

*Current Perspective***Interleukin (IL)-33: New Therapeutic Target for Atopic Diseases**Takeshi Nabe<sup>1,\*</sup><sup>1</sup>Laboratory of Toxicology, Faculty of Pharmaceutical Sciences, Setsunan University,  
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**Abstract.** Interleukin (IL)-33, a member of the IL-1 family of cytokines, is produced when epithelial and endothelial cells are exposed to stimuli. Hematopoietic cells such as macrophages also produce IL-33. IL-33 is considered to function as an ‘alarmin’, activating various immune cells through its receptor ST2, which leads to the production of various molecules. The IL-33-induced production of pro-inflammatory cytokines is a critical event that aggravates atopic diseases such as asthma, atopic dermatitis, and pollenosis and suggests that IL-33-blocking agents could represent new therapeutic drugs. The anti-IL-33 antibody was effective in allergic models, whereas the anti-ST2 antibody has yielded controversial results because soluble ST2 functions as a decoy receptor for IL-33. IL-33-mediated pulmonary inflammation may be glucocorticoid-resistant especially when other cytokines act synergistically. Anti-tumor necrosis factor (TNF)- $\alpha$  therapy may also be effective against IL-33-mediated diseases. ERK1/2 inhibitors have also been shown to suppress the production of IL-33. On the other hand, activation of  $\beta_2$ -receptors enhanced the expression of IL-33 mRNA in dendritic cells by activating protein kinase A (PKA), suggesting that PKA inhibitors may be candidates for IL-33-blocking agents. The effects of IL-33-blocking agents on atopic diseases need to be pharmacologically assessed in experimental and clinical studies.

**Keywords:** Interleukin (IL)-33, atopic disease, glucocorticoid, anti-allergic drug, asthma

**1. Introduction**

Atopic diseases including asthma, atopic dermatitis, and pollenosis are characterized by persistent eosinophilic tissue inflammation, which is dependent on Th2 cell activation. Glucocorticoids can suppress the recruitment and activation of those inflammatory cells, leading to attenuation of the tissue inflammation. However, there are severe phenotypes of atopic diseases, which are sometimes uncontrolled by glucocorticoids. Especially, some groups of asthmatic patients poorly respond to inhaled glucocorticoids (1). In order to develop new pharmacotherapy, it is required to elucidate new target molecules, which are definitely involved in the severe phenotypes of atopic diseases.

IL-33 is a member of the IL-1 family of cytokines that

includes IL-1 $\alpha$ , IL-1 $\beta$ , IL-1 receptor antagonists, and IL-18; and it is released when first-line cells, such as airway epithelial cells, are exposed to exogenous stimuli including allergens and microbes (2). IL-33 is considered to function as an ‘alarmin’ belonging to the larger family of damage-associated molecular pattern (DAMP) molecules, which activates various immune cells through the cell surface IL-33 receptor ST2, leading to the production of various molecules. The IL-33-induced production of pro-inflammatory cytokines has been suggested as a critical event that aggravates atopic diseases. IL-33-mediated allergic airway inflammation in particular has been suggested as one of the characteristic features of the severe phenotype of asthma, including steroid-resistant asthma (2 – 4). Thus, IL-33-blocking agents that inhibit the production and actions of IL-33 could represent new types of therapeutic drugs for atopic diseases.

In this review the basic pathophysiology of IL-33 and its roles in asthma, atopic dermatitis, and pollenosis (allergic rhinitis and conjunctivitis) have been summarized, in addition to candidates for IL-33-blocking agents.

