

Innate-Type and Acquired-Type Allergy Regulated by IL-33

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ABSTRACT

We propose two types of allergic response: IgE-dependent and IgE-independent, and designate these as 'acquired-type allergy' and 'innate-type allergy', respectively. IL-33 stimulates both innate (basophils, mast cells, or group 2 innate lymphoid cells) and acquired (Th2 cells) allergy-related cells to induce and/or augment Th2 cytokine production, which leads to eosinophilic inflammation *in vivo*. Thus, IL-33 is an essential regulator for both 'innate-type allergy' and 'acquired-type allergy', and might be an attractive therapeutic target for allergic diseases.

KEY WORDS

asthma, basophils, eosinophils, IL-33, innate lymphoid cells

INTRODUCTION

It is well documented that basophils and mast cells release large amounts of IL-4 and IL-13 after cross-linkage of the IgE receptor, Fcε receptor I (FcεRI), by complexes of antigen plus antigen-specific IgE.^{1,2} IL-4 initiates and promotes Th2 responses and additionally activates these effector cells,³ while IL-13 contributes to the development of allergic responses by inducing mucus formation and eosinophilic infiltration via the production of eotaxin.⁴ Upon linkage of FcεRI, basophils and mast cells produce various other bioactive chemical mediators such as histamine and lipid metabolites.¹ Thus, cross-linkage of FcεRI is associated with the development of 'acquired-type allergy', and IgE antibody is therefore an essential molecule in this process (Fig. 1 left).

In contrast, we identified a type of allergy that does not require IgE antibody. Transgenic mice over-expressing IL-18 in keratinocytes spontaneously develop atopic dermatitis even in the absence of STAT6 activation, which is required for Th2 cell development and IgE production.⁵ Moreover, cultured bone-marrow-derived murine basophils and mast cells express IL-18Rα chain and produce Th2 cytokines (IL-4, IL-6, IL-9 and IL-13) and histamine in response to stimulation with IL-3 and IL-18, even without FcεRI cross-linkage⁶ (Fig. 1 right). In addition, both baso-

phils and mast cells express ST2 (IL-33Rα chain), recently identified as the receptor for IL-33, a member of the IL-1 family.⁷ Like IL-18, IL-33 can stimulate basophils and mast cells to produce Th2 cytokines without cross-linkage of FcεRI.⁷ From these results, we concluded that there are two types of allergy, one of which requires allergen and IgE antibody and another that does not require these molecules. We have designated these two types of allergy, 'acquired-type allergy' and 'innate-type allergy'.⁸ IL-18 and IL-33 are essential regulators for 'innate-type allergy' (Fig. 1 right).

In addition, basophils can produce Th2 cytokines in response to proteases from allergens and helminths, or pathogen-associated molecular patterns (PAMPs), via Toll-like receptors (TLRs). Papain, a cysteine protease allergen, can strongly induce the expression of transcripts encoding Th2 cytokines (IL-4, IL-6 and IL-13), thymic stromal lymphopoietin (TSLP) and CC chemokine ligand (CCL)1, which are associated with Th2 cell differentiation and recruitment, in bone-marrow-derived murine basophils without cross-linkage of FcεRI.⁹ It has been also reported that bone-marrow-derived murine basophils selectively express TLR 1, 2, 4 and 6 and produce significant amounts of Th2 cytokines in response to IL-3 plus peptidoglycan or IL-3 plus lipopolysaccharide via TLR2 or TLR4, respectively, in the absence of FcεRI

