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Interleukin-33 in tissue homeostasis, injury and inflammation

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Summary

Interleukin-33 (IL-33) is a nuclear-associated cytokine of the IL-1 family originally described as a potent inducer of allergic type 2 immunity. IL-33 signals via the receptor ST2, which is highly expressed on group 2 innate lymphoid cells (ILC2s) and T helper 2 (Th2) cells, thus underpinning its association with helminth infection and allergic pathology. Recent studies have revealed ST2 expression on subsets of regulatory T cells, and for a role for IL-33 in tissue homeostasis and repair that suggests previously unrecognized interactions within these cellular networks. IL-33 can participate in pathologic fibrotic reactions, or, in the setting of microbial invasion, can cooperate with inflammatory cytokines to promote responses by cytotoxic NK cells, Th1 cells and $CD8^+$ T cells. Here, we highlight the regulation and function of IL-33 and ST2, and review their roles in homeostasis, damage and inflammation, suggesting a conceptual framework for future studies.

Introduction

In 1989, a primary response gene was identified in serum-stimulated fibroblasts that resembled the extracellular portion of the interleukin-1 (IL-1) receptor. This protein, named T1 (Werenskiold et al., 1989), ST2 (Tominaga, 1989), Der4 (Lanahan et al., 1992), or Fit1 (Bergers et al., 1994), was the soluble form of the IL-33 receptor. Now designated IL-1-receptor-like 1 (IL1RL1), we will here use the common designation ST2. The ligand for ST2 was identified in 2005 during a search for unknown IL-1 family members (Schmitz et al., 2005), which revealed a sequence originally identified as a canine gene induced in endothelial cells in response to subarachnoid hemorrhage (Onda et al., 1999). T helper 2 (Th2) cells and mast cells expressed ST2, and IL-33 promoted Th2-associated allergic

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immunity when administered to mice(Coyle et al., 1999; Löhning et al., 1998; Schmitz et al., 2005; Townsend et al., 2000; Xu et al., 1998; Yanagisawa et al., 1997). Although IL-33 is most frequently characterized as an epithelial cytokine that promotes type 2 immune responses, recent studies have extended its biology to include roles in basal tissue regulation, organ-specific injury and repair (which promote fibrosis when dysregulated), and immunity to viruses, microbes and neoplasms. Despite this pleiotropic spectrum, surprising gaps remain in our knowledge regarding the molecular control and diverse functionalities of this cytokine. Here, we review the literature and propose a progressive model for conceptualizing the role of IL-33 in homeostasis and inflammation. In the *homeostatic stage*, constitutive pools of IL-33 become active locally to sustain basal physiology by activating $ST2^+$ resident cells in a cell- and tissue-specific manner. In the *amplification stage*, tissue-specific pools of IL-33 increase and $ST2^+$ cells increase in numbers in attempting to maintain homeostasis, usually in response to perturbations like parasites or allergens and resulting in overt manifestations of type 2 immunity. When continued over long periods, pathologic fibrosis can occur. In the *conversion stage*, inflammation from damaged tissues leads to the acquisition of IL-33 responsiveness through induced expression of ST2 on inflammatory cells, including NK cells, Th1 cells and $CD8^+$ T cells, and resulting in overt manifestations of type 1 immunity. This facilitates clearance of pathogens but often at the cost of tissue damage. Consideration of this model may have implications in considering therapeutic strategies for altering IL-33 activities *in vivo*.

Molecular characterization of IL-33

IL-33 is a member of the IL-1 family, which includes IL-1α, IL-1β, IL-18, IL-36α, IL-36β, IL-36γ and IL-37, and the receptor antagonists IL-1Ra, IL-36Ra, and possibly IL-38 (Garlanda et al., 2013a). IL-33 is localized in the cell nucleus but also functions as a cell-free cytokine (Carriere et al., 2007), and in this way is similar to IL-1α and HMGB1 (Garlanda et al., 2013a; Moussion et al., 2008). Human and mouse IL-33 consist of seven coding exons, which produce a ~31 kDa protein of 270 and 266 amino acids, respectively. Exons 1–3 encode the N-terminal domains required for IL-33 nuclear localization, whereas exons 4–7 encode the C-terminal IL-1-like cytokine domain (Carriere et al., 2007). The nuclear localization domain (amino acids 1–65 in human) includes a chromatin-binding motif (amino acids 40–58) (Roussel et al., 2008), which mediates interaction of IL-33 with histone dimers and promotes chromatin compaction; mutation at R48 results in diffuse cytoplasmic localization of IL-33 and abolishes IL-33-mediated transcriptional repression in Gal4 reporter assays (Roussel et al., 2008). IL-33 has also been shown to bind the p65 subunit of NF-κB via the RelA interaction domain (amino acids 66–111) and inhibit NF-κB transcriptional activity in HEK293RI cells (Ali et al., 2011). Despite these data, evidence that nuclear IL-33 regulates normal transcriptional activity as part of its functionality requires further study.

The remainder of the IL-33 protein (amino acids 109–266 in mouse) encodes the IL-1-like cytokine domain, a 12-stranded β-trefoil fold similar to IL-1α, IL-1β, IL-1Rα and IL-18 (Lingel et al., 2009). This domain binds to the IL-33 receptor ST2, thus facilitating recruitment of IL-1RAcP to form the heterotrimeric signaling complex. Unlike IL-1β and IL-18, the N-terminal portion of IL-33 does not require cleavage by caspase 1 for release

from the cell or to initiate signaling via ST2 (Cayrol and Girard, 2009; Luthi et al., 2009; Talabot-Ayer et al., 2009). Apoptosis-associated caspase-3 and caspase-7 cleave and inactivate IL-33 at a conserved residue, Asp178 (Asp175 in mouse), within the IL-1-like domain(Cayrol and Girard, 2009; Luthi et al., 2009). N-terminal processing of full-length IL-33 can also occur via a short stretch of amino acids between the nuclear-binding domain and the IL-1-like cytokine domain. These residues are targeted by extracellular proteases common at inflammatory sites, including neutrophil cathepsin G, neutrophil elastase and mast cell serine proteases, resulting in IL-$33_{95–270}$, IL-$33_{99–270}$, and IL-$33_{109–270}$. The resulting 19 kDa cytokine forms of IL-33 exhibit 10- to 30-fold higher bioactivity, and are functionally similar to the 18 kDa recombinant IL-$33_{112–270}$ available commercially(Lefrancais and Cayrol, 2012; Lefrancais et al., 2014; 2012). The relative contributions of full-length and cleaved IL-33 *in vivo* are incompletely resolved.

Whether or not it is necessary for underlying function, the nuclear localization of full-length IL-33 is highly regulated, since mislocalization has drastic consequences. Gene-targeted knock-in mice in which the IL-33 nuclear domain was replaced by DsRed reporter sequence express a fusion protein consisting of the cytokine domain but lacking nuclear localization. Heterozygous mice are born normally but develop high serum IL-33 and lethal inflammation characterized by splenomegaly with multi-organ infiltration by myeloid cells, particularly eosinophils, neutrophils and monocytes/macrophages (Bessa et al., 2014). These pathologic changes resemble those induced by constitutive over-expression of full-length IL-33 (Talabot-Ayer et al., 2015).