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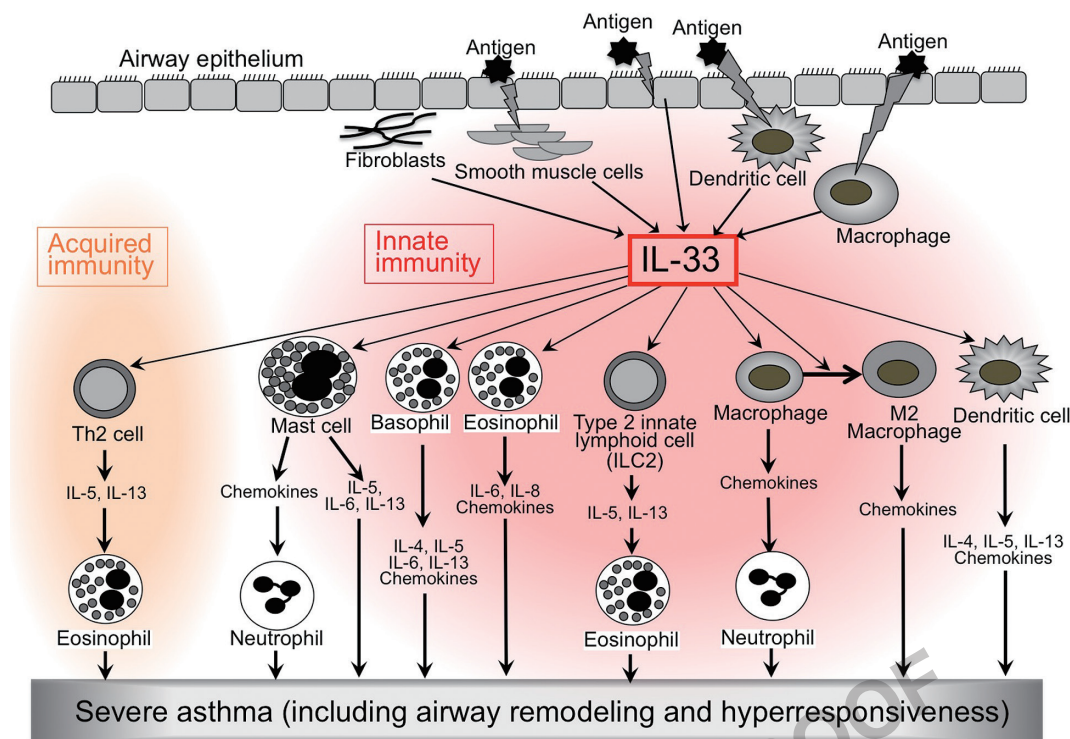


**Fig. 1.** Roles of interleukin (IL)-33 in the pathogenesis of asthma by bridging between innate and acquired immunity.

## 2. Production of IL-33

As reviewed elsewhere (2, 5), IL-33 is expressed by various organs such as the lungs, skin, and central nervous system. IL-33 was originally identified as a nuclear factor protein in endothelial cells. It was then shown to be produced by not only endothelial cells, but also epithelial cells, smooth muscle cells, and fibroblasts. In addition to the structural cells in various tissues, hematopoietic cells, especially macrophages, were also reported to produce IL-33. The IL-1 and IL-18 proteins are matured by the cleavage of caspase-1 under pro-inflammatory conditions. IL-33 is also considered to be processed in a similar manner. However, a previous study showed that this protein maturation process was not needed for IL-33 to display its biological activity because full-length IL-33, which is released during necrosis, also exhibited its actions *in vivo* (6). In the case of apoptosis, IL-33 is cleaved by caspase-3 and caspase-7 to become inactivated. Murine pollenosis models have revealed that IL-33 is constitutively expressed in conjunctival and nasal epithelial cells (8, 23). It is considered that IL-33 can be released after epithelial cell damage or injury, which may be caused by allergen proteins, enzymes, and bioactive molecules contained in pollens. Scratching episodes could also cause epithelial damage, resulting in the release of IL-33.

The expression of IL-33 mRNA was previously shown to be up-regulated by inflammatory stimuli including allergens and pro-inflammatory cytokines. IL-33 mRNA levels in airway smooth muscle cells were up-regulated when these cells were incubated with tumor necrosis factor (TNF)- $\alpha$  for 24 h (3). Regarding hematopoietic cells, an IgE-dependent stimulation upregulated the expression of IL-33 mRNA and protein in murine mast cells within 24 h (7). Under *in vivo* conditions, a topical ragweed allergen challenge elevated IL-33 mRNA levels in conjunctival tissue 24 h after the challenge (8). In a murine model of asthma, IL-33 mRNA and protein were up-regulated within as short as 4 h after an intratracheal antigen challenge in sensitized mice (Nabe et al., unpublished). Further studies are required to clarify whether increases in the amount of IL-33 mRNA are always relevant for IL-33-related diseases.

