

## Minireview

# Targeting IL-33 in Autoimmunity and Inflammation

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### ABSTRACT

Interleukin-33 (IL-33) belongs to the IL-1 family of cytokines. Whereas IL-1 is processed and released by live immune cells in response to infection or other triggers, IL-33 is mostly released as a danger signal ("alarmin") from damaged cells. IL-33 may also be processed and released from activated mast cells (MCs) with subsequent autocrine and paracrine actions. IL-33 augments the stimulatory effects of IgE and substance P on MCs but can also trigger release of cytokines from MCs on its own. Blood IL-33 levels are increased in asthma, atopic dermatitis,

multiple sclerosis, rheumatoid arthritis, and Sjögren's syndrome. However, prolonged elevation of IL-33 downregulates Fc $\alpha$ RI and may be protective in atherosclerosis, suggesting different roles in immune-regulated diseases. Even though neutralizing IL-33, knocking-down its receptor, or using its soluble "decoy" receptor has resulted in anti-inflammatory effects, there appear to be different outcomes in different tissues. Hence, selective regulation of IL-33 synthesis, release, and signaling may be required to provide effective treatment options.

### Introduction

**Interleukin-33 Structure and Function.** There are 11 known members of the interleukin (IL)-1 family. IL-33 is a new member of the IL-1 family that regulates innate and adaptive immune systems to promote inflammatory responses (Dinarello, 2009). IL-33 is mainly expressed by keratinocytes, epithelial and endothelial cells (Moussion et al., 2008), as well as by human monocytes (Nile et al., 2010) and mouse astrocytes (Kempuraj et al., 2013). IL-33 acts as an alarmin against injury-induced stress, pathogens, or cell death by activating local immune cells (Lukens et al., 2012; Lunderius-Andersson et al., 2012).

IL-1 $\alpha$  and IL-1 $\beta$  are both synthesized in proforms and require proteolytic cleavage for their activation and release through what has been termed the NOD-like receptor family, pyrin domain-containing 3 (NLRP3) "inflammasome" (Schroder et al., 2010; Franchi and Nunez, 2012). The cysteine protease caspase 1 must be cleaved and activated from its

proform and it is then organized into the NLRP3 inflammasome (Schroder et al., 2010). Pro-IL-1 $\alpha$  (31 kDa) must be cleaved by caspase 1 to generate the active form (17 kDa) (Arend et al., 2008), which is normally conserved within the cell, mainly bound to the plasma membrane, or localized in the nucleus (Dinarello et al., 2012).

IL-33 is synthesized in its proform (30 kDa), but its processing does not appear to involve the NLRP3 inflammasome (Schroder et al., 2010). In contrast, caspase-1 cleaves pro-IL-33 into an inactive form (Cayrol and Girard, 2009). Moreover, unlike pro-IL-1 $\alpha$ , the proform of IL-33 is biologically active and also contains nuclear localization sequences (like pro-IL-1 $\alpha$ ) allowing it to act both as an intracellular nuclear factor and as an extracellular cytokine (Zhao and Hu, 2010). Proteases such as calpain, cathepsin G, and elastase can cleave pro-IL-33 into more potent mature forms (Lefrançois et al., 2012; Garlanda et al., 2013) (Fig. 1). It was recently reported that chymase and tryptase secreted from mast cells (MCs) can generate IL-33 forms that are 30-fold more potent than full-length IL-33 (Lefrançois, et al., 2014).

IL-33 primarily induces the production of Th2-associated cytokines (Dinarello, 2002) but can also activate CD8<sup>+</sup> cells

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ABBREVIATIONS: AD, atopic dermatitis; CCL2, chemokine ligand 2; hBD2, human b-defensin 2; IFN, interferon; IL, interleukin; JNK, c-Jun N-terminal kinases; MC, mast cell; MS, multiple sclerosis; NF- $\kappa$ B, nuclear factor- $\kappa$ B; NLRP3, NOD-like receptor family, pyrin domain-containing 3; SCF, stem cell factor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

