Published in final edited form as:

Curr Opin Immunol. 2010 December ; 22(6): 800–806. doi:10.1016/j.coi.2010.10.006.

IL-33 family members and asthma – bridging innate and adaptive immune responses

Clare M Lloyd

Leukocyte Biology Section, National Heart and Lung Institute, Sir Alexander Fleming Building, Faculty of Medicine, Imperial College, South Kensington, London SW7 2AZ, UK

Abstract

The discovery of IL-33 as the ligand for the orphan Th2 associated receptor ST2 has uncovered a whole range of different avenues for this pathway. Although the extracellular functions of ST2 as a marker for Th2 cell and mast cell activity were well defined, the complexities of IL-33 regulation, nuclear function and secretion are only just being realised. The well documented expression pattern of ST2 has identified a role for the IL-33/ST2 axis in the classical Th2 cell and mast cell driven pathogenesis of asthma and anaphylaxis. However, the induction of IL-33 expression by environmental or endogenous triggers now suggests a wider role for the pathway during infection, inflammation and tissue damage.

Introduction

IL-33 and its receptor are part of the IL-1 family, and their interactions promote a variety of actions from a number of different cell types. Unique within the IL-1 family, IL-33 is associated with the promotion of systemic Th2 responses. The IL-33/ST2 axis is thought to be intimately involved in the promotion and maintenance of allergic inflammation via a number of cell types that include Th2 cells, mast cells and basophils, and structural cells such as airway epithelium and smooth muscle cells. Although first identified as a protein expressed by lymph node-associated endothelial cells bioinformatic analysis identified IL-33 as the ligand for the former orphan receptor ST2 [1]. IL-33 binds a heterodimeric receptor complex consisting of ST2 and the ubiquitously expressed IL-1R accessory protein (IL-1R-AP) which promotes signalling via the TIR domain of IL-1RAP and activates several signalling proteins including, NFkB and mitogen activated protein (MAP) kinases such as p38 and JNK [2,3] (Figure 1). This signalling cascade distinguishes IL-33 from the classical Th2 type cytokines which signal through JAK-STAT pathways. ST2 (also known as IL1RL1, T1, DER-4, Fit-1 or IL1R4) is a member of the TLR/IL-1R (TIR) family, and has 38% amino acid homology to the IL-1R. Due to differential splicing the ST2 gene encodes at least three isoforms of protein, a soluble form (sST2), a membrane bound form (ST2L) and a variant ST2 [4]. ST2 gene expression is widespread but the membrane bound form is most highly expressed on mast cells and T helper (Th2) cells [5,6]. This led to the association between the ST2/IL-33 axis and Th2 type pathologies such as asthma. More recent analysis has determined that IL-33 interacting with ST2 on a range of different leukocytes promotes a number of key inflammatory pathways that have the potential to initiate and propagate allergic inflammation [3].

IL-33 signalling

IL-33 localises to the nucleus of resting cells and binds chromatin via H2A–H2B histone complex, exerting a potential transcriptional repressor effect [7]. How it migrates from this nuclear localization for interaction with its extracellular receptor, ST2, is less clear. IL-33 lacks a specific signal peptide to enable it to be processed for secretion via the ER-Golgi pathway. Caspase-1 cleavage of pro-IL-33 has been reported *in vitro*, although IL-33 lacks a classical caspase-1 cleavage site. Also, in comparison to cleavage of IL-1 β , caspase-1 cleavage of IL-33 is inefficient and requires non-physiologic concentrations of caspase-1. In the absence of other caspases, caspase-1 is unable to cleave IL-33, suggesting that caspase-1 activates other proteases to mediate cleavage, and likely candidates include caspase 7 and 3, as well as calpain. Cleavage products are biologically inactive, and since protease cleavage of IL-33 occurs during apoptosis, release of biologically active full length IL-33 is thus limited [8*,9]. By contrast during necrotic processes uncleaved but biologically active IL-33 was released [10]. Although a substantial proportion of secreted IL-33 is actually full-length pro-IL33, its biologic potency remains questionable. The fact that IL-33 may be released by damaged cells undergoing necrotic cell death during infection or trauma, suggests it may function as an endogenous danger signal or ‘alarmin’ [11]. This function has also been attributed to IL-1 α and HMGB1, two proteins that have dual functions as nuclear proteins and extracellular cytokines. All three proteins lack classical secretion signals and display cytokine activity independent of processing, as well as being released by necrotic cells, but not apoptotic cells. Pathogens or allergens as well as other environmental agents (such as pollution) may trigger tissue damage which results in IL-33 secretion following necrotic cell death. This ‘alarmin’ function of IL-33 may thus propagate the exacerbations of asthma that complicate severe disease.