Regulation of IL-33 mRNA is also not well understood. In the mouse, IL-33 transcription initiates from one of two non-coding exons which are associated with constitutive or induced production of IL-33 (Polumuri et al., 2012; Talabot-Ayer et al., 2012). There are also a number of potential high-quality miRNA binding sites within the long 3′ UTR of IL-33 (www.microrna.org; A. Savage, unpublished observations). Among these, miR-9, miR-145, miR-214 and miR-499-5p have been linked to vascular and coronary function (Gidlöf et al., 2013; Hu et al., 2014; Jin et al., 2015; Shimizu et al., 2013; Turczy ska et al., 2012; Wang et al., 2010), and could be of interest because IL-33 from cardiac fibroblasts can promote cardioprotection (Sanada et al., 2007).

IL-33 release and/or secretion

Because IL-33 lacks a traditional signal sequence (Garlanda et al., 2013a) or a non-canonical processing and export pathway, cell death by necrosis and/or active necroptosis may be dominant mechanisms by which the cytokine reaches the extracellular milieu (Cayrol and Girard, 2014; Kaczmarek et al., 2013), leading to its designation as an ‘alarmin’. Indeed, receptor-interacting protein kinase 1 (Ripk1) knockout mice succumb to perinatal necroptosis-driven inflammation and exhibit marked increases in extracellular IL-33 (Rickard et al., 2014). However, it is unclear if cell death can account entirely for the biologic effects of IL-33. IL-33 release from living cells was reported in human bronchial epithelium exposed to *Alternaria*(Kouzaki et al., 2011) and from mechanically-stressed fibroblasts *in vitro* and *in vivo* (Kakkar et al., 2012). Several studies suggest extracellular ATP can promote IL-33 production or secretion in models of allergic inflammation(Byers et

al., 2013; Hudson et al., 2008; Kouzaki et al., 2011). Human IL-33 transcripts lacking exon 3, 4 and/or 5 have been recovered from cell lines and primary cells (Hong et al., 2011; Tsuda et al., 2012). However, these splice forms appear to be minor components in primary cells and further work is required to determine their physiologic relevance. Other nuclear alarmins such as HMGB1 and IL-1α may be useful in understanding IL-33 regulation and activity. HMGB1 is ubiquitously expressed and, while it can be liberated from the cell by necrosis, active release from inflammatory macrophages may constitute an additional release mechanism (Harris et al., 2012). In contrast, IL-1α appears to require necrosis to access the extracellular space (Rider et al., 2013). Further study is necessary to elucidate these various pathways and how they are controlled.

The IL-33 receptor subunit ST2

The receptor complex for IL-33 consists of the specific subunit ST2 and the shared signaling chain, IL-1RAcP (Figure 1). ST2 is in a conserved locus on human chromosome 2 and mouse chromosome 1 with other IL-1 receptors, including those for IL-1 (IL1R1, decoy receptor IL1R2), IL-18 (IL18R1, IL18RAP), and IL-36 (IL1RL2) (Garlanda et al., 2013a). IL-1 family receptors are present throughout vertebrates together with their cytokine ligands, suggesting their co-evolutionary development. Although ST2 exhibits a similar distribution, its ligand IL-33 apparently arose later in evolution, as it is present in mammals but absent in non-mammalian vertebrates (Sattler et al., 2013). Despite this disconnect, there is no evidence for unidentified ST2 ligands in humans or mice. Further, ST2 is the only well-documented receptor for IL-33. In support of this, mice with loss of IL-33 nuclear localization signals or constitutive over-expression of IL-33 develop systemic inflammation that is abrogated by crossing onto the ST2-deficient background(Bessa et al., 2014; Talabot-Ayer et al., 2015).

Soluble ST2

An additional layer of complexity in the biology of IL-33 is the occurrence of two ST2 isoforms, ST2L and sST2 (Yanagisawa et al., 1993). ST2L is the full-length protein and includes the extracellular Ig-like domains, a short extracellular spacer, the transmembrane domain and an intracellular TIR domain(Liu et al., 2013). sST2 is a short form which lacks the final three exons, resulting in a soluble secreted protein consisting of the extracellular cytokine-binding domains. sST2 is present constitutively in human serum (Kuroiwa et al., 2000; Oshikawa et al., 2001), where it acts as a decoy receptor by binding free IL-33. sST2 is increased by diverse inflammatory stimuli and in cardiovascular, rheumatologic and allergic diseases, potentially restricting the deleterious effects of elevated systemic IL-33 (Hayakawa et al., 2007; Kumar et al., 1997; Oshikawa et al., 2002; Weinberg et al., 2002; Yanagisawa et al., 1993). In humans, genome wide association studies (GWAS) have identified ST2 variants associated with altered levels of serum sST2(Ho et al., 2013), which could influence susceptibility to IL-33-mediated responses.

ST2L signaling

The crystal structure of the ectodomain of ST2 complexed with IL-33 has been solved (Liu et al., 2013). The ectodomain of ST2 consists of 3 Ig-like domains and resembles IL-1R1.

The two distal domains (D1D2) pack together and connect via a flexible linker to the membrane-proximal third (D3) domain; IL-33 binds between the D1D2 and D3 domains (Liu et al., 2013). The binary IL-33-ST2 complex recruits IL-1RAcP, a shared signaling component of receptors for IL-1α and β and IL-36α, β and γ, to initiate signaling. IL-1RAcP signaling induces recruitment to the receptor complex of MyD88, IRAK, IRAK4 and TRAF6; activation of MAP kinases Erk1/2, p38 and JNK; activation of AP-1 transcription factors; and degradation of IκBα leading to translocation of NFκB to the nucleus (Andrade et al., 2011; Schmitz et al., 2005). IL-33 signaling may also require JAK2 activation (Funakoshi-Tago et al., 2011). As these signaling pathways are largely conserved with TLR, IL-1 and IL-18 signaling, the unique biologic effects of IL-33 are likely mediated by ST2L expression. ST2L signaling pathways can be inhibited by the IL-1 receptor-like molecule SIGIRR (TIR8), such that in Th2 cells, SIGIRR negatively regulates ST2 signaling and inhibits type 2 inflammatory processes (Bulek et al., 2009). IL-23 signaling impairs IL-33-mediated signaling in intestinal Tregs by restricting phosphorylation and activation of the Th2-associated transcription factor GATA3 (Schiering et al., 2014). IFN-γ potently inhibits IL-33 activation of ILC2 *in vitro* and *in vivo* and may be critical in suppressing this pathway during infections by bacteria and viruses (see below; Molofsky et al., 2015). Whether other described inhibitors of MyD88-dependent pathways, such as A20 (TNFAIP3), IRAK-M, or SOCS family members restrict IL-33/ST2 signaling is unknown (Garlanda et al., 2013b; Tamiya et al., 2011; Turer et al., 2008). The regulation, interaction, and signaling of IL-33 and ST2 are summarized in Figure 1.