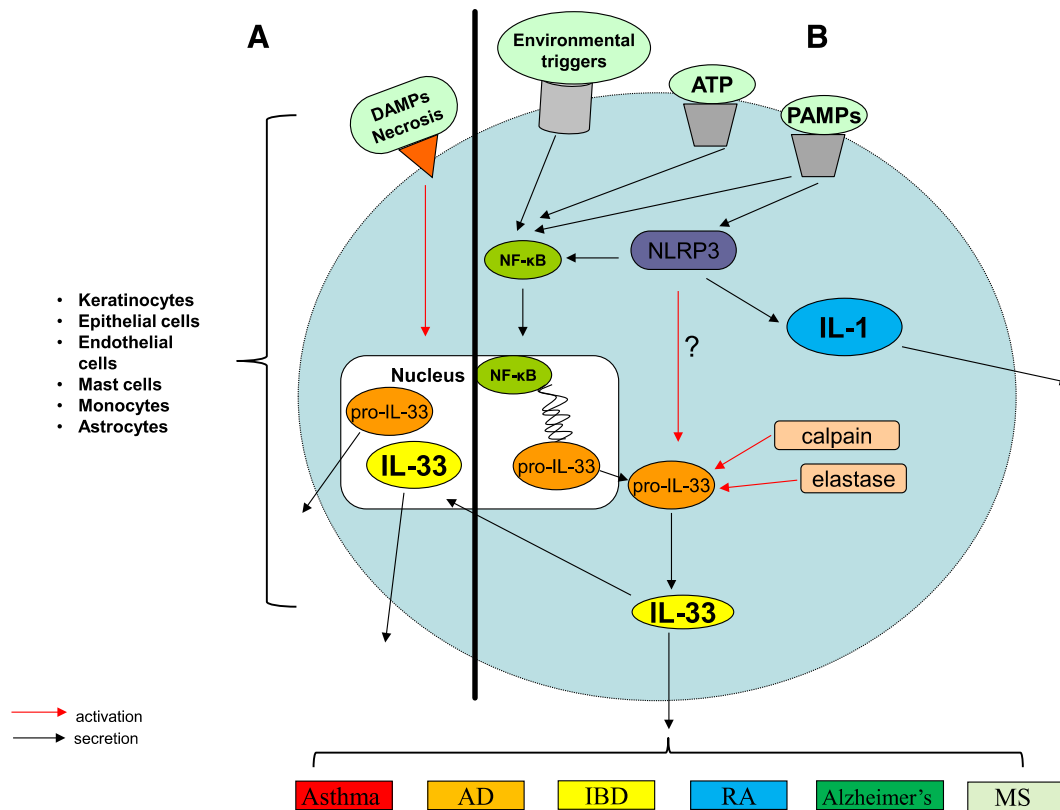


Fig. 1. Diagrammatic representation of the proposed steps for the activation and release of IL-33. (A) Damage-associated molecular patterns (DAMPs), IFN- $\gamma$ , and other triggers activate immune cells, including mast cells, to release both active pro-IL-33 and active IL-33 extracellularly, where they act as alarmins for other cells. (B) Pathogen-associated molecular patterns (PAMPs), ATP, and other environmental or innate triggers activate either NF- $\kappa$ B directly or the inflammasome (NLRP3) to generate IL-1. In addition, NF- $\kappa$ B induces the synthesis of pro-IL-33, which is then acted upon by calpain and elastase to generate active IL-33. The vertical black line is meant to distinguish (A) from (B). IL-33 is mainly expressed by keratinocytes, epithelial and endothelial cells, as well as by monocytes, mast cells, and astrocytes (the cell types are listed on the basis of the strength of the evidence). IL-33 is involved in the pathogenesis of a number of diseases that are listed in boxes with the colors of the rainbow meant to indicate the strength of the evidence. IBD, inflammatory bowel disease; RA, rheumatoid arthritis.

(Villarreal and Weiner, 2014). IL-33 induces lymphoid cell-mediated airway inflammation by also activating the mammalian target of rapamycin (Salmond et al., 2012).

