Functional and clinical translation of asthma and allergy associated genetic variants in IL33 and IL1RL1

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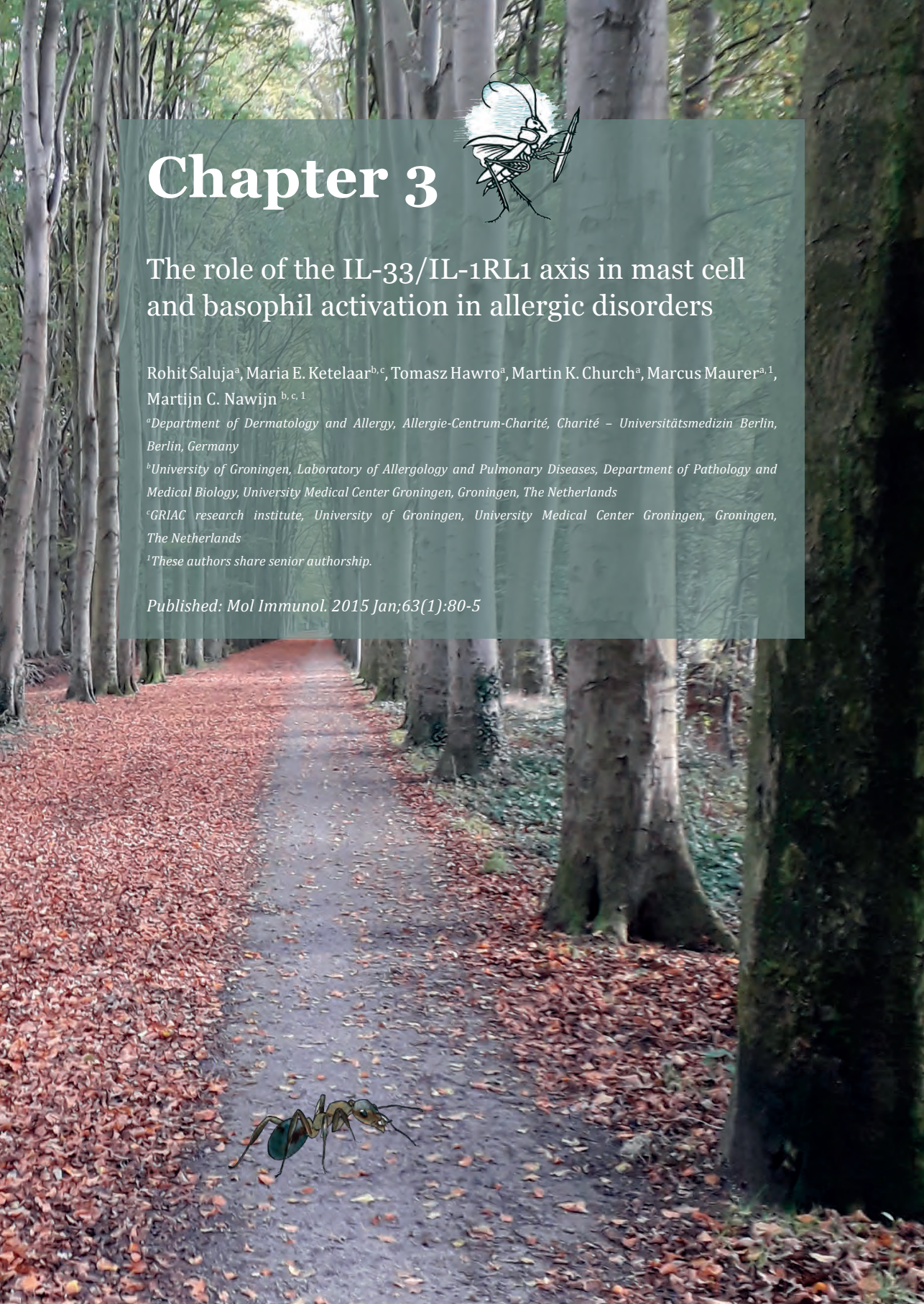

Chapter 3

The role of the IL-33/IL-1RL1 axis in mast cell and basophil activation in allergic disorders