Sources and production of IL-33

IL-33 protein is constitutively present in healthy mice and humans, primarily in nuclei of non-hematopoietic cells (Schmitz et al., 2005), with particular abundance in specialized populations of epithelial and endothelial cells(Moussion et al., 2008; Pichery et al., 2012). IL-33 was first identified in human lymph node high endothelial venules (HEV; originally named NF-HEV or DVS-27) and its expression was induced in canine cerebral vasculature after subarachnoid hemorrhage(Baekkevold et al., 2003; Onda et al., 1999). IL-33 is highly expressed in lymph node and spleen fibroblastic reticular cells (FRC) in mice and humans, although not in mouse HEV (Moussion et al., 2008; Pichery et al., 2012). In contrast to humans, mouse endothelial expression of IL-33 appears restricted to adipose tissue, liver and female reproductive tract (Carlock et al., 2014; Marvie et al., 2010; Pichery et al., 2012). IL-33 expression in endothelial cells *in vitro* has been linked to cellular quiescence and confluence, and may require Notch signals (Küchler et al., 2008; Sundlisaeter et al., 2012). Human and mouse share constitutive IL-33 expression at epithelial surfaces, including in skin, stomach, intestine, salivary gland, vagina and lung, where expression is particularly high in alveolar type 2 cells (Mohapatra et al., 2015; Moussion et al., 2008; Pastorelli et al., 2010; Schmitz et al., 2005); species-specific differences may exist (Sundnes et al., 2015). This epithelial expression pattern partially overlaps with other cytokines that target ILC2s, including TSLP and IL-25, suggesting potentially shared functions (Bulek et al., 2010; Mohapatra et al., 2015). During inflammation additional populations express IL-33, such as epithelial progenitor cells in models of COPD (Byers et al., 2013). In myeloid cells, IL-33 transcription can be induced by allergic challenge (Hardman et al., 2013) and TLR

signaling. Mouse peritoneal macrophages express IL-33 mRNA in response to TLR activation by a process dependent on TBK1, RIG-I and IRF3 (Polumuri et al., 2012). TLR2-dependent induction of IL-33 mRNA in human monocytes and mouse macrophages was dependent on TRAF6 and IRF7 (Sun et al., 2014). Experimental demonstration of pathways that induce IL-33 protein in hematopoietic cells *in vivo*, as well as the physiologic relevance of hematopoietic sources of IL-33, require further study.

IL-33 in tissue homeostasis

IL-33 expression is regulated by diverse stimuli and in a cell- and tissue-specific manner, reflecting interactions in tissue between constitutive and induced components. Here, it may be useful to consider cell types that constitutively express high amounts of ST2, thus revealing cells and tissues that likely orchestrate initial responses to IL-33. Non-hematopoietic cells, including endothelial cells, epithelial cells and fibroblasts, are reported to express ST2L and respond to IL-33, although the *in vivo* consequences of signaling in these populations are not well described. In hematopoietic cells, IL-33 acts primarily on immune cells associated with type 2 and regulatory immune responses, including ILC2s, Th2 cells, eosinophils, mast cells, and basophils, as well as subsets of dendritic cells, myeloid-derived suppressor cells and Tregs (Cayrol and Girard, 2014). ILC2s, some Tregs, and mast cells are the primary tissue-resident cells that constitutively express high levels of ST2, positioning these cells as initial targets of IL-33. Mast cells are present in most tissues, can be activated by IL-33 to release mediators (Lunderius-Andersson et al., 2012), and may interact with ILC2s to maintain epithelial integrity(Roediger et al., 2013). ILC2s are systemically distributed in tissues, including skin, lung, gastrointestinal tract, uterus and adipose tissue. When activated they comprise the major innate source of type 2 cytokines such as IL-5, IL-13, IL-9 and GM-CSF, in addition to epithelial growth factors such as amphiregulin (Cheng and Locksley, 2015; von Moltke and Locksley, 2014; Moro et al., 2010; Neill et al., 2010; Price et al., 2010). Studies comparing responses to IL-33 in ILC2-replete Rag-knockout and ILC2-deficient Rag x γc – knockout mice suggest that ILC2s comprise the major innate target of exogenous IL-33 (Brestoff et al., 2014; Mchedlidze et al., 2013; Moro et al., 2010). IL-33-mediated ILC2 activation typically leads to tissue accumulation of eosinophils and alternatively activated macrophages (AAM), and is associated with elevated numbers of tissue Tregs.

Certain subsets of Tregs, including those in adipose tissue, express high amounts of the Th2-associated transcription factor GATA3 as well as ST2, and require IL-33 for their maintenance and function (Molofsky et al., 2015; Schiering et al., 2014; Vasanthakumar et al., 2015)). These tissue Tregs are highly suppressive and express IL-10 together with other markers associated with activation, including ICOS, KLRG1 and GITR. *In vitro*, IL-33 promotes proliferation of $ST2^+$ Tregs and further enhances GATA3 expression, which stabilizes FoxP3 expression while increasing ST2 expression in a feed-forward reinforcing manner (Schiering et al., 2014; Vasanthakumar et al., 2015). Although IL-33 has direct effects on Treg stabilization and function, IL-33 also promotes ILC2 and/or dendritic cell subsets that enhance Treg numbers and function by indirect mechanisms (Besnard et al., 2015; Duan et al., 2012; Matta et al., 2014; Molofsky et al., 2015). Tregs generated during the perinatal period express ST2 and are highly suppressive and proliferative (Yang et al.,

2015). These perinatal Tregs restrict the tissue autoimmune manifestations of Aire deficiency, a model of the human autoimmune disorder, APECED (autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy), hinting at a possible role for IL-33 in supporting perinatal tissue tolerance.

Although further work is needed, these data suggest a model whereby ILC2s, a subset of Tregs and possibly mast cells are positioned in tissues through a developmentally regulated process, where they can respond to local fluctuations in extracellular IL-33. In certain tissues, additional resident hematopoietic or tissue cells may also respond to IL-33, although this remains poorly explored. Serum sST2 serves to localize endogenous IL-33, where it might mediate processes involved in normal growth and development while sustaining tolerance by the developing adaptive immune system (Figure 2A).

Adipose tissue

The best-studied model of IL-33 function in tissue homeostasis is in white adipose tissue (Figure 2). White adipose tissue (WAT) is the major storage site for high-energy triglycerides, which are released as free fatty acids by lipolysis during periods of energy need. WAT of lean mice is populated with $ST2^+$ ILC2s and Tregs that promote WAT eosinophils and AAM (Brestoff and Artis, 2015; Hams et al., 2013; Mathis, 2013; Molofsky et al., 2013b; Moro et al., 2010). IL-33 is abundant in adipose tissue, where expression has been confirmed in endothelial cells and fibroblast-like reticular cells, although further study is needed (Kolodin et al., 2015; Molofsky et al., 2015; Pichery et al., 2012; Wood et al., 2009; Zeyda et al., 2013). In mice, loss of IL-33 or ST2 leads to worsening obesity and insulin resistance, a hallmark of type 2 diabetes (Brestoff et al., 2014; Lee et al., 2015; Miller et al., 2010; Vasanthakumar et al., 2015). These changes are associated with a shift in the function and population of normal WAT immune cells, characterized by diminished ILC2 activation and decreased numbers of eosinophils, AAM and Tregs (Kolodin et al., 2015; Molofsky et al., 2015; Vasanthakumar et al., 2015)). Each of these cell types has been shown to protect in mouse models of obesity-induced insulin resistance (Brestoff and Artis, 2015; Mathis, 2013; Wu et al., 2011), supporting the concept whereby IL-33 sustains the architecture and function of $ST2^+$ resident cells that limit infiltration of adipose tissue by inflammatory lymphocytes and myeloid cells that lead to insulin resistance and metabolic syndrome.