Despite IL-33 sharing the IL-1 receptor accessory protein with other members of the IL-1 family that are known to upregulate an inducible antimicrobial peptide human b-defensin 2 (hBD2), IL-33 downregulates serum-induced hBD2 in human primary keratinocytes; this finding may explain the increased colonization rate of *Staphylococcus aureus* seen in atopic dermatitis (AD) patients (Alase et al., 2012). Interestingly, hBD2 has been reported to activate human MCs (Subramanian et al., 2013).

**Regulation of IL-33 Expression.** IL-33 expression is induced by pathogen-associated molecular patterns and environmental triggers (Lloyd, 2010). Interestingly, extracellular ATP was reported to act as a sensor for airborne allergens (Kouzaki et al., 2011). IL-33 can also be induced by triggers of Toll-like receptors (Zhang et al., 2011b) that are also present on MCs and can be activated by bacterial and viral DNA sequences, leading to release of different cytokines (Abraham and St. John, 2010).

IL-33 and its surface receptor ST2 were upregulated by interferon- $\gamma$  (IFN $\gamma$ ) in keratinocytes derived from patients with AD (Seltmann et al., 2013). Tumor necrosis factor (TNF), but not IL-17, stimulates secretion of IL-33, which induces expression of IL-6, monocyte chemoattractant protein-1, and

vascular endothelial growth factor (VEGF) (Balato et al., 2012). However, it appears that the type of cytokines/chemokines produced by IL-33 may depend on the particular tissue since the extent and type of such mediators varies between sensitized skin and asthmatic airways (Savinko et al., 2013).

**IL-33/ST2 Signaling.** IL-33 was discovered as a main ligand to ST2 (IL-1R4) receptor, which is mostly expressed on the surfaces of epithelial cells, fibroblasts, and MCs (Liew et al., 2010). The ST2 receptor is found in either the transmembrane ST2L form, which is the more abundant form, or in the cytoplasm as the soluble sST2 form, which may be acting as a decoy by binding and neutralizing IL-33 (Liew et al., 2010). The receptor complex comprises the ST2 and IL-1 receptor accessory proteins (Chackerian et al., 2007). IL-33 binding recruits the IL-1R AcP coreceptor, the adaptor protein MyD88, along with the associated protein IL-1R kinase.

ST2 activation leads to stimulation of mitogen-activated protein kinase via TNF receptor-associated factor 6, which can signal activator protein-1 via c-Jun N-terminal kinases (JNKs). TNF receptor-associated factor 6 can also activate nuclear factor- $\kappa$ B (NF- $\kappa$ B), resulting in its nuclear translocation and proinflammatory gene transcription (Kakkar and Lee, 2008). ST2 activation of the chronic myelogenous leukemia cell line, KU812, resulted in release of multiple cytokines through stimulation of NF- $\kappa$ B, JNKs, and p38

mitogen-activated protein kinase, but not extracellular signal-regulated kinase 1/2; however, IL-13 production in these cells apparently did not require JNKs or extracellular signal-regulated kinase 1/2 signaling (Tare et al., 2010). IL-33 can also act as a DNA binding factor (Kakkar and Lee, 2008).

**IL-33 and Mast Cells.** The effect of IL-33 on MCs was reviewed recently (Sabatino et al., 2012). ST2 is expressed on MCs, for which it acts as a chemoattractant and augments the effect of other triggers (Fux et al., 2014). MCs respond to cell injury through IL-33 (Lunderius-Andersson et al., 2012) and have therefore been considered “sensors of cell injury” (Enoksson et al., 2011). A murine MC line (MC/9) was reported to produce significant amounts of IL-33 after stimulation with IgE and antigen (Hsu et al., 2010). More recently, bone marrow–derived cultured mast cells stimulated by ovalbumin and specific IgE induced the expression and release of IL-33, which has autocrine action on IL-6 and IL-13 expression (Tung et al., 2014).

