inflammation (IL-33 KO mice)	-Demonstrate that IL-33 role in production of Th2 cytokines -Demonstrate EOS infiltrates to lung -Demonstrate histopathologic changes in the lung	[64]
mechanisms of IL-2 production from MCs in chronic allergic dermatitis in response to IL-33	- Further IL-2 production by binding FcεRI -IL-2 led to considerable expansion of Tregs - Increased numbers of IL-2 expressing MCs	[159]
IL-33 and ST2 receptor in allergic airway inflammation mice	-Elevated levels of soluble ST2 in the serum	[156, 160]
Mice treated with anti-IL-33-neutralizing Ab in OVA-induced AR	-Reduced eosinophilia during -Suggesting the role of IL-33 in the disease development	[109]

Table 1 (continued)

Model of study	Result	Ref
mAbs to IL-25, IL-33, and TSLP cytokines in food allergy mice	- Strongly inhibited FA development - FA suppression required treatment with a cocktail of all three mAbs - Treatment 3-mAb cocktail during induced FA tolerance.	[122]
IL-33 used in wildtype mice after exposure to Alternaria alternata allergen	- Increase airway eosinophilia - Increase bone marrow eosinophilopoies - Activation of ILC2 and their production of IL-5	[161, 162]
IL-33 in ova induced asthma model in mice	-Induces eosinophil-mediated massive airway inflammation of the lung tissue -Elevated local concentrations of IL-5, IL-13 -Induced goblet cell hyperplasia	[163]
Repeated systemic administration of recombinant IL-33	-Induces eosinophilia splenomegaly -Production of Th2 cytokines -Increased IgE serum levels	[154, 155]

advancement and aggravation of atopic keratoconjunctivitis [137]. IL-33 protein has been reported to be highly stated in human vascular endothelial cells and conjunctival epithelium in giant papillae gained from patients with atopic keratoconjunctivitis [138]. After administration of ragweed pollen, IL-33 is released, leading to penetration of eosinophils and CD4 + T cells with stimulated ST2 on the surface of the conjunctival stroma [139]. These activations are significantly reduced in IL-33 knockout mice [140].

Chronic spontaneous urticaria (CSU) and anaphylaxis

CSU is a common skin condition considered by the presence of itchy wheals that last less than 24 h and persist for at least six weeks and often for several decades [141]. CSU is an autoimmune disorder with hive formation instruments reliant on IgG and IgE [142]. Despite a favorable prognosis, CSU is a debilitating disease as its primary symptom, pruritus, can cause sleep trouble and harmfully affect quality of life and work performance [143]. There are signs of a role for IL-33 in the pathogenesis of CSU [144]. In particular, studies of skin biopsies from patients with CSU have shown significantly elevated levels of IL-33 in contrast to healthy controls, proposing that the appearance of Th2-promoting cytokines may play an essential role in healing [145]. Another study proposes that IL-33 signaling may be a critical orientation of histaminergic itch in mast cell-associated pruritic situations such as CSU [146]. This suggests that IL-33 plays a character in causing and expressing CSU.

IL-33 levels in the serum of atopic patients increase significantly during anaphylaxis [147, 148], suggesting that IL-33 may play a character in advancing anaphylaxis. Similarly, IL-33 can induce mast cell degranulation via ST2, leading to systemic and passive cutaneous anaphylaxis in IgE-sensitized mice, even in the nonappearance of a specific IgE antigen [147, 149]. This suggests that the IL-33-ST2 pathway plays a vital role in inflammation during the later stages of passive cutaneous anaphylaxis in mice.

Concluding remark

IL-33 is a tissue-derived nuclear cytokine from the IL-1 family, expressed in endothelial cells, epithelial cells, and fibroblast-like cells under both homeostasis and inflammation. It has been identified as an alarmin cytokine from the IL-1 family; IL-33 has appeared as a central modulator of tissue Tregs and ILC2s, with significant characteristics in type-2, type-1, and regulatory immune responses. Current studies suggest that IL-33 promotes the manufacture of substantial quantities of IL-5 and IL-13 by ILC2s, potentially contributing to the initiation of allergic inflammation. The intense activity of IL-33 on ILC2s, and the pivotal role of these cells in the early

Table 2 Human studies of IL-33 in allergic diseases

Model of study	Result	Ref
placebo-controlled phase 2a study, for Etokimab(an anti–IL-33 biologic) to desensitize peanut-allergic adults(ClinicalTrials.gov NCT02920021)	- Reduce atopy-related adverse events - Reduced IL-4, IL-5, IL-9, IL-13, ST2 levels - Reduced peanut-specific IgE	[123]
Role of IL-33 and ST2R in human asthma patients	- Increased serum levels of soluble ST2	[17, 164]
Evaluate serum IL-33 in patients with asthma.	-Higher level of IL-33 in patients with asthma -Higher IL-33 in the allergic asthma -Higher serum IL-33 level in eosinophilic asthma -No difference in serum IL-33 level between different asthma severity groups	[165]
IL-33 polymorphisms with asthma (rs4742170 and rs7037276, and rs1342326)	- rs4742170 and rs7037276 are associated with intermediate-onset wheeze - rs1342326 is associated with persistent wheeze - rs928413 and rs1342326 are relevant to asthma	[68, 166]
SNP in IL-33, rs1888909, rs1041973 and rs873022 are associated with	-Decreased production of sST2 in atopic -Increases asthma risk -Associated with post-bronchiolitis asthma	[167, 168]
IL-33 in HDM induced AR	-Stimulated Th2 cells to produce IL-5 -Responsible for induction of local inflammation -IL-33 is crucial in the pathogenesis of chronic rhinosinusitis, nasal polyps	[106, 169]
IL-33 in asthma	-Greater IL-33 mRNA expression in epithelial cells of airway biopsies -High levels of sST2 and IL-33 in the plasma and sputum	[72, 77]
Etokimab, a humanized immunoglobulin subtype G1/κ monoclonal Ab	-Inhibits IL-33 activity -Inhibition of IL-33/IL-12–induced IFN-γ release in whole blood	[170]
24 Japanese cedar (JC) pollinosis patients and 14 HDM-sensitized patients with AR	-IL-33 protein level is increased in sinus mucosa -significant correlation with the total nasal symptom score	[171]

stages of allergic airway inflammation, may help explain the involvement of the IL-33/ST2 pathway in the genetic susceptibility to human allergic diseases. Beyond its pathological role in allergic diseases, IL-33 also contributes to various immune regulatory processes. However, further studies are needed to clarify the precise therapeutic potential of targeting the IL-33/ST2 axis in different disease contexts and its physiological roles, as current evidence is still evolving.

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No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

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