Although WAT is responsible for lipid storage, brown adipose tissue (BAT) expresses high amounts of uncoupling protein 1 (UCP1) and converts energy into heat, an important component of cold adaptation. BAT is abundant in newborns and decreases in adults (Frontini and Cinti, 2010). Recent studies have shown that white adipose tissue can convert to a brown-like depot, termed ‘beige’ or ‘brite’ adipose (Bartelt and Heeren, 2014; Harms and Seale, 2013). This occurs predominantly in subcutaneous WAT depots and may facilitate BAT-mediated adaptive thermogenesis (Bartelt and Heeren, 2014; Harms and Seale, 2013). Both BAT and beige adipose dissipate energy and influence glucose and VLDL-triglyceride metabolism (Bartelt et al., 2011; Chondronikola et al., 2014), potentially protecting against metabolic disorders such as type 2 diabetes. Type 2 immune cells have been implicated in promoting cold-induced adipose tissue beiging (Brestoff and Artis, 2015;

Qiu et al., 2014; Rao et al., 2014), and IL-33 can act on ILC2s to promote beiging even at room temperature (Brestoff et al., 2014; Lee et al., 2015). In one study, ILC2-derived IL-13 was shown to act on adipose precursors to promote a beige fate (Lee et al., 2015), whereas a second study demonstrated ILC2s induce beiging by secreting the endogenous opioid methionine-enkephalin (Brestoff et al., 2014). Fundamental questions remain, including the relevant source(s) and direct target(s) of adipose tissue IL-33 and the signals and mechanisms that promote adipose tissue IL-33 production and release.

Female reproductive tissues

IL-33 and ST2 are expressed in uterine endometrial cells and increase with decidualization before fetal implantation (Salker et al., 2012). IL-33 was reported in placental macrophages and shown to promote the growth of trophoblasts (Fock et al., 2013). Ovarian IL-33 and ST2 increase with ovulation (Carlock et al., 2014), where IL-33 is expressed by endothelial cells surrounding developing follicles (Wu et al., 2015). IL-33 is required for recruitment of macrophages to mediate ovarian atresia post-ovulation, and IL-33-deficient mice show a 33% reduction in reproductive lifespan (Wu et al., 2015). These findings suggest IL-33 may promote the physiologic clearance of atretic ovarian follicles and possibly promote uterine and placental remodeling in the course of the estrous cycle and pregnancy. ILC2s are present in the uterus (Nussbaum et al., 2013), where they may coordinate aspects of the IL-33 response.

In the mammary gland, cells and cytokines associated with type 2 immunity mediate ductal branching and outgrowth during pubescent morphogenesis (Gjorevski and Nelson, 2011; Khaled et al., 2007; Sternlicht et al., 2006), a process that occurs within an adipose tissue matrix (Gjorevski and Nelson, 2011). The cytokines IL-4, IL-5 and IL-13, the epithelial growth factor amphiregulin, and eosinophil and AAM infiltration are all necessary for normal ductal outgrowth (Aupperlee et al., 2014; Colbert et al., 2005; Khaled et al., 2007); all of these findings are consistent with a role for ILC2s, which promote adipose tissue eosinophils and AAM (Molofsky et al., 2013b), produce a majority of tissue IL-5 and IL-13 (Nussbaum et al., 2013), and are a source of amphiregulin (Monticelli et al., 2011). Definitive studies, including the potential role of mammary gland IL-33, ILC2s, and Tregs, are needed.

Central nervous system

Prenatally, IL-33 is expressed in discrete regions of the central nervous system (CNS), including eye and spinal cord (Molofsky et al., 2013a; Pichery et al., 2012) and postnatally in the thalamus, cerebellum, spinal cord, and optic nerve (Hudson et al., 2008; Pichery et al., 2012; Wicher et al., 2013; Yasuoka et al., 2011). IL-33 is abundant in macroglia, including grey-matter astrocytes and oligodendrocytes (Hudson et al., 2008; Yasuoka et al., 2011). Microglia, the primary immune cells of the CNS, can express ST2 and are positioned to respond to glial signals (Yasuoka et al., 2011). In models of CNS damage, IL-33 promotes microglial and macrophage alternative activation and limits glial scarring (Luo et al., 2015; Pomeshchik et al., 2015). Astrocytes and microglia also participate in neural circuit formation during development, and immune molecules can fundamentally shape and alter

these circuits(Clarke and Barres, 2013). A role for glial-derived IL-33 in shaping CNS neural circuits remains unknown.

Despite the widespread constitutive pool of nuclear IL-33 and strategically positioned ST2-expressing cells, both IL-33-deficient and ST2-deficient mice are grossly normal and suffer no overt developmental abnormalities. As previously noted, IL-33 is also expressed at barrier surfaces that contact the environment and commensals, including the skin, lung and gastrointestinal tract (Pichery et al., 2012). The potential homeostatic functions of IL-33 at these sites and others during normal growth and development have not been systematically explored.

IL-33 in type 2 immune responses

At the time of its discovery as a cytokine binding to the ST2 receptor, IL-33 was administered to mice exogenously by a variety of routes and methods (Humphreys et al., 2008; Kondo et al., 2008; Miller et al., 2008; Schmitz et al., 2005). In each case, massive infiltrations of tissues by eosinophils, epithelial goblet cell hyperplasia and elevations of typical type 2 cytokines were noted. These responses also occurred in Rag-deficient mice, indicating that innate cells were the primary target of IL-33 (Kondo et al., 2008). Importantly, these observations formed the cornerstone of experiments that later contributed to the discovery and characterization of ILC2s (Moro et al., 2010; Neill et al., 2010; Price et al., 2010). As such, these first experiments revealed that ILC2s are a dominant $ST2^+$ cell responsive to IL-33 in the intact animal, and have prompted further investigations into the role of IL-33 in type 2 immune responses that accompany helminth infections, allergy and asthma.