MCs are hemopoietically derived cells located close to blood vessels and nerves, where they proliferate primarily in response to stem cell factor (SCF) (Galli et al., 1995) but also nerve growth factor (Matsuda et al., 1991). MCs are important for allergic reactions but also for mastocytosis, mast cell activation disorders, and other inflammatory diseases (Theoharides et al., 2015). IL-33 has also been reported to drive maturation of human MCs (Allakhverdi et al., 2007) and promote MC survival (Iikura et al., 2007). IL-33 promoted proliferation of mouse mast cell independent of c-Kit (Saluja et al., 2014). Nevertheless, IL-33 was reported to cross-activate the SCF c-Kit receptor on MCs (Drube et al., 2010). Evidently, IL-1RAcP interacts with c-Kit constitutively and IL-33R binds upon stimulation with SCF leading to cytokine release (Drube et al., 2010). Apparently, inhibition of c-Kit signaling also blocked human MC release of IL-1b (Drube et al., 2012), which had been shown to occur selectively without degranulation (Kandere-Grzybowska et al., 2003).

IL-33 augmented the activating effect of IgE and SCF on MC and basophils (Silver et al., 2010). IL-33 induced release of proinflammatory cytokines, especially IL-6, without degranulation from bone marrow–derived MCs (Moulin et al., 2007), and enhanced IL-8 production from human cord blood–derived cultured mast cells stimulated by IgE/anti-IgE, but without histamine release (Iikura et al., 2007). IL-33 augmented human MC release of VEGF in response to substance P, but not on its own (Theoharides et al., 2010). Moreover, IL-33 production of IL-13 independently of FcεRI stimulation (Ho et al., 2007) stimulated prostaglandin D<sub>2</sub>, but not tryptase, release from activated human MCs (Nicoletti et al., 2012). IL-33 was also able to prime murine MCs for enhanced activation by IgG immune complexes (Drube et al., 2010; Kaieda et al., 2012), and stimulated MC-dependent neutrophil influx (Hueber et al., 2011; Enoksson et al., 2013). In addition to activation through cross-linking of the high-affinity IgE receptor (FcεRI) (Blank and Rivera, 2004), MCs are also stimulated by a variety of other triggers (Theoharides et al., 2007), such as the neuropeptide neurotensin (Donelan et al., 2006) and substance P (Zhang et al., 2011a).

MCs secrete numerous inflammatory mediators including histamine; leukotrienes; prostaglandins and tryptase; cytokines such as IL-6, IL-9, IL-13, TNF; chemokines like CCL2 and IL-8 (CXCL8); as well as VEGF (Theoharides et al., 2012a). MCs are the only cell type in which preformed TNF is

stored in secretory granules (Olszewski et al., 2007) and released bound to heparin particles that can reach draining lymph nodes and contribute to inflammation (Kunder et al., 2009). TNF can also activate T cells (Nakae et al., 2005; Kempuraj et al., 2008). MC-derived IL-6 and transforming growth factor-β are critical for the development of Th-17 cells (Nakae et al., 2007; Suurmond et al., 2011), and MCs secrete IL-17 themselves (Kenna and Brown, 2013).

IL-33 also augments the action of thymic stromal lymphopoietin (Nakae et al., 2007), which may be acting as another early immune alarmin through MCs (Kaur et al., 2012).

## Functional and Pathologic Features of IL-33 in Allergic Diseases

IL-33 is thought to contribute to disease pathology (Liew et al., 2010), especially inflammatory (Dinarello, 2002; Lukens et al., 2012; Milovanovic et al., 2012), allergic (Saluja et al., 2015), and autoimmune (Pei et al., 2014) diseases, through activation of MCs (Castellani et al., 2009).

**Allergic Inflammation.** There is substantial evidence that IL-33 is involved in airway inflammation (Oboki et al., 2011) and it appears to facilitate allergic airway responses to subthreshold exposure to dust mites (Llop-Guevara et al., 2014) and to ovalbumin in mice (Sjoberg et al., 2015). IL-33 induced Th-17–mediated airway inflammation via MCs (Hsu et al., 2010). In fact, there is evidence that IL-33 modulates cross-talk between MCs and smooth muscle cells in human airways (Kaur et al., 2015). Genetic polymorphism of ST2 and ST2L provides susceptibility for asthma development (Moffatt et al., 2010). ST2L expression was significantly increased in patients with severe asthma, and multiple single nucleotide polymorphisms in IL1RL1 were found in these patients (Traister et al., 2015).

