Interleukin (IL)-33 and the IL-1 Family of Cytokines—Regulators of Inflammation and Tissue Homeostasis

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Cytokines play an integral role in shaping innate and adaptive immune responses. Members of the interleukin (IL)-1 family regulate a plethora of immune-cell-mediated processes, which include pathogen defense and tissue homeostasis. Notably, the IL-1 family cytokine IL-33 promotes adaptive and innate type 2 immune responses, confers viral protection and facilitates glucose metabolism and tissue repair. At the cellular level, IL-33 stimulates differentiation, maintenance, and function of various immune cell types, including regulatory T cells, effector CD4⁺ and CD8⁺ T cells, macrophages, and type 2 innate lymphoid cells (ILC2s). Other IL-1 family members, such as IL-1 β and IL-18 promote type 1 responses, while IL-37 limits immune activation. Although IL-1 cytokines play critical roles in immunity and tissue repair, their deregulated expression is often linked to autoimmune and inflammatory diseases. Therefore, IL-1 cytokines are regulated tightly by posttranscriptional mechanisms and decoy receptors. In this review, we discuss the biology and function of IL-1 family cytokines, with a specific focus on regulation and function of IL-33 in immune and tissue homeostasis.

Interleukin (IL)-1 family cytokines are potent initiators and amplifiers of immune responses and inflammation. Because they are secreted by damaged cells and are crucial for eliciting inflammatory responses, these cytokines are also called “alarmins.” Deregulated expression of IL-1 family members aggravates inflammation, autoimmunity, and allergic responses. Consequently, IL-1 blockade is used for the treatment of a variety of inflammatory diseases, including rheumatoid arthritis, psoriasis, atherosclerosis, ischemia, and reperfusion and graft rejection (Garlanda et al. 2013; Jesus and Goldbach-Man-

sky 2014). However, IL-1 family cytokines also play critical roles in facilitating tissue repair and preserving homeostasis. Thus, expression of IL-1 family members is tightly regulated at multiple levels, including transcriptional and posttranslational mechanisms as well as the expression of decoy and antagonist receptors (Garlanda et al. 2013). IL-1 family cytokines can also function as nuclear factors and influence gene expression by interacting with transcription factors or the chromatin (Martin and Martin 2016). IL-1 family members also act as RNA-splicing factors to regulate the expression of genes that are involved

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in diverse physiological roles, which include survival and thermogenesis (Pollock et al. 2003; Odegaard et al. 2016).

IL-33 is a prominent member of the IL-1 family, which was discovered in 2003 (Baekkevold et al. 2003) after more than two decades of search to identify a ligand for the orphan IL-1 receptor ST2 (Tominaga 1989). IL-33 was first recognized for its critical role in the induction of allergic asthma by coordinating the expansion and function of adaptive and innate immune cells (Hardman and Ogg 2016). Consistent with this notion, genome-wide association studies (GWAS) have implicated polymorphisms in IL-33 or its receptor ST2 (IL1RL1) in a range of diseases that includes asthma, cardiovascular diseases, and allergy (Hardman and Ogg 2016). More recently, however, novel roles for IL-33 were uncovered that extend beyond immunity. For example, IL-33 was identified to play a prominent role in adipose tissue homeostasis, where it facilitates the expansion of anti-inflammatory immune cells, including type 2 innate lymphoid cells (ILC2)s and regulatory T (Treg) cells, thereby suppressing obesity-induced inflammation and preserving insulin sensitivity (Brestoff et al. 2015; Lee et al. 2015; Vasanthakumar et al. 2015). Similar functions in repair and maintenance of nonlymphoid tissues were also described for other tissues such as the colon or injured muscle tissue (Burzyn et al. 2013b; Schiering et al. 2014; Kuswanto et al. 2016). IL-33 therefore plays critical and context-specific roles in lymphoid and nonlymphoid tissues by preserving tissue homeostasis or mediating inflammation. This review focuses on the multifaceted functions of IL-33; however, we will also discuss the biology of other IL-1 family cytokines.

SOURCES OF IL-33 AND OTHER IL-1 FAMILY CYTOKINES

The IL-1 family consists of 11 members with diverse and complex functions (Garlanda et al. 2013). Most members of this family are expressed constitutively as full-length isoforms in a wide range of hematopoietic and nonhematopoietic cells, but are only processed and released by cells stimulated through Toll-like receptors