Regulation of IL-33 activity

The secretion capabilities of IL-33 have the potential to drive harmful inflammation, thus mechanisms have evolved to regulate IL-33 functions *in vivo*. A soluble form of the IL-33R, termed sST2, is able to sequester and neutralise IL-33. This sST2 develops as an alternatively spliced mRNA induced by serum as well as anti-inflammatory signals such as vitamin D. sST2 shares a common extracellular domain with ST2 but lacks the transmembrane and intracellular Toll-interleukin-1R domains [12]. Soluble ST2 acts as a decoy receptor to bind and functionally inhibit IL-33 activity *in vitro* and *in vivo* [13]. Pre-treatment of mice with sST2 reduced Th2 cytokine production in a murine model of asthma [14]. Another IL-1R family member termed single Ig IL-1 Receptor-related molecule/Toll IL-1R8 (SIGIRR, also referred to as TIR8) is also a negative regulator for IL-33 (as well as IL-1R1, TLR4 and TLR9) [15*]. SIGIRR forms a complex with ST2 upon IL-33 stimulation and specifically inhibits IL-33/ST2 signalling *in vitro* and *in vivo*. IL-33 induced Th2 responses are enhanced in SIGIRR deficient mice and stronger allergen specific Th2 pathology develop in the absence of SIGIRR during an asthma model [15*].

Expression of ST2 on leukocytes involved in the asthmatic response

ST2 is expressed on Th2 cells and IL-33 is able to influence Th2 function *in vitro* and *in vivo* (Figure 2). IL-33 promotes secretion of the Th2 cytokines IL-5 and IL-13 from Th2 cells derived from allergic donors after TCR-dependent or independent stimulation [16]. Interestingly, substantial amounts of IFN γ were also produced. In the presence of allergen, IL-33 is able to polarise mouse or human naive CD4⁺ T cells into a population of T cells that produce mainly IL-5 but not IL-4 [17*]. This polarisation is dependent upon MyD88 and SIGIRR, together with phosphorylation of MAPKs and NF- κ B. However, neither IL-4 nor STAT-6 was involved, and the Th2/Th1 lineage transcription factors GATA-3 and T-bet

were not induced [17*]. In addition, IL-33 is able to recruit and activate both mouse and human Th2 cells via an undefined mechanism [18].

ST2 is a lineage marker for mast cells as well as for Th2 cells, and is expressed during multiple stages of development, including the earliest detectable committed precursors in the mouse [19]. Human CD34+ progenitor cells express ST2 *in vivo* and *in vitro*, and respond to IL-33 stimulation by producing large amounts of Th2 cytokines and chemokines, such as IL-5, IL-13, IL-6 and CXCL8, CCL1 and CCL17 – all of which can escalate allergic inflammatory reactions [20]. Addition of IL-33 to *in vitro* cultures of CD34+ cells rapidly accelerates their maturation into tryptase-containing mast cells [21]. IL-33 synergises with IgE receptor cross linking to enhance production of CXCL8 in mast cells [22]. Moreover, IL-33 enhanced IgE-mediated degranulation and leukotriene synthesis in primary human mast cells. Since IL-33 augments mast cell survival and adhesion to fibronectin, ST2/IL-33 interactions on mast cells may serve not only to promote maturation and activation, but also to maintain their localisation within the tissue [23]. IL-33 also exerts distinct effects on basophils. IL-33/ST2 interactions enhanced degranulation in response to IgE cross-linking stimuli and enhanced basophil migration to eotaxin without effect on surface expression of CCR3 [22,24]. Moreover, IL-33 synergises with IL-3 to promote IL-4 production and CD11b expression by basophils.

Human eosinophils, but not neutrophils express ST2 mRNA. Although protein was undetectable on freshly isolated eosinophils, an *in vitro* culture in medium induced expression of ST2 protein, which increased with addition of GM-CSF [25]. Consequently IL-33 induced eosinophil superoxide anion production and degranulation as potently as IL-5. Moreover these responses were blocked after incubation with anti-ST2. IL-33 also potently induces eosinophil adhesion via up-regulation of CD11b expression and enhances eosinophil survival [26].

Macrophages express ST2 and receptor expression is enhanced by IL-13 [27]. IL-33 has a profound effect on the phenotype of alveolar macrophages, driving them towards an alternatively activated (AAM) phenotype that express the mannose receptor, IL-4Ra and produce high levels of CCL24 and CCL17, both of which are critical during allergic inflammation. Similarly IL-33 amplified the IL-13 induced polarisation of alveolar and bone marrow derived macrophages *in vitro* by increasing expression of arginase-I, Ym1 and CCL24 and CCL17. IL-33 sequesters in the nucleus of monocytes undergoing apoptosis, but is released into the extracellular milieu by LPS-stimulated cells in which necrosis had been induced by 'freeze-thawing' [28].