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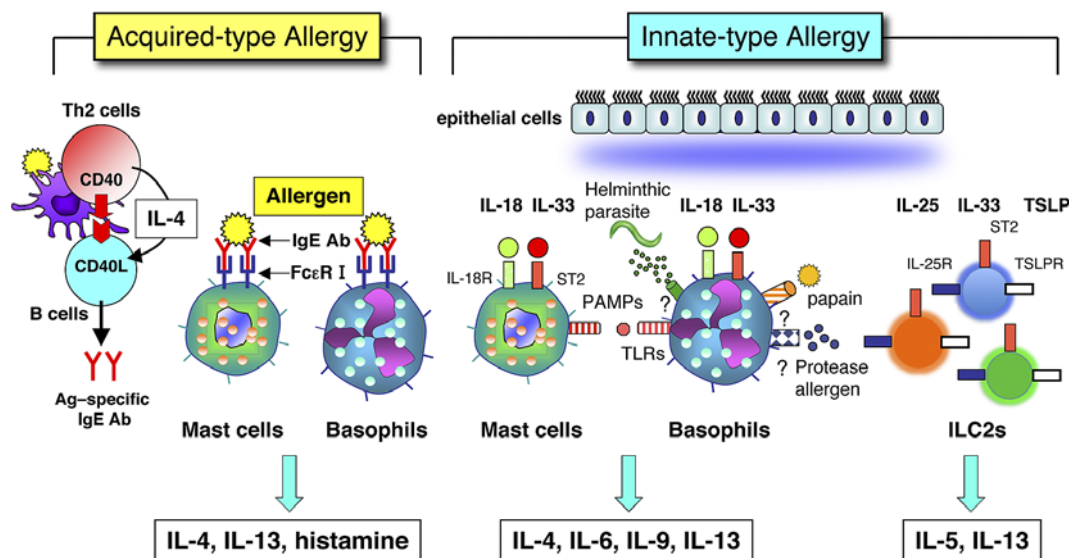


Fig. 1 Acquired-type allergy and innate-type allergy. IgE antibody is an essential molecule in allergy induced by mast cells or basophils stimulated by complexes of antigen and antigen-specific IgE that interact with FcεR1 to stimulate the production of Th2 cytokines and histamine. In contrast, IL-18/IL-33 stimulation of basophils induces the production of Th2 cytokines without FcεR1 cross-linkage. Furthermore, basophils produce Th2 cytokines in an IgE-independent manner after exposure to components of allergens and helminths via unknown receptors or after stimulation by pathogen-associated molecular patterns (PAMPs) via Toll-like receptors (TLRs). Furthermore, group 2 innate lymphoid cells (ILC2s) produce large amounts of IL-5 and IL-13 in response to epithelial cell-derived cytokines, IL-33, IL-25 and TSLP. Because of the relative involvement of the acquired/innate immune systems, we propose the former type of allergic response be termed 'acquired-type allergy' and the latter 'innate-type allergy'.

cross-linkage¹⁰ (Fig. 1 right). These results suggest basophils stimulated by protease allergen and PAMPs may play a key role in the induction of innate-type allergy.

Furthermore, recently identified natural helper cells,¹¹ nuocytes,¹² and innate helper 2 (IH2) cells,¹³ currently termed group 2 innate lymphoid cells (ILC2s)¹⁴ that are negative for lineage markers, express ST2 and produce large amounts of IL-5 and IL-13 in response to IL-33 as well as IL-25 and TSLP. All of these cytokines (IL-25, IL-33 and TSLP) including IL-18 are epithelial cell-derived cytokines and are essential regulators of innate-type allergy. Furthermore, they are a link between innate-type allergy and acquired-type allergy.

This review describes the nature of IL-33 and then provides details of 'innate-type' or 'acquired-type' allergic diseases regulated by IL-33, based mainly on the findings of our research group.

THE NATURE OF IL-33

EXPRESSION, LOCALIZATION, AND SECRETION OF IL-33

IL-33, the latest member of the IL-1 family is the ligand for ST2 (IL-33Rα)¹⁵ and shares a signaling pathway with IL-1 and IL-18.¹⁵⁻¹⁷ However, unlike IL-1 and IL-18, protein maturation is not necessary for IL-

33 bioactivity. Full-length IL-33, a 30-kDa protein, is biologically active.^{18,19} IL-33 is most likely released through cell necrosis or injury rather than cleavage by caspase.¹⁹ Thus, IL-33 is similar to an alarmin or damage-associated molecular patterns (DAMPs), such as IL-1α and high mobility group box 1 (HMGB1), which are endogenous proinflammatory factors released from damaged cells.^{17,20,21} However, necrotic cell death may not be the only way of releasing IL-33. An aeroallergen, the fungus *Alternaria alternata*, has been identified as an inducer of IL-33 release in the absence of cell death. *Alternaria* extract stimulation induces IL-33 secretion from *in vitro* cultured epithelial cells via the acute accumulation of extracellular ATP.²²

IL-33 was originally identified as a nuclear factor protein in endothelial cells of high endothelial venules (HEV)²³; hence, it was initially called NF-HEV. Indeed, IL-33 is constitutively expressed and localized in the nucleus of epithelial and endothelial cells from various tissues with a few exceptions.^{21,24} Thus, it was considered that IL-33 functioned as a nuclear factor. However, very little is known at present regarding the role of IL-33 as a nuclear factor.

