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Interleukin-33 in Asthma: How Big of a Role Does It Play?

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Abstract

In complex disorders such as asthma and allergic disease, the goal for developing disease-modifying biotherapeutics is to find a target that is a central instigator of immunologic activity. Interleukin (IL)-33 seems to be such a molecule, as it is one of the earliest-released signaling molecules following epithelial damage and can orchestrate the recruitment and activation of the cells responsible for disease. Unregulated IL-33 activity leads to activation of T-helper type 2 cells, mast cells, dendritic cells, eosinophils, and basophils, ultimately leading to increased expression of cytokines and chemokines that define the disease. As such, IL-33 is an attractive candidate for therapeutic intervention with the goal of ameliorating disease. This review focuses on the role of IL-33 in promoting and maintaining the asthma phenotype.

Keywords

Asthma; Interleukin-33; ST2; Interleukin-1 family

Introduction

Members of the interleukin (IL)-1 family play a critical role in the early immune and inflammatory response following tissue injury or infection. The family consists of 11 members that share a common β -trefoil structural motif (composed of 12 β -strands) and are highly proinflammatory [1]. The best characterized members of the family include IL-1 α , IL-1 β , IL-1Ra, IL-18, and IL-33. With the exception of IL-18 (chromosome 11) and IL-33 (chromosome 9), all identified members of the IL-1 family are located on human chromosome 2, implying origin from a common ancestor [2]. IL-1 α/β and IL-18 are expressed as a prodomain and contain polypeptide precursors that are proteolytically cleaved by caspase-1 to generate the active molecule. Dysregulation of the IL-1 family has been implicated in many diseases, including asthma, rheumatoid arthritis, Crohn's disease, periodontitis, and sepsis.

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IL-1 α/β production is stimulated by a variety of agents, many of which target molecular pattern receptors. Cells involved in their production include mononuclear phagocytic cells, endothelial cells, keratinocytes, synovial cells, osteoblasts, neutrophils, glial cells, and many others. As part of the innate inflammatory response, IL-1 α/β stimulates production of cytokines such as tumor necrosis factor- α , IL-6, and IL-8. IL-1 α/β activates T lymphocytes by enhancing IL-2 production and IL-2 receptor expression.

IL-18 synergizes with IL-12 to produce interferon (IFN)- γ ; however, it does not directly promote T-helper (Th)1 cell development [3]. Additionally, IL-18 shares with IL- α/β the ability to induce adherence and recruitment of cells through upregulation of intracellular adhesion molecule-1, vascular adhesion molecule-1, and E-selectin.

IL-1Ra is secreted in response to inflammatory stimuli but serves an anti-inflammatory function by binding to the IL-1 receptor without inducing signal transduction and preventing IL-1 α/β from binding to the receptor [4].

This review focuses on the role of the newest member of the IL-1 family, IL-33, in promoting and maintaining the asthma phenotype.

Interleukin-33

IL-33 was identified through a database search of the human genome using a profile derived from a compilation of the other IL-1 family members [5]. As deduced from the cDNA sequence, IL-33 contains 270 amino acids with a predicted molecular mass of 30 kDa [5]. IL-33 is expressed by many cells and tissues, including the stomach, brain, spleen, heart, bronchial epithelial cells, fibroblasts, smooth muscle cells, keratinocytes, macrophages, and dendritic cells (DCs) [5]. It was initially thought that like IL-1 and IL-18, IL-33 would be produced as an inactive precursor, and its secretion and activation would be dependent upon cleavage by caspase-1 within a specialized proinflammatory cellular processing center termed the *inflammasome*. Although this can occur in vitro with a truncated version of the protein, it does not appear that this is true in vivo. These initial reports suggested that IL-33 would be cleaved by caspase-1 at Asp110. However, this site is not conserved between humans and mice [5]. When the sequence was further examined, a conserved caspase cleavage motif was identified at Asp178 [6•]. Studies revealed that cleavage did occur at this site, though it was mediated by caspase-3 and caspase-7, which are not components of the inflammasome and are activated during apoptosis [6•]. It was also demonstrated that full-length IL-33 is an active molecule, and cleavage reduces its half-life [6•]. The current model for IL-33 action is that it is released from cells undergoing necrosis (eg, in response to infection or inflammation) and then acts as a proinflammatory endogenous “danger signal.” When cells alternatively undergo apoptosis, IL-33 is cleaved, and the proinflammatory activity of the cytokine is reduced [6•]. In addition to being secreted, IL-33 can function intracellularly. Within the N-terminal region of the protein, IL-33 contains a conserved homodomain-like helix-turn-helix motif. This domain associates in vivo with heterochromatin and mitotic chromatin, where it acts as a transcriptional repressor [7]. A similar activity has been described for IL-1 α [8,9].