IL-33 serum levels were significantly increased compared with the control nonasthmatic individuals (Pushparaj et al., 2009; Raeiszadeh et al., 2014). IL-33 was secreted from human bronchial epithelial cells after stimulation with an extract of *Alternaria*, a common fungus causing allergic respiratory diseases (Lefrançois and Cayrol, 2012). IL-33 also mediated maximum responses in allergen-induced airway inflammation (Kamijo et al., 2013). IL-33 is also involved in allergic rhinitis (Haenuki et al., 2012) and allergic conjunctivitis (Lin et al., 2013).

Additional studies from rodent models support the role of IL-33 in lung diseases (Eiwegger and Akdis, 2011; Kamijo et al., 2013). Intranasal administration of IL-33 triggered an immediate allergic inflammatory response in the airways, which was absent in IL-33–deficient mice (Louten et al., 2011). In another study, IL-33–deficient mice did not develop sneezing (early) or accumulate eosinophils and basophils (late) when challenged with ragweed pollen (Haenuki et al., 2012). In a model using ST2-deficient mice, ST2 receptor signaling was the main inducer of Th2 cytokines in the asthmatic airways, but receptor presence was dispensable for Th2-dependent inflammation in the sensitized skin (Savinko et al., 2013).

The IL-33/ST2 pathway appears to be involved in AD (Cevikbas and Steinhoff, 2012; Savinko et al., 2012). Serum levels of IL-33 were increased in patients with AD compared with healthy controls and were significantly reduced after

clinical improvement of skin lesions (Tamagawa-Mineoka et al., 2014). IL-33 was reported to stimulate innate lymphoid cells in AD (Salimi et al., 2013). IL-33 was also elevated in the skin, but not in the serum, of patients with psoriasis, a chronic inflammatory condition the pathogenesis of which is also associated with MC activation (Theoharides et al., 2010).

**IL-33 in Autoimmunity and Inflammation.** The IL-33/ST2 axis has been increasingly implicated in immunopathology and inflammation (Milovanovic et al., 2012). Blood levels of IL-33 are increased in a number of autoimmune and inflammatory (Milovanovic et al., 2012) diseases, such as rheumatoid arthritis (Kritas et al., 2013), systemic lupus erythematosus (Yu et al., 2013), Sjögren's syndrome (Awada et al., 2014), Grave's disease (Celik et al., 2013), and inflammatory bowel disease (Beltran et al., 2010). Genetic polymorphism studies have identified IL-33R1 as a susceptibility gene in inflammatory bowel disease (Jostins et al., 2012), Crohn's disease (Franke et al., 2010), and AD (Hirota et al., 2012). In addition to IgE-mediated allergic reactions, MCs also participate in innate and acquired immunity (Galli et al., 2005; Sismanopoulos et al., 2012), autoimmunity (Rottem and Mekori, 2005), and inflammation (Theoharides et al., 2007). In particular, MCs play a crucial role in the pathogenesis of AD (Vasiadi et al., 2013), psoriasis (Theoharides et al., 2010), rheumatoid arthritis (Askenase, 2003; Kritas et al., 2013), multiple sclerosis (MS) (Karagkouni et al., 2013), and autism (Theoharides, 2013), possibly through the "selective" release of mediators (Theoharides et al., 2007).

A recent study reported strong expression of IL-33 and ST2 around amyloid plaques in diseased patients with Alzheimer's disease compared with control brains (Xiong et al., 2014). Release of IL-33 from astrocytes was induced by glial maturation factor, implicating them in neurodegenerative diseases (Kempuraj et al., 2013). Moreover, incubation of mouse astrocytes with amyloid- $\beta$ 1-42 increased IL-33 expression (Xiong et al., 2014). In fact, increasing evidence implicates brain inflammation and cytokines in the pathogenesis of Alzheimer's disease (Griffin and Barger, 2010; Rubio-Perez and Morillas-Ruiz, 2012; Griffin, 2013). Brain inflammation may be evident in the earlier stages of the disease and may constitute a more reasonable target for drug development (Kozauer and Katz, 2013). Interestingly, IL-33 was also upregulated in astrocytes and peripheral leukocytes of MS patients (Christophi et al., 2012). Moreover, expression of IL-33 and IL-33 genes was increased in patients with remitting-relapsing MS (Zhang et al., 2014). Mast cells have been implicated in brain inflammation (Theoharides and Zhang, 2011).