These findings strongly suggested that an antigen challenge and subsequent events can release IL-33 and induce the transcription of IL-33 mRNA, leading to the synthesis of the IL-33 protein in hematopoietic and non-hematopoietic cells.

## 3. IL-33 receptors

As reviewed elsewhere (2, 5), IL-33 binds to the IL-33 receptor, ST2, which is also called IL-1RL1 and T1, and

belongs to the Toll-like receptor (TLR)/IL-1R superfamily. IL-33-bound ST2 then forms a complex with the IL-1R accessory protein (IL-1RAcP), which is expressed ubiquitously. ST2 is expressed on various cells including hematopoietic cells, such as mast cells, basophils, eosinophils, Th2 cells, macrophages, dendritic cells, NK cells, NKT cells, and type 2 innate lymphoid cells (ILC2), which contribute to the induction and development of allergic inflammation. Structural cells including endothelial cells, epithelial cells, and fibroblasts also express ST2. When activated by IL-33, these cells secrete various kinds of mediators corresponding to the nature of respective cells, leading to the aggravation of allergic inflammation.

Regarding intracellular events after the activation of ST2 by IL-33, the heterodimeric ST2/IL-1RAcP receptor complex activates an adaptor protein, MyD88, and IRAK-1/4 and MAP kinases. In addition, inflammatory mediators are produced via activation of transcription factor, NF- $\kappa$ B.

#### 4. Targets of IL-33

Th2 cells play central roles in acquired immunity by producing IL-4, IL-5, and IL-13, which are involved in asthma mainly by the synthesis of IgE, activation of eosinophils, and hypersecretion of mucus, respectively. Th2 cells express ST2 on their cellular membrane and produce IL-5 and IL-13, but not IL-4 in response to IL-33 (2). Sensitized mast cells possess antigen-specific IgE, which binds on the high-affinity IgE receptors, Fc $\epsilon$ RI, on the cellular membrane. IgE-bearing mast cells respond to specific invading allergens by rapidly releasing histamine and arachidonic acid metabolites and producing various cytokines. Human mast cells stably express ST2 and produce cytokines and chemokines, such as TNF, granulocyte macrophage colony stimulating factor, IL-5, IL-6, IL-10, IL-13, CXCL8, and CCL1, but not the arachidonic acid metabolites, prostaglandin D<sub>2</sub> and leukotriene C<sub>4</sub>, when exposed to IL-33 (9). Basophils also possess Fc $\epsilon$ RI on their cellular membranes and predominantly release IL-4 in response to antigens following the antigen-IgE antibody reaction. Basophils are known to function as antigen-presenting cells that differentiate Th2 cells after antigen exposure. Isolated human basophils also express high amounts of ST2 (10). This type of granulocyte responds to IL-33, leading to the enhanced production of IL-4 and expression of CD11b by IL-3–primed human basophils (10). The number of eosinophils is locally and systemically increased by atopic diseases. Human eosinophils also express ST2 (11). This study demonstrated that IL-33 induced superoxide anion production and degranulation

as potently as IL-5 and also enhanced eosinophil survival and induced the production of IL-8 (11). The severe asthma phenotype is characterized by airway neutrophilia. Thus, a target for the accumulation of neutrophils may be useful as a therapy for severe asthma. A previous study reported that IL-33 enhanced the tissue infiltration of neutrophils (12). However, the effects of IL-33 on neutrophils were found to be indirect through the activation of other cells, such as mast cells (12). It was previously reported that human neutrophils did not possess ST2 (11).

Among innate lymphoid cells, ILC2s were shown to respond to IL-33. ILC2s have been identified by many investigators and referred to by various names including natural helper (NH) cells, multi-potent progenitor type 2 cells, and nuocytes (6). They express similar cell surface molecules to each other, including ST2 and CD25, and secrete IL-5, IL-13, and IL-6, but not IL-4 in response to IL-33 (6). Polarized macrophages can be broadly classified into two types: M1 and M2 macrophages. Classically activated M1 macrophages are differentiated by type 1 inflammatory cytokines and microbes, and they function as effector cells against microorganisms and tumor cells. In contrast, alternatively activated M2 macrophages are differentiated by type 2 immune responses, angiogenesis, and tissue repair processes. A previous study demonstrated in mice that IL-33 contributed to M2 macrophage polarization and chemokine production by polarized macrophages, which were involved in airway inflammation (13). IL-33 was found to stimulate mouse bone marrow–derived DC to express the maturation markers, CD40 and CD80, and pro-inflammatory cytokines and chemokines, IL-4, IL-5, IL-13, CCL17 TNF- $\alpha$ , and IL-1 $\beta$  (14). This effect of IL-33 on DCs was blocked by an anti-ST2 antibody and soluble ST2 (14).

