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Emerging Functions of IL-33 in Homeostasis and Immunity

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Abstract

Our understanding of the functions of the IL-1 superfamily cytokine and damage-associated molecular pattern IL-33 continues to evolve with our understanding of homeostasis and immunity. The early findings that IL-33 is a potent driver of type 2 immune responses promoting parasite expulsion, but also inflammatory diseases like allergy and asthma, have been further supported. Yet, as the importance of a type 2 response in tissue repair and homeostasis has emerged, so has the fundamental importance of IL-33 to these processes. In this review, we outline an evolving understanding of IL-33 immunobiology, paying particular attention to how IL-33 directs a network of $ST2^+$ regulatory T cells, reparative and regulatory macrophages, and type 2 innate lymphoid cells that are fundamental to tissue development, homeostasis, and repair.

1. INTRODUCTION

Despite its widespread expression in the body, IL-33 has always been an elusive and complicated molecule. It was first described in 2003 as an mRNA- and nucleus-targeted protein abundantly expressed in endothelial cells of human lymphoid organs and designated nuclear factor from high-endothelial venules (NF-HEV) (1, 2). The carboxy-terminal part of the human IL-33 protein was subsequently identified using computational tool–based GenBank searches for novel members of the IL-1 cytokine family (3). Because the IL-33 protein had a three-dimensional structure similar to those of other IL-1 family members, it was declared a new IL-1 cytokine (3). Subsequent chromosomal anatomy and sequence assessments, however, found little evidence that IL-33 evolved from a common IL-1 ancestor, and it is more appropriate to describe IL-33 as an IL-1 superfamily member (4). Schmitz et al. (3) provided the seminal evidence that IL-33 cytokine activity is due to ligation of a previously defined orphan receptor in the IL-1 receptor (IL-1R) superfamily, stimulation 2 (ST2). This interaction induces type 2 cytokine secretion by type 2 helper T (Th2) cells, which were the first cells pinpointed as expressing detectable levels of the IL-33 receptor (5). NF-HEV and IL-33 were later confirmed to be the same protein, and IL-33 was further characterized as a chromatin-associated nuclear cytokine in vivo. Several comprehensive reviews provide excellent descriptions of the studies that identified and characterized IL-33 and ST2 (1, 5, 6). Likewise, the study of the role of IL-33 in immunity is a mature field and well-reviewed (5, 7–10). Therefore, we have kept our discussion of the details of the molecular biology of IL-33 and its role in immunity focused on more recently discovered pro- and anti-inflammatory activities of IL-33, especially those outside the realm of type 2–mediated immune responses. This is not to minimize the importance of this work but to allow for an in-depth discussion of the recent findings regarding the roles that this fascinating, pervasive, and often perplexing molecule plays in tissue development, homeostasis, and repair.

2. MOLECULAR BIOLOGY OF IL-33

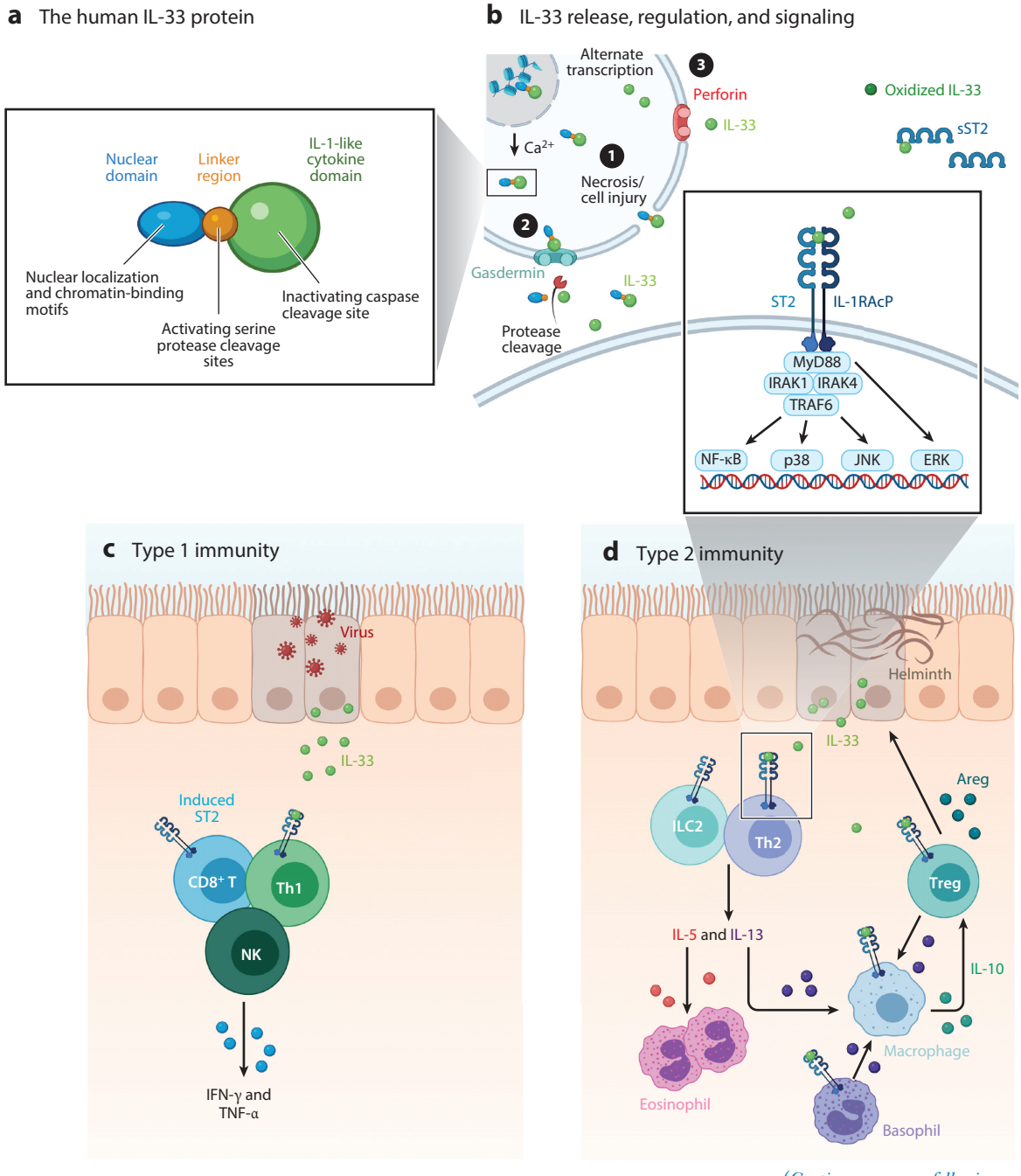
2.1. Gene

The human *IL33* gene is located on chromosome 9 at 9p24.1, and the mouse *Il33* ortholog is situated on the same chromosome at 19qC1 (1, 5). In mice and humans, the gene has eight exons (1, 5). Two promoters have been identified, one in humans upstream of an untranslated exon (exon 1 or 1a), and another in both humans and mice before exon 2. The first promoter contains an interferon-stimulated response element and several IFN-γ activation sites (11). These two promoters generate two transcripts (*Il33a* and *Il33b* mRNAs) that include unique 5′-untranslated regions, but they encode the same protein (1, 5, 11).

2.2. Protein Structure and Function

IL-33 (**Figure 1**) is synthesized as a full-length, 270–amino acid protein that consists of two evolutionarily conserved domains. The first is an N-terminal nuclear domain (amino acids 1–65) that enables nuclear localization and chromatin association of IL-33. The second domain is a C-terminal IL-1-like cytokine domain (amino acids 112–270) that confers the cytokine-like activities of IL-33. These two domains are separated by a divergent central linker region (amino acids 66–111) (1, 5). High-resolution structures of most of the IL-1 superfamily members, including IL-33, have been determined by X-ray crystallography or solution-state nuclear magnetic resonance. IL-33 contains a conserved β-trefoil conformation and central hydrophobic core

composed of 12 β sheets, similar to the structure originally described for IL-1 (1, 5). The cytokine domain is an IL-1-like structure with folding properties similar to those of IL-1α, IL-1β, and IL-18 (12, 13). Human IL-33 exhibits high identity with the murine form, with the central linker region the most divergent (1).