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Abstract

Interleukin-33 (IL-33) is a recently discovered cytokine that belongs to the IL-1 superfamily and acts as an important regulator in several allergic disorders. It is considered to function as an alarmin, or danger cytokine, that is released upon structural cell damage. IL-33 activates several immune cells, including Th2 cells, mast cells and basophils, following its interaction with a cell surface heterodimer consisting of an IL-1 receptor-related protein ST2 (IL-1RL1) and IL-1 receptor accessory protein (IL-1RAcP). This activation leads to the production of a variety of Th2-like cytokines that mediate allergic-type immune responses. Thus, IL-33 appears to be a double-edged sword because, in addition to its important contribution to host defence, it exacerbates allergic responses, such as allergic rhinitis and asthma. A major purported mechanism of IL-33 in allergy is the activation of mast cells to produce a variety of pro-inflammatory cytokines and chemokines. In this review, we summarize the current knowledge regarding the genetics and physiology of IL-33 and IL-1RL1 and its association with different allergic diseases by focusing on its effects on mast cells and basophils.

Keywords

Mast cell; Basophil; IL-33; IL-1RL1; IL-1RAcP; Signal transduction

Abbreviations

BMMCs, bone marrow-derived murine mast cell;
ECM, extracellular matrix;
eQTLs, expression quantitative trait loci;
ERK, extracellular signal-regulated kinases;
GATA1, globin transcription factor 1;
GATA2, globin transcription factor 2;
GI tract, Gastrointestinal tract;
GWA, genome-wide association;
Hck, hematopoietic cell kinase;
HUCBMCs, human umbilical cord blood mast cells;
IL-1RAcP, IL-1 receptor accessory protein;
IL-1RL1, IL-1 receptor-like 1;
JNK, c-Jun N-terminal kinases;
MyD88, myeloid differentiation primary response gene (88);
NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells;
p38 MAPK, p38 mitogen-activated protein kinases;
PGD2, prostaglandin D2;
SCF, stem cell factor;
SNPs, single-nucleotide polymorphisms;
TIR, toll/interleukin-1 receptor;
TLRs, Toll Like Receptors;
TNF-α, tumour necrosis factor alpha;
TRIF, TIR-domain-containing adapter-inducing interferon-β;
TSLP, thymic stromal lymphopoietin;
VEGF, vascular endothelial growth factor.

Introduction

IL-33 is a recently discovered 30 kDa member of the IL-1 superfamily of cytokines. It is a central regulator of innate and adaptive type-2 immune responses and is thought to play a critical role in the initiation and maintenance of allergic disorders, such as atopic dermatitis, allergic asthma and allergic rhinitis. Novel insights from large-scale studies on the genetic basis for allergic disorders have identified both IL-33 and its receptor IL-1RL1 as critical genes for asthma susceptibility, indicating a central role for this pathway in disease pathogenesis. Dysregulated activity of the IL-33/IL-1RL1 pathway is thought to contribute to allergic disorders through several mechanisms. Here, we will discuss recent progress in identifying the role of the IL-33/IL-1RL1 pathway in activation and effector functions of mast cells and basophils.

IL-33 and IL-1RL1 as susceptibility genes for allergic disorders

Atopy and allergic diseases are the result of an interaction between a susceptible host and a permissive environment, both contributing to the inception of disease. The identity of the genes contributing most prominently to disease susceptibility has been revealed by genome-wide association (GWA) analyses in large cohorts of patients and controls. In these studies, IL-33 has been identified as a susceptibility gene for asthma (21,22), while IL-1RL1 has been identified as a susceptibility gene not only for asthma (21,22,57,67), but also inflammatory bowel disease (132), Crohn's disease (133), celiac disease (134,135) and atopic dermatitis (62), as well as for eosinophil counts in the blood (15). These studies strongly indicate that polymorphisms in these genes contribute to the pathogenesis of these disorders. Polymorphisms in the IL-33 and IL-1RL1 genes can result in altered activity of the IL-33/IL-1RL1 pathway by multiple mechanisms. First, genetic polymorphisms can directly affect mRNA expression levels in a certain cell type or tissue. Such polymorphisms are referred to as expression Quantitative Trait Loci, or eQTLs. In some, but not in all cases, altered mRNA expression levels will also result in altered protein levels (protein QTL or pQTL). Alternatively, polymorphisms might alter the coding sequence of the gene, resulting in the expression of a functionally different protein, even if expression levels are not affected. For instance, a recent study by Ho and colleagues (136) elegantly showed that IL-33 induced signalling through IL-1RL1 is affected by common genetic variation at the IL-1RL1 locus, not only through effects of the polymorphisms on IL-1RL1 gene expression levels, but also by effects of amino-acid substitutions on the activity of the receptor in transmitting the IL-33-induced signal.