(TLRs) or by damaged cells undergoing necrosis (Sims and Smith 2010). IL-33 was first identified as a nuclear factor expressed in high endothelial venules of the human Peyer's patches, tonsils, and lymph nodes (Baekkevold et al. 2003). It was later found to be produced by endothelial and epithelial cells and by some hematopoietic cell types, including dendritic cells (Schmitz et al. 2005), mast cells (Hsu et al. 2010), and macrophages (Fock et al. 2013). IL-33 protein is constitutively expressed in astrocytes and oligodendrocytes within the central nervous system (CNS); however, its expression and secretion is elevated upon CNS injury (Yasuoka et al. 2011; Gadani et al. 2015). High expression of IL-33 was also found in endothelial cells of various tissues, including the adipose tissue, liver, ovaries, vagina, skin, lung, stomach, and salivary gland (Villaret et al. 2010; Lopetuso et al. 2012; Pichery et al. 2012; Byers et al. 2013; Carlock et al. 2014). In steady state, IL-33 is found predominantly in the nucleus of these cells with no evidence of cytoplasmic localization. Inflammation induces IL-33 expression in epithelial cells, but only tissue damage is thought to result in efficient IL-33 release (Martin and Martin 2016). Similarly, expression of IL-33 is heightened in the liver during lipopolysaccharide (LPS)-induced endotoxin shock, and in the lung alveoli during papain-induced allergic airway inflammation (Pichery et al. 2012). A similar phenomenon was observed in colonic epithelium where IL-33 expression increased after inflammation and injury (Schiering et al. 2014) and in retinal Müller cells during macular degeneration (Xi et al. 2016). IL-33 can be detected in the serum of patients with inflammatory diseases or cancer and can potentially be used as a diagnostic and prognostic marker for a range of diseases, including hepatitis B infection (Wang et al. 2012), psoriasis (Mitsui et al. 2016), acute ischemic stroke (Qian et al. 2016), and non-small-cell lung cancer (Hu et al. 2013).

Similar to IL-33, other members of the IL-1 family are produced by a variety of hematopoietic and nonhematopoietic cells. Full-length IL-1 α protein is expressed constitutively in healthy epithelial cells of the intestine, kidney, liver, endothelial cells, and astrocytes (Sims and Smith

2010). Sterile inflammation caused by tissue injury facilitates the release of IL-1 α , aiding the recruitment of macrophages to the injured site, which may augment tissue damage (Rider et al. 2011). In contrast, during programmed apoptosis, IL-1 α is retained in the nucleus to prevent tissue damage (Cohen et al. 2010). In macrophages, de novo synthesis of IL-1 α occurs after stimulation with LPS (Arango Duque and Descoteaux 2014). IL-1 β is produced predominantly by cells of the hematopoietic compartment, including macrophages, blood monocytes, and dendritic cells. In contrast to IL-1 α , which is largely constitutively expressed, transcription of *Il1b* is induced by components of the complement system, tumor necrosis factor (TNF), TLR ligands, and IL-1 β itself (Sims and Smith 2010). IL-18 is produced by two major immune cell populations, macrophages, and dendritic cells (Dinarello et al. 2013). However, stromal cells, including endothelial cells, keratinocytes, and intestinal epithelial cells constitutively express the IL-18 precursor (Dinarello et al. 2013). Similar to IL-1 β and IL-33, mature IL-18 is released from tissues undergoing necrosis (Mommsen et al. 2009). IL-36 is expressed in several tissues, including skin, gut, lung, keratinocytes, and brain, and in some hematopoietic cells, including macrophages, neutrophils (Bozoyan et al. 2015), and T cells (Vigne et al. 2011). Similar to other IL-1 family members, IL-36 expression can be up-regulated by inflammatory stimuli, including LPS. In skin epithelial cells, IL-36 is upregulated during psoriasis, and in bronchial cells during viral or bacterial infection (Boutet et al. 2016). Unlike other IL-1 family members, IL-37 expression can be induced by the anti-inflammatory cytokine transforming growth factor (TGF)- β (Nold et al. 2010). However, in peripheral blood monocytic cells and dendritic cells, IL-37 expression was also elevated by stimulation through TLRs (Sharma et al. 2008; Nold et al. 2010). Expression of the little-known IL-38 cytokine is restricted to few tissue sites, including skin and the spleen (Lin et al. 2001). In summary, while IL-1 family cytokines are expressed by a wide variety of tissues, they are usually released only in response to “danger” signals.

IL-33 AND T HELPER (Th)2 RESPONSES

Extracellular pathogens such as helminths and nematodes induce a Th2-type inflammation mediated by the cytokines IL-4 and IL-5. IL-33 was originally classified as a Th2 cytokine owing to its role in amplifying type 2 immune responses and exacerbating allergic asthma. This idea was supported by the finding that expression of IL-33 receptor ST2 appeared to be restricted to the Th2 lineage (Lohning et al. 1998). Indeed, IL-33 stimulation increases IL-5 and IL-13 but not IL-4 secretion by Th2 cells (Kurowska-Stolarska et al. 2008). In line with this finding, Th2 cells expressing ST2 secrete IL-5 and are highly pathogenic (Endo et al. 2015). Consistent with a central role in Th2 responses, ST2 was indispensable for Th2 responses in specific helminth infection models (Hoshino et al. 1999). Notably, IL-33 also acts as a chemoattractant for human Th2 cells (Komai-Koma et al. 2007).