(Caption appears on following page)

Figure 1 (*Figure appears on preceding page*)

Structure and function of IL-33 in immunity. (*a*) Full-length IL-33 comprises two highly conserved domains, an N-terminal nuclear domain with nuclear localization and chromatin-binding motifs (*blue*) and an IL-1-like cytokine domain (*green*). These are separated by a divergent central linker region (*orange*). Activating and inactivating cleavage sites are indicated. (*b*) IL-33 is released from damaged or stressed cells by several potential mechanisms. (❶) Necrosis or injury allows full-length IL-33 to be released from the nucleus, where it is typically sequestered by the nuclear domain–binding nucleosomes. (❷) Full-length IL-33 can be translocated to the cytoplasm in a Ca^{2+}-dependent manner and then released via a gasdermin D–dependent process. (❸) IL-33 lacking its nuclear domain is generated from alternative splicing transcripts, enabling cytoplasmic localization and secretion via perforin-2-mediated pores. Full-length IL-33 is functional, but cleavage by serine proteases generates mature, more active forms. IL-33 is regulated via sequestration in the nucleus, oxidation, and sequestration by sST2. Binding of ST2 and IL-1RAcP, an IL-1 superfamily member coreceptor, by full-length or mature IL-33 leads to binding of MyD88, IRAK1, and IRAK4 kinases and TRAF6 and the activation of several MAP kinases and NF-κB. (*c*) The binding of IL-33 to ST2 that is upregulated on activated $CD8^+$ T cells and $CD4^+$ Th1 cells, as well as NK cells, leads to augmented proliferation and increased production of proinflammatory cytokines. (*d*) Cells mediating type 2 immunity express ST2 and respond to IL-33 with proliferation and production of cytokines that support the clearance of pathogens and restore epithelial health. IL-13 production by ILC2s, $CD4^+$ Th2 cells, Tregs, and basophils is vital to generate reparative and regulatory macrophages that aid repair and support local Tregs. IL-5 production by ILC2s controls the accumulation of eosinophils that aid in parasite expulsion. Abbreviations: Areg, amphiregulin; ILC2, group 2 innate lymphoid cell; NK, natural killer; sST2, soluble ST2; Th1, type 1 T helper; Treg, regulatory T cell. Figure adapted from images created using BioRender.com.

2.3. Regulation of Expression and Cellular Sources

Ongoing investigations into IL-33 expression continue to lead to important insights into how modulated cellular sources and expression patterns determine IL-33 activities.

2.3.1. Constitutive expression. In the steady state, full-length IL-33 is constitutively expressed in various cell types in human and mouse tissues and located in their nuclei (1, 5). Major identified sources include human endothelial cells and mouse adventitial stromal cells of the vascular tree; epithelial cells in barrier tissues; fibroblast reticular cells (FRCs) in the lymphoid organs; and glial cells, neurons, and astrocytes in the nervous system (1, 5, 14–17).

2.3.2. Induced or transient expression. Although IL-33 is constitutively expressed by many cells during the steady state, cellular stress or exposure to inflammation can augment or induce cellular expression of IL-33. For example, IL-33 expression increases in the mucosal barrier tissues after irradiation or chemotherapy (18), in the intestine of patients developing graft-versus-host disease (GVHD) following allogeneic hematopoietic cell transplantation (alloHCT) (18), and in airway epithelial cells of patients with asthma or chronic obstructive pulmonary disease (COPD) (1). IL-33 expression is increased in mouse type 2 alveolar epithelial cells (AEC2s) by pathogens, allergens, or irritants (1). In addition to epithelial and endothelial cells expressing induced levels of IL-33, stromal cells that include fibroblasts, myofibroblasts, and fibroblast-like cells are critical sources of IL-33 during inflammation and tissue repair (1, 19). Proinflammatory cytokines like IFN-γ (20), IL-4, and IL-13 (14); Notch signaling (21); and mechanical stress (22, 23) have all been shown to increase IL-33 expression in tissue parenchyma and stroma.

2.3.3. Leukocyte expression. Early studies reported IL-33 expression in $CD45^+$ hematopoietic cells (1, 3, 24). However, IL-33 levels detected at baseline in $CD45^+$ hematopoietic cells were much lower than levels identified in nonhematopoietic cells (24), and it has remained unclear whether leukocytes are important sources of IL-33 protein in vivo in both humans and mice. Studies identifying induced IL-33 expression in mast cells pointed toward a role for IL-33 in myeloid cells and mast cell–mediated inflammation (25, 26) and autoimmunity (27). Recent studies have also provided strong evidence for IL-33 expression in mucosal mouse $CD103^+CD11c^+$ conventional dendritic cells (cDCs) and related human $HLA\text{-}DR^+$ cells (28). These studies used precise, cell-specific deletion of IL-33 to supply compelling evidence for the importance of myeloid

cell–derived, but not epithelial cell–derived, IL-33 in the generation of intestinal $ST2^+$ regulatory T cells (Tregs) that regulate helminth immunity (28). Other recent rodent studies have suggested the importance of intrinsic IL-33 activity to B cell development (29) and Treg suppressive function and stability (30). However, neither of these studies established robust evidence of IL-33 protein in Tregs or B cells, but instead, reporter signatures were used to support their conclusions. It will be exciting to watch as investigators continue to use models allowing IL-33 to be targeted or tracked in lymphocyte subsets to determine whether and when IL-33 is expressed during lymphocyte development and how it contributes to later adaptive immune cell subset functions.

2.4. Nuclear Localization, Chromatin Association, and Gene Regulation

The full-length, 270–amino acid IL-33 protein is localized to the nucleus of expressing cells and biologically active when freed after cellular injury or necrotic cell death (1). This nuclear localization is due to the N-terminal domain of IL-33, which contains a nuclear localization sequence (amino acids 61–78) that is sufficient for nuclear localization and chromatin association. The N-terminal domain also includes a short chromatin-binding motif (amino acids 40–58) that binds to the nucleosome in an acidic pocket formed by the histone heterodimer H2A-H2B (1, 5, 6) (**Figure 1**). The binding strength of IL-33 to chromatin via the N terminus is strong and comparable to that of histone H3 (31). Deletion of only the N-terminal nuclear domain results in loss of nuclear IL-33 retention of the truncated forms and leads to ST2-dependent inflammation–induced lethality (31, 32). Surprisingly, chromatic binding actually limits IL-33 release during necrosis, but released IL-33 and chromatin synergistically activate ST2 signaling (31). These studies established that an important function of IL-33 chromatin binding is to regulate its extracellular release and the activity of the cytokine domain (**Figure 1**).

Nuclear IL-33 has also been suggested to mediate gene regulation through various mechanisms (4). In overexpression experiments, a region of IL-33 made up of amino acids 66–109 can interact with the N-terminal domain of NF-κB p65 and act as a transcriptional repressor that blunts and delays NF-κB-triggered gene expression in vitro (33). Negative regulation of NF-κB activity downstream of TNF-α, poly(I:C), or IL-1β signaling by IL-33 was observed in fibroblast-synoviocytes from patients with rheumatoid arthritis (34). Separate assessment of IL-33-overexpressing cells in vitro demonstrated that IL-33 can increase IL-13 transcription by binding regions in the *IL13* gene locus (35). FAK (focal adhesion kinase) associates with IL-33 in the nucleus of murine squamous cell carcinoma cells (36). This complex interacts with a network of chromatin modifiers and transcription regulators to control the expression of CCL5, which attracts tumor-infiltrating Tregs (36). Transcriptional profiling of IL-33- and ST2-deficient kidneys in an obstructive fibrosis model suggested that nuclear IL-33 contributes to fibroblast differentiation through gene expression modulation (37). Yet, high-throughput proteomic assessment of endothelial cells with IL-33 knocked down or exposed to IL-33 lacking the N terminus (amino acids 95–270) found that extracellular, but not nuclear, IL-33 could regulate protein expression in endothelial cells (38). These data are analogous to those obtained from genome-wide analysis of esophageal epithelial cells lacking ST2 and IL-33 in which no transcriptional changes were observed after expression of full-length wild-type IL-33 was induced (31). Thus, while there is accumulating evidence that nuclear IL-33 has transcriptional regulatory functions, these functions appear highly situational and potentially cell-type specific.

2.5. Release and Secretion

While mechanisms of IL-33 release have been studied extensively, there remain critical gaps in our knowledge of the mechanisms by which IL-33 leaves the nucleus and transits outside the

cell. IL-33 lacks a signaling sequence and is not secreted from cells by the classical endoplasmic reticulum–Golgi apparatus secretory pathway. Instead, IL-33 is described as a nuclear alarmin that is released after injury in a functional, full-length form to alert the immune system to tissue damage (1, 5, 6). Agents causing cellular damage, necrotic cell death, or necroptosis release IL-33 in extracellular fluids (1). In vivo, IL-33 is released following viral infection–induced lung damage and can be detected in the cerebrospinal fluid after spinal cord injury (1). IL-33 is also evident in the bronchoalveolar lavage (BAL) fluids of asthma patients after lung challenge with pollen and house dust mite antigen (1). The fungal allergen *Alternaria alternata* induces the release of IL-33 from lung epithelial cells by causing cellular stress and reactive oxygen species generation, extracellular ATP secretion, and increased intracellular Ca^{2+} concentrations (1). Unfortunately, it is challenging to exclude cell death as a mechanism in this setting because intranasal exposure to *Alternaria* is also associated with a significant loss of IL-33^{+} cells at 1 h (1). While mechanical stress appears to contribute to IL-33 release, further studies are needed to clarify the mechanism involved (22, 23, 39). Release mechanisms other than necrosis-induced cell death may require that nuclear IL-33 be translocated to the cytoplasm or generated without the N terminus, as proposed recently, to support the release of cytoplasmic IL-33 via perforin-2-mediated pores (**Figure 1**) by CD103^{+}CD11c^{+} cDCs (28). A recent study of COPD clinical specimens documented an IL-33 isoform that lacks the N-terminal domain and could be tonically secreted from airway basal cells on the surface of small extracellular vesicles, or exosomes (40). This pathway supported *Alternaria* extract–mediated type 2 airway inflammation (40). Momota et al. (41) recently identified a mechanism for IL-33 release in vitro that is regulated by two signals. First, IL-33 is translocated from the nucleus to the cytoplasm in a Ca^{2+}-dependent manner. Second, nigericin, a *Streptomyces hygroscopicus*–derived potassium ionophore, triggers gasdermin D–dependent, pyroptosis–mediated IL-33 release through membrane rupture (**Figure 1**). Thus, several scenarios have emerged where divergent pathways allow necrosis- or pyroptosis-mediated release of full-length IL-33, as well as nonclassical secretion of truncated IL-33 proteins. Further investigations should shine additional light on each pathway's prevalence and functional outcomes in different biological conditions.