IL-33 and helminth infection

In the mouse, infection with the helminth *Nippostrongylus brasiliensis* causes IL-33 release (Moro et al., 2010) and activation of ILC2s (Moro et al., 2010; Neill et al., 2010; Price et al., 2010) which cooperate with Th2 cells to mediate intestinal worm expulsion (Neill et al., 2010; Oliphant et al., 2014; Price et al., 2010). IL-33 signaling is not absolutely required for the generation of $CD4^+$ Th2 cells (Hoshino et al., 1999; Townsend et al., 2000), *N. brasiliensis* intestinal clearance (Neill et al., 2010; Senn et al., 2000), or IgE responses (Hung et al., 2013; Townsend et al., 2000), although it expedites these processes in part via efficient ILC2 activation (Hung et al., 2013; Neill et al., 2010). During infection with *Schistosoma mansoni*, IL-33 signaling was required for optimal granuloma formation, lung eosinophilia and Th2 cytokine production (Townsend et al., 2000). IL-33 promotes Th2 cells necessary to clear *Trichuris muris* (Humphreys et al., 2008), and IL-33 signaling limited *Trichinella spiralis* encystation in muscle (Scalfone et al., 2013). IL-33 can cooperate with other epithelial cytokines, including IL-25 (Neill et al., 2010), to mediate helminth clearance. *In vitro*, ILC2s are synergistically activated by IL-33 when combined with other cytokines such as IL-2, IL-7, IL-9 and TSLP (Martinez-Gonzalez et al., 2015; Oliphant et al., 2014; Turner et al., 2013; Wilhelm et al., 2011), suggesting environmental perturbations are integrated to mediate these responses. Thus, IL-33 is a partially redundant but important component of type 2 immune responses in the context of helminth infection.

Th1 cell-associated inflammatory responses can counter-regulate IL-33-associated Th2 cell immunity. Thus, IL-1β can impair intestinal IL-33 upregulation during helminth infection and limit the ability to clear chronic gastrointestinal infection (Zaiss et al., 2013). Similarly, mice lacking the IL-1β receptor, IL-1R, or the adaptor MyD88, had more robust intestinal granuloma formation when infected with *Heligmosomoides polygyrus* (Reynolds et al., 2014). In models of cerebral malaria, IL-33 administration protected against Th1 cell-associated lethality by inducing ILC2s and Tregs (Besnard et al., 2015). IFN-γ potently inhibits IL-33-mediated ILC2 activation *in vitro* and *in vivo* following *Listeria* infection (Molofsky et al., 2015). IL-33 has been implicated in protection or pathology in a variety of additional bacterial and parasitic infections, as recently reviewed, (Rostan et al., 2015), although the mechanisms of action in these models are not well defined.

IL-33 in allergic pathology

Large-scale GWAS implicate both IL-33 and ST2 in susceptibility to asthma; other loci associated with ILC2 and Th2 cell function, including IL-13, TSLP and RORα were also noted (Gudbjartsson et al., 2009; Moffatt et al., 2010; Torgerson et al., 2011). IL-33 was required for ovalbumin- and papain-induced type 2 airway inflammation (Oboki et al., 2010). Additional allergic challenges, including *Alternaria* (Bartemes et al., 2012; Kouzaki et al., 2011; Snelgrove et al., 2014), house dust mite extract (Willart et al., 2012), and chitin polymers (Van Dyken et al., 2014) were found to induce lung IL-33 that promoted Th2 immune responses and airway hyperreactivity. IL-33 induction occurred in both hematopoietic and non-hematopoietic cells, particularly in alveolar type 2 cells (Kouzaki et al., 2011; McSorley et al., 2014; Mohapatra et al., 2015). Activation of lung ILC2s (Bartemes et al., 2012; Beamer et al., 2013; Doherty et al., 2012; Halim et al., 2012; Van Dyken et al., 2014), Th2 cells (Endo et al., 2015; Kurowska-Stolarska et al., 2008), or both (Iijima et al., 2014), were required to mediate the allergic phenotype, depending on the model system. ILC2s may indirectly support the generation of Th2 cells via IL-13 induction of dendritic cell migration or through direct ILC2/Th2 interactions (Halim et al., 2014; Martinez-Gonzalez et al., 2015; Oliphant et al., 2014). Additionally, Th2 and Th9 cells produce γ_c receptor-binding cytokines such as IL-2, IL-4 and IL-9, which can potentiate ILC2 activation (Mirchandani et al., 2014; Wilhelm et al., 2011). IL-33 can also act directly on $ST2^+$ Th2 cells *in vitro* (Guo et al., 2009; Schmitz et al., 2005) and *in vivo* (Endo et al., 2015; Kurowska-Stolarska et al., 2008) to promote cytokine production.

IL-33 plays a role in other models of allergic disease, including allergic rhinitis and chronic rhinosinusitus through activation of ILC2s, basophils and mast cells (Haenuki et al., 2012; Kato, 2015; Mjösberg et al., 2011; Nakanishi et al., 2013). In humans, chronic eosinophilic rhinosinusitis with nasal polyps is associated with increased epithelial IL-33 and $IL\text{-}13^+$ ILC2s (Shaw et al., 2013). IL-33 is expressed in skin keratinocytes and is elevated in humans and mouse models of atopic dermatitis (Kim and Artis, 2015). In mice, overexpression of IL-33 in the skin can cause atopic dermatitis-like immune pathology (Imai et al., 2013). The role of endogenous IL-33 in murine atopic dermatitis models has been inconsistent (Kim et al., 2013; Salimi et al., 2013), suggesting IL-33 may be one of several signals that together promote disease (Kim and Artis, 2015). IL-33 may contribute to gastrointestinal food allergy (Chu et al., 2013; Muto et al., 2014) and other eosinophilic

gastrointestinal diseases, although further study is required to delineate these roles. Together, these findings indicate that IL-33 can promote pathologic type 2 immune responses, particularly at barrier surfaces such as the lung and skin. Similar to helminth infections, IL-33 frequently acts in combination with additional signals such as IL-2, IL-9, TSLP, IL-25, leukotrienes, prostaglandins, or TL1A, to promote ILC2 and/or Th2 functions (von Moltke and Locksley, 2014). Inhibition of the IL-33 pathway may be a promising therapeutic approach for limiting these pathologic responses (Fahy, 2015).

IL-33 promotes both protective and pathologic type 2 immune responses in the setting of tissue injury (Figure 2b), which may represent extensions of the role of IL-33 during tissue homeostasis, here termed *amplification*. Indeed, type 2 immunity plays active roles in both wound healing and helminth immunity (Gause et al., 2013). Helminths induce adaptive Th2 cells and low-affinity IgE antibody production, but these responses typically cause little acute tissue pathology, likely due to the concomitant activation of regulatory cells, such as Treg (Finlay et al., 2014; McSorley and Maizels, 2012). Although helminths actively elicit regulatory responses in part through secretion of immune-modulatory products (Finlay et al., 2014; McSorley and Maizels, 2012), IL-33 itself has direct and indirect effects in stimulating these regulatory pathways (Molofsky et al., 2015). In contrast, allergic pathologic states are characterized by chronic elevations in tissue IL-33 and activated ILC2s with Th2 cells, and are associated with tissue pathology and a failure to activate or maintain regulatory responses, including Treg. In these chronic settings, Th2 cells likely become activated during repetitive rounds of antigenic stimulation, further driving maladaptive cycles of immune dysfunction.