Regarding non-hematopoietic structural cells, as described above, IL-33 is known to be produced in large amounts by epithelial and endothelial cells. Both structural cells express ST2 on their cellular membranes; therefore, IL-33 can function in an autocrine fashion in these structural cells, leading to the enhanced production of cytokines by epithelial and endothelial cells (15).

#### 5. Roles of IL-33 in atopic diseases

##### 5.1. Asthma

IL-33 was shown to be expressed at higher levels in the lungs of human asthma patients than in those of control subjects (3). The expression of IL-33 was particularly evident in the lungs of patients with the severe phenotype of asthma (3). IL-33 promoted collagen synthesis in asthmatic fibroblasts from pediatric patients

with severe steroid-resistant asthma (3), suggesting that IL-33 plays a role in the development of airway remodeling, a characteristic feature of severe asthma. Asthma has been regarded as CD4<sup>+</sup> Th2 cell-driven airway inflammation. Th2 cells produce large amounts of IL-4, IL-5, and IL-13. However, we previously reported that the almost complete depletion of CD4<sup>+</sup> cells by an anti-CD4 antibody could not completely reduce the production of IL-4, IL-5, or IL-13 in the lungs of a murine model of asthma (16), indicating that other cellular sources of these Th2 cytokines must exist. IL-33 is capable of producing IL-5 and IL-13 from ST2-expressing ILC2s (6), which indicates that IL-5-induced eosinophilia and IL-13-induced mucus production could be induced even in the absence of Th2 cells. The intraperitoneal or intranasal administration of IL-33 to mice induced ST2/MyD88-dependent airway hyper-responsiveness and goblet cell hyperplasia through production of IL-4, IL-5, and IL-13 in the lungs (17). In addition, allergic airway inflammation was attenuated by a treatment with an anti-IL-33 antibody (18). Because IL-33 is capable of activating ST2-expressing Th2 cells, IL-5, and IL-13 produced by both Th2 cells and ILC2s are involved in asthma.

IL-33-related allergic airway inflammation was previously suggested to be steroid-resistant. It was reported that the TNF- $\alpha$ -induced expression of IL-33 mRNA in human airway smooth muscle cells in vitro could not be inhibited by dexamethasone (3). In an in vivo study using a house dust mite-induced murine asthma model, IL-33 production and collagen deposition in the lung were not significantly reduced by budesonide, whereas airway hyperresponsiveness, cellular inflammation, and IL-13 production were suppressed by this glucocorticoid (1). Neutrophilic airway inflammation is known to be involved in the severe phenotype of asthma. The infiltration of neutrophils is mainly induced by IL-8. As described above, IL-33 indirectly induced neutrophilic inflammation (12), suggesting that IL-33 may play roles in the phenotype of severe asthma. Neutrophilic airway inflammation is generally resistant to glucocorticoids. IL-33-mediated airway inflammation has also been suggested to be steroid-resistant (1). These two phenomena may be related to each other. IL-33-mediated airway inflammation augmented by the neutrophil-related cytokine, IL-17, could not be suppressed by dexamethasone (19).

Taken together, these findings indicate that IL-33 could orchestrate a bridge between innate and acquired immunity to develop severe asthma phenotype.

## 5.2. Atopic dermatitis

Atopic dermatitis is characterized by severe skin

inflammation and long-lasting itching, the latter of which markedly reduces the quality of life of patients. The expression of IL-33 and ST2 were found to be increased in the skin of patients with atopic dermatitis after a challenge with an allergen or staphylococcal enterotoxin B (20). TNF- $\alpha$  dose-dependently induced IL-33 gene expression in healthy human skin (21). Furthermore, the expression of IL-33 was found to be enhanced in psoriatic skin and reduced by an anti-TNF- $\alpha$  therapy (21). In IL-33 transgenic mice, which show skin-selective IL-33 gene expression, various atopic dermatitis-like skin symptoms such as spontaneous itching, eosinophil infiltration, and mast cell hyperplasia were induced (22). However, the precise roles of IL-33 in atopic dermatitis remain unclear.