2.6. Regulation of Protein Functions

As discussed above, mRNA-transcribed, full-length, or N-terminally truncated forms of IL-33 are biologically active. However, shorter forms of IL-33 generated by protease cleavage in the linker region (**Figure 1**) remove the N-terminal domain from the full-length protein to generate more potent, mature forms. Cleavage in the cytokine domain, however, inactivates IL-33, as do other protein modifications (1, 5, 6).

2.6.1. Positive regulation. IL-33 is processed to the mature form by inflammatory serine proteases produced by neutrophils and mast cells. Yet, processing of full-length IL-33 can also occur in mice deficient in immune cell proteases, suggesting a functional role for exogenous allergen proteases and endogenous calpains (42). In mouse models of lung injury, allergen exposure, and helminth infection, mature forms of IL-33 have been detected in BAL fluids of recovered animals (1). These findings suggest that proteolytic maturation of full-length IL-33 is an important component of IL-33 regulation and contributes to the diverse activities of this cytokine.

2.6.2. Negative regulation. Nuclear localization and retention regulate the release and proinflammatory activity of IL-33 and are vital for immune homeostasis (32). In addition, IL-33 is cleaved and inactivated by caspases during apoptosis, limiting its capacity to trigger

inflammation when cell death occurs in a controlled manner (1). The caspase cleavage site is in the middle of the IL-1 cytokine domain (amino acid 178 in humans) and is not found in other IL-1 superfamily members. Once IL-33 reaches the extracellular space, it is regulated by several known mechanisms that are only briefly reviewed here (1, 5, 6). First, IL-33 is rapidly oxidized at critical cysteine residues within the cytokine domain, which causes the formation of disulfide bridges and inactivates IL-33. Free IL-33 is also sequestered by a soluble decoy receptor, soluble ST2 (sST2). Alternative splicing of ST2 generates sST2, which lacks the transmembrane domain and binds IL-33 in biological fluids to prevent it from triggering ST2 signaling (43). Both adaptive and innate immune cells, as well as nonhematopoietic cells, produce sST2 in response to proinflammatory cytokines, Toll-like receptor (TLR) ligands, and mechanical stress (7). sST2 is elevated in the sera of patients with trauma and various inflammatory diseases and is associated with reduced IL-33-mediated immune responses (44, 45).

2.7. Splice Variants and Isoforms

Single-nucleotide sequence variations identified in the human *IL33* gene are found in the promoter region and are associated with increased susceptibility to asthma (46). Conversely, a loss-of-function mutation before exon 8 likely results in a biologically inactive, truncated IL-33 protein, causing reduced numbers of eosinophils in the blood and conferring protection to individuals against asthma, which parallels the reduced asthma susceptibility observed in IL-33-deficient mice (47). In human airway epithelial cells, alternative transcript splicing deletes exons 3 and 4. This splicing variation confers cytoplasmic localization of a functional molecule with signaling capacity and is associated with type 2 inflammation in patients with asthma (48). These data substantiate the contributions of IL-33 to human type 2 responses and corroborate the contributions of IL-33 to type 2–associated clinical immunopathologies. Importantly, they also endorse the appropriateness of using transgenic rodent models; similar phenotypes have been observed in IL-33-deficient mice (24), mice with cytoplasmic localized IL-33 (32), and humanized mice (49).

2.8. IL-33-Induced ST2 Signaling

IL-33 signals to cells through the membrane-bound receptor ST2 (**Figure 1**). To date, no other receptor for IL-33 or ligand for ST2 has been identified. Studies of the crystal structure of the IL-33-ST2 complex reveal that two binding sites in the cytokine domain of IL-33 interact with all three immunoglobulin-like domains of ST2. Specific single-point mutations in the IL-33 binding site acidic residues significantly decreased the ST2 binding affinity, demonstrating that IL-33 binds to ST2 through acidic residues forming salt bridges with ST2 basic residues at each binding site. Details regarding the crystal structure of IL-33 interacting with ST2 can be found in other reviews (1, 5, 6). Binding of IL-33 allows ST2 to interact with IL-1RAcP, an IL-1 superfamily member coreceptor, and this IL-33 receptor complex signals through MyD88, IRAK1, and IRAK4 kinases and TRAF6 to culminate in the activation of several MAP kinases and NF-κB (**Figure 1**). These signaling intermediates and pathways are shared with IL-1R and IL-18R, as well as other members of the TLR/IL-1R superfamily. Yet stimulation by IL-33, IL-1, IL-18, and TLR ligands induces unique biological effects on the same cell type. For example, we revealed that TLR4 and ST2 produce contrasting impacts on cellular metabolism when these closely related pathways are stimulated on macrophages (50). In brief, IL-33-exposed macrophages can utilize oxidative phosphorylation, whereas TLR4-stimulated cells will be locked into a metabolic program relying on glycolysis and associated with proinflammatory activities (51). Regulated expression of each of these surface receptors during development or throughout an immune response is also likely important in dictating distinct effects of IL-33 versus other members of the TLR/IL-1R

superfamily (1, 5, 8). Additionally, the location and timing of IL-33 release relative to TLR or IL-1R ligation may direct the distinct outcomes modulated by IL-33 stimulation.

Recently, we have shown that naturally occurring nanovesicles embedded within the extracellular matrix, defined as matrix-bound vesicles (MBVs), contain bioactive IL-33 that is protected from proteolytic degradation (52). Using MBVs isolated from wild-type or IL-33-deficient mice and ST2-deficient macrophages, we showed that IL-33 encapsulated within MBVs can bypass the classical IL-33/ST2 receptor signaling pathway and direct macrophage differentiation into the reparative, $Arg1^+$ pro-remodeling phenotype. This anti-inflammatory property of IL-33-containing MBVs may explain their therapeutic capacity to limit inflammation and tissue injury after heart transplantation (50) and ocular pressure–induced ischemia in the eye (53). Unlike recombinant IL-33 (rIL-33), IL-33 in MBVs does not activate p38 or NF-κB and induces arginase 1 expression independent of STAT6 phosphorylation (52). While it can be speculated that full-length IL-33 released from MBVs mediates transcriptional regulatory functions to support $Arg1^+$ macrophage generation, further investigation is needed to establish this, as well as the mechanisms of MBV uptake and release from MBVs.

$Arg1^+$ macrophages are historically described as M2, or alternatively activated, macrophages to align with the type 2 cytokines (IL-4, IL-10, IL-13) that support their generation from nondifferentiated, or M0, macrophages (54). These are typically contrasted to M1, or classically activated, macrophages generated by stimulation of type 1 cytokines (IFN-γ and TNF-α) and identified by inducible NO synthase (iNOS) expression (54). However, this binary classification is an overly simplistic view based on in vitro conditions that do not reflect the diverse in vivo conditions that generate heterogeneous macrophage phenotypes (54). Thus, we use functional terminology to describe macrophage subsets. For instance, regulatory macrophages secrete IL-10 and TGF-β and express programmed cell death ligands to suppress a local immune response (55). Expression of Arg1 by regulatory and reparative macrophages causes them to generate ornithine from L-arginine to support tissue repair and produce immunosuppressive metabolites (55). Reparative macrophages produce growth factors, including platelet-derived growth factor, TGF-β1, insulin-like growth factor, and VEGFα, to aid injury resolution. These factors promote cellular proliferation and blood vessel development, attract tissue fibroblasts, and differentiate fibroblasts into myofibroblasts (55). Conversely, proinflammatory macrophages express iNOS to generate large quantities of NO and are highly phagocytic to aid in debris and pathogen clearance (55). Proinflammatory macrophages display costimulatory molecules; present antigens on MHC; and secrete TNF-α, IL-1β, IL-6, and IL-12, which amplify innate and adaptive immune responses (55).

3. IL-33 AND ITS ROLE IN IMMUNITY

After the discovery of IL-33 and ST2 in the late 1990s and early 2000s, it was shown that administration of rIL-33 to mice consistently elicits a profound type 2 immune response. Eosinophils infiltrated into tissues; goblet cell hyperplasia was observed; and elevated type 2 cytokines, particularly IL-5 and IL-13, were detected (1–5, 56). Such evidence for type 2–mediated inflammation by IL-33 was soon followed by the demonstration that IL-33 released from cells plays an important role in parasite clearance and type 2–mediated pathologies, such as asthma and allergic skin disorders. In the period since these early discoveries, the dominant immune targets of IL-33 have been shown to be adaptive and innate tissue-resident immune cells that express ST2 constitutively. Yet, many other immune, stromal, and parenchymal cells are induced to express ST2 during activation. This induced expression leads to situations briefly outlined below, where IL-33 exhibits pleiotropic functions supporting IFN-γ-, IL-9-, and IL-17-dominated immune responses as part

of the host response to pathogens or immune-mediated inflammatory diseases (for reviews with comprehensive details, see References 5, 7, and 57).