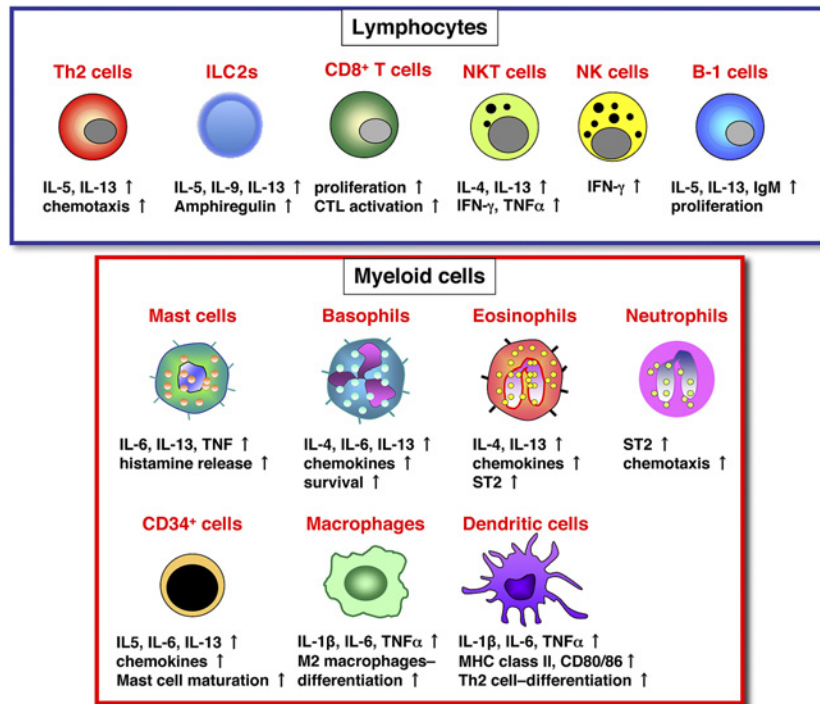


Fig. 2 Multifaceted bioactivity of IL-33. Various lymphocytes and myeloid cells express ST2 and can respond to IL-33 to promote the expression and/or production of various cytokines and functions. In particular, IL-33 is a potent inducer of Th2 cytokines from allergy-related cells (Th2 cells, basophils, mast cells, eosinophils, and group 2 innate lymphoid cells [ILC2s]). This broad array of effector functions of IL-33 on various cells indicates the importance and complex involvement of IL-33 in a wide range of diseases.

TARGET CELLS AND THEIR RESPONSES TO IL-33

ST2 (IL-33Rα) is expressed on a variety of cell types, epithelia, and endothelia in various tissues, fibroblasts, T cells, B-1 cells, basophils, mast cells, eosinophils, neutrophils, natural killer cells, invariant natural killer T cells, monocytes, macrophages, dendritic cells, and ILC2s^{16,17} (Fig. 2). Therefore, these cells respond to the presence of IL-33. ST2 was initially shown to be abundant on Th2 cells²⁵ and IL-33 is a potent inducer of Th2 cytokines. IL-33 treatment of Th2 cells augments IL-5 and IL-13 production.¹⁵ Similarly, the culture of naive T cells with IL-33 induces IL-5- and IL-13-, but not IL-4-, producing T cells.²⁶ IL-33 also potently activates innate Th2 cytokine producers. As mentioned above, IL-33 induces IL-6 and IL-13 production from basophils and mast cells in the absence of FcεRI cross-linkage.^{7,27-30} Eosinophils stimulated with IL-5 and/or GM-CSF up-regulate ST2, and are responsible for IL-33 induced IL-4 production.³¹ Furthermore, IL-33 stimulates ILC2s to produce large amounts of IL-5, IL-9, and IL-13.³² Th2 cytokines produced from innate-type cells play critical roles in the development of IgE-independent ‘innate-type’ allergy as well as in exacerbating IgE-dependent ‘acquired-