## 5.3. Pollenosis (allergic rhinitis and conjunctivitis)

Typical symptoms of allergic rhinitis are sneezing, rhinorrhea, and nasal blockage. Anti-histaminic drugs effectively relieve sneezing and rhinorrhea. The IL-33 protein was shown to be constitutively expressed in the nasal epithelial cells of healthy human subjects and down-regulated in the inflamed nasal epithelial cells of patients with allergic rhinitis (23). On the other hand, the expression of IL-33 mRNA in nasal epithelial cells during a pollen season was significantly higher in allergic rhinitis patients than in healthy control subjects (23). In murine studies, Haenuki et al. (23) demonstrated that the induction of sneezing and eosinophilic and basophilic nasal inflammation in a ragweed pollen-induced allergic rhinitis model was reduced in IL-33-deficient mice. Thus, these nasal allergic responses were mediated by endogenously released IL-33. However, it has yet to be determined whether IL-33 is involved in nasal blockages, which causes these patients the most discomfort. Allergic conjunctivitis is clinically characterized by mucosal congestion and edema, as well as itching in the conjunctiva. IL-33 was shown to be expressed in the vascular endothelial cells and conjunctival epithelium of human allergic conjunctival tissue, (24). In a murine study, exogenously applied IL-33 augmented allergic conjunctivitis (8); however, the roles of endogenous IL-33 have yet to be elucidated in detail.

## 6. Target therapy for IL-33

### 6.1. Anti-IL-33 antibody and anti-ST2 antibody

The neutralization of IL-33 should suppress the development of allergic diseases. Anti-IL-33 monoclonal antibody (mAb) treatments have been reported to inhibit allergen-induced eosinophilic airway inflammation, mucus hypersecretion, and Th2 cytokine production in mice (18). Ovalbumin-induced allergic rhinitis was also attenuated by an anti-IL-33 treatment: this mAb reduced

the frequency of nose scratching, serum IgE increases, and eosinophil infiltration into the airway tissue (25). Thus, an antibody drug that neutralizes IL-33 may represent a therapeutic drug for atopic diseases. On the other hand, the IL-33 receptor ST2 on the cellular membrane could also be a therapeutic target. However, ST2 has been detected not only on the cellular membrane, but also in serum in a soluble form, which can serve as a decoy receptor for IL-33 (5, 6). Thus, soluble ST2 may function as a regulator for IL-33 function. Strategies to neutralize ST2 require further attention.

## 6.2. Glucocorticoids

Glucocorticoids non-specifically and broadly suppress various inflammatory events mainly through binding to glucocorticoid receptors in the cytoplasm and inhibiting the mRNA expression of pro-inflammatory mediators. As described above, IL-33-mediated airway inflammation may be resistant to corticosteroids. Dexamethasone was previously shown to effectively suppress intranasal IL-33 alone-induced airway inflammation manifested by the accumulation of NH cells and increases in IL-5 and IL-13 levels. However, when an allergen was co-administered with IL-33, airway inflammation was altered to become corticosteroid-resistant (26). Steroid-resistant airway inflammation was reduced by a treatment with an antibody against thymic stromal lymphoprotein (TSLP), indicating that TSLP expressed by the allergen challenge changed the asthma phenotype to corticosteroid-resistant (26). Steroid resistance may be attributed to activation of the STAT5 signaling pathway by TSLP, which cannot be suppressed by corticosteroids in NH cells (26). Similar to this finding, airway inflammation induced by a combined treatment with IL-33 and IL-17 was also found to be resistant to dexamethasone (19).

However, it remains controversial whether the production of IL-33 is susceptible to glucocorticoids. The TNF- $\alpha$ -induced expression of IL-33 mRNA in human airway smooth muscle cells in vitro were not inhibited by a treatment with dexamethasone, although it was slightly inhibited by higher concentrations of dexamethasone (3). Allergic airway IL-33 production in a house dust mite-induced murine asthma model was also found to be corticosteroid-resistant (1). In contrast, regarding in vivo IL-33 in a murine model of asthma, a systemic treatment with dexamethasone dose-dependently inhibited the production of IL-33 after an intratracheal antigen challenge (Nabe et al., unpublished).