3.1. IL-33 Effects in the Lymphoid Compartment

ST2 was first shown to be expressed on both human and mouse Th2 cells both in vitro and ex vivo, and these cells were the early focus of the study of ST2 immunobiology (5, 7, 57). Th2 cells are classically described by their expression of the transcription factor GATA3 and production of type 2 effector cytokines. ST2 expression on Th2 cells is independent of IL-4, IL-5, and IL-10 expression but can be induced through IL-2-STAT5-mediated induction of GATA3 in vitro. IL-33 stimulation of Th2 cells increases their proliferation and IL-5 and IL-13 production (3, 5, 7, 57). In addition to Th2 cells, a subset of Tregs expressing ST2 have been identified. $ST2^+$ Tregs are typically $CD4^+Foxp3^+GATA3^+$ and preferentially accumulate in the nonlymphoid tissues (58–62). $ST2^+$ Tregs are especially enriched in the mucosal barrier tissues and can be either thymus-derived or peripherally induced Tregs (61). IL-33 stimulation of $ST2^+$ Tregs enhances their proliferation and expression of IL-13 and amphiregulin (Areg) (**Figure 1**), which support their regulatory functions and direct tissue repair as described below (58–61, 63, 64). Furthermore, $CD4^+$ Th1 cells and type 1 $CD8^+$ T cells express ST2 and sST2 transiently following an antigen encounter (65–68). Th1 cells upregulate ST2 in a STAT4- and T-bet-dependent manner (65) (**Figure 1**). A loss of ST2 on Th1 or $CD8^+$ T cells results in an impaired type 1 effector response to lymphocytic choriomeningitis virus (LCMV) in mice (65, 66). In 2010, several groups identified a population of lineage-negative and $ST2^+c\text{-}Kit^+Sca\text{-}1^+IL\text{-}7aR^+$ cells in the lymphoid gate that were GATA3 dependent and profound producers of IL-5 and IL-13. These novel cells secrete type 2 cytokines but lack antigen receptors and are now designated group 2 innate lymphoid cells (ILC2s) (69).

3.2. IL-33 Effects in the Myeloid Compartment

Early studies using recombination activating gene 2 (Rag2)-deficient mice, which lack T and B cells, revealed the potent impacts of IL-33 on innate cells of the myeloid compartment (56, 70). We know now that myeloid precursors and differentiated myeloid subsets express modulated levels of ST2 that are important for their development, differentiation, and function. For example, IL-33 acts directly on mast cells to promote their survival through the upregulation of BCLXL and supports their maturation and production of effector cytokines, including IL-13 and IL-22 (71, 72). Basophils also express low levels of ST2, and IL-33 stimulation provokes the release of cytokines, especially IL-4, IL-8, and IL-13 (73). This relationship is critical to basophil direction of alveolar macrophage generation and lung development (74). IL-33 acts directly on macrophages following IL-13-mediated ST2 upregulation to support the generation of type 2 cytokine–differentiated, reparative, and regulatory macrophages (75, 76). IL-33 also enhances the expansion, survival, and adhesiveness of human eosinophils that mediate reparative and proinflammatory roles throughout the body (77, 78). IL-33 stimulates myeloid cells to secrete IL-2, which synergizes with IL-33 to support $ST2^+$ Treg expansion and functions (28, 79, 80). ST2 expression on $CCR2^+$ monocytes is essential for the metabolic reprogramming necessary for differentiation into regulatory and reparative macrophage subsets (50).

3.3. IL-33 in Type 2 Immunity

A wealth of information regarding IL-33 support of type 2 immunity to parasites can be found in other reviews (5, 7, 8). In brief, helminth infection in mice increases IL-33 levels in the barrier tissues, and the administration of rIL-33 confers protection due to enhanced type 2 cytokine

expression. Free IL-33 levels are also elevated in the peritoneal fluid shortly after infection to support ILC2 effector cytokine secretion (**Figure 1**) that causes goblet cell hyperplasia (5, 7, 8). Patients infected with *Schistosoma* have increased levels of IL-33 in their sera, which correlates with increased type 2 cytokine production and eosinophilia. IL-33 signaling is necessary for granuloma formation, eosinophilia, and Th2 effector cytokine production in the lung in response to *Schistosoma* infection. Dahlgren et al. (14) recently identified a new feedback role for IL-33 in helminth infection. They determined that a critical source of IL-33 is fibroblast-like adventitial stromal cells (ASCs). IL-33 and TSLP from ASCs are required for ILC2 and Th2 cell accumulation in the lung during helminth infection, and ILC2s promote IL-13-mediated ASC expansion and IL-33 production (14).

3.4. IL-33 in Type 1 Immunity

Although IL-33 is predominantly associated with type 2 immune responses mediated by cells constitutively expressing ST2, it can augment protective type 1 immunity. IL-33 is effective at promoting expansion of $CD8^+$ T cells and their production of type 1 effector cytokines IFN-γ and TNF-α during viral infections and supports an effective recall response upon reinfection (66, 81–83) (**Figure 1**). This may be because the typically $ST2^-$ leukocytes involved in type 1 immune responses, such as natural killer (NK) cells, NK T cells, Th1 cells, and $CD8^+$ T cells, are induced to express ST2 by poorly understood inflammatory signals. One signal known to upregulate ST2 on these lymphocytes is IL-12 (18, 65, 67, 84, 85). STAT4 and the type 1–associated transcription factor T-bet were required for induced ST2 upregulation, which is necessary for an effective Th1 response following an LCMV infection (65). Effective antiviral T cell responses are initiated in the secondary lymphoid organs, where antigen-presenting cells (APCs) activate T cells. High-endothelial venules and FRCs within the lymphoid organs mediate lymph node remodeling and enlargement during a viral infection (86), and they are the primary sources of IL-33 in the lymph nodes (1). During LCMV infection, FRCs lose IL-33 expression by an undefined mechanism, which correlates with induced $CD8^+$ T cell expression of ST2 and expansion (19). How ST2 expression is coordinated on $CD8^+$ T cells in vivo and how IL-33 is released from FRCs during injection to support type 1 antiviral immune responses are important outstanding questions.

3.5. IL-33 in Immune Responses to Fungal and Bacterial Pathogens

During a *Candida albicans* infection, IL-33 delivery can boost an antifungal neutrophil response by enhancing macrophage secretion of CXCL1 and CXCL2 to drive neutrophil recruitment and by increasing the surface expression of the corresponding receptor CXCR2 on neutrophils (87). In a related model of systemic *C. albicans* infection, IL-33 treatment improves the ability to control *Candida*-induced immunopathologies by stimulated $CD4^+$ T cells to produce IL-13 that acts synergistically with IL-33 to promote reparative and regulatory macrophage differentiation (88). Yet, mice deficient in ST2 display improved outcomes due to the reduced type 2 lung inflammation arising from over-robust accumulation of ILC2s and Th2 cells (89–91). Alvarez et al. (92) recently demonstrated that there is a delicate balance maintained by IL-33 and IL-1 signaling supporting the regulatory immune response during fungal infections. IL-33 stimulation supports Treg stability, as $ST2^{-/-}$ Tregs are prone to acquire RORγt and IL-1R1 and lose their suppressive function. *Il1r1*$^{-/-}$ mice infected with *Cryptococcus neoformans* have a greater number of $ST2^+$ Tregs, which maintain Foxp3 and resist change to a Th17 phenotype, resulting in reduced fungal clearance and augmenting susceptibility to fungal infection (92). Similarly, IL-33 negatively regulates the pathogen-clearing Th17 response to colitis induced by the enteric pathogen

Citrobacter rodentium by enhancing gut epithelium permeability, suppressing antimicrobial REG3γ upregulation, increasing Treg frequency, and impairing Th17 differentiation (93).

Several studies have shown that patients with sepsis have elevated IL-33 or sST2, suggesting an association between IL-33 and bacterial infections (94–97). These have been thoroughly reviewed recently (98), but briefly, the administration of IL-33 significantly reduces mortality in the cecal ligation and puncture mouse model of sepsis and is associated with increased neutrophil infiltration into the peritoneal cavity and increased bacterial clearance compared to untreated mice (94). Survivors of sepsis can develop long-term sequelae from immune dysfunction due to an expanded Treg population. Patients who survive sepsis have increased Tregs, IL-33, and IL-10 in their peripheral blood. High levels of IL-33 activate IL-4- and IL-13-producing ILC2s, which support the polarization of IL-10-secreting macrophages that ultimately enhance Treg expansion (99). IL-33 increases in cutaneous wounds challenged with *Staphylococcus aureus*, which is a common wound pathogen (100, 101). Delivery of rIL-33 increased neutrophil localization to the wound and increased antimicrobial activity of local macrophages to reduce bacterial colonization (100, 101). IL-33 also increased healing, suggesting that the functions of IL-33 in immunity and homeostasis, like the two processes themselves, are tightly linked.