The functional consequences of IL-33 polymorphisms have not yet been experimentally validated (26). In case of IL-1RL1, the genetic signals are highly complex, given that certain gene polymorphisms are often inherited together with polymorphisms in the neighbouring IL-18R1 gene (26). Here, the IL-1RL1 SNPs are non-synonymous exonic SNPs resulting in amino-acid changes within the intracellular signalling domain. These are always inherited together with a number of IL-18R1 SNPs that have been found to be eQTLs, resulting in

altered IL-18R1 expression levels. Given these limitations in the resolution of the genetic analyses, causal involvement of either gene in the associated disorders is difficult to establish definitively. Hence, while these genetic analyses are very powerful in identifying the genetic basis for the susceptibility to disease, the interpretation of their functional consequences requires careful dissection of the biology underlying disease pathogenesis. Therefore, this review will offer a detailed discussion of the effects of the IL-33/IL-1RL1 pathway on mast cells and basophils in the context of atopic disorders.

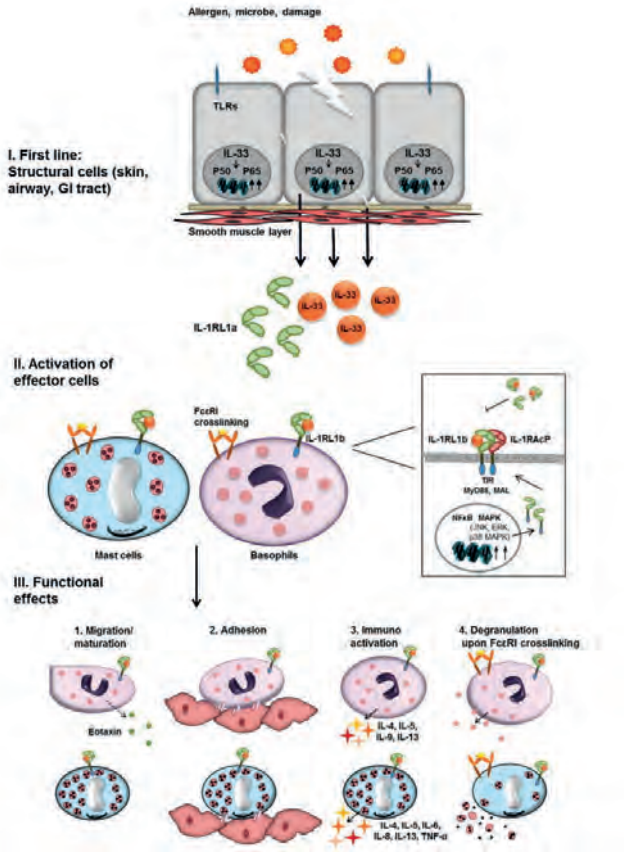


Figure: Schematic representation of IL-33 release by structural cells and its action as a modulator of mast cell and basophil functions. Tissue damage induced by exposure to allergens, microbes or by physico-chemical stress leads to induction of necrotic cell death and release of IL-33 from structural cells such as epithelial and smooth muscle cells. IL-33 bioavailability may be limited by binding to the decoy receptor IL1-RL1a (also called sST2). IL-33 acts on mast cells and basophils through a heterodimeric receptor complex IL-1RAcP and IL-1RL1b, which initiates a MyD88-dependent signalling pathway and results in JNK, ERK and p38 MAPK activation. IL-33 regulates different functions of mast cells and basophils, including maturation, adhesion, cytokine release and degranulation.

IL-33: an alarmin of the IL-1 cytokine family

IL-33 is a member of the IL-1 cytokine family with intracellular localization. It is constitutively expressed in the nucleus of several cell types, including epithelial cells (124,137), endothelial cells (137) and innate immune cells such as macrophages (122) and dendritic cells (96). IL-33 expression can also be induced under inflammatory conditions. While mast cells express IL-33 (138), basophils have not been reported to express the cytokine.