The IL-33 repertoire was recently expanded to include effects on DC function [29]. IL-33 is able to promote the generation of myeloid DC (CD11c⁺CD11b⁺CD205⁺) in cultures of murine BM via a process involving GM-CSF production from other cells, which the authors propose to be basophils. Although they showed normal dendritic morphology, these IL-33 generated DCs were functionally immature. Specifically, they expressed only low levels of MHC Class II, did not respond to TLR ligands and failed to activate naive T cells. These DCs are likened to maturation-resistant 'tolerogenic' DC such as those generated with IL-10 or pharmacologic agents [30]. Although this finding has yet to be confirmed *in vivo*, it is interesting to speculate whether the IL-33/ST2 axis is able to regulate professional APC function during immune responses.

Purified iNKT cells express ST2 and respond to IL-33, although on TCR engagement IFN- γ rather than IL-4 is induced [16,31]. A combination of IL-33 and IL-12 enhanced IFN- γ from both NKT and iNKT cells. Moreover IL-33 together with α -galactosylceramide induced both

IL4 and IFN- γ . These data show that IL-33 can enhance both Th1-type and Th-2-type responses, which is likely to be of importance in development of severe asthma [32].

Expression of IL-33 in the lung

Constitutive expression of IL-33 has been determined in a number of tissues, primarily stromal cells, including fibroblasts, cardiomyocytes, keratinocytes, adipocytes and epithelial cells at mucosal surfaces [33]. A recent study used a combination of tissue microarrays and antibody staining and showed widespread expression of IL-33 in the endothelial cells of large and small vessels in most normal human tissues, as well as tumours [11]. Constitutive nuclear expression of IL-33 was also observed in fibroblastic cells of lymphoid tissues, and epithelial cells of certain tissues exposed to the environment, including skin keratinocytes, epithelial cells in the gut, tonsillar crypts and salivary glands. Considerable variation was observed in staining patterns between tissue samples and within each sample, suggesting that expression may be influenced by environmental cues, such as microflora, allergens and certain pathogens. Interestingly the authors did not comment on expression in the lung. However, analysis of mouse and human cDNA libraries and quantitative PCR has shown that IL-33 is constitutively expressed in epithelial cells of the bronchus and small airways [1]. In addition, recent endobronchial biopsy studies have revealed an association between IL-33 and severe asthma [34*,35]. IL-33 expression was determined in airway smooth muscle cells (ASMC) by a number of methods including PCR, ELISA and Western blotting to show higher expression of IL-33 in subjects with asthma compared to non-asthmatic controls, and a particular association with severe asthma [35]. TNF α was shown to increase IL-33 expression in ASMC *in vitro*, and dexamethasone failed to block this up-regulation. The same group have also determined that epithelial cells in bronchial asthma show increased expression of IL-33 [34*]. Widespread staining of IL-33 was observed throughout the epithelium in sections from asthmatic subjects. Quantitative assessment revealed that there was an increase in staining intensity in severe asthmatics compared with healthy controls. Moreover, significant levels of IL-33 were measured in bronchiolar lavage from moderate, but not mild, asthmatics compared to normal controls.

IL-33/ST2 interactions drive allergic pathology *in vivo*

Evidence that IL-33/ST2 interactions are functionally important in allergic inflammation comes from mouse model studies which have manipulated ligand/receptor interactions. Administration of blocking anti-ST2 antibodies or ST2-Ig fusion protein to allergic mice abrogated Th2 cytokine production *in vivo*, eosinophilic pulmonary inflammation and AHR but had no effect on Th1 driven airway inflammation [5]. Similarly, anti-IL-33 antibodies ameliorated eosinophil recruitment, Th2 cytokine production, serum IgE and mucus production [36]. Conversely administration of IL-33 directly into the lung induces AHR and goblet cell hyperplasia, and lung IL-4, IL-5 and IL-13 [27,37*]. Strikingly, intranasal IL-33 also induced this allergic pathology even in the absence of T and B cells [37*]. Moreover, when instilled concurrent with antigen sensitisation IL-33 induces antigen-specific IL-5⁺ T cells and promotes allergic airway disease even in the absence of IL-4 [17*]. Genetic overexpression of IL-33 also leads to spontaneous eosinophilic inflammation in a mIL-33 transgenic mouse [38]. Blockage studies have also determined that the IL-33/ST2 pathway not only promotes Th2 responses but also maintains AHR during allergen challenge [39]. However, the role of the IL-33/ST axis in promoting allergic airway disease is not straightforward, since ST2 knockout mice are not protected from OVA-induced inflammation and eosinophilia [40,41]. The fact that ST2 mice are protected in a short term priming model of allergic inflammation might indicate the contribution of mast cells since in the short term model mast cells play a more dominant role. However it is clear that the

IL-33/ST2 pathway exerts distinct effects in the lung although the precise role of IL-33 and sST2 and membrane bound ST2 in different models of asthma remains unclear.