3.6. IL-33 in Respiratory Inflammation and Allergy

IL-33 is upregulated in allergic and chronic respiratory diseases, including asthma, atopic dermatitis, allergic rhinitis, and COPD. Large-scale genome-wide association studies implicate IL-33 in human asthma, as both *IL33* and *IL1RL1* are linked to susceptibility (46, 102). IL-33 expression is upregulated in the bronchial epithelial cells of patients with asthma and in the epidermal keratinocytes of patients with atopic dermatitis (103, 104). Rodent models of these respiratory and allergic diseases implicate IL-33 and ST2 as important to the immunopathology of these diseases (see Reference 105 for a comprehensive review). Yi et al. (106) have recently identified a unique lectin, intelectin-1, that plays an important role in the innate immune response to pathogens as a critical regulator of IL-33 expression in epithelial and epidermal cells in both asthma and atopic dermatitis. Knockdown of intelectin-1 expression reduces IL-33 expression in two asthma and two atopic dermatitis models, and its expression in humans correlates with increased disease (106). IL-33 promotes anaphylaxis and allergic reactions through mast cell degranulation (107, 108). During asthma, mast cells migrate from the submucosa to the airway epithelium and produce IL-33-mediated type 2 cytokines that stimulate the epithelium to upregulate IL-33 in a feed-forward loop (109). IL-33 is implicated in IL-9 signaling, and IL-9-deficient mice challenged with IL-33 have attenuated inflammatory cell infiltrate, goblet cell hyperplasia, collagen deposition, and cytokine expression (110). A role for IL-33 in IL-9 production in mouse models of allergic conjunctivitis has been suggested, where IL-9 production is induced by IL-33-stimulated $CD4^+$ T cells (111).

Smoking is a key contributor to the chronic and progressive inflammation of the lung in COPD patients, where increased levels of IL-33 and ST2 are observed (112, 113). Neutralizing IL-33 abrogates the pathogenic changes induced by cigarette smoke, suggesting a role for IL-33 in COPD-associated tissue damage (114). A recent phase 2a clinical trial tested the anti-IL-33 monoclonal antibody etokimab in a limited number of atopic dermatitis patients. It provided clinical benefits, reduced peripheral eosinophils, and inhibited skin neutrophil infiltration in response to skin challenge (115). The early identification of IL-33 as a mediator of type 2 immunopathology is leading to therapeutics to hopefully improve life quality for individuals with asthma and other type 2–driven pathologies.

3.7. Tumor Immunity

Unsurprisingly, the pleiotropy of IL-33 evident in immunity to pathogens is also apparent in immunity to malignancies. IL-33 is implicated in tumor growth and metastasis due to actions on myeloid cells and Tregs, but it also promotes the antitumorigenic activities of $CD8^+$ T cells and NK cells. Specifically, IL-33 promotes tumor proliferation through mast cell activation, which results in chemotactic accumulation of tumor-associated macrophages that support tumor angiogenesis (116). Free IL-33, and potentially intrinsic IL-33, promotes the recruitment and immunosuppressive functions of Tregs to favor tumor growth and immune evasion (30, 117–119). The secretion of reparative growth factors, such as Areg, by IL-33-stimulated $ST2^+$ Tregs leads to an increased tumor burden in a mouse model of metastatic mammary carcinoma (120). Yet, ectopic expression or overexpression of IL-33 by B16 or 4T1 tumor cells or administration of the recombinant IL-33 increased both recruitment to the tumor microenvironment (TME) and activation of effector $CD8^+$ T cells and NK cells (121, 122). IL-33 also contributes to antitumorigenic immunity by stimulating eosinophils. IL-33 indirectly recruits eosinophils to the TME through tumor-released CCL5 and CCL24 or IL-5-secreting ILC2s (123–127). While counterintuitive given eosinophil association with type 2 immune responses, a link between IL-33 antitumor activities and eosinophils has been demonstrated by several studies (123, 128). A recent study revealed that an IL-33-ILC2-eosinophil axis suppresses tumor growth in a pathway that can be disrupted by tumor-derived lactate, which attenuates ILC2 function and survival (129).

alloHCT is a common treatment for hematological malignancies. alloHCT protocols use varied intensities of chemotherapy and irradiation to remove residual malignant cells, facilitate engraftment of donor stem cells, and prevent host immune cell rejection of donor stem cells. Such conditioning treatments have both damaging and beneficial effects. Recipient APCs can be activated to secrete high levels of IL-12, which supports the generation of Th1 cells and potent $CD8^+$T-bet^{high} effectors that clear malignant cells. Yet, the release of cytolytic molecules in these type 1 responses can mediate organ and tissue injury culminating in GVHD. IL-33 is upregulated by irradiation or chemotherapy conditioning and remains elevated at least through day 14 in small intestine epithelial cells and fibroblasts (18). A lack of IL-33 in the HCT recipient or the use of $St2^{-/-}$ donor cells limits GVHD by blunting type 1 immune responses in this setting (18). ST2 on donor T cells is not required, however, for malignancy clearance (18). These findings in mice parallel clinical data showing that IL-33 is increased in colon biopsies from alloHCT patients with GVHD relative to those from alloHCT patients without GVHD (18). GVHD is also less severe when donor $CD4^+$ T cells lack MyD88, which is required for TLR, IL-1R, and ST2 signaling (130, 131) and favors their survival and differentiation into Th1 and Th17 cells (130, 131). Transfer of donor T cells that lack MyD88 signaling results in peripheral $Foxp3^+$ Treg expansion after alloHCT and reduced GVHD lethality (131). The timing of immune system exposure to IL-33 after alloHCT affects GVHD outcomes. Delivery of IL-33 after alloHCT increases morbidity (18), whereas preconditioning with IL-33 increases the number of recipient-derived $ST2^+$ Tregs, which persist after alloHCT and decrease GVHD morbidity and mortality (63). The recent study of IL-33 in tumor immunity and alloHCT has demonstrated IL-33 pleiotropy and provided insights into when the ST2-IL-33 axis should be modulated to achieve optimal outcomes.

4. IL-33 AND ITS ROLE IN HOMEOSTASIS

Immune responses to pathogens and injury create states of inflammation that can disrupt systemic and local homeostasis. Immunity and homeostasis are often viewed as opposing states, yet this view is outdated. Recent ideas in immunology and systems biology indicate that the immune system and its responses to pathogens, injury, and acute or chronic inflammation need to be viewed as another

part of the body's effort to establish and maintain a functional equilibrium between the organ systems and tissues (132). Given the diverse expression of IL-33 in the organ systems, paired with its release during cell turnover, stress, and injury, it is not surprising that IL-33$^+$ and ST2$^+$ immune cells are appreciated as critical to the body's response to fluctuating nutritional availability, energy expenditure, environmental conditions, traumas, stresses, and microbial insults. In addition, IL-33 has emerged as critical for the proper development of tissues and organs needed to establish initial homeostasis (**Figure 2**).

4.1. Adipose Tissue and Energy Homeostasis

In lean individuals, the adipose tissue depots are replete with anti-inflammatory immune cells, many of which express ST2 and promote adipose tissue homeostasis by maintaining an anti-inflammatory environment (127). ST2$^+$ ILC2s are found in the white adipose tissues, primarily used for energy storage, of both mice and humans (8). Treatment of mice with IL-33 or IL-33-cultured ILC2s increases ILC2s in adipose tissue depots and induces genes associated with thermogenesis and energy expenditure in adipocytes via secretion of the opioid-like pentapeptide methionine-enkephalin. IL-33 stimulates ILC2 secretion of the cytokines IL-5 and IL-13, which support local eosinophils and anti-inflammatory macrophages. IL-33-activated ILC2s also recruit Tregs to the adipose tissue depots via an ICOSL-ICOS interaction (8). Mechanistically, IL-33 acts on ILC2s to stimulate phosphorylation of AMPK at Thr172 via TAK1, an effect that is negatively regulated by adiponectin, a soluble mediator secreted by adipocytes (134). Additionally, peroxisome proliferator–activated receptor gamma (PPARγ) expression in adipose tissue ILC2s helps increase ILC2 responsiveness to IL-33 (135). ILC2s clearly constitute an important immune cell population in the adipose tissue that is highly sensitive to IL-33 and essential to promote adipose tissue homeostasis via promotion of thermogenesis in adipocytes and recruitment of anti-inflammatory immune cells (8).

Visceral adipose tissue (VAT) is primarily composed of white adipocytes that function as energy storage depots. Tregs constitute >40% of the CD4$^+$ T cell population in the VAT and are required to maintain VAT homeostasis (133). Adipose tissue Tregs express ST2 and are highly dependent on IL-33 for their survival and homeostatic turnover (136–138). Indeed, Treg-specific deletion of *St2* results in significant loss of Tregs in the visceral and subcutaneous fat depots, while Tregs in the lymphoid tissues are unaffected (139). The addition of exogenous IL-33 protects mice fed a high-fat diet (HFD) from insulin resistance, in part by promoting the survival and homeostasis of adipose tissue–resident Tregs (136–138). Eosinophils are also sensitive to IL-33 in the adipose tissue microenvironment. Activation of ILC2s with IL-33 initiates the secretion of IL-5, an eosinophil activation factor, which helps to support eosinophils indirectly. However, VAT eosinophils are also directly responsive to IL-33, causing their expansion and activation (140, 141). Eosinophils are typically beneficial in maintaining adipose tissue homeostasis by promoting regulatory macrophage survival (8).