A recent study using an ovalbumin mouse model reported that inhalation of hypochlorite [CID (2)] induced non-allergic lung hypersensitivity, an effect absent in ankyrin 1-null mice or W/W<sup>v</sup> MC-deficient mice (Hox et al., 2013). These results are interesting in view of the fact that ankyrin 2 was strongly associated with autism (De Rubeis et al., 2014; Iossifov et al., 2014). Many children with autism are characterized by allergic symptoms (Angelidou et al., 2011; Theoharides, 2013) and the risk of autism is much more common in children with mastocytosis (Theoharides, 2009). In fact, autism involves brain inflammation (Ashwood and Van de Water, 2004; Zhang et al., 2010) and microglial activation (Suzuki et al., 2013; Gupta et al., 2014). Moreover, there is evidence of cross-talk between microglia and MCs (Skaper

et al., 2014). It is interesting that the diseases discussed above worsen with stress (Theoharides and Cochrane, 2004; Vasiadi et al., 2012; Theoharides et al., 2012b; Karagkouni et al., 2013), and MCs are activated by corticotropin-releasing hormone secreted under stress (Theoharides et al., 2004; Cao et al., 2005).

## Treatment Possibilities

Targeting IL-33 has been considered as a therapeutic target for atopic (Nabe, 2014), rheumatic (Duan et al., 2013), and autoimmune diseases (Wang et al., 2012). Administration of sST2 to murine splenocytes inhibited production of Th2 cytokines (e.g., IL-4 and IL-5) but not of Th1 (e.g., IFN- $\gamma$ ) (Lohning et al., 1998). Additionally, when murine thymoma cells were stably transfected with ST2L and then treated with sST2, IL-33 binding to the ST2L was inhibited and so was the induction of NF- $\kappa$ B (Hayakawa et al., 2007).

Intranasal anti-IL-33 antibody significantly inhibited cigarette smoke-induced lung inflammation in mice, as evidenced by reduced levels of IL-33 and ST2, as well as decreased number of neutrophil and macrophage infiltration along with decreased expression of inflammatory cytokines (IL-1 $\beta$ , TNF, IL-17) (Qiu et al., 2013). Mice challenged with ovalbumin and then treated with anti-IL-33 antibody or sST2 showed negative regulation of ovalbumin-induced allergic airway inflammation (Lee et al., 2014); both treatments decreased Th2 cytokine levels in bronchoalveolar lavage fluid and decreased the count of eosinophils (Lee et al., 2014). One company has announced the production of a humanized anti-IL-33 antibody for clinical use ([www.anaptysbio.com/anti-il33](http://www.anaptysbio.com/anti-il33)). One study on human corneal epithelial cells reported that ST2 antibody or soluble anti-ST2 protein blocked IL-33-stimulated thymic stromal lymphopoietin and chemokine (CCL2, CCL20, CCL22) production from these cells at both mRNA and protein levels, (Lin et al., 2013).

On the basis of the evidence discussed above, the IL-33/ST2 signaling pathway could serve as novel biomarker or target for the development of new treatments (Kakkar and Lee, 2008; McLean et al., 2014). One recent paper reported the inhibitory effect of fingolimod and newly synthesized analogs on IL-33/ST2 signaling in dendritic cells; they reported variable effects on inhibition of IL-13 and IFN- $\gamma$  production possibly through regulation of intracellular calcium levels and protein phosphatase 2A activity (Ruger et al., 2014). However, the role of ST2/IL-33 appears to differ according to the tissue target(s). Surprisingly, IL-33 was reported to reduce the development of atherosclerosis in ApoE knockout mice, in spite of the fact that it elevated serum IgE levels, and treatment with sST2 led to development of larger atherosclerotic plaques (Oboki et al., 2010). This finding appears contrary to the well known role of MCs in the development of atherosclerosis (Sun et al., 2007; Theoharides et al., 2011).