type’ allergy (described below in detail). Furthermore, considering type 2 inflammation, IL-33 enhances differentiation of alternatively activated or M2 macrophages that are characterized by the surface expression of mannose receptor and IL-4Rα and the production of CCL17 and CCL24. IL-33 directly induces M2 macrophage differentiation from bone marrow cells or alveolar macrophages in concert with IL-13.³³ In addition, IL-33-activated eosinophils enhance M2 macrophage polarization.³⁴ IL-33 also induces proinflammatory cytokines, such as IL-1β, IL-6, and TNF-α, from mast cells³⁵⁻³⁷ and basophils^{7,29,30} as well as the Th1 cytokine IFN-γ from NK cells and NKT cells.^{29,38} IL-33 is a chemoattractant for human Th2 cells.³⁹ Furthermore, IL-33 recruits eosinophils, basophils, and neutrophils to the site of inflammation by facilitating the production of chemokines.^{7,15,33,40,41}

This broad array of IL-33 effector functions on various cell types indicates the importance and complex involvement of IL-33 in a wide range of diseases. Indeed, IL-33 acts as an exacerbating factor in various inflammatory diseases, such as rheumatoid arthritis and inflammatory bowel diseases. However, reports indicate IL-33 can improve several diseases such as ischemic heart diseases, atherosclerosis and Al-

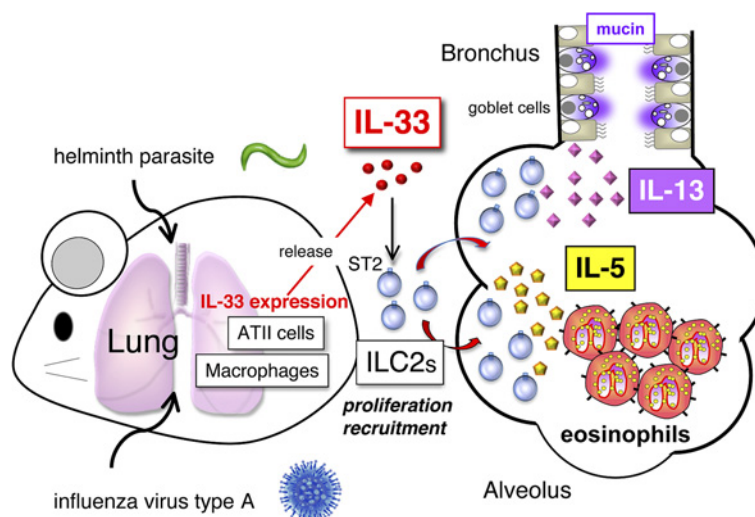


Fig. 3 IL-33-mediated innate-type allergic responses in the lung. In mice infected with a helminth parasite or influenza virus, rapid IL-33 production by alveolar epithelial type II (ATII) cells or macrophages, respectively, stimulates group 2 innate lymphoid cells (ILC2s) in the lung to produce IL-5 and IL-13, which results in lung eosinophilia and goblet cell hyperplasia.

zheimer's disease.¹⁷ Considering the physiological functions of IL-33 in target cells (Fig. 2), it plays an important role in the pathogenesis of allergic inflammation. It has been speculated that aeroallergen (such as pollen grain or fungus)-induced IL-33 from the nuclei of airway epithelial cells induces the recruitment of allergic cells (Th2 cells, eosinophils, basophils, mast cells, or ILC2s) to the airways and stimulates them to induce cytokines or chemokines, which results in exacerbated allergic inflammation.

INNATE-TYPE ALLERGY REGULATED BY IL-33

INNATE-TYPE ASTHMA

Intranasal administration of IL-33 to mice induces airway hyperresponsiveness (AHR), goblet cell hyperplasia, and airway eosinophilic infiltration by an ST2/MyD88-dependent mechanism by induction of IL-5 and IL-13 in the lungs.⁷ Administration of IL-33 induces goblet cell hyperplasia in the airways of wild-type mice but not in those of IL-13 deficient (IL-13^{-/-}) mice, which clearly indicates that IL-33 produces these responses by the induction of endogenous IL-13. Furthermore, similar treatment of RAG2^{-/-} mice, lacking T and B cells, induced more severe AHR with marked goblet cell hyperplasia and eosinophilic infiltration in the lungs. Thus, IL-33 induces asthma-like symptoms independently of the acquired immune system. We have designated this type of Th2 cells/IgE-independent- and IL-33-dependent asthma "innate-type asthma".⁷ In contrast to RAG2^{-/-} mice, γ c^{-/-} RAG2^{-/-} mice fail to develop innate-type asthma, which suggests that unidentified bone marrow-derived cells

are the target cells for IL-33. Indeed, recently identified innate lymphoid cells (ILC2s) have been identified as the predominant IL-5 and IL-13-producing population induced by IL-33 in murine lungs.³²