Recently, single-cell RNA sequencing (scRNA-seq) analysis of CD45$^-$ cells in the VAT of mice revealed that IL-33 expression is detectable in distinct mesenchymal stromal cell (MSC) populations (142), a finding that was corroborated by flow cytometric analysis of CD45$^-$ populations (143). Both studies showed that the dominant IL-33-expressing cells in the stromal vascular cell fraction are CD45$^-$Sca-1$^+$ and also express platelet-derived growth factor receptor alpha (PDGFRα). While Mahlakoiv and colleagues (143) showed that the majority of VAT MSCs express transcripts that identify them as adipose stem cell progenitors, they also determined that approximately 15% of VAT MSCs expressed podoplanin (PDPN) and CD9. In contrast, Spallanzani and colleagues (142) used scRNA-seq analysis of the Sca-1$^+$PDGFRα$^+$PDPN$^+$ VAT MSCs

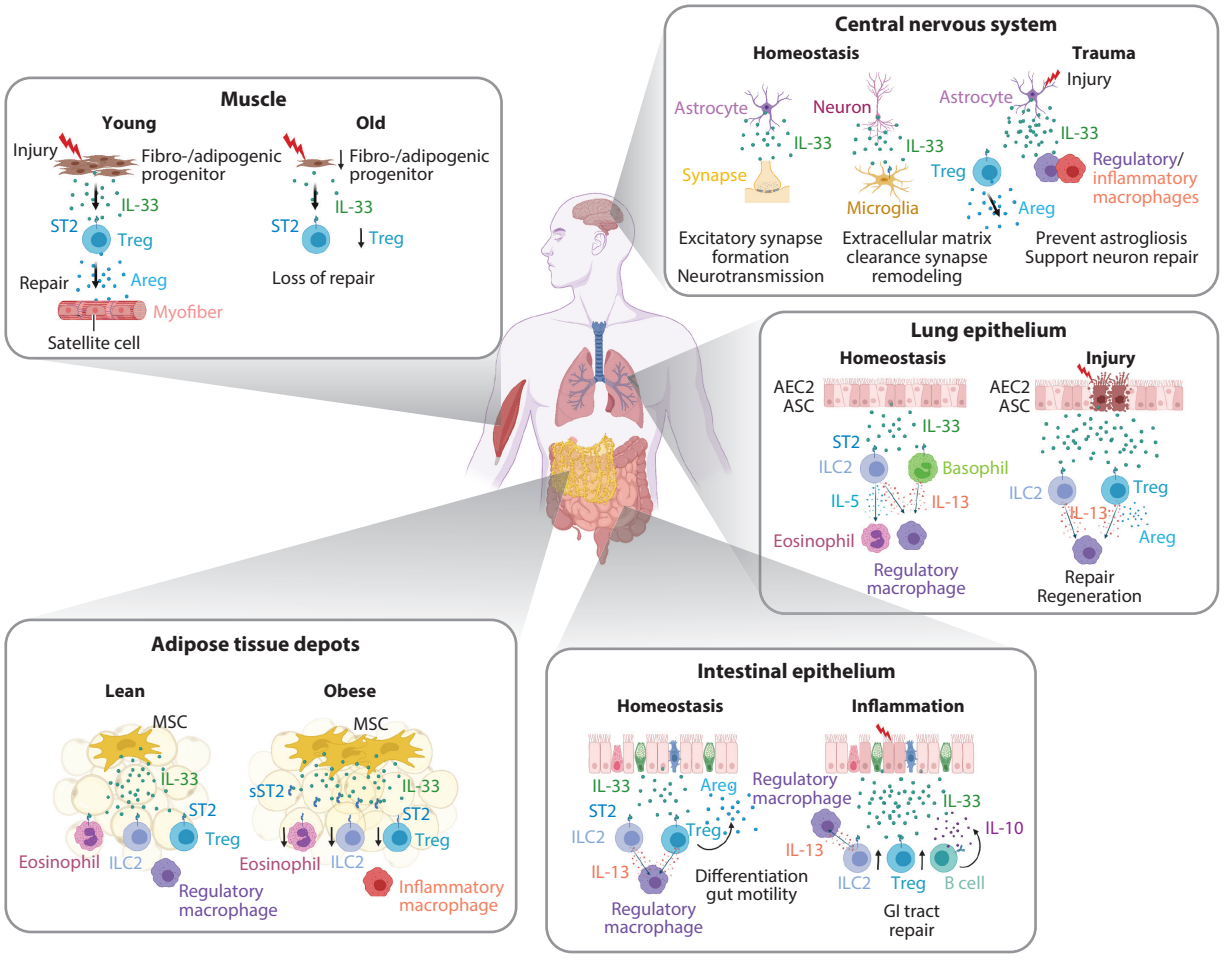


Figure 2

Functions of IL-33 in tissue homeostasis and repair. In the adult mouse CNS, IL-33 is produced primarily by astrocytes and neurons and promotes excitatory synapse formation and neurotransmission. By activating microglia, IL-33 promotes extracellular matrix clearance and synapse remodeling. After CNS injury, astrocytes increase IL-33 release, which promotes $CD4^+Foxp3^+$ Treg secretion of Areg and maintains a balance between inflammatory and regulatory macrophages to promote neuron repair and prevent astrogliosis. After a skeletal muscle injury, IL-33 is released by fibro-/adipogenic progenitor cells to cause Areg secretion by Tregs. Areg expands satellite muscle cells to improve muscle repair. In older mice, the frequency of satellite muscle cells is reduced, and thus the IL-33-Treg repair axis becomes perturbed. In the lung, AEC2s and ASCs release IL-33, promoting $ST2^+$ ILC2 secretion of IL-13 and IL-5, which support reparative eosinophils and alveolar macrophages. IL-33 secretion also promotes $ST2^+$ basophil secretion of IL-13 that orchestrates a homeostatic type 2 environment. After lung damage or injury, IL-33 secretion is increased to help initiate a repair cascade in which both $ST2^+$ Tregs and ILC2s secrete the reparative cytokine IL-13 and Areg. In the adipose tissue depots, particularly the visceral and subcutaneous adipose tissues, MSCs secrete IL-33 to maintain $ST2^+$ eosinophils, Tregs, and ILC2s that support regulatory macrophages. In obesity, the frequency of IL-33-secreting MSCs increases, but the additional IL-33 is likely sequestered by sST2. Targeting of IL-33 by increased sST2 during obesity reduces the frequency of $ST2^+$ anti-inflammatory immune cells in the adipose tissues and increases inflammatory macrophage populations. In the gastrointestinal tract, IL-33 is released predominantly by epithelial cells, supporting $ST2^+$ ILC2s, regulatory macrophages, and Tregs. IL-33 directly acts on Paneth cell differentiation to support bacterial clearance and on enteric neurons to control gut motility by promoting the release of serotonin. During tissue injury and inflammation in the gut, IL-33 secretion is increased. IL-33 promotes goblet cell hyperplasia and IL-13 secretion by ILC2s. It also supports both Tregs and IL-10-producing B cells that help mediate repair and promote gut tissue homeostasis. Abbreviations: AEC2, type 2 alveolar epithelial cell; Areg, amphiregulin; ASC, adventitial stromal cell; CNS, central nervous system; GI, gastrointestinal; ILC2, group 2 innate lymphoid cell; MSC, mesenchymal stromal cell; sST2, soluble ST2; Treg, regulatory T cell. Figure created from images created with BioRender.com

to reveal five distinct VAT MSC subtypes, three of which express high levels of IL-33 transcripts. Fluorescence microscopy revealed that IL-33-expressing VAT MSCs were interspersed among the adipocyte populations. γδ T cells secrete IL-17A and initiate IL-33 secretion by VAT MSCs (144), which is critical to the survival, proliferation, and turnover of the cells that maintain adipose tissue homeostasis: ILC2s, Tregs, and eosinophils.

During overnutrition and obesity development, the adipose tissue environment becomes perturbed, and adipocytes release TNF-α, IL-6, and CCL2 to recruit NK cells, $CD8^+$ T cells, and proinflammatory macrophages. These drive adipose tissue inflammation and cause loss of local and systemic energy homeostasis. While exogenous IL-33 protects mice on an HFD and reduces adipose tissue inflammation (145), surprisingly, the frequency of IL-33-secreting MSCs increases and IL-33 in the serum is elevated in these mice (142). However, counterintuitively this increase in IL-33 availability does not promote increased survival and accumulation of Tregs or ILC2s (142, 143). The loss of IL-33 protection may be due to increased adipocyte secretion of sST2, which likely sequesters extracellular IL-33, thus limiting IL-33-mediated Treg and ILC2 survival and homeostasis (146). Thus, therapeutics that target sST2 while leaving IL-33 intact to support Tregs, ILC2s, and other type 2 cells may be beneficial for treating obesity and its comorbidities, including cardiovascular disease and type 2 diabetes.