IL-33 has been described to have a dual function, showing activity both as a transcription factor and as a cytokine. IL-33 has been shown to bind directly to chromatin (94) and the NF-κB proteins p50 and p65 (38,39). This activity can induce expression of pro-inflammatory genes, such as IL-6 and IL-8. Alternatively, when secreted or released into the extracellular environment, IL-33 can bind to IL-1RL1 and induce signal transduction, as detailed below. Cells that have been described to respond to IL-33 include a range of innate and adaptive immune cells such as innate type-2 helper cells (ILC2s) (116), NK and NKT cells (44), eosinophils (46,47), macrophages (107,139), dendritic cells and Th2 cells (44,107,121,140,141). Both basophils (44,46,47,120,141) and mast cells (42,118,120) have been reported to respond to IL-33, resulting in markedly increased production of type-2 cytokines, including IL-4, and enhanced effector functions as discussed in detail below.

IL-33 signal transduction in responsive cells

Upon release, IL-33 binds to a receptor complex consisting of two transmembrane proteins: IL-1RL1 and IL-1RAcP. Both receptor subunits carry an intracellular TIR domain, which is critical for signal transduction. Binding of IL-33 to the heterodimeric receptor complex results in the sequestration of TIR-domain containing signalling adapter proteins such as MyD88 and MAL, and subsequent downstream signalling leading to activation of the NF-κB and mitogen activated protein kinases (MAPK) pathways (47,142).

MAPK are categorized into three groups; first, ERK (extracellular relate kinases), which are mainly activated by growth hormone receptors; second, JNK (c-Jun N-terminal kinases), which are mainly activated in stress; and third, p38 MAPK, which are mainly activated via cellular stress including reactive oxygen species and inflammatory cytokines. IL-33 can induce MAPK signalling pathways (p38 MAPK, JNK and ERK) downstream of IL-1RL1 and MyD88 adapter protein (82). In the human mast cell-line LAD2, IL-33 reportedly phosphorylates p38 MAPK prominently, and IL-33 induced activation of p38 MAPK leads to the upregulation of IL-13 production (143). Moreover, IL-33 induces phosphorylation of p38 MAPK, JNK as well as ERK in mast cells derived from human umbilical cord blood (HUCB)-MCs. IL-33 leads to the production of IL-8 in HUCB-MCs through a p38 MAPK dependent pathway. Inhibition of p38 MAPK with SB203580 abolishes the production of IL-8 by IL-33 in HUCB-MCs without affecting their viability (118). The soluble receptor for IL-33 (an isoform of IL-1RL1 or sST2), acts as a decoy receptor for IL-33 by binding IL-33 and reducing its level in the serum. In LAD2 mast cells, sST2 was found to have an inhibitory role on p38 MAPK and may have therapeutic effects in various allergic diseases (143).

The effects of IL-33 in mouse mast cells are similar to those observed in human mast cells. In mouse bone-marrow derived mast cells (BMMCs), IL-33 induces phosphorylation of p38 MAPK leading to the production of different cytokines such as IL-6 (43). IL-33 induces phosphorylation of p38 MAPK as well as ERK in mouse mast cells that has been found to be inhibited by anti-ST2 antibody (96). IL-33 induced p38 MAPK signalling leads to the production of IL-6 and IL-13 through the MyD88-dependent and TIR-domain-containing adapter-inducing interferon-β (TRIF)-independent pathway. IL-33 mediated phosphorylation of p38 MAPK and ERK is diminished in BMMCs of MyD88 knockout mice (119).

A recent report (144) showed that the exposure of BMMCs to IL-33 increases the activation of all of the three signalling molecules (JNK, ERK and p38 MAPK), which lead to the production of IL-6 and IL-13. Incubation of BMMCs with PD98059 (ERK inhibitor), SP600125 (JNK inhibitor) and SB203580 (p38 MAPK inhibitor) diminishes the IL-33 induced production of both IL-6 and IL-13. However, SB203580 (p38 MAPK inhibitor) has a more prominent effect compared with the other inhibitors.

Taken together, IL-33 can induce the phosphorylation of signalling molecules such as JNK, ERK and p38 MAPK in both human and mouse mast cells that may further govern cell differentiation and activation. Inhibition of IL-33 mediated signalling pathways may be a therapeutic target for a range of disorders including allergic asthma, rhinitis and might be used for anti-rheumatic therapy (95).