In addition to Th2 cells, ILC2s play a key role in promoting airway inflammation. They express high amounts of ST2 and are exquisitely responsive to IL-33, which induces secretion of IL-5 and IL-13 (Moro et al. 2010; Neill et al. 2010). IL-33 administration expands the lung ILC2s, leading to airway hyperresponsiveness (Moro et al. 2010; Barlow et al. 2012). ROR α -deficient mice, which lack ILC2, were unable to initiate Th2 responses when treated with papain (Halim et al. 2014). Notably, IL-33-expanded ILC2s also produce the tissue repair and growth factor amphiregulin (AREG), an epidermal growth factor (EGF) receptor ligand (Monticelli et al. 2011). IL-5 and IL-13, secreted by both Th2 cells and ILC2s, contribute to the recruitment of eosinophils, which amplifies allergic airway inflammation (Yamaguchi et al. 1988; Pope et al. 2001; Nussbaum et al. 2013). In allergic asthma, eosinophils are a major source of IL-4 and mediate inflammation by releasing cytotoxic granules and lipid mediators that induce tissue damage and bronchoconstriction (Kita 2011). IL-33 contributes to this process not only by mediating the expansion of Th2 cells and ILC2s, but additionally it can promote the differentiation of eosinophils from CD117⁺ progenitors in an IL-

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Figure 1. Illustration shows the diverse cellular sources of interleukin (IL)-33, sensing of IL-33 by adaptive and innate immune cells, and the plethora of immunological and nonimmunological functions regulated by IL-33 to preserve immune and tissue homeostasis. CNS, Central nervous system; Th, T helper; Treg, regulatory T cells; ILC2s, type 2 innate lymphoid cells.

5-dependent manner (Stolarski et al. 2010). Eosinophils in the airway express high levels of ST2 and respond to IL-33 secreted by lung epithelial cells (Kurowska-Stolarska et al. 2008). IL-33 not only promotes differentiation of eosinophils, but also improves their function by augmenting the expression of IL-13, IL-6, CCL-17, and TGF- β (Stolarski et al. 2010). IL-33 also induces the differentiation and expansion of alternatively activated M2 macrophages, which express the IL-4R, secrete CCL-24 and CCL-17 and cooperate with Th2 cells and eosinophils in airway inflammation (Kurowska-Stolarska et al. 2009). In agreement with its role in promoting and amplifying airway inflammation, mutations in *Il33* and *Il1rl1* (encoding ST2) are closely associated with increased asthma risk (Gudbjartsson et al. 2009; Moffatt et al. 2010). Taken together, IL-33 initiates and amplifies Th2 inflammation by promoting the differentiation, maintenance, and function of Th2 cells, ILC2s, eosinophils, and alveolar macrophages (Fig. 1; Table 1).

IL-33 AND Th1 RESPONSES

Intracellular pathogens, including bacteria and viruses, induce type 1 inflammation executed by CD4⁺ and CD8⁺ T cells, macrophages, and B cells. Recent studies have shown that IL-33 is also involved in the establishment of Th1 inflammation and cytotoxic T-cell responses. During lymphocytic choriomeningitis virus (LCMV) infection, Th1 cells were found to express ST2 in a T-bet- and signal transducers and activators of transcription (STAT)4-dependent manner (Baumann et al. 2015). ST2 expression in Th1 cells, however, was transient compared to the constitutive high levels observed in Th2 cells. ST2 contributed to the expansion of antigen-specific Th1 cells and promoted the expression of Th1 transcription factor T-bet (Baumann et al. 2015). Another study found that IL-33 induced Th1 cell differentiation by potentiating the activity of the Th1-polarizing cytokine IL-12; however, IL-33 by itself was unable to pro-

Table 1. Cytokine and receptor nomenclature of the interleukin (IL)-1 family and their functions mediated by immune cells.