It is well known that asthma is enhanced by viral and bacterial infections. Recently, Chang *et al.* revealed that both ILC2s and IL-33 play an important role in asthma-like symptoms caused by influenza virus type A (H3N1).⁴² They demonstrated that influenza virus-induced IL-33 from alveolar macrophages increases the number of ILC2s in the lung, which produce IL-13 from ILC2s in response to IL-33, resulting in innate-type asthma (Fig. 3). These findings indicate IL-33 is critically involved in the pathogenesis of innate-type asthma, suggesting IL-33 might be a therapeutic target for the treatment of innate-type asthma.

PROTEASE ALLERGEN-INDUCED AIRWAY EOSINOPHILIA

It has been shown that intranasal administration of papain, a cysteine protease allergen, induced IL-33-dependent innate type eosinophilia in wild-type mice and RAG2^{-/-} mice.⁴³ Recently, Kamijo *et al.* demonstrated that intranasal administration of papain twice (days 0 and 7) induces eosinophilic infiltration in the lungs and papain-specific IgE and IgG1 antibodies in wild-type mice but not in IL-33^{-/-} mice,⁴⁴ indicating the papain-induced IL-33 production in the lung. Indeed, papain induced IL-33 in the bronchoalveolar lavage (BAL) fluid in a dose dependent manner. Papain-induced IL-33 stimulated lung ILC2s to produce significant amounts of IL-5 and IL-13, resulting

in severe lung eosinophilia.^{44,45} Furthermore, Kamijo *et al.* demonstrated that RAG2^{-/-} mice showed significant, but less severe papain-induced airway eosinophilia, which suggests possible cooperation of acquired immune cells, such as Th2 cells, and IL-33-mediated innate immune cells, such as ILC2s, in protease allergen-induced allergic airway inflammation.

EOSINOPHILIC PNEUMONIA

Eosinophilic pneumonia (Löfller syndrome) is a very common complication of gastrointestinal nematode infections, including the *Strongyloides*, *Ascaris*, and *Ancylostoma* species.⁴⁶ Nevertheless, the physiological relevance and pathogenesis of eosinophilic pneumonia are still not thoroughly understood. Recently, Yasuda *et al.* demonstrated that *Strongyloides venezuelensis* (*S. venezuelensis*)-infection induces severe eosinophilic inflammation and goblet cell hyperplasia in the lungs. In contrast, IL-33^{-/-} mice did not develop such allergic inflammation, indicating IL-33 has a critical role in the induction of pulmonary eosinophilia.⁴¹ They further demonstrated that alveolar epithelial type II cells (ATII) express IL-33 protein in their nuclei and that infection with *S. venezuelensis* or intranasal administration of chitin (a polysaccharide found on the surface of helminths) increases the number of ATII cells and the level of IL-33 expression. *S. venezuelensis* infection could induce pulmonary eosinophilia in RAG2^{-/-} mice, suggesting the contribution of IL-33-stimulated ILC2s in the induction of pulmonary eosinophilic inflammation (Fig. 3). Indeed, ILC2s were induced in the lung of *S. venezuelensis*-infected mice in an IL-33-dependent manner. They finally revealed that IL-33-stimulated ILC2s protects against *S. venezuelensis* by inducing pulmonary eosinophilic inflammation through the production of IL-5 and IL-13.

These results suggest that *S. venezuelensis* infection provokes these alterations principally through the action of chitin. However, the precise mechanism whereby IL-33 is released from ATII cells by nematode infection remains unclear. One report demonstrated IL-33 release is dependent on prior production of trefoil factor 2 (TFF2), an epithelial cell-derived repair molecule, during migration through the lung by gastrointestinal *Nippostrongylus brasiliensis* larvae and that TFF2^{-/-} mice consequently show impaired Th2 responses and worm expulsion.⁴⁷ Both ATII cells and TFF2 contribute to wound healing. Thus, IL-33 released from damaged bronchial epithelial cells by nematodes has a host defense role via ILC2s driven by IL-5 and IL-13 production.