IL-33 induced effects in basophils

Basophils express IL-1RL1 and respond to IL-33. Expression of IL-1RL1 in basophils is induced by IL-3 (47)) and IL-33 itself (46). IL-1RL1 gene expression is induced by activation of GATA2, while GATA1 represses IL-1RL1 expression (145). IL-33 induces the expression of a range of cytokines in basophils, and induces basophil adhesion and migration towards eotaxin (46). For instance, IL-33 induces expression of IL-4 and IL-13 in freshly isolated basophils, a response which is greatly amplified by FcεRI crosslinking (46). Peripheral blood basophils have also been found to express IL-5 and IL-9 in response to IL-33. IL-3 amplifies this response, most likely by upregulating expression levels of IL-1RL1 (44,141). IL-33, as a single agent, does not induce degranulation of human primary basophils ex vivo, even from subjects with high serum-IgE levels (146). Degranulation of basophils upon IgE crosslinking, however, is greatly enhanced by IL-33 (46). We have summarized the influence of IL-33 on basophils in Fig. 1.

IL-33 induced effects in mast cells

The binding of IL-33 to IL-1RL1 can modulate many aspects of mast cell function, including adhesion, maturation, degranulation and cytokine production. The primary effect on mast cells appears to be subsequent to its interaction with cell surface IL-1RL1.

Adhesion

Mast cell adherence to the blood vessel wall is initiated by upregulated expression of ICAM-1 and VCAM-1 on endothelial cells, which is mediated partly by IL-33-induction of NF-κB (39). In addition to facilitating adhesion, these adhesion molecules may influence several mast cell functions, such as cytoskeleton reorganization, cell signalling and mediator secretion (147).

Mast cells adhesion to fibronectin is induced primarily by the stimulation of KIT by stem cell factor (SCF) (148). However, IL-33, together with IL-1β, another member of the IL-1 cytokine family, enhances the adhesion of human mast cells (HUCB-MCs) to fibronectin (118). A previous study has reported that mast cells activated with calcium ionophore A23187 or IgE crosslinking show increased adhesion to laminin (149). However, a recent study has suggested that IL-33 is produced following IgE crosslinking (138) and, thus, it may be speculated that this IL-33 may further facilitate strong adhesion of mast cells to extracellular matrix (ECM) (Fig. 1).

Maturation

Mast cell maturation is governed by many cytokines, including IL-3, IL-4 and IL-9. IL-33 is also considered a potent stimulus for human mast cell maturation via an IL1-RL1 dependent pathway (42) (Fig. 1). CD34+ precursor cells isolated from human umbilical cord blood show expression of the full-length IL-1RL1 (IL-1RL1b or ST2L) that is crucial for recognition of IL-33 (42). IL-33 alone or in combination with thymic stromal lymphopoietin (TSLP) has been shown to enhance the maturation of CD34+ MC precursors. IL-33 stimulation of CD34+ progenitor cells reportedly enhances the expression of tryptase, a marker of mast cell maturation (42).

Thus, the importance of IL-33 mediated mast cell maturation may have great clinical significance, especially in autoimmune diseases where mast cell-derived tryptase has an important role in the pathology of conditions such as arthritis (150).

Activation and secretion of mast cell mediators

The mast cell activating effects of IL-33 are somewhat controversial. The ability of IL-33 to induce cytokine release from cultured mast cells is well established (118,136,151,152) as is its ability to enhance IgE-dependent cytokine generation (118,119,138,151). However, while some publications report that IL-33 also stimulates or enhances degranulation and PGD2 generation (120,152) others state that IL-33 has no detectable effect on the release of histamine and PGD2 (31,42,118,151). Moreover, and interestingly, in contrast to the potentially pro-allergenic effects of short-term exposure of mast cells to IL-33, prolonged exposure to IL-33 has been found to down-regulate mast cell signalling proteins, such as phospholipase Cγ1 and Hck (153). This suggests that IL-33 may show opposite effects on mast cell activation under chronic conditions compared to the acute allergic phase. This certainly requires further study, but would potentially have important implications for the design of IL-33 focused treatment strategies in allergic disease.