Cytokine	Receptor	Coreceptor	Immune cell target	Function
IL-33	ST2	IL-1RAcP	Th2 and Th1 cells, Treg cells, macrophages, CD8 ⁺ T cells, eosinophils, ILC2s, NK cells, NKT cells	Type 1 and type 2 immunity, maintenance of organismal metabolism, thermogenesis, tissue repair
IL-1 α	IL-1R1 IL1-R2	IL-1RAcP	Macrophages	Sterile inflammation
IL-1 β	IL-1R1 IL1-R2	IL-1RAcP	Th17 cells, Th1 cells, ILC1s, regulatory B cells	CNS inflammation, type 1 immunity, gut homeostasis
IL-18	IL-18R α	IL-18R β	Th1 cells, CD8 ⁺ T cells, NK cells, ILC1s	Type 1 immunity
IL-36 α , β , γ	IL-1Rrp2	IL-1RAcP	CD8 ⁺ T cells, NK cells, and $\gamma\delta$ T cells	Type 1 immunity, antitumor immunity
IL-37	IL-18R α		Dendritic cells, macrophages, Treg cells	Immune suppression
IL-38	IL-1Rrp2		T cells	Immune suppression
IL-1RA	IL-1R1		Macrophages, dendritic cells, Th17	Restrains inflammation
IL-36RA	IL-1Rrp2		Unknown	Restrains inflammation

Th, T helper; Treg cell, regulatory T cell; ILC2, type 2 innate lymphoid cell; NK, natural killer; NKT cell, natural killer T cell; CNS, central nervous system.

mote Th1 differentiation (Komai-Koma et al. 2016). IL-33 was also found to induce ST2 expression in CD8⁺ T cells in vitro and augmented TCR-signaling-dependent interferon (IFN)- γ production (Yang et al. 2011). In line with these findings, during infection with an acute strain of the LCMV, IL-33 promoted the clonal expansion and function of effector CD8⁺ T cells (Fig. 1) (Bonilla et al. 2012). IL-33 also expanded a population of ST2⁺ natural killer T (NKT) cells and augmented TCR signaling and IL-12-dependent expression of IFN- γ (Bourgeois et al. 2009). Similarly, IL-33 also induced IFN- γ production in NK cells and promoted the NK cell response against murine cytomegalovirus (Nabekura et al. 2015). Overall, these data suggest that IL-33 is a potent but context-specific amplifier of Th1 inflammation; however, its precise role needs to be further evaluated.

IL-33 IN ORGANISMAL METABOLISM

Visceral adipose tissue (VAT) is an important endocrine organ that secretes soluble factors such as leptin and adiponectin to regulate organismal metabolism (Coelho et al. 2013). VAT

is also a reservoir for multiple pro- and anti-inflammatory immune cells (Cipolletta et al. 2011; Wensveen et al. 2015). Obesity leads to the expansion of proinflammatory immune cells, which induce insulin resistance and, subsequently, type 2 diabetes (Cipolletta et al. 2011; Wensveen et al. 2015). Over the last few years, it has become apparent that IL-33 plays a central role in VAT homeostasis. IL-33 facilitates the differentiation and maintenance of Foxp3⁺ Treg cells and ILC2s in the VAT, both of which play critical roles in limiting VAT inflammation and maintaining insulin sensitivity (Table 1) (Feuerer et al. 2009; Cipolletta et al. 2012; Brestoff et al. 2015; Vasanthakumar et al. 2015). Treg cells are a subset of CD4⁺ T cells that potently suppress autoreactive and inflammatory T cells. The majority of Treg cells develops in the thymus; however, they undergo further differentiation and diversification in the periphery, which allows them to acquire full suppressive function and the ability to enter nonlymphoid tissues, including the VAT (Burzyn et al. 2013a; Teh et al. 2015). VAT Treg cells co-opt the adipose tissue transcription factor PPAR- γ for their differentiation and maintenance (Cipolletta et al.

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2012). While development and survival of Treg cells in most tissues is strictly dependent on IL-2 (Liston and Gray 2014), VAT-resident Treg cells in addition require IL-33 for their survival and maintenance (Vasanthakumar et al. 2015). VAT Treg cell numbers significantly decrease in the absence of IL-33 signaling. In vitro, IL-33 facilitated population expansion of VAT Treg cells even in the absence of IL-2 or TCR signaling (Vasanthakumar et al. 2015). IL-33 expression in the adipose tissue increased with age, which also correlates with an increase in VAT Treg cells, suggesting that IL-33 is the rate-limiting cytokine for Treg-cell expansion in the adipose tissue. In keeping with this notion, administration of IL-33 expanded Treg cells specifically in the adipose tissue (Kolodin et al. 2015; Molofsky et al. 2015; Vasanthakumar et al. 2015). Obesity leads to the decline of VAT Treg cell numbers, which coincides with exacerbation of inflammation in the VAT and development of insulin resistance (Fig. 1) (Feuerer et al. 2009; Vasanthakumar et al. 2015). When administered to obese mice, IL-33 rescued Treg cell numbers in the VAT, which coincided with suppression of inflammation and improved glucose tolerance (Han et al. 2015; Vasanthakumar et al. 2015). Besides facilitating survival and proliferation, IL-33 also enhances the expression of GATA3 and Foxp3 in VAT Treg cells, and preserves expression of PPAR- γ , suggesting a pivotal role for IL-33 in preserving VAT Treg cell function and phenotype (Vasanthakumar et al. 2015).