The function of IL-33 secretion from epithelium is likely of critical importance. Several lines of evidence show that administration of IL-33 to the lung results in initiation of Th2 type immunity via IL-4 and IL-13. Interestingly, this can occur in the absence of T and B cells or IL-4 [17*]. An explanation for this may come from the recent finding that treatment of mice with either IL-33, or IL-25, results in a novel type of 'innate lymphoid cell' in the gut. These cells have been termed nuocytes [42*], multi-potent progenitor type-2 cells [43*] or natural helper cells [44*] and express IL-13 and IL-4 and promote type 2 immune activity in the gut. It seems likely that these innate lymphoid helper cells may provide immunity earlier but less specifically than conventional type 2 cells. It remains to be seen if they occur following immune responses other than worm infection but since allergen directly promotes release of IL-33, and IL-25 from the pulmonary epithelium it seems likely that generation of innate lymphoid cells will occur following allergen exposure.

IL-33 and heterogeneity of asthma phenotypes

Asthma has classically been viewed as a Th2 mediated disease with therapeutic efforts directed towards blocking Th2 cytokines and preventing eosinophil recruitment and survival. However, this view is rapidly changing with the realisation that distinct clinical phenotypes of asthma exist coupled with the fact that results from trials targeting the Th2 response have been underwhelming [45]. A central role for the pulmonary epithelium in directing and propagating allergic responses has been proposed (Figure 3). The discovery that allergens can trigger pattern recognition receptors such as Toll-like receptors on the epithelium is central to this theory [46*]. Interestingly, allergen activated TLR4 signalling results in the generation of IL-33, as well as IL-25 and TSLP. This group of innate pro-allergic cytokines are able to promote allergen specific Th2 responses via dendritic cell recruitment and activation, but since IL-33 (and IL-25) is able to promote allergic type inflammation even in the absence of Th2 cytokines, this pathway represents an important mechanism for development of allergic pathology. Importantly, these results were generated using an allergen challenge protocol involving inhalation of the environmental allergen house dust mite in naive animals, and in the future it will be interesting to determine the effects of manipulating the IL-33/ST2 axis during this type of model, rather than the classical OVA Th2 driven model, which uses peritoneal sensitisation with a Th2 skewing adjuvant [45].

SNPS in asthma

Genetic evidence is accumulating to increase the association between IL-33/ST2 and development of asthma. IL-33 levels have been shown to be increased in severe asthma [35] as well as patients with allergic pollinosis [47] and in atopic patients with anaphylaxis [48]. Genetic analysis has linked polymorphisms in the IL-33 and ST2 genes with asthma and allergy-related traits [2]. Single nucleotide polymorphisms (SNPs) in the IL-33 gene have been associated with asthma, eosinophils and also allergic rhinitis [47,49] whereas SNPs in the ST2 locus have been associated with childhood asthma, asthma and airway function [49–51]. In addition, a genome wide association study of over 10,000 asthmatics revealed associations with IL-33 [52]. Although further analysis is required to ensure that these genetic associations have functional correlates these large scale analyses provide further evidence for the involvement of the IL-33/ST2 axis in development of human disease.

Conclusions

IL-33 is a central player in the development of allergic inflammation. Although the expression pattern of its receptor, ST2 implicated an association in generating type 2 immune reactions some of the novel functions assigned to this receptor/ligand axis indicate an expanding role. The fact that IL-33 is able to function as an 'alarmin' and will be secreted following tissue damage is important in the context of the lung. The pulmonary epithelium is prone to damage from pathogens such as viruses, air pollution and also protease activity of allergens. All of these molecules promote epithelial damage that results in IL-33 production. IL-33 can then exert profound effects on the adaptive immune system to promote Th2 differentiation and eosinophil and mast cell activation. However, the exciting novel effects of IL-33 on the innate immune system to promote innate lymphoid cells outline a dual role for IL-33 to activate both arms of the immune system.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest

- Schmitz J, Owyang A, Oldham E, Song Y, Murphy E, McClanahan TK, Zurawski G, Moshrefi M, Qin J, Li X, et al. IL-33, an interleukin-1-like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines. *Immunity*. 2005; 23:479–490. [PubMed: 16286016]
- Smith DE. IL-33: a tissue derived cytokine pathway involved in allergic inflammation and asthma. *Clin Exp Allergy*. 2010; 40:200–208. [PubMed: 19906013]
- Liew FY, Pitman NI, McInnes IB. Disease-associated functions of IL-33: the new kid in the IL-1 family. *Nat Rev Immunol*. 2010; 10:103–110. [PubMed: 20081870]
- Tago K, Noda T, Hayakawa M, Iwahana H, Yanagisawa K, Yashiro T, Tominaga Si. Tissue distribution and subcellular localization of a variant form of the human ST2 gene product, ST2 V. *Biochem Biophys Res Commun*. 2001; 285:1377–1383. [PubMed: 11478810]
- Coyle AJ, Lloyd C, Tian J, Nguyen T, Eriksson C, Wang L, Ottoson P, Persson P, Delaney T, Lehar S, et al. Crucial role of the interleukin 1 receptor family member T1/ST2 in T helper cell type 2-mediated lung mucosal immune responses. *J Exp Med*. 1999; 190:895–902. [PubMed: 10510079]
- Xu D, Chan WL, Leung BP, Huang Fp, Wheeler R, Piedrafita D, Robinson JH, Liew FY. Selective expression of a stable cell surface molecule on type 2 but not type 1 helper T cells. *J Exp Med*. 1998; 187:787–794. [PubMed: 9480988]
- Roussel L, Erard M, Cayrol C, Girard JP. Molecular mimicry between IL-33 and KSHV for attachment to chromatin through the H2A-H2B acidic pocket. *EMBO Rep*. 2008; 9:1006–1012. [PubMed: 18688256]
- Lüthi AU, Cullen SP, McNeela EA, Duriez PJ, Afonina IS, Sheridan C, Brumatti G, Taylor RC, Kersse K, Vandenabeele P, et al. Suppression of interleukin-33 bioactivity through proteolysis by apoptotic caspases. *Immunity*. 2009; 31:84–98. [PubMed: 19559631] [This paper reports that IL-33 is inactivated by caspase cleavage, but that biologically active IL-33 is released after cellular damage, and that it may function as 'alarmin'.]
- Talabot-Ayer D, Lamacchia C, Gabay C, Palmer G. Interleukin-33 is biologically active independently of caspase-1 cleavage. *J Biol Chem*. 2009; 284:19420–19426. [PubMed: 19465481]
- Cayrol C, Girard JP. The IL-1-like cytokine IL-33 is inactivated after maturation by caspase-1. *PNAS*. 2009; 106:9021–9026. [PubMed: 19439663]
- Moussion C, Ortega N, Girard JP. The IL-1-like cytokine IL-33 is constitutively expressed in the nucleus of endothelial cells and epithelial cells *in vivo*: a novel "alarmin"? *PLoS ONE*. 2008; 3:e3331. [PubMed: 18836528]