4.2. Support of Maternofetal Homeostasis

Pregnancy is a unique state where the maternal immune system must establish and maintain homeostasis with a semi-allogeneic fetus and its developing immune system. IL-33 is ample during pregnancy in the placenta (147), uterus (148), and trophoblast cells (149). Given high cell turnover during pregnancy, the bioavailability of IL-33 is more than sufficient at the maternofetal interface, where it restores or maintains local homeostasis. Reduced IL-33 levels are associated with preeclampsia (149), and IL-33 supports successful pregnancy by stimulating the proliferation and invasiveness of maternal decidual stromal cells, which promote the establishment of maternofetal tolerance. These events are a result of IL-33-mediated upregulation of CCL2/CCR2 on decidual cells via NF-κB and ERK1/2 signaling pathways (150). IL-33 also acts on decidual NK cells that contribute to the development of a local Th2 bias and support decidual regulatory macrophage polarization and efferocytosis (151, 152). Certain stress conditions, such as infection-induced inflammation, cause the release of IL-33, which targets decidual B cells, including a B1 subset (145). IL-33 induces B cell production of progesterone-induced blocking factor 1 (PIBF1), which is an anti-inflammatory molecule that restores immune homeostasis and prevents preterm birth (154, 155). While IL-33 expression is ample, B1 cell expression of ST2 is tightly regulated; it peaks at the transition between the first and second trimesters and drops to pre-pregnancy levels at the end of pregnancy (153). This suggests that $ST2^+$ B1 cells may play a vital role in modulating the transitions between pregnancy stages.

4.3. IL-33 in Organ System Development and Homeostasis

The body's tissues and organs are functional collections of parenchymal and stromal cells made up of specific subsets of nonhematopoietic-derived fibroblasts; epithelial, endothelial, mural (pericytes and smooth muscle cells), and mesothelial cells; and hematopoietic cell–derived immune cells (156–159). Tissue formation and function during embryonic, neonatal, and postnatal development require coordinated cross talk between these cell subsets. These communications are equally important to restore homeostasis after pathology due to injury or infection. IL-33 plays a role in both these processes.

4.3.1. Respiratory system. The lung requires a large surface area for optimal uptake of oxygen and release of carbon dioxide, and recent studies have revealed fundamental roles for IL-33 in lung development and function. Mechanical stress directs essential aspects of lung development, including tube morphogenesis, branching, and pneumocyte differentiation (160). Interestingly, mechanical stress caused by lung inflation also augments IL-33 expression and release to shape the immunological environment of the lung (22, 161). The first breaths of life increase postnatal IL-33 in AEC2s, orchestrating an IL-33-rich, type 2 environment that drives the expansion and accumulation of IL-5- and IL-9-secreting ILC2s and eosinophils (161). The early lung is also dense with basophils and mast cells (161). The appearance of IL-13-producing ILC2s coincides with the arrival of alveolar macrophages, which are polarized by IL-13 toward a reparative and regulatory subset. It is hypothesized that the type 2–dominated environment of the lung is poised to support tissue remodeling while protecting against loss of function by limiting excessively destructive type 1 inflammatory responses to microbes (161, 162). A type 2 homeostatic state in the lung appears to come at a cost, as the type 2–dominated immune responses also contribute to allergy and asthma (162).

IL-33 expressed in the lung also has essential direct and lasting functional impacts on the immune cells that dictate the immunological response in the lung and maintain a local type 2–skewed homeostasis. IL-33 stimulation of ILC2s during the neonatal period is necessary to train ILC2s that seed the lung and persist there to respond with potent type 2 cytokine production in response to subsequent IL-33 (163). Cohen et al. (74) used scRNA-seq to characterize the cellular composition of the developing and adult lung and assess potential ligand-receptor interactions required for the development of the local immune system. They described that lung-resident basophils localize near alveoli and have a distinct lung-specific phenotype imprinted on them by IL-33 and granulocyte-macrophage colony-stimulating factor (GM-CSF) secreted by AEC2s (74). This local training of $ST2^+$ basophils initiates secretion of IL-13 by the basophils, thus guiding their orchestration of alveolar macrophage differentiation and function in the lung (74). Dahlgren et al. (14) established that $ST2^+$ ILC2s, Tregs, and $ST2^+$ type 2 cDCs exist in the adventitial niche around larger vessels in lung tissues under homeostatic conditions. They showed that IL-33^+ ASCs, but not AEC2s, are crucial to these niches, as they produce TSLP to support ILC2 accumulation and production of IL-13. ILC2 IL-13 drives reciprocal ASC expansion and increases ASC production of IL-33. In total, IL-33 is an important early signal that initiates the expansion and function of ILCs, eosinophils, and basophils to set up a homeostatic type 2 environment that is sustained through early IL-33 imprinting on long-lasting resident cells that respond more efficiently to challenges later in life.

4.3.2. Digestive system. The gastrointestinal (GI) tract carries out diverse functions that are crucial to organismal homeostasis. It is the site of food digestion and nutrient uptake, supports water and electrolyte regulation, and provides a home to beneficial microbial flora, all while protecting against infection by ingested pathogens. GI tract epithelial cells are predominantly absorptive enterocytes that enable nutrient and water uptake. Still, the GI tract epithelium also contains highly specialized cells, including antimicrobial peptide–secreting Paneth cells in the small intestine, mucus-producing goblet cells, and IL-25-generating tuft cells to modulate the microbiome and clear pathogens (164, 165). The GI tract is also a sensory organ system where enteroendocrine cells provide spatial and temporal information about intestinal contents by activating local sensory neurons with neurotransmitters and neuropeptides (166). IL-33 is prominently expressed in both GI tract epithelial cells and pericryptal fibroblasts (14, 167). How it is released in the GI tract is poorly understood, but IL-33 is a necessary instructive signal to $ST2^+$ tissues and immune cells that reside there. Both IL-33- and ST2-deficient mice have decreased goblet cells and increased

susceptibility to experimental colitis (168). IL-33 also directs the differentiation of epithelial progenitor cells into Paneth cells to support bacterial clearance (169). Moreover, IL-33 is sensed by a subset of enteroendocrine cells and causes the release of serotonin, which acts on enteric neurons to promote gut motility (167).

4.3.3. Central nervous system. The central nervous system (CNS) comprises the brain and spinal cord, which act together to control bodily functions. IL-33 is expressed at high levels by astrocytes in the brain and spinal cord and at lower levels by oligodendrocyte precursors, neurons, and glial cells (16, 170). During neonatal development, the brain initially makes many more neuronal synapses than needed. Excessive synapses are pruned away by microglia, ultimately resulting in mature neuronal circuits. As neuronal synapses are developing, IL-33 expression increases in a subpopulation of astrocytes (16). Ablation of IL-33 in these cells results in excessive excitatory synapse formation and abnormal thalamic and sensorimotor circuit function, which manifest as defective acoustic startle responses in mice (16). Mechanistically, IL-33 expression by astrocytes helps to recruit microglia cells to these excessive neuronal synapses, where they engulf and destroy the redundant synapses. Astrocyte-specific IL-33 expression plays a critical role in adult mouse neuron synaptic plasticity, which is needed for learning and memory formation (171). Administration of IL-33 to mice or conditional deletion of *Il33* in astrocytes promoted or decreased the formation of excitatory synapses and neurotransmission, respectively (171). The loss of IL-33 secretion by astrocytes resulted in impairment in spatial memory formation, indicating that IL-33 is required to maintain homeostatic synaptic plasticity in the CNS (171). In recent studies, neurons in the hippocampus were shown to express IL-33 in an experience-dependent manner (15). Ablation of neuronal IL-33 manifested in impairment of spine plasticity, newborn neuron integration, and generation of remote fear memories (15). IL-33 secretion by neurons instructed microglia in extracellular matrix engulfment, and loss of IL-33 resulted in an accumulation of extracellular matrix between synapses, leading to a loss of homeostatic synaptic plasticity (15). Thus, IL-33 is a critical factor for CNS function and homeostasis throughout all stages of life.

4.4. IL-33 in Tissue Repair and Homeostasis Restoration

As elaborated above, the developmental and homeostatic functions of IL-33 are a result of its ability to support type 2–promoting cells and their activities. These activities are consistent with the role of type 2 cytokines in tissue repair and wound healing, with IL-33 emerging as a dominant signal to $ST2^+$ type 2–promoting cells that are instrumental to the repair process. However, similar to the well-documented involvement of type 2 cytokines, such as IL-4 and IL-13 in fibrosis, IL-33 is also implicated in failed repair processes or fibrotic disease, particularly in the lung and skin.

4.4.1. Trauma. In the face of blunt trauma, many patients admitted to an intensive care unit present with rapid elevations in plasma IL-33 levels and increases in sST2, which is a potent negative regulator of IL-33 (45). In fact, early increases in IL-33 in the absence of a corresponding rise in sST2 were positively correlated with increased IL-4, IL-5, and IL-13 and more favorable clinical outcomes (45). In contrast, high sST2 and low IL-33 plasma concentrations after blunt trauma were associated with in-hospital mortality and adverse clinical outcomes (44). These observations align with an essential role for IL-33 stimulation of local and systemic type 2 responses needed to establish homeostasis and repair after major traumas.

4.4.2. Tissue repair. After tissue damage, freed IL-33 not only alerts the immune system to the injury but is intimately involved in the repair process of various tissues.