ACQUIRED-TYPE ALLERGY REGULATED BY IL-33

ALLERGIC RHINITIS

Allergic rhinitis (AR) is one of the most common allergic inflammatory diseases, with an incidence of

over 600 million people worldwide.⁴⁸ The prevalence of seasonal AR is increasing in the developed world. Among allergenic weeds, ragweed pollen is common and has been reported to be a major source of airborne allergenic protein in the United States and many countries of central Europe.⁴⁹ AR is divided into two categories, seasonal and perennial AR. Nasal responses in AR comprise two phases: IgE-dependent early-phase responses and Th2 cytokine-dependent late-phase responses.⁵⁰ Clinical symptoms, such as sneezing and rhinorrhea, occur because of the early-phase responses within 5-30 min. The late-phase responses consist of congestion, fatigue and malaise at 6-24 h after exposure to an allergen. The major pathological changes associated with late-phase responses are eosinophilic accumulation into the nasal mucosa.⁵⁰ The mechanisms underlying the development of bronchial asthma have been well analyzed using a murine model. However, the precise mechanisms underlying the development of nasal responses in AR have not been clearly defined.

A previous study of ours showed that the serum level of IL-33 is significantly elevated in Japanese patients with seasonal AR, and that there is a significant association between susceptibility to AR and polymorphisms in the *IL33* gene.⁵¹ However, very little is known regarding the role of IL-33 in the development of AR. Recently, we established a novel murine model of ragweed pollen-specific AR and examined the pathological role of ragweed-induced IL-33 in the development of AR using IL-33^{-/-} mice.⁴⁰ After nasal challenge with ragweed pollen, ragweed-immunized wild-type mice manifested early-phase (sneezing) and late-phase (eosinophilic and basophilic accumulation) responses. In contrast, IL-33^{-/-} and FcεRIα^{-/-} mice failed to develop either phase of AR response. Furthermore, we found that ragweed-immunized mice but not naïve mice developed a significant and time-dependent increase in basophil accumulation in the nasal mucosa after ragweed exposure. In addition, this accumulation of basophils was diminished in IL-33^{-/-} mice, suggesting that both endogenous IL-33 and ragweed-specific Th2 immunity contribute to the nasal accumulation of basophils in AR. IL-33 protein is constitutively expressed in the nucleus of nasal epithelial cells and is promptly released into nasal fluids in response to nasal exposure to ragweed pollen. This ragweed pollen-driven IL-33 is essential for the development of sneezing and the nasal accumulation of eosinophils and basophils by increasing histamine release and inducing the production of chemoattractants from FcεRI⁺ mast cells and basophils, respectively. Together with the contribution of IL-33 in stimulating eosinophils, basophils, and mast cells to produce allergic inflammatory mediators, this process may lead to the recurrent seizures and irreversible mucosal hypertrophy observed in AR (Fig. 4).