12. Palmer G, Lipsky BP, Smithgall MD, Meininger D, Siu S, Talabot-Ayer D, Gabay C, Smith DE. The IL-1 receptor accessory protein (AcP) is required for IL-33 signaling and soluble AcP enhances the ability of soluble ST2 to inhibit IL-33. *Cytokine*. 2008; 42:358–364. [PubMed: 18450470]
13. Hayakawa M, Hayakawa H, Matsuyama Y, Tamemoto H, Okazaki H, Tominaga Si. Mature interleukin-33 is produced by calpain-mediated cleavage *in vivo*. *Biochem Biophys Res Commun*. 2009; 387:218–222. [PubMed: 19596270]
14. Hayakawa H, Hayakawa M, Kume A, Tominaga Si. Soluble ST2 blocks interleukin-33 signaling in allergic airway inflammation. *J Biol Chem*. 2007; 282:26369–26380. [PubMed: 17623648]
15. Bulek K, Swaidani S, Qin J, Lu Y, Gulen MF, Herjan T, Min B, Kastelein RA, Aronica M, Kosz-Vnenchak M, Li X. The essential role of single Ig IL-1 receptor-related molecule/toll IL-1R8 in regulation of Th2 immune response. *J Immunol*. 2009; 182:2601–2609. [PubMed: 19234154]
[This paper outlines a functional role for SIGIRR in regulating allergic inflammation *in vivo*.]
16. Smithgall MD, Comeau MR, Yoon BR Park, Kaufman D, Armitage R, Smith DE. IL-33 amplifies both Th1- and Th2-type responses through its activity on human basophils, allergen-reactive Th2 cells, iNKT and NK Cells. *Int Immunol*. 2008; 20:1019–1030. [PubMed: 18550585]
17. Kurowska-Stolarska M, Kewin P, Murphy G, Russo RC, Stolarski B, Garcia CC, Komai-Koma M, Pitman N, Li Y, McKenzie ANJ, et al. IL-33 induces antigen-specific IL-5+ T cells and promotes allergic-induced airway inflammation independent of IL-4. *J Immunol*. 2008; 181:4780–4790. [PubMed: 18802081] [The first report that IL-33 may direct allergic pathology *in vivo*, even in the absence of IL-4 and Th2 lineage transcription factors, indicating that IL-33 may exert its effects via mechanisms that do not involve T cells.]
18. Komai-Koma M, Xu D, Li Y, McKenzie ANJ, McInnes IB, Liew FY. IL-33 is a chemoattractant for human Th2 cells. *Eur J Immunol*. 2007; 37:2779–2786. [PubMed: 17853410]
19. Moritz DR, Rodewald HR, Gheyselinck J, Klemenz R. The IL-1 receptor-related T1 antigen is expressed on immature and mature mast cells and on fetal blood mast cell progenitors. *J Immunol*. 1998; 161:4866–4874. [PubMed: 9794420]
20. Allakhverdi Z, Michael RC, Dirk E, Smith, Dean T, Leandra ME, Martin D, Yong-Jun L, Karen JH, Judah AD, Gail MG, Guy D. CD34+ hemopoietic progenitor cells are potent effectors of allergic inflammation. *J Allergy Clin Immunol*. 2009; 123:472–478. [PubMed: 19064280]
21. Allakhverdi Z, Smith DE, Colmeau MR, Delespesse G. Cutting edge: the ST2 ligand IL-33 potently activates and drives maturation of human mast cells. *J Immunol*. 2007; 179:2051–2054. [PubMed: 17675461]
22. Silver M, Margulis A, Wood N, Goldman S, Kasaian M, Chaudhary D. IL-33 synergizes with IgE-dependent and IgE-independent agents to promote mast cell and basophil activation. *Inflamm Res*. 2010; 59:207–218. [PubMed: 19763788]
23. Iikura M, Suto H, Kajiwarra N, Oboki K, Ohno T, Okayama Y, Saito H, Galli SJ, Nakae S. IL-33 can promote survival, adhesion and cytokine production in human mast cells. *Lab Invest*. 2007; 87:971–978. [PubMed: 17700564]
24. Suzukawa M, Iikura M, Koketsu R, Nagase H, Tamura C, Komiya A, Nakae S, Matsushima K, Ohta K, Yamamoto K, Yamaguchi M. An IL-1 cytokine member, IL-33, induces human basophil activation via its ST2 receptor. *J Immunol*. 2008; 181:5981–5989. [PubMed: 18941187]
25. Cherry WB, Juhan Y, Kathleen RB, Koji I, Hirohito K. A novel IL-1 family cytokine, IL-33, potently activates human eosinophils. *J Allergy Clin Immunol*. 2008; 121:1484–1490. [PubMed: 18539196]
26. Suzukawa M, Koketsu R, Iikura M, Nakae S, Matsumoto K, Nagase H, Saito H, Matsushima K, Ohta K, Yamamoto K, Yamaguchi M. Interleukin-33 enhances adhesion, CD11b expression and survival in human eosinophils. *Lab Invest*. 2008; 88:1245–1253. [PubMed: 18762778]
27. Kurowska-Stolarska M, Stolarski B, Kewin P, Murphy G, Corrigan CJ, Ying S, Pitman N, Mirchandani A, Rana B, van Rooijen N, et al. IL-33 amplifies the polarization of alternatively activated macrophages that contribute to airway inflammation. *J Immunol*. 2009; 183:6469–6477. [PubMed: 19841166]
28. Nile CJ, Emma B, Paiboon J, Philip MP, John JT. Expression and regulation of interleukin-33 in human monocytes. *Immunology*. 2010; 130:172–180. [PubMed: 20070408]