ST2

Members of the IL-1 family exert their function through a group of receptors that belong to the Toll-like receptor-IL-1 receptor superfamily, which is defined by the presence of an intracellular Toll-IL-1R domain [10]. This superfamily is separated into two groups: Toll-like receptors and IL-1 receptors. The IL-1 receptor family is composed of 10 members that form a heterodimeric complex consisting of two members of the family. One member binds the cytokine, while the other transmits the signal to the intracellular space [10]. The first

component of the IL-33 receptor was originally identified in 1989 as a serum-inducible secreted protein from murine fibroblasts [11,12]. The receptor was termed *ST2* (also called *DRE4*, *Fit-1*, or *T1* in the older literature). This receptor is highly expressed on mast cells and is a highly selective marker of Th2 cells. Additional cells include macrophages, hematopoietic stem cells, natural killer cells, natural killer T cells, eosinophils, basophils, nuocytes, and fibroblasts [13–15]. Two forms of the receptor exist; a membrane-bound form expressed on hematopoietic tissues and lung and a soluble form induced upon stimulation of fibroblasts [16]. It is hypothesized that the soluble isoform is expressed as a homeopathic response aimed at decreasing ongoing Th2 responses through its function as a decoy receptor. ST2 remained an orphan receptor until the cloning of IL-33 in 2005 [5]. It was subsequently shown that the coreceptor for ST2 was the IL-1R accessory protein (IL-1RAcP), a receptor component used by other members of the IL-1 family (IL-1 α , IL-1 β , IL-1F6, IL-1F8, and IL-1F9) [17]. Binding of IL-33 to its receptor triggers activation of the nuclear factor (NF)- κ B and mitogen-activated protein kinase pathways (specifically p38, JNK, and extracellular signal-regulated kinase [ERK]1 and ERK2) to initiate cell signaling.

Evidence for a Role of Interleukin-33 in Asthma

Two of the most important cytokines responsible for Th2 immune deviation are IL-33 and thymic stromal lymphopoietin (TSLP). Using differential polymerase chain reaction display to identify molecules that distinguish Th2 cells from Th1 cells, two groups found that expression of ST2 was the best marker that characterized Th2 cells [18,19]. The levels of ST2 on Th2 cells were independent of expression of IL-4 or IL-5 [18]. The requirement for IL-33 in Th2-cell generation and activity was demonstrated in a pulmonary granuloma model driven by *Schistosoma mansoni* eggs and in a murine model of allergic disease driven by ovalbumin sensitization. In these models, IL-33 drove development of Th2 cells that produced mainly IL-5, with lesser amounts of IL-4, but not IFN- γ [20,21]. Polarization toward Th2 cells by IL-33 involved activation of the NF- κ B and mitogen-activated protein kinase pathways [22]. Similarly, differentiation of human CD4⁺ cells in vitro in the presence of IL-33 enhanced antigen-dependent IL-5 and IL-13 production [14]. In addition to influencing CD4 cellular differentiation, IL-33 is a chemoattractant for Th2 cells, recruiting Th2 cells to lymph nodes and tissue [23]. IL-33 can influence DC maturation and activity, leading to their enhanced expression of major histocompatibility complex-II, CD86, and IL-6. These activated DCs, when cultured with naïve CD4⁺ T cells, lead to their differentiation in a fashion characterized by production of IL-5 and IL-13 [24•]. In the bone marrow, IL-33 induces granulocyte-macrophage colony-stimulating factor (GM-CSF) expression that promotes the development of CD11c⁺ DCs [25].