IL-33 is also a critical growth factor for VAT ILC2s, which promote the conversion of white adipose tissue to brown adipose tissue (BAT) (Brestoff et al. 2015; Lee et al. 2015). BAT is critically important for thermogenesis of newborns but also contributes to weight loss as it generates heat from chemical energy (calories). ILC2-derived methionine-enkephalin peptides induce the expression of brown adipocyte factor uncoupling protein-1 (UCP-1), required for thermogenesis (Brestoff et al. 2015). It has also been proposed that ILC2s were involved in mediating the IL-33-dependent VAT Treg cell expansion, as VAT Treg cells from IL-5-deficient mice, which lacked ILC2s, failed to expand upon

IL-33 treatment (Molofsky et al. 2015). However, such a mechanism has not yet been supported by additional studies. IL-33 also directly acted on adipose tissue to induce the expression of UCP-1 by an unconventional mechanism as discussed later (Odegaard et al. 2016). Thus, while it is clear that IL-33 plays a central role in maintaining adipose homeostasis, precisely how IL-33-responsive cells and IL-33-dependent mechanisms cooperate in the adipose to maintain tissue health remains to be elucidated. Of note, IL-18 also plays a protective role in obesity (Lee et al. 2016; Murphy et al. 2016), while IL-1 β drives adipose tissue inflammation and insulin resistance (Lee et al. 2016).

IL-33 IN TISSUE HOMEOSTASIS AND REPAIR

As outlined earlier, IL-33 is released predominantly by inflamed or injured tissue. Remarkably however, IL-33 is also involved in tissue repair, a mechanism that is likely to have evolved as a feedback to restrain tissue damage. IL-33-dependent Treg-cell-mediated tissue repair has been demonstrated in skeletal muscle and the lung (Fig. 1). Skeletal muscle regeneration critically depends on a self-renewing population of cells called satellite cells. Upon injury, satellite cells proliferate and differentiate into new myofibers or fuse to existing ones and promote regeneration. While inflammatory CD4⁺ and CD8⁺ T cells impede this process (Tidball and Villalta 2010), IL-33-dependent Treg cells maintain an environment conducive for satellite cell differentiation and muscle regeneration (Burzyn et al. 2013b). Treg cells that reside and expand in the muscle after injury critically depend on IL-33 (Kuswanto et al. 2016). Similar to the injured muscle, IL-33-dependent Treg cells play an important role in restraining inflammation in the gastrointestinal tract (Schiering et al. 2014). Consistent with this finding, Treg cells deficient for ST2 could not control experimental colitis. IL-23, a cytokine known to drive intestinal inflammation and inflammatory bowel disease, inhibited the function of IL-33 (Schiering et al. 2014).

Finally, IL-33 has been shown to induce expression of AREG in Treg cells. This function

was shown to play a role in Treg-cell-mediated lung tissue repair after influenza virus infection. Lung epithelial cell-derived IL-33 induced up-regulation of AREG in lung-resident Treg cells, which facilitated repair of damaged lung epithelium and improved lung function after resolution of the infection (Fig. 1) (Arpaia et al. 2015). AREG is also highly expressed in Treg cells in the adipose tissue (Vasanthakumar et al. 2015), suggesting that tissue repair is a common IL-33-induced mechanism of action for Treg cells residing in nonlymphoid tissues. Indeed, IL-33 also induces AREG expression in ILC2s to promote tissue repair in the lung and intestinal epithelia (Monticelli et al. 2011, 2015). Treatment of mice with recombinant IL-33 increased the expression of tight junction proteins claudin1 and mucin and improved intestinal integrity, thereby preserving barrier function (Monticelli et al. 2015). IL-33 also plays an important role in limiting brain tissue damage. Upon brain injury, damaged oligodendrocytes release IL-33, which acts on microglial cells and astrocytes to secrete chemokines and cytokines to attract neuroprotective M2 macrophages that facilitate neural tissue repair (Gadani et al. 2015). Similarly, ILC2s that reside in the meninges are activated by IL-33 secreted upon CNS injury and contribute to limiting CNS injury (Gadani et al. 2017). Finally, IL-33 has also been shown to induce the expansion of IL-10-producing B cells, thereby limiting inflammation in the intestine and protecting from inflammatory bowel disease (Sattler et al. 2014).