29. Nobuyasu M, Hironori M, Akira T. IL-33 promotes DC development in BM culture by triggering GM-CSF production. *Eur J Immunol.* 2009; 39:3331–3342. [PubMed: 19750479]
30. Turnquist HR, Thomson AW. IL-33 broadens its repertoire to affect DC. *Eur J Immunol.* 2009; 39:3292–3295. [PubMed: 19877020]
31. Elvire B, Linh PV, Michel S, Séverine D, Anne B, Stéphane R, Jean-Marc G, Elke S, Michel D, Pierre G, et al. The pro-Th2 cytokine IL-33 directly interacts with invariant NKT and NK cells to induce IFN-gamma production. *Eur J Immunol.* 2009; 39:1046–1055. [PubMed: 19266498]
32. Bulek K, Swaidani S, Aronica M, Li X. Epithelium: the interplay between innate and Th2 immunity. *Immunol Cell Biol.* 2010; 88:257–268. [PubMed: 20065993]
33. Haraldsen G, Balogh J, Pollheimer J, Sponheim J, Kochler AM. Interleukin-33-cytokine of dual function or novel alarmin? *Trends Immunol.* 2009; 30:227–233. [PubMed: 19359217]
34. Prefontaine D, Jessica N, Fazila C, Severine A, Abdelhabib S, Jamila C, James GM, Qutayba H. Increased IL-33 expression by epithelial cells in bronchial asthma. *J Allergy Clin Immunol.* 2010; 125:752–754. [PubMed: 20153038] [The first direct demonstration that IL-33 is found in the epithelium during asthma and correlates with disease severity.]
35. Prefontaine D, Lajoie-Kadoch S, Foley S, Audusseau S, Olivenstein R, Halayko AJ, Lemiere C, Martin JG, Hamid Q. Increased expression of IL-33 in severe asthma: evidence of expression by airway smooth muscle cells. *J Immunol.* 2009; 183:5094–5103. [PubMed: 19801525]
36. Liu X, Li M, Wu Y, Zhou Y, Zeng L, Huang T. Anti-IL-33 antibody treatment inhibits airway inflammation in a murine model of allergic asthma. *Biochem Biophys Res Commun.* 2009; 386:181–185. [PubMed: 19508862]
37. Kondo Y, Yoshimoto T, Yasuda K, Futatsugi-Yumikura S, Morimoto M, Hayashi N, Hoshino T, Fujimoto J, Nakanishi K. Administration of IL-33 induces airway hyperresponsiveness and goblet cell hyperplasia in the lungs in the absence of adaptive immune system. *Int Immunol.* 2008; 20:791–800. [PubMed: 18448455] [With Ref. [17*], shows that IL-33 is able to promote Th2 type immune pathology, including changes in airway function, even in mice that do not have T or B cells.]
38. Zhiguang X, Wei C, Steven R, Wei D, Wei Z, Rong M, Zhanguo L, Lianfeng Z. Over-expression of IL-33 leads to spontaneous pulmonary inflammation in mIL-33 transgenic mice. *Immunol Lett.* 2010; 131:159–165. [PubMed: 20412815]
39. Kearley J, Buckland KF, Mathie SA, Lloyd CM. Resolution of allergic inflammation and AHR is dependent upon disruption of the T1/St2-IL-33 pathway. *Am J Respir Crit Care Med.* 2009
40. Townsend MJ, Fallon PG, Matthews DJ, Jolin HE, McKenzie ANJ. T1/St2-deficient mice demonstrate the importance of T1/St2 in developing primary T helper cell type 2 responses. *J Exp Med.* 2000; 191:1069–1076. [PubMed: 10727469]
41. Hoshino K, Kashiwamura Si, Kuribayashi K, Kodama T, Tsujimura T, Nakanishi K, Matsuyama T, Takeda K, Akira S. The absence of interleukin 1 receptor related T1/St2 does not affect T helper cell type 2 development and its effector function. *J Exp Med.* 1999; 190:1541–1548. [PubMed: 10562328]
42. Neill DR, Wong SH, Bellosi A, Flynn RJ, Daly M, Langford TKA, Bucks C, Kane CM, Fallon PG, Pannell R, et al. Nuocytes represent a new innate effector leukocyte that mediates type-2 immunity. *Nature.* 2010; 464:1367–1370. [PubMed: 20200518]
43. Saenz SA, Siracusa MC, Perrigoue JG, Spencer SP, Urban JF Jr, Tocker JE, Budelsky AL, Kleinschek MA, Kastelein RA, Kambayashi T, et al. IL25 elicits a multipotent progenitor cell population that promotes TH2 cytokine responses. *Nature.* 2010; 464:1362–1366. [PubMed: 20200520]
44. Moro K, Yamada T, Tanabe M, Takeuchi T, Ikawa T, Kawamoto H, Furusawa Ji, Ohtani M, Fujii H, Koyasu S. Innate production of TH2 cytokines by adipose tissue-associated c-Kit +Sca-1+lymphoid cells. *Nature.* 2010; 463:540–544. [PubMed: 20023630] [This series of papers describe novel innate type lymphocytes in the gut, that in Refs. [42*,43*,44*] were induced by administration of IL-33. These results highlight IL-33 as a key factor in early innate responses as well as during adaptive Th2 responses.]
45. Lloyd CM, Saglani S. Asthma and allergy: the emerging epithelium. *Nat Med.* 2010; 16:273–274. [PubMed: 20208514]