IL-33 in tissue damage, repair and fibrosis

Work in models of cardiovascular disease demonstrated IL-33 induction following vascular and cardiac stress that was correlated with improved outcomes (Miller et al., 2008; Onda et al., 1999; Sanada et al., 2007; Sánchez-Más et al., 2014). IL-33 reduced atherosclerosis (Miller et al., 2008), limited pressure overload-induced cardiac hypertrophy (Sanada et al., 2007), and improved cardiac function and cardiomyocyte survival after myocardial infarction (Seki et al., 2009). IL-33 administration expands ILC2s and Tregs and protects in models of allograft rejection, tissue injury and pathology driven by excess type 1 immune responses (Brunner et al., 2011; Duan et al., 2012; Liang et al., 2013; Schiering et al., 2014; Turnquist et al., 2011; Yin et al., 2013). $ST2^+$ Tregs are also increased during helminth infection (Layland et al., 2010; Molofsky et al., 2015) and in models of muscle damage (Burzyn et al., 2013), suggesting damage-induced IL-33 may participate in these responses. However, elevated serum IL-33 can also be associated with autoimmune disease and chronic pathology (Palmer and Gabay, 2011). Human patients with systemic sclerosis have elevated IL-33 levels that correlated with the extent of skin and lung fibrosis (Yanaba et al., 2011). In mouse models of liver damage, IL-33 activates ILC2s to expand, produce IL-13 and promote hepatic stellate cell activation and liver fibrosis (Mchedlidze et al., 2013). IL-33 can also cause skin fibrosis in an ILC2- and eosinophil-dependent manner (Rankin et al., 2010). These findings suggest IL-33 promotes tissue repair, likely coordinated by ILC2s and Tregs, but that these pathways can become maladaptive when chronic or excessive, resulting in allergic pathology and fibrosis. These changes may reflect the outgrowth of pathologic

Th2 effector cells, loss of regulatory cells, and/or damage or depletion of tissue niches for critical precursor cells required to sustain tissue homeostasis.

IL-33-ST2 in infection and non-allergic inflammation

During inflammatory, infectious and neoplastic insults, other white blood cells, including neutrophils, macrophages, NK cells, NKT cells, Th1 cells and $CD8^+$ T cells, are recruited to damaged tissues and gain responsiveness to IL-33, a process we term *conversion* (Figure 2C). These cells express little ST2 at rest, but transient expression, particularly in inflammatory lymphocytes, can be induced in response to signals such as IL-12 (Bourgeois et al., 2009; Smithgall et al., 2008; Sun et al., 2009; Yang et al., 2011). Th1 cells required STAT4 signaling and the Th1-associated transcription factor Tbet to induce transient up-regulation of ST2 (Baumann et al., 2015). In these inflammatory settings, IL-33 drives cell expansion and IFN-γ production, and is required for optimal protection against viral infection (Bonilla et al., 2012; Nabekura et al., 2015; Villarreal and Weiner, 2014). After immune stimulation, dendritic cells (DC) which reside near high endothelial venules (HEV) in lymphoid organs are major sources of IL-12 (Reinhardt et al., 2006). Inflammatory DCs also interact with fibroblastic reticular cells (FRC), which mediate lymph node remodeling and enlargement during infection (Acton et al., 2014). HEV and FRC are primary sources of lymph node IL-33 in mice and humans (Moussion et al., 2008; Pichery et al., 2012), and release of IL-33 in these cells might reflect mechanical forces inherent in the rapid inflammation-induced changes in lymph node size, akin to findings in fibroblasts (Kakkar et al., 2012). In contrast, ILC2s, mast cells and $ST2^+$ Tregs are rare in lymphoid tissues (Molofsky et al., 2015; Nussbaum et al., 2013), potentially limiting competition for IL-33 and allowing IL-12 to drive low amounts of ST2 expression on inflammatory lymphocytes that enables competence to detect IL-33. As such, IL-33 may have a role as a vaccine adjuvant, as revealed in studies in which IL-33 promoted protective $CD4^+$ and $CD8^+$ T cells against human papilloma virus(Villarreal et al., 2014). The success of this approach may depend on the route of the vaccine and its ability to promote a Th1 cell-prone environment, including IL-12 production (Villarreal and Weiner, 2015).

In mice exposed chronically to tobacco smoke, the IL-33 tissue pool in lung is massively increased and ST2 expression becomes up-regulated on inflammatory leukocytes; in this setting, IL-33 enhances inflammation and worsens disease(Kearley et al., 2015). In mouse models of virally driven COPD, lung precursors increased expression of IL-33; similar findings were noted in humans with COPD (Byers et al., 2013). These studies suggest states of chronic inflammation, such as COPD, can increase tissue IL-33 pools and IL-33 may cooperate with persistent inflammatory signals to further promote inflammation and tissue damage. There are likely additional signals that directly repress tissue ILC2s and Tregs during chronic inflammation (Kearley et al., 2015).

IL-33 has diverse effects in cancer models. Direct overexpression of IL-33 in neoplasms promoted NK and $CD8^+$ T cell infiltration and restriction of cancer growth and metastasis (Gao et al., 2015). However, IL-33 can signal on cancer cells that themselves express ST2L, thereby promoting survival and metastasis (Kim et al., 2014; Levescot et al., 2014; Yu et al., 2015). In a model of breast cancer, exogenous IL-33 drove a mixed regulatory/type 2

immune infiltrate that promoted tumor growth and metastasis (Jovanovic et al., 2013). Elevated levels of blood ILC2s were identified in patients with gastric cancer and were associated with a suppressive immune state (Bie et al., 2014). Together, the effects of IL-33 on cancer appear context-specific, and may depend on the types of immune cells in the tumor environment, the amount of available IL-33, the amount of sST2 and the tumor cell-intrinsic expression of ST2L.

Integrating the spectrum of IL-33 activities

Understanding of IL-33 biology has evolved and expanded from its predominant role in allergic pathology to unexpected participation in basic physiologic processes connected with development and metabolism, to tissue repair and fibrosis, and to roles in classic inflammation. A framework for conceptualizing the spectrum of IL-33 biology hypothesizes a stepwise process by which the size of the tissue IL-33 nuclear pool, the presence of supporting cytokines, and the types of responding cells create a dynamic element embedded within the functionality of tissues (Figure 3).

Stage 1: Homeostasis

The role of IL-33 during tissue homeostasis is most informed from studies in adipose tissue, but similar mechanisms may occur in female reproductive organs and elsewhere (Figure 2A). At rest, IL-33 is maintained as a reservoir in the nuclei of certain endothelial and epithelial cells, and perhaps certain fibroblast reticular stromal cells. In response to poorly defined cues, which may be mechanical, hormonal or metabolic, active IL-33 is translocated to the extracellular space, perhaps through regulated secretion or cellular turnover associated with focal areas of cell death. The primary targets of constitutive IL-33 production are likely ILC2s and subsets of Tregs, which are positioned during development and whose activation leads to accumulation of AAMs and eosinophils to create a tissue environment that suppresses inflammation and promotes a reparative state characterized by tolerance. At these homeostatic concentrations, effects of IL-33 are restricted to local tissue by the constitutive presence of the decoy receptor, sST2, in serum. Similar pathways may be elicited during localized tissue injury (Brunner et al., 2011; Duan et al., 2012; Liang et al., 2013; Schiering et al., 2014; Turnquist et al., 2011; Yin et al., 2013), where the target of these and related activities may include resident precursor-like stromal cells (Burzyn et al., 2013; Goh et al., 2013; Heredia et al., 2013; Lee et al., 2015). While speculative at this time, the ability of IL-33, ILC2 and Tregs to regulate the tissue regenerative compartment remains an important area for further study.