Inflammatory mediators within the tumor microenvironment can either promote an anti-tumor immune response or support tumor pathogenesis. In keeping with this notion, IL-33 plays a context-dependent role in tumor biology where it can be protective or deleterious. For example, IL-33 facilitates the expansion of NK cells and cytotoxic CD8⁺ T cells to promote tumor eradication (Gao et al. 2015). On the other hand, IL-33 augments tumor growth by promoting colorectal cancer cell stemness (Fang et al. 2017) and metastasis in lung cancer (Wang et al. 2016a). The multifaceted role of IL-33 in the tumor environment was reviewed in more detail recently (Wasmer and Krebs

2016). Thus, while IL-33 maintains tissue homeostasis by augmenting population expansion and function of immune cells that facilitate tissue repair, it can also drive tumor growth (Fig. 1; Table 1).

IMMUNE REGULATION BY OTHER IL-1 FAMILY MEMBERS

In addition to IL-33, other IL-1 family cytokines play critical roles in the differentiation and function of multiple immune cells. IL-18 was originally identified as a costimulator of IFN- γ production and subsequently established to contribute to Th1 differentiation (Yoshimoto et al. 1998). IL-18 was also required for the efficient production of IFN- γ and TNF in antigen-specific CD8⁺ T cells, suggesting a prominent role for IL-18 in viral defense (Denton et al. 2007). Similarly, IL-18 promotes IFN- γ production in NK cells and ILC1 (Table 1) (Chaix et al. 2008; Malloy and Uhlig 2013).

IL-1 β promotes the differentiation of IL-17-producing Th17 cells and $\gamma\delta$ T cells in vivo and have been implicated in autoimmune and inflammatory diseases that affect the CNS (Chung et al. 2009; Sutton et al. 2009). IL-6 induced IL-1R1 expression on CD4⁺ T cells, thereby facilitating Th17 differentiation and induction of experimental autoimmune encephalomyelitis (Chung et al. 2009). Notably, Th17 cells themselves are equipped with NLRP3 and caspase-8, allowing for the secretion of bioactive IL-1 β , creating an autocrine loop that facilitates differentiation of Th17 cells (Martin et al. 2016). IL-1 β also contributes to Th1 inflammation and cytotoxic T-cell differentiation by activating dendritic cells to produce IL-12 (Wesa and Galy 2001). Interestingly, IL-1 β cooperates with IL-33 in ILC2 biology. While IL-33 is critical for ILC2 cell differentiation, IL-1 β is required for their activation. IL-1 β also induces the expression of IL-12 receptor, which facilitates T-bet expression and transdifferentiation to ILC1 lineage cells (Ohne et al. 2016). Finally, gut microbiota-induced IL-1 β is required for the differentiation of regulatory B cells, which contribute to immune homeostasis by producing the anti-inflammatory cytokine IL-10 (Rosser et al. 2014).

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Several lines of evidence suggest that IL-1 α and IL-1 β promote tumorigenesis by inducing the expression of growth factors that facilitate tumor growth and metastasis. IL-1 induces the expression of several tumorigenic and metastatic mediators, such as matrix metalloproteinases (MMPs), vascular endothelial growth factor (VEGF), IL-8, IL-6, TNF, and TGF- β . Tumor tissue-derived IL-1 β itself attracts immune cells, including macrophages and neutrophils, which further produce IL-1 β to promote angiogenic response, tumor invasiveness, and metastasis (Apte et al. 2006; Perrier et al. 2009; Voronov et al. 2014). In contrast, IL-36 γ , which is also highly expressed in the tumor environment, plays a protective role in cancer by polarizing CD8⁺ T cells, NK cells, and $\gamma\delta$ T cells to produce IFN- γ and establishes a conducive setting for tumor eradication (Wang et al. 2015). Th1 cells have also been shown to express IL-36R, signaling through which synergized with IL-12 in Th1 differentiation in vivo (Vigne et al. 2012).

The anti-inflammatory cytokine of the IL-1 family, IL-37, plays a role in restraining activation of antigen-specific T cells by suppressing dendritic cell activation and limiting the expression of proinflammatory cytokines IL-1 β , IL-6, and IL-12 (Luo et al. 2014). IL-37 also repressed the expression of IL-6 in LPS-induced macrophages, suggesting its role in dampening innate immune responses (Li et al. 2015). Finally, IL-37 promoted the suppressive properties of Treg cells by inducing up-regulation of IL-10, TGF- β , and CTLA-4 (Wang et al. 2016b). Thus, IL-1 cytokines play diverse roles in infection autoimmunity and cancer.