Cytokine production

Mast cells are the first line of defence and have the capacity to produce multiple cytokines in response to numerous different stimuli, including allergens and bacterial, viral and fungal infections (154). IL-33 is mainly released by necrotic structural cells and is considered a key danger signal or alarmin. IL-33 seems to be a potent inducer of innate type-2 lymphocytes and Th2 cells to produce type 2 cytokines such as IL-4, IL-5 and IL-13. IL-33 is also one of the strongest stimuli for the production of different cytokines by mast cells (155) (Fig. 1).

In human mast cells, IL-33 induces IL-8 and IL-13 secretion (118) and enhances substance P-induced VEGF mRNA transcription and secretion of VEGF protein; however, IL-33 alone is not able to induce secretion of VEGF (156). In vivo studies suggest that mast cells could be the main source of the production of type II cytokines (IL-4, IL-5 and IL-13) in serum (121). However, IL-33 has no effect on the production of anti-inflammatory cytokines such as IL-10 (152).

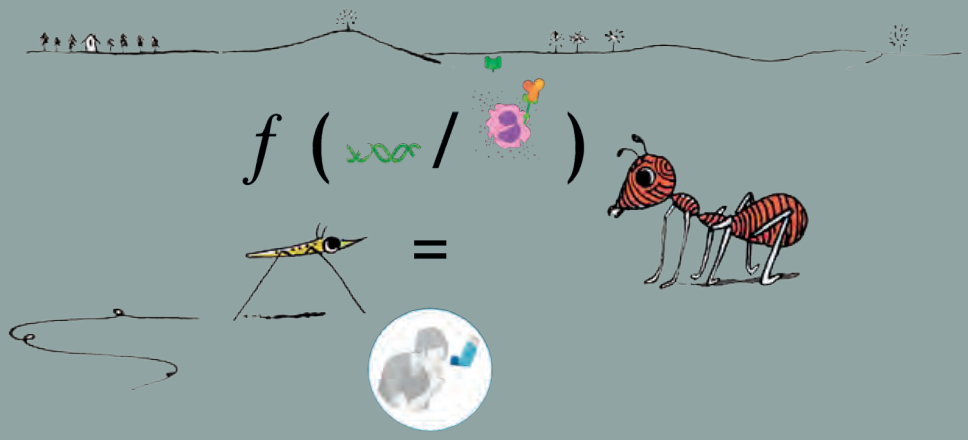
IgE cross linking is a main mechanism through which mast cells produce cytokine release. However, IL-33 can induce IL-13 and IL-6 production by BMMCs independently of IgE (119). IL-33 may enhance cytokine production through a MyD88-dependent pathway (119). In contrast, IL-1β or IL-18 does not induce IL-13 and IL-6 production. IL-33 has been reported to not induce several other cytokines in BMMCs, e.g. IFN-γ, IL-1α, IL-1β, IL-2, IL-3, IL-4, IL -10, IL-12, IL-15, IL-17, IL-18, IL -19, IL-20, IL-21, IL -22, IL-23 and IL-27 (119).

Concluding remarks

This review has provided a brief survey of the role of IL-33 and IL-1RL1 focussing mainly on its modulation of mast cell and basophil functions. Single nucleotide polymorphisms in the IL-33 and IL-1RL1 genes indicate a significant role for IL-33/IL-1RL1 signalling in asthma and other allergic diseases. IL-33 is released mainly by structural cells after tissue injury and it can be recognized by innate-type immune cells, including mast cells and basophils. IL-33 has major role in various allergic disorders, such as asthma and allergic rhinitis. Thus, targeting the IL-33 pathway may provide a new potential therapeutic approach to treat allergic diseases. Whereas the role of IL-33 on various cell types has been explored in great detail, further studies are necessary to understand how the SNPs associated with the various disorders affect the IL-33 pathway in different allergic diseases and have their effects on the mast cell/basophil axis.

To take home

- SNPs in the IL-33 and IL-1RL1 genes play a crucial role in asthma and allergic diseases.
- The IL-33/IL-1RL1 pathway modulates several functions in mast cells and basophils under physiological and pathological conditions.
- Dysregulated activity of the IL-33/IL-1RL1 pathway could contribute to allergic disorders via altered functioning of mast cells and basophils.
- Targeting the IL-33/IL-1RL1 pathway could form a novel therapeutic approach to treat allergic diseases.



Part II

Functional translation of *IL33* and *IL1RL1* genotypes into asthma pathophysiology

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