Moreover, long term exposure (. 72 hour) of human and mouse MCs to IL-33 resulted in significant reduction of MC activation by antigen, suggesting that IL-33 may have the ability to induce "a hyporesponsive phenotype" in MCs (Jung et al., 2013). Blocking IL-33 also may not be as critical as blocking ST2, as was previously reported for the TNF- $\alpha$  and its receptor in experimental allergic encephalomyelitis (Kassiotis and Kollias, 2001).

There is also some controversy about the role of IL-33 in cancer. Some authors have reported that IL-33 promotes metastasis of gastric (Yu et al., 2015) and colorectal (Liu et al., 2014) cancers. However, other papers have reported that IL-33 may act as an adjuvant to enhance antigen-specific tumor immunity (Villarreal et al., 2014).

The natural flavonoid quercetin can block the ability of IL-1 to stimulate selective release of IL-6 from human MCs (Kandere-Grzybowska et al., 2006), and its structural analog luteolin can block the stimulatory effect of IL-33 on MC TNF release (data not shown). Quercetin and luteolin have potent antioxidant and anti-inflammatory actions (Middleton et al., 2000). They both inhibit the release of histamine, leukotrienes, and prostaglandin D<sub>2</sub> from human cultured MCs in response to cross-linkage of Fc $\epsilon$ RI (Kimata et al., 2000). Quercetin also inhibits histamine, IL-6, IL-8, TNF- $\alpha$ , and tryptase release from human MCs (Kempuraj et al., 2005; Park et al., 2008), as well as asthma in a guinea pig model (Moon et al., 2008) and contact dermatitis in humans (Weng et al., 2012). Luteolin has also been reported to inhibit stimulation of activated T cells (Kempuraj et al., 2008), keratinocytes (Weng et al., 2014a), and microglia (Jang et al., 2008).

IL-33 has been implicated in MS (Christophi et al., 2012; Zhang et al., 2014). Luteolin has synergistic effect with IFN- $\beta$  in inhibiting activation of peripheral blood mononuclear cells from MS patients (Sternberg et al., 2008, 2009). A novel luteolin analog, tetramethoxyluteolin, is more potent than luteolin (Weng et al., 2014b), making it an attractive molecule for drug development especially since it is also less metabolized (Walle, 2007). Black ginger is rich in methoxyluteolin (Wei et al., 2014) and it is interesting that a ginger extract was recently reported to reduce the clinical symptoms of experimental immune encephalomyelitis and IL-33 expression in the spinal cord of the mice (Jafarzadeh et al., 2014). Recent reviews have discussed the possible use of flavonoids in the treatment of neurodegenerative diseases (Jäger and Saaby, 2011; Jones et al., 2012; Solanki et al., 2015). Strangely, IL-33 has been reported to improve functional recovery after contusion spinal cord injury in a mouse model (Pomeshchik et al., 2015) and to attenuate experimental autoimmune uveitis (Barbour et al., 2014). These apparently opposite results may be attributable to species differences or the involvement of different IL-33 isoforms (Villarreal and Weiner, 2015).

## Conclusion

IL-33 has emerged as a major “alarm signal” that can be released either from damaged cells or from live MCs sensing danger. IL-33 augments the effect of other triggers but can also stimulate cytokine release directly. IL-33 levels and ST2 expression are high in allergic inflammation and certain autoimmune diseases. Regulation of the release and action of IL-33 on specific target tissues may prove to be a useful therapeutic approach (Kakkar and Lee, 2008). However, the apparent divergent functions of IL-33 in different tissues, organs, and diseases need to be further investigated. For instance, it was recently shown that two IL-33 isoforms facilitate the production of protective Th1 and CD8 T cells (Villarreal and Weiner, 2015). Hence, some isoforms may be pathologic, whereas others may be protective.

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## Authorship Contributions

Wrote or contributed to the writing of the manuscript: Theoharides, Petra, Taracanova, Panagiotidou, Conti.

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