REGULATION OF EXPRESSION OF ACTIVE IL-33 AND OTHER IL-1 FAMILY CYTOKINES

Production of IL-1 family members is tightly regulated at several levels. Notably, all IL-1 family members with the exception of IL-1 receptor antagonist (IL-1Ra) are translated without a signal peptide that would be required for active secretion via the endoplasmic reticulum and Golgi apparatus (Sims and Smith 2010; Afonina et al. 2015). Therefore, they need to be cleaved

by caspases and proteases to release bioactive forms (Garlanda et al. 2013). For example, IL-1 β is secreted as a pro-IL-1 β , which is cleaved by caspase-1 to release the bioactive IL-1 β into circulation. While most immune cells express caspase-1, its activity is regulated by the inflammasome NLRP3. Neutrophil-secreted enzymes elastase and proteinase-3 also cleave pro-IL-1 β efficiently to generate the bioactive forms. In contrast, the IL-1 α precursor, which is released upon necrosis of source tissues, is readily available for the induction of inflammation, as it can activate signaling directly by binding to its receptor.

Similar to IL-1 β , IL-18 is translated as a 24-kDa protein, which then is cleaved by NLRP3-activated caspase-1 to become 17-kDa active IL-18. Thus, NLRP1-deficient mice also have reduced amounts of active IL-18, manifesting in spontaneous obesity (Murphy et al. 2016). Pro-IL-18 can be also cleaved by neutrophil-derived proteases and proteinase-3 to generate the active form. The biological activity of IL-36 also requires posttranslational processing (Towne et al. 2011); however, precisely how pro-IL-36 is cleaved is unclear. Similarly, the mechanisms underlying IL-37 processing are unknown, although they are likely to involve caspase-1 (Li et al. 2015).

IL-33, unlike most other members of the family, is released by necrotic cells as a 29-kDa full-length protein that has bioactivity and does not require proteolytic processing (Martin and Martin 2016). Although originally believed to be processed by caspase-1, later studies revealed caspase-1 to be redundant for IL-33 activity (Talabot-Ayer et al. 2009). In contrast, proteases secreted by neutrophils, macrophages, and mast cells cleave the amino-terminal end of human IL-33, resulting in a 10-fold increase in activity (Lefrancais et al. 2012). On the other hand, caspase-3 and -7 released by apoptotic cells can effectively cleave and inactivate IL-33. Thus, the expression of the active forms of IL-1 family cytokines is controlled by multiple post-translational mechanisms that have evolved to balance the fine line between the beneficial and detrimental functions of the members of this cytokine family.

REGULATION OF IL-33 AND IL-1 FAMILY SIGNALING

Most members of the IL-1 family signal by binding to heterodimeric receptors. IL-33, IL-1 α , IL-1 β , and IL-36 utilize a common receptor chain called IL-1RAcP. IL-1 α , IL-1 β , and IL-1RA share yet another common receptor chain, IL-1R1. In contrast, ST2 is exclusively used by IL-33, while IL-1Rrp2 is specific to IL-36. IL-36RA is an IL-36R antagonist that has more than 50% similarity to IL-1RA. IL-1 α and IL-1 β can also signal by binding to IL-1R2. IL-18 and IL-37 bind and signal through a heterodimeric receptor composed of IL-18R α and IL-18R β (Fig. 2; Table 1) (Garlanda et al. 2013). Despite the diversity in receptor recognition, all IL-1 family receptors possess a cytoplasmic Toll-IL-1R (TIR) domain and initiate a common signaling cascade, which is similar to TLRs and requires the adaptor Myd88 (O'Neill 2000). Signaling downstream of Myd88 involves IRAKs, TRAF6, and TAK1, leading to the activation of Janus kinase (JNK), extracellular signal-regulated kinase (ERK), and mitogen-activated protein kinase (MAPK) pathways. Eventually, transcription factors, including RelA/p65 (nuclear factor [NF]- κ B) and c-Jun establish the transcriptional program activated by IL-1 family members (O'Neill and Greene 1998).

Proximal IL-1 family signaling is regulated tightly by decoy and antagonistic receptors (Sims and Smith 2010; Garlanda et al. 2013). For example, the IL-33 receptor is generated in two distinct forms that differ functionally: membrane-bound ST2 that allows functional IL-33 signaling and a shorter soluble form that sequesters available IL-33 (Yanagisawa et al. 1993; Garlanda et al. 2013; Martin and Martin 2016). Notably, increased soluble ST2 is a prognostic marker for several inflammatory diseases (Kim et al. 2015). Similarly, the soluble receptor isoform of IL-1R2 can bind to IL-1 β extracellularly and render it unavailable for signaling. IL-1R signaling is also inhibited by the IL-1R antagonist, IL-1RA, which competes with IL-1 β for IL-1R1 receptor binding (Aksentijevich et al. 2009). Furthermore, soluble IL-1R2 and IL-1RAcP can also bind to pro-IL-1 β efficiently and prevent its proteolytic processing. Similar mechanisms exist for other IL-1-like cytokines, for example, for IL-36, through expression of an antagonist receptor for IL-36, and for IL-18 through the expression of IL-18-binding protein (IL-18BP), which prevents IL-18 interaction with the receptor (Fig. 2; Table 1) (Sims and Smith 2010; Garlanda et al. 2013).