Stage 2: Amplification

Migratory helminths, which are highly adapted to their hosts, elicit the second stage of IL-33 biology characterized by increased numbers and amounts of IL-33 in involved tissues (Figure 2B). This is accompanied by expansion of $ST2^+$ immune cells, particularly ILC2s and Th2 cells which help to restrict the helminth, but also Tregs, which repress the pro-inflammatory effects of chronic infestation and together promote the healing of involved tissue. sST2 levels may increase to contain effects of the expanded IL-33 pool, which can be buffered over many years before pathologic effects of fibrosis and other tissue injuries

become apparent. Over time, niches for key precursor cells may become disturbed, such that tissue architecture can no longer be sustained. Tissue tolerance and metabolic alterations necessary to sustain the massive egg-laying capacity of long-lived helminths may represent adaptations that have co-evolved with these parasites, which are widespread among vertebrates (Finlay et al., 2014; Maizels et al., 2012; McSorley and Maizels, 2012). During allergic pathology, such as asthma and atopic dermatitis, expansion of ILC2s becomes dissociated from Treg stimulation, enabling the activation of adaptive immunity and associated accumulation of Th2 cells and the development of high-affinity IgE capable of activating mast cells and basophils. Why Tregs are poorly induced in allergy to environmental allergens remains perplexing, but may reflect developmental anomalies related to changes in the early postnatal environment in westernized countries, the so-called 'hygiene' hypothesis. As such, further research investigating the early postnatal development, tissue positioning and differentiation of ILC2s and Tregs might be particularly informative. Indeed, perinatal Tregs may have specialized properties that endow them with functionalities related to tissue-specific tolerance (Yang et al., 2015).

Stage 3: Conversion

Inflammatory and infectious conditions associated with loss of epithelial integrity, microbial invasion at damaged barriers, and damage to precursor populations define the third stage of IL-33 (Figure 2C). Inflammatory cells such as NK cells, Th1 $CD4^+$ T cells, and $CD8^+$ T cells acquire ST2 and thus IL-33 sensitivity in response to IL-12 and other inflammatory mediators, such that classical immune inflammatory pathways become engaged, a process we term *conversion* (Villarreal and Weiner, 2014). Regulatory and type 2 responses are also actively repressed by inflammatory signals such as IFN-γ (Molofsky et al., 2015). In certain tissues (lymph nodes, spleen), a relative lack of otherwise constitutively $ST2^+$ immune cells may establish permissive conditions for acquiring responsiveness to IL-33, which is greatly expanded during the amplification of the fibroblastic reticular cell network and (in human) HEV in the enlarging lymph node. Here, IL-33 becomes critical in mediating host defense against damaged barriers in the setting of bacterial or viral infection. In the chronic phases of inflammation, nuclear pools of IL-33 become greatly expanded in tissue, such that periodic challenges lead to massive release of active IL-33 that overwhelms local sST2 levels and systemic effects of IL-33 begin to dominate. Although such a dramatic shift from type 2-associated to type 1-associated inflammation seems unusual, IL-18, another member of the IL-1 family, can mediate similarly disparate responses (Fabbi et al., 2015; Smith, 2011; Voehringer, 2012). Expression of novel IL-1 family receptors by cells constitutes an economical mechanism to rapidly re-direct conserved signaling networks to alternative effector programs in response to life-threatening challenges.

While much of this model remains conjectural, it provides a framework for organizing the complexities of IL-33 biology while exposing areas in need of further investigation. Details of IL-33 production and access to the extracellular environment, of sST2 production and regulation, and of factors determining the expression of ST2 on distinct populations of ILC2s and Tregs remain unclear. The precise role of ST2 on myeloid cells is largely undefined, and the mechanisms by which IL-12 and potentially other signals enable the expansion of ST2 expression and IL-33 responsiveness onto inflammatory cytotoxic cells

remains understudied. The next few years will be marked by further understanding of the remarkable spectrum of biologic processes affected by IL-33 and its role in homeostasis, repair, host defense and immunopathology.

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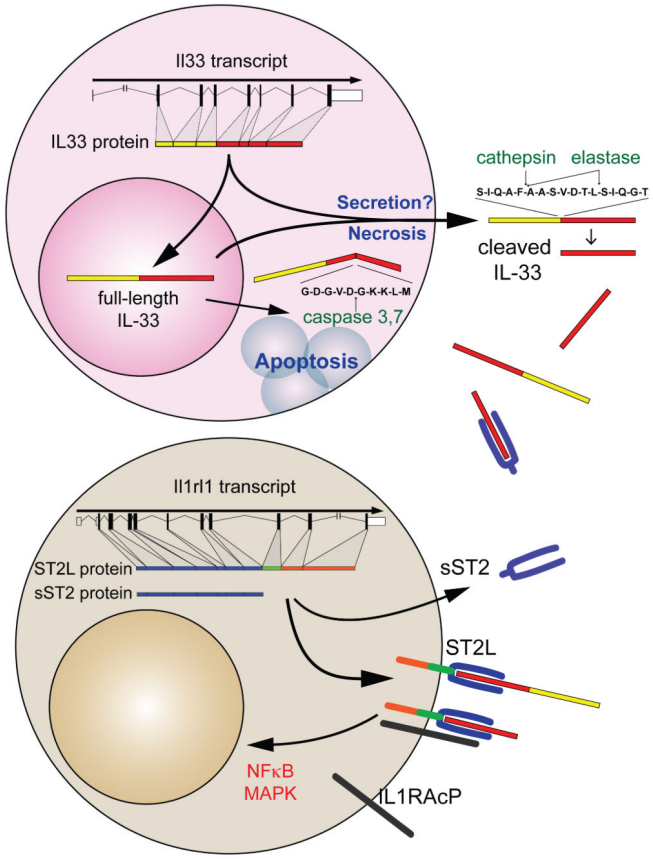

Figure 1. IL-33-ST2 molecular characteristics

IL-33 is transcribed from seven coding exons and transported to the nucleus. During lytic cell death associated with necrosis or necroptosis, or possibly via direct secretion from intact cells, full-length IL-33 is released from the nucleus into the extracellular environment. Activation of apoptotic pathways leads to inactivation of IL-33 via caspase 3- or 7-mediated cleavage. Once released, full-length IL-33 can be further processed by serine proteases, such as cathepsin-G and elastase, into forms with increased activity. The IL-33 receptor ST2 is produced in two forms, a short soluble (sST2) or longer membrane-bound form (ST2L). sST2 is constitutively expressed, but can be induced during tissue damage, and binds IL-33 and restricts its availability. In contrast, both full-length and actively processed IL-33 bind to ST2L in combination with IL-1RAcP on target cells and induces canonical NFκB and MAPK signaling pathways leading to cellular activation and proliferation.