The susceptibilities of IL-33-induced responses and IL-33 production to glucocorticoids may be dependent on the disease state, in which various pro-inflammatory molecules such as TSLP and IL-17 are locally produced and act synergistically.

## 6.3. Anti-TNF- $\alpha$ therapy

The expression of IL-33 in normal and psoriatic skin was up-regulated by TNF- $\alpha$ , while an anti-TNF- $\alpha$  antibody suppressed its expression (22). In addition, TNF- $\alpha$  induced IL-33 mRNA expression in human airway smooth muscle cells in vitro (3). Thus, the association between TNF- $\alpha$  and IL-33 suggests that anti-TNF- $\alpha$  therapy could suppress the production of IL-33, leading to relief from asthma. Clinical trials evaluating the effectiveness of anti-TNF- $\alpha$  therapy have yielded controversial findings. One study showed that an anti-TNF- $\alpha$  antibody was effective against severe asthma (27).

## 6.4. ERK1/2 (extracellular signal-regulated kinase 1/2) inhibition

The expression of IL-33 mRNA and protein was up-regulated in active lesions from patients with ulcerative colitis (28). The expression of IL-33 in human colonic subepithelial myofibroblasts was shown to be induced by IL-1 $\beta$  and TNF- $\alpha$  in vitro (28). Furthermore, the expression of IL-33 was blocked by p42/44 mitogen-activated protein kinase (MAPK, ERK1/2) inhibitors, but not by a p38 MAPK inhibitor or PI3K inhibitor (28). This finding indicated that the activation of ERK1/2 was involved upstream of the production of IL-33. If these intracellular signals also contribute to the production of IL-33 in atopic diseases, p42/44 MAPK inhibitors could be used as effective therapeutic drugs.

## 6.5. Adrenaline $\beta$ -receptor antagonist and protein kinase A (PKA) inhibitor

Yanagawa et al. (29) first reported that lipopolysaccharide (LPS)-induced IL-33 mRNA expression in dendritic cells (DC) in vitro was markedly enhanced by noradrenaline and adrenaline, and that this enhancement was mediated by the activation of PKA following intracellular cyclic AMP elevations through the activation of  $\beta_2$  receptors on DC membranes. However, the release of inflammatory mediators from various cells is generally suppressed when intracellular cyclic AMP is elevated. Indeed, the previous study confirmed that IL-1 and IL-18 mRNA expression was attenuated by  $\beta$ -receptor agonists (29). The mechanisms underlying these conflicting findings for IL-33 and other IL-1 family cytokines (IL-1 and IL-18) remain unclear. Furthermore, when cyclic AMP was decreased by  $\beta$ -receptor blockers and the PKA inhibitor H89, the expression of IL-33 mRNA was clearly suppressed (29). The finding that IL-33 mRNA expression by TLR and non-TLR agonist from murine macrophages was significantly inhibited by the PKA inhibitor, but not by tyrosine kinase inhibitor, and PKC inhibitor was also reported by another group (30).

Taken together, the production of IL-33 in atopic

diseases could also be suppressed by  $\beta$ -receptor blockers and PKA inhibitors. However,  $\beta$ -receptor blockers must generally be avoided for asthma patients because of their bronchoconstrictive activity. This strategy might be useful for atopic dermatitis patients who have no defect in their respiratory organs. Strategies to reduce intracellular cyclic AMP levels may be useful in the development of therapeutic drugs for atopic diseases mediated by IL-33.

## 7. Closing remarks

IL-33 plays important roles in atopic diseases to orchestrate the activation of various ST2-expressing structural cells and hematopoietic cells. The mechanisms underlying IL-33-mediated inflammation have been immunologically analyzed. It has also been suggested that IL-33-blocking agents could be good therapeutic drugs, especially for the severe phenotypes of atopic diseases. However, pharmacological evaluations to develop IL-33-blocking agents have not been extensively conducted. Agents including natural products that inhibit the production and actions of IL-33 need to be pharmacologically assessed.

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