46. Hammad H, Chieppa M, Perros F, Willart MA, Germain RN, Lambrecht BN. House dust mite allergen induces asthma via Toll-like receptor 4 triggering of airway structural cells. *Nat Med*. 2009; 15:410–416. [PubMed: 19330007] [This shows that allergens with proteolytic activity can directly trigger TLR4 on the pulmonary epithelial surface resulting in the production of IL-33. These data indicate that exposure to allergen results in IL-33 activity from the epithelium which can initiate or amplify allergic immunopathology.]
47. Sakashita M, Yoshimoto T, Hirota T, Harada M, Okubo K, Osawa Y, Fujieda S, Nakamura Y, Yasuda K, Nakanishi K, Tamari M. Association of serum interleukin-33 level and the interleukin-33 genetic variant with Japanese cedar pollinosis. *Clin Exp Allergy*. 2008; 38:1875–1881. [PubMed: 19037964]
48. Pushparaj PN, Tay HK, H'ng SC, Pitman N, Xu D, McKenzie A, Liew FY, Melendez AJ. The cytokine interleukin-33 mediates anaphylactic shock. *PNAS*. 2009; 106:9773–9778. [PubMed: 19506243]
49. Gudbjartsson DF, Bjornsdottir US, Halapi E, Helgadottir A, Sulem P, Jonsdottir GM, Thorleifsson G, Helgadottir H, Steinthorsdottir V, Stefansson H, Williams C, et al. Sequence variants affecting eosinophil numbers associate with asthma and myocardial infarction. *Nat Genet*. 2009; 41:342–347. [PubMed: 19198610]
50. Ali M, Zhang G, Thomas WR, McLean CJ, Bizzintino JA, Laing IA, Martin AC, Goldblatt J, Le S, Hayden CM. Investigations into the role of ST2 in acute asthma in children. *Tissue Antigens*. 2009; 73:206–212. [PubMed: 19254249]
51. Naomi E, Reijmerink, Dirkje S, Postma, Marcel B, Ilja MN, Deborah AM, Eugene RB, Gerard HK. Association of IL1RL1, IL18R1, and IL18RAP gene cluster polymorphisms with asthma and atopy. *J Allergy Clin Immunol*. 2008; 122:651–654. [PubMed: 18774397]
52. Moffatt MF, Gut IG, Demenais F, Strachan D, Bouzigon E, Heath S, von Mutius E, Farrall M, Lathrop M, Cookson WOC, the GABRIEL consortium. A GABRIEL consortium large-scale genome-wide association study of asthma. *New Engl J Med*. 2010 in press.

Figure 1.

IL-33 signalling pathways. IL-33 mediates its function by binding to a receptor complex comprising ST2 and IL-1 receptor accessory protein (IL-1RAP) leading to the recruitment of the myeloid differentiation primary-response protein 88 (MYD88) complex. Although the mechanism is unclear, the complex is thought to activate at least two independent pathways involving the mitogen activated protein kinase (MAPK) pathway as well as the phospholipase D (PLD)-sphingosine kinase (SPHK) pathway, ultimately leading to activation of MAP kinases and NFκB. SIGIRR acts as a negative regulator for signalling, and soluble ST can bind directly to IL-33 thus acting as a decoy receptor. Although biologically active IL-33 is generated passively by necrotic cells, caspase cleavage during apoptosis leads to inactivation.

Leukocyte		Effect of IL-33/ST2 interaction
Th2 cell		Th2 generation ↑IL-5, IL-13
Eosinophil		<ul style="list-style-type: none"> •↑Superoxide anion release •↑Degranulation •↑Adhesion via CD11b •↑survival
Macrophage		Development of Alternatively activated phenotype <ul style="list-style-type: none"> •↑IL-4Rα •↑Mannose Receptor •↑CCL11, CCL24, CCL17
Mast cell		Maturation <ul style="list-style-type: none"> •↑IL-5, IL-13, IL-6 production •↑CXCL8, CCL1, CCL17
NK cell		<ul style="list-style-type: none"> •+ IL-12 leads to ↑ IFN-γ production •+α-gal-cer leads to ↑IL-4 and IFN-γ production

Figure 2.

Leukocyte expression of ST2 and effect of interaction with IL-33. ST2 is expressed on a number of leukocytes involved in the asthmatic response and binding of IL-33 results in a wide variety of effects that influence the course of allergic reactions.

Figure 3.

IL-33 in asthma. Exposure to airborne allergens, pollution, respiratory viruses causes damage to the pulmonary epithelium and/or activation of pattern recognition receptors such as TLRs leading to the release of IL-33 from lung structural cells such as epithelial cells. IL-33 likely drives allergen sensitisation via effects on airway dendritic cells and development of Th2 mediated pathology via generation of IL-4, IL-5 and IL-13. IL-33 leads to the generation of macrophages with an alternatively activated phenotype and to the recruitment, maturation and survival of eosinophils. Importantly, IL-33 is able to induce airway hyperresponsiveness via mast cells and IL-13.