In humans, constitutive expression of IL-33 protein

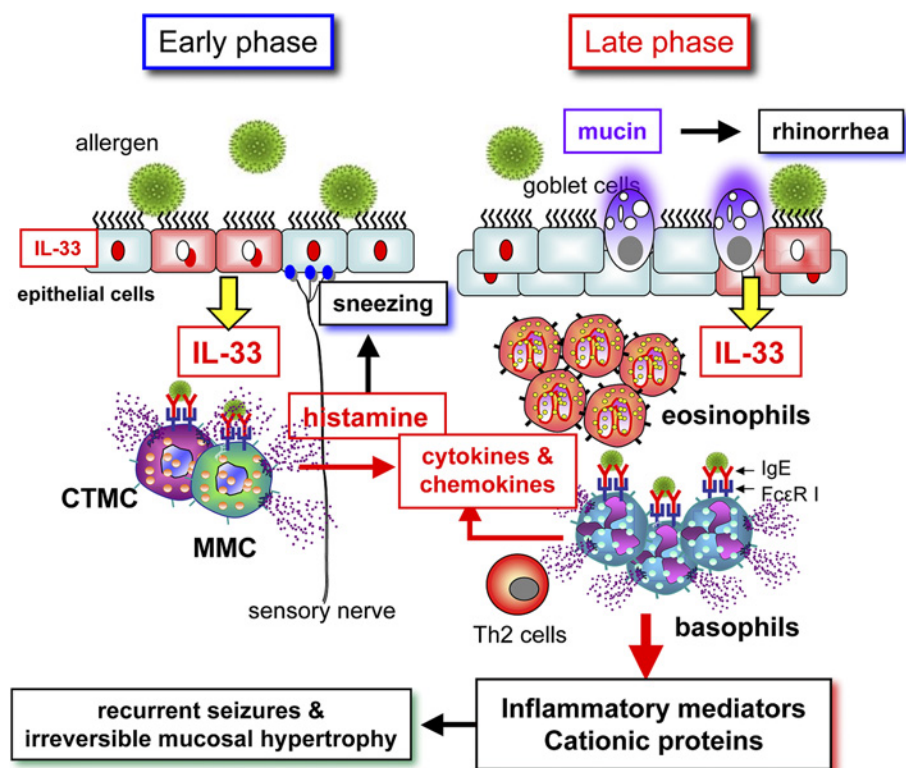


Fig. 4 Pathogenic role of IL-33 in allergic rhinitis. Ragweed pollen-driven endogenous IL-33 from nasal epithelial cells contributes to both early-phase (sneezing) and late-phase (nasal accumulation of eosinophils and basophils) responses in allergic rhinitis (AR) by increasing histamine release and inducing the production of chemoattractants from mast cells and basophils, respectively. Together with the contribution of IL-33 in the stimulation of Th2 cells, eosinophils, basophils, and mast cells to produce allergic inflammatory mediators, this process may lead to recurrent seizures and irreversible mucosal hypertrophy in AR.

in the nasal epithelial cells of healthy controls has been demonstrated as well as the down-regulated expression of IL-33 protein in the inflamed nasal epithelial cells of AR patients. However, IL-33 mRNA expression in the nasal epithelial cells of AR patients is significantly up-regulated during the pollen season,⁴⁰ which indicates that enhanced extracellular IL-33 release is associated with reduced IL-33 protein expression in inflamed nasal epithelial cells. Although the mechanism of ragweed pollen-driven IL-33 release from nasal epithelial cells remains unclear, taken together these results indicate that IL-33 may present an important therapeutic target for the prevention of AR.

ATOPIC DERMATITIS

Atopic dermatitis (AD) is a major allergic disorder. The morbidity of AD reaches 20-30% in developed countries.⁵² AD is characteristic of chronic dermatitis with severe, long-lasting itching. Clinically, eosinophils and mast cells accumulate in the lesional skin of

patients with AD, often with elevated peripheral blood levels of histamine and total IgE.⁵³ Genetic links have been identified between AD and polymorphisms in the gene encoding ST2. A SNP in the distal promoter of the *ST2* gene (chromosome 2q12) is significantly associated with AD, and there is a strong correlation with high soluble ST2 (ST2 lacking transmembrane and intracellular domains) and total IgE levels in the sera of AD patients.⁵⁴ These results indicate this ST2 genetic polymorphism is a candidate for conferring susceptibility to AD. Less is known about circulating IL-33; however, mRNA levels for IL-33 and ST2 are substantially increased in the lesional skin of patients with AD compared with non-lesional skin and healthy controls. Immunohistochemical staining revealed the numbers of IL-33⁺ cells were increased in keratinocytes and in endothelial cells, whereas those of ST2⁺ cells were increased in infiltrating inflammatory cells in the dermis of lesional skin compared with non-lesional skin.⁵⁵ However, it was still unclear how IL-33 contributes to these skin inflamma-