4.4.2.1. Mucosal tissue repair. Repair of the injured lung epithelium involves transition through several regulated phases involving inflammation, progenitor proliferation, and differentiation, followed by tissue regeneration and remodeling. Early studies established an important role for $ST2^+$ Tregs in the resolution of epithelial injury after virus-induced lung injury due to their secretion of Areg, a bifunctional growth factor (58). Areg supports stem cell proliferation and differentiation and is secreted by $ST2^+$ Tregs in response to IL-33 and independently of TCR stimulation (58). IL-33 also induces TCR-independent secretion of IL-13 that mediates the direct generation of regulatory and reparative $Arg1^+$ macrophages to restore local homeostasis after lung injury (60). In a similar manner, IL-33 mediates IL-13 secretion by ILC2s, which promotes $Arg1^+$ reparative macrophage generation to support lung regeneration after unilateral pneumonectomy (172). In addition to priming IL-13 secretion by ILC2s or Tregs, IL-33 promotes the proliferative self-renewal of local macrophages and their differentiation into reparative subsets that aid club cell regeneration (173). This is significant, as club cells are the major secretory cells of the airway epithelium and promote protection of the bronchiolar epithelium. IL-33 also expands lung ILC2s and elicits their secretion of IL-9 to prevent pyroptosis-mediated loss of endothelial cells (174).

Tissue insults, inflammation, and infections upregulate IL-33 in the intestines (18, 169) to support the regulation of intestinal inflammation and restore intestinal homeostasis. IL-33 expression is increased in the inflamed mucosae of people suffering inflammatory bowel disease and of mice during experimental colitis (175). IL-13 secretion by ILC2s during helminth infections increases expression of IL-33 in ASCs (14). This IL-13-mediated increase in IL-33 appears to support a feed-forward mechanism where local IL-33 promotes goblet cell hyperplasia through IL-13 secretion by ILC2s. This axis also directs type 2 macrophage differentiation to mediate tissue repair and support a return to homeostasis (176). IL-33 stimulation of $ST2^+$ Tregs and IL-10-producing regulatory B cells has also been implicated in the immune cell network stimulated by IL-33 to resolve GI tract injury and inflammation (61, 177). IL-33 also mediates repair and resolution of colitis by inducing microRNAs, particularly miR-320, to drive the proliferation of $ST2^+$ intestinal epithelial cells (178). These recent findings suggest that IL-33 expression supports the regulation of intestinal inflammation and maintains or restores GI tract homeostasis through actions on local injured tissues as well as a local network of Tregs, ILC2s, and regulatory and reparative macrophages.

4.4.2.2. Skin wounds. The skin was among the first sites identified to have high constitutive IL-33 expression (3, 179), and IL-33 expression is upregulated after acute skin injury (180, 181). Cutaneous wound closure and re-epithelialization are delayed in mice lacking IL-33, a condition associated with decreased $IL\text{-}13^+$ ILC2s (182). ST2-deficient mice display increased proinflammatory macrophages and reduced re-epithelialization (176). Delivery of IL-33 increases the numbers of local ILC2s and reparative macrophages in the wound to accelerate wound healing (182, 183). These studies support a role for released IL-33 targeting $ST2^+$ ILC2s and macrophages; yet, it has also been suggested that nuclear IL-33 in keratinocytes plays an important role in wound healing (181). This nuclear function is based on the observation that IL-33-deficient keratinocytes displayed delayed closure in an in vitro scratch assay. This phenomenon was suggested to be the result of intracellular regulation of NF-κB signaling. But further investigation of this mechanism is needed to rule out direct impacts of free IL-33 on keratinocytes in this system.

4.4.2.3. Skeletal muscle and cardiac tissue repair. Skeletal muscle has significant regenerative capacity due to the presence of satellite cells, a resident stem cell population. Early after injury, neutrophils, proinflammatory macrophages, and local proinflammatory cytokines expressed by

these cells drive the activation and proliferation of satellite cells that function as myogenic precursors. This activity is followed by precursor differentiation into myotubes and muscle in a type 2 cytokine–dominated microenvironment supported by eosinophils, reparative macrophages, and Tregs (184). Fibro-/adipogenic progenitor cells in the skeletal muscle express IL-33 and act on local ST2$^+$ Tregs present at the injury site. These ST2$^+$ Tregs orchestrate muscle regeneration through the secretion of Areg, which supports the function of muscle satellite cells (59, 185). Interestingly, IL-33 expression spikes early after skeletal injury in young mice, whereas old mice lose IL-33-expressing cells (185). These findings suggest that the regenerative potential of tissues is directly tied to the availability of IL-33 and lead to speculation that chronic injury, wound magnitude, or age may lead to restriction of IL-33 to cause dysregulated or failed tissue repair.

The major cell types making up the human heart have been categorized based on comprehensive scRNA-seq analysis of heart regions (158). An interactive viewer (**https://www.heartcellatlas.org/**) can be used to observe that the predominant *Il33*-expressing cells are stromal in nature and include fibroblasts, smooth muscle cells, endothelial cells, and mesothelial cells. This aligns with early studies describing IL-33 expression in cardiac fibroblasts (39) and vasculature (reviewed in 5). These studies demonstrate that IL-33 directly protected ST2$^+$ cardiac myocytes from apoptotic and hypertrophic signaling to limit fibrosis (5, 39). Free IL-33 also drives type 2 responses by ST2$^+$ Tregs and ILC2s that protect against atherosclerosis, heart transplant rejection, and catecholamine-induced fibrosis (186). Yet, IL-33 administration in these studies makes it difficult to separate the systemic regulatory functions of ILC2s and Tregs versus their importance in local repair or injury resolution. Using a heart transplant model to assess the impact of local IL-33 on early inflammation and its resolution after transplantation, Li et al. (50) found that grafts lacking IL-33 suffered increased fibrosis and vasculopathy, leading to premature graft failure. This early graft loss was not due to failed early ST2$^+$ Treg accumulation, as observed for skeletal muscle injury (185). Instead, it resulted from the need for IL-33-mediated metabolic reprogramming of monocytes to enable their differentiation into reparative macrophages (50). A similar increase in proinflammatory immune infiltration has been observed in IL-33-deficient mice, which also suffered augmented pressure overload–induced fibrosis and heart failure (187).

4.4.2.4. IL-33 in CNS injury and restoration. The concentrations of both IL-33 and sST2 increase in the blood after stroke (188–191). IL-33 secretion from astrocytes after ischemia acts in a cell-intrinsic fashion to support astrocyte survival and secretion of protective neurotrophic factors (192). IL-33 also helps to support the survival and function of brain Tregs that prevent astrogliosis and neuronal damage during brain injury (193). In mice and humans, IL-33 is secreted by astrocytes and oligodendrocytes in response to traumatic brain injury (194, 195). This release of IL-33 improves recovery by preventing astrogliosis (196), expanding ILC2s, and recruiting macrophages to the damage, while also repressing the inflammatory activity of other innate cells in the meninges (197, 198).

4.5. Unknowns Involving IL-33 in Development, Repair, and Homeostasis

A new understanding of the importance of IL-33 to the development and homeostatic functions of tissues and organ systems has been established through the recent innovative study of ST2- and IL-33-deficient mice. These studies have shown IL-33 communicates tissue conditions to various immune cells as they also receive other signals that orchestrate their efforts to clear pathogens, maintain homeostasis, and restore a functional equilibrium across organ systems. The ability of IL-33 released during injury or cellular death or stress to promote restorative and regulatory responses is unique in the IL-1 family, and there are numerous mechanistic questions that remain

to be answered. First, IL-33-driven ST2$^+$ Treg and ILC2 reparative functions appear especially potent early after injury. Yet, it remains difficult to truly separate the suppressive functions of these cells in controlling early inflammation and limiting excess damage from their subsequent ability to promote tissue repair. This overlap is especially true for IL-13 and Areg, which support repair but have long been appreciated to generate immunosuppressive myeloid cells. Second, there remains a significant gray area, especially between mouse and human systems, as to which cells express IL-33 constitutively, during active inflammation, and during inflammation resolution and tissue repair. Studies with new IL-33 reporter mice have recently expanded the scope of cells thought to routinely express IL-33 and revived the potential of involvement of nuclear IL-33 in cell development and function (28–30). Thus, more than 15 years since the identification of IL-33, it seems much remains to be uncovered about the role IL-33 plays in and on the cells of the body. Furthermore, it is not only the who but also the how and when of IL-33 release and ST2 expression that need to be clarified. The roles of ST2$^+$ cells and IL-33 in lung development and adipose energy homeostasis are clear. Yet, what are the kinetics and mechanisms of IL-33 release in these healthy tissues? It must be assumed that IL-33 release in injured and inflamed tissue looks quite different, and IL-33 signals stimulate a now broader known network of cells expressing de novo ST2. Do the IL-33-driven networks involving immunity and repair untangle themselves to restore homeostasis by controlling IL-33 release or the expression of sST2 and ST2? Hopefully, these important questions will be answered with newly available tools allowing timed cell and tissue-specific deletion of IL-33 or ST2 in various disease models. This knowledge will clarify where and how best to modulate the IL-33 and ST2 axis to resolve injury and restore dysregulated local or systemic homeostasis. It will also help identify the factors that dysregulate the ST2-IL-33 axis and cause pathology because they are overrepresented, undersupplied, or delivered in the wrong time frame.

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