In addition to the above-described mechanisms that control the availability of IL-1-like

Figure 2. A schematic representation of interleukin (IL)-1 family receptors, coreceptors, ligands, and negative regulators. TIR, Toll-IL-1R.

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cytokines, the expression of some receptors is tightly governed by transcriptional mechanisms. This is particularly well known for ST2, the expression of which is controlled by the Th2 lineage-determining transcription factor Gata3 (Hayakawa et al. 2005). Similarly, ST2 expression in ILC2s (Hoyler et al. 2012; Mjosberg et al. 2012) and colonic Treg cells (Schiering et al. 2014) is regulated by Gata3. In contrast, Th1 cells expressed ST2 in a T-bet- and STAT4-dependent manner (Baumann et al. 2015). ST2 expression on Treg cells also required the TCR signaling-induced transcription factor IRF4 and its binding partner BATF (Vasanthakumar et al. 2015). A recent study has shown that PPAR- γ is required for efficient ST2 expression on Th2 cells (Chen et al. 2017). It remains to be seen whether PPAR- γ contributes to regulation of ST2 expression in other cell types.

NUCLEAR FUNCTIONS OF IL-33, IL-1 α , AND IL-37

Unlike other cytokines, some IL-1 family members are known to have nuclear functions. IL-33, IL-1 α , and IL-37 possess a nuclear localization sequence (NLS) that facilitates nuclear entry. IL-33 also possesses an amino-terminal homeodomain like helix-turn-helix (HTH) DNA-binding domain (Carriere et al. 2007). Nuclear IL-33 can act both as a transcriptional activator and repressor in a context-specific manner. It can interact with histone H2A and H2B and regulate chromatin architecture and partner with the methyltransferase SUV39H1 to facilitate repression of genes (Carriere et al. 2007). Furthermore, IL-33 can cooperate with NF- κ B transcription factors p65/RelA and p50 and sequester them to the cytoplasm, thereby, preventing the expression of inflammatory genes (Ali et al. 2011). Although not a nuclear function, a recent study has also shown that intracellular IL-33 can regulate the splicing of uncoupling protein-1 (UCP-1) gene in adipocytes, thereby regulating thermogenesis and brown fat differentiation (Odegaard et al. 2016). Similar to IL-33, IL-1 α can also translocate to the nucleus and activates transcription by interacting with chromatin (Garlanda et al. 2013). The range of functions

regulated by nuclear IL-1 α includes proliferation, cell migration, apoptosis, and expression of cytokines, including IL-18 and TNF (Garlanda et al. 2013; van de Veerdonk and Netea 2013). Nuclear IL-1 α also interacts with NF- κ B transcription factors to regulate gene expression and, similar to IL-33, facilitates the splicing of prosurvival molecule Bcl-xL (Pollock et al. 2003). Finally, IL-37 was shown to translocate to the nucleus and to repress the expression of inflammatory genes in LPS-treated macrophages (Sharma et al. 2008).

CONCLUDING REMARKS

IL-1 has long been known to play a central role in inflammation. More recently, IL-33 has emerged as another crucial regulator of immunity and tissue homeostasis (Fig. 1). However, while substantial advances were made over the last decade, there are many aspects of the biology of IL-1 family cytokines that remain unexplored. Processing of the procytokine forms into biologically active forms is a key and the foremost regulatory mechanism in IL-1 biology. Yet, the precise mechanism by which IL-33 is cleaved or the exact function of long versus short forms of IL-33 in immunity and inflammation are still a matter of intense debate. It is also incompletely known how specificity of signaling is achieved by members of the IL-1 cytokine family, given that the receptor chains are shared by many of the IL-1-like cytokines. For example, it is unclear whether ST2 or IL-1R compete for IL-1RAcP or interact with different affinities. In such a scenario, ST2 or IL-1R may sequester IL-1RAcP and thereby limit signaling through the other receptor. This may be critical when designing blocking antibodies for a particular cytokine as such antibodies may affect the activity of other cytokines that share the receptor chain. Similarly, while it is clear that soluble ST2 can limit the signaling of IL-33, it is unknown how the expression of the soluble and membrane-bound forms of ST2 is regulated. Importantly, although IL-33 is localized in the nucleus, its role in transcription has not been studied fully. It is also unclear whether the IL-33 released extracellularly by necrotic or in-

flamed tissue can act as a transcription factor in the target cell. Given the considerable “resource sharing” between IL-1 family members, which share molecules that activate them as well as receptors and signaling components, fully understanding the biology of IL-1 family cytokines, will be essential to exploit their therapeutic potential.

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