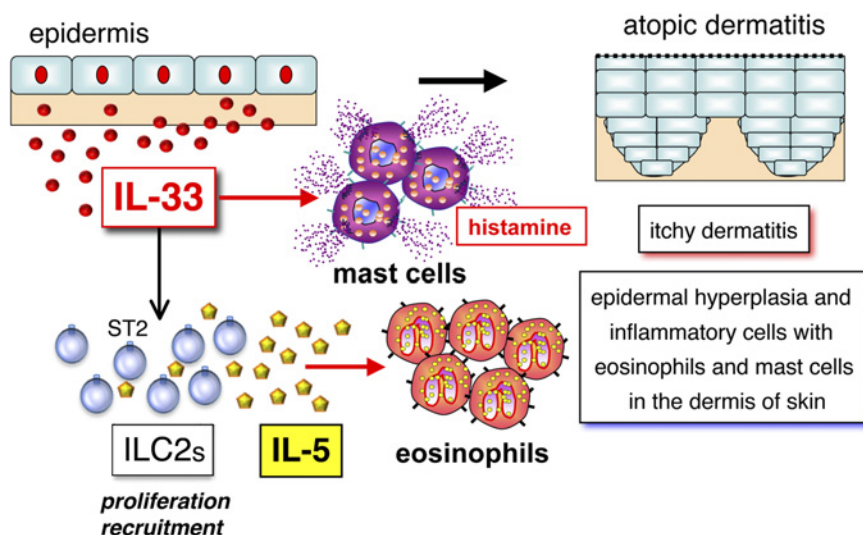


Fig. 5 Pathogenic role of IL-33 in atopic dermatitis. In transgenic mice over-expressing IL-33 in keratinocytes, IL-33 induces the recruitment of group 2 innate lymphoid cells (ILC2s) in the skin and stimulates the production of IL-5 to induce eosinophil infiltration in the dermis of skin. IL-33 also contributes to the induction of recruitment of mast cells and histamine release. Together, these processes lead to spontaneous itchy dermatitis.

tory conditions.

Recently, our group established transgenic mice with skin-specific overexpression of IL-33, termed hK14mIL33tg mice.⁵⁶ IL-33 was localized in the nuclei of the epidermis, and the intensity of staining for IL-33 was higher in hK14mIL33tg mice than in wild-type mice. Interestingly, spontaneous itchy dermatitis developed in hK14mIL33tg mice at 6-8 weeks of age in specific pathogen-free conditions. In the lesional skin, the epidermis was thickened, numbers of activated eosinophils and mast cells were increased, and blood histamine and total IgE levels were significantly higher than controls, traits that closely resemble the features of atopic dermatitis. The protein concentration of IL-5 and chemokines (RANTES and eotaxin) were markedly higher in the serum and lesional skin from hK14mIL33tg mice than in wild-type mice. In addition, IL-5-producing ILC2s were significantly increased in the lesional skin, peripheral blood, and regional lymph nodes. When anti-IL-5 antibody was administered to hK14mIL33tg mice every 2 days for 2 weeks, dermatitis with thickened epidermis with eosinophil infiltration was markedly improved. These results suggest that IL-33 from epidermal keratinocytes induces ILC2s in the skin and stimulates their production of IL-5, which induces AD-like dermatitis with eosinophilic infiltrates (Fig. 5). IL-33 is involved both in the increased numbers of mast cells in the skin,⁵⁷ and in histamine release from mast cells.⁴⁰ Thus, IL-33 from epidermal keratinocytes can result in the induction of recruitment of mast cells and histamine release (Fig. 5).

AD is often associated with increased serum allergen-specific IgE (IgE associated form); however, about 20% of patients with clinically diagnosed AD have no allergen-specific IgE (non-IgE associated form).⁵⁸ This form of AD might represent innate-type AD. Further studies using hK14mIL33tg mice backcrossed to RAG2^{-/-} mice will help understand the importance of IgE in AD.

CONCLUSIONS

IL-33 stimulates both innate (basophils, mast cells, or ILC2s) and acquired (Th2 cells) allergic cells to induce/augment Th2 cytokine production, which leads to eosinophilic inflammation *in vivo*. Thus, IL-33 is an essential regulator for both 'innate-type allergy' and 'acquired-type allergy', and might be an attractive therapeutic target for allergic diseases. To accomplish the therapeutic application of IL-33, however, a number of issues need to be addressed. The most important issue is to identify the exact mechanism of IL-33 release *in vivo*. Currently, there is a limited understanding of the pathways for IL-33 release. Studies suggest IL-33 is not released by a single mechanism, so specific neutralizing antibodies to IL-33 or inhibitors to the IL-33-signaling pathway might help treat allergic diseases.

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