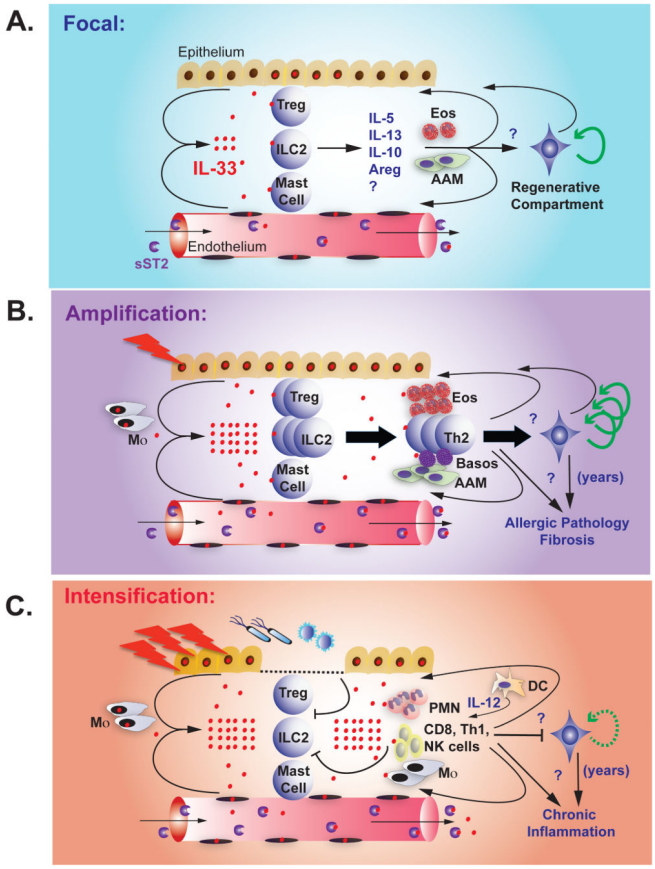

Figure 2. Progressive stages of IL-33-ST2

A. Homeostasis. IL-33 is present in the nuclei of a subset of epithelial and endothelial cells at rest. Poorly understood signals promote IL-33 release or focal cellular necrosis. IL-33 acts on tissue-resident ST2-expressing ILC2, Treg, and possibly mast cells, inducing the production of IL-5, IL-13, IL-10, amphiregulin (Areg), and other signals that promote eosinophils (Eos) and alternatively activated macrophages (AAM). These cells and signals feed back on the tissue and may regulate remodeling and limit inflammation, in part by activating tissue progenitor cells. sST2 in the blood prevents systemic IL-33 effects.

B. Amplification. During tissue allergic insults and injury, epithelial and endothelial cells release IL-33, likely via necrosis, and IL-33 expression is further induced. Increased extracellular IL-33 activates and expands tissue ILC2 and Treg, and promotes recruitment and survival of additional immune cells (eosinophils, AAM, Th2 cells, basophils). These cells and signals feed back on the tissue to promote remodeling and limit inflammation, in part by activating tissue progenitor cells. In acute injury (infarction, tissue damage, helminth infection) these pathways help resolve injury and limit helminth infection. Chronic stimuli, such as allergens and repetitive tissue damage, lead to multiple cycles of IL-33 release that promote chronic allergic pathology, tissue fibrosis, increased Th2 cells, loss of Treg and other regulatory components, and increased tissue stores of IL-33. sST2 production is increased, but IL-33 concentrations may exceed blood buffering capacity in chronic damage and lead to systemic effects.

C. Conversion. Infectious or inflammatory triggers elicit tissue damage and epithelial breaches in the context of pathogen-associated molecular patterns. Pre-formed tissue IL-33 stores are released, likely via necrosis, and IL-33 is further induced in tissue cells. Inflammation and foreign antigen induces dendritic cell activation and IL-12 production, trafficking of inflammatory leukocytes from blood, and increased responsiveness to IL-33 through upregulation of ST2 on additional cell types. Activated inflammatory cells and cytokines, including IFN-γ, repress the Treg and type 2 immune response and facilitate killing of microbial and viral pathogens. In chronic inflammatory states, such as COPD and possibly autoimmune disease, IL-33 pools are increased and promotes repetitive cycles of IL-33 release, increasing tissue damage. sST2 production is increased, but IL-33 levels may exceed blood buffering capacity in chronic damage and lead to systemic effects.

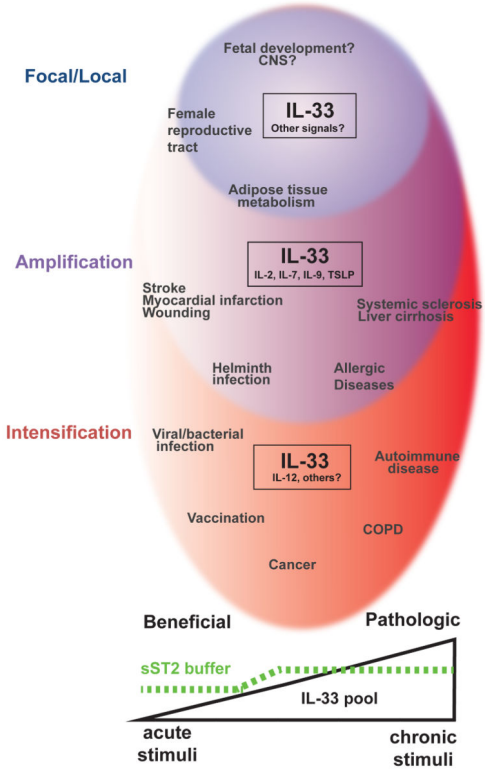

Figure 3. Spectrum of IL-33 biology

A model of the spectrum of IL-33 effects on tissue during beneficial and pathologic immune responses, with IL-33 cellular pools increasing from left to right. (**Homeostasis, Blue**) IL-33 is present in a restricted subset of cells and cooperates with unknown signals to maintain tissue integrity, limit excess inflammation and promote tissue adaptation to remodeling and other physiologic stressors. (**Amplification, Purple**) During acute tissue injury and damage, IL-33 synergizes with other epithelial cytokines and lymphokines to promote tissue homeostasis and repair (stroke, myocardial infarction, wounding). Helminths elicit similar responses. With repetitive tissue damage, IL-33 pools increase, regulatory mechanisms are suppressed, inflammation is amplified and fibrosis ensues (sclerosis, cirrhosis, allergic disease). (**Conversion, Red**) Generation of IL-12 and other inflammatory signals promotes IL-33 signaling on inflammatory cells that are normally unresponsive, while repressing type 2-associated responses. Activation of this pathway promotes beneficial responses to infection and possibly vaccination, and may support anti-cancer immune responses in certain settings. With chronic unresolved inflammation, however, tissue IL-33 increases and ultimately contributes to tissue damage (COPD, autoimmune diseases).