Mast cells play a central role in allergic inflammation and asthma through their release of a variety of mediators. Several studies have demonstrated ST2 and IL-1RAcP receptor expression on mast cells. Binding of IL-33 and subsequent signaling leads to expression of many proinflammatory cytokines, chemokines, and lipid mediators, including CXCL8 (IL-8), IL-5, IL-13, IL-6, IL-1 β , tumor necrosis factor- α , GM-CSF, CCL2 (monocyte chemoattractant protein-1), and prostaglandin D₂ [26–28]. The ability of IL-33 to stimulate mast cell cytokine production depends in part on its ability to form a receptor complex composed of a combination of the ST2/IL-1RAcP heterodimer with c-Kit; the combination of signaling from the two receptors results in activation of multiple pathways leading to increased cytokine expression [29]. A similar synergy is observed with IL-33 and TSLP. On its own, IL-33 promotes maturation of CD34⁺ mast cell precursors, which was accelerated with the addition of TSLP as measured by the acquisition of tryptase [28]. In a follow-up study, this group confirmed that circulating CD34⁺ cells express both the TSLP and IL-33 receptors and that specific allergen challenge in individuals with allergic asthma increases their numbers [30]. Expression of IL-33 may play a role in homing of mast cells to tissues,

as IL-33 promotes adhesion to a fibronectin matrix [26]. The above data indicate that IL-33 could influence mast cells to influence allergic reactions but do not definitively demonstrate a role in disease. Using a murine model of cutaneous and systemic anaphylaxis, IL-33 was critical for the induction of anaphylaxis that occurred in a T-cell-independent and mast cell-dependent manner in IgE-sensitized animals [31]. The same study also showed that mast cells sensitized with IgE expressed higher levels of ST2 than nonsensitized mast cells, a step critical for the anaphylactic response [31].

In the article describing the cloning of IL-33, it was shown that intraperitoneal administration of IL-33 in mice induces Th2 immune deviation and cytokine production, causes elevated IgE, and generates profound mucosal eosinophilic inflammation in the lung and gastrointestinal tract [5]. The eosinophilic infiltration was localized beneath the endothelium, both adjacent to the blood vessels and within the vessel wall. In addition to the increased mucus, the epithelial lining of the lungs was hypertrophied [5]. Others have demonstrated that administration of an IL-33 receptor antagonist reduces production of Th2 cytokines and airway inflammation in these models of murine allergic disease [32,33]. The role of IL-33 in eosinophil biology has been further examined using purified human eosinophils from healthy and atopic individuals. Microarray analysis indicated that ST2 was constitutively expressed on eosinophils, although on the surface, only low levels of the protein were detected [34]. Receptor levels increased following stimulation with GM-CSF [34]. When treated with IL-33, eosinophils responded by increasing superoxide, eosinophil-derived neurotoxin, CXCL8, CCL2, and IL-6 production [34,35]. The increased cytokine and chemokine production was mediated by activation of the NF- κ B, p38 mitogen-activated protein kinase, and ERK signaling pathways [35]. In addition, IL-33 promoted eosinophil survival—although not as efficiently as IL-5—and increased the cell surface expression of intracellular adhesion molecule-1 [34,35]. Recently, there has been a renewed interest in the role that the basophil plays in allergic disease through production of IL-4 in response to IgE-cross-linking. Incubation of human basophils with IL-33 results in increased mRNA expression of IL-4 and IL-13 [36]. On the protein level, IL-4 secretion was increased, as was cell surface expression of CD11b. The increased expression of CD11b synergistically enhanced the migration of basophils to CCL11 (eotaxin) [36].

Where does the IL-33 come from to cause problems in asthma and atopy? The most likely source is the airway epithelium in the lung and sinus cavity. When endobronchial biopsies were performed and epithelial cells were cultured *ex vivo*, increased expression of IL-33 was found in the epithelial cells of individuals with bronchial asthma as compared with healthy individuals [37]. This finding was verified when bronchoalveolar lavage fluid was collected, and again, IL-33 levels were higher in bronchoalveolar lavage fluid from those with moderate asthma compared with those with mild asthma or controls [37]. In chronic sinusitis, sinonasal epithelial cells were cultured from patients who were responsive or recalcitrant to medical or surgical treatment. IL-33 was expressed in the epithelium of both groups, with higher levels found in the epithelial cells from patients recalcitrant to treatment [38].

Model for the Role of Interleukin-33 in Asthma

The collective data suggest a role for IL-33 in asthma and allergic disease. However, can these be tied together to present a cohesive mode of action? Our proposed model is summarized in Fig. 1. Primary production of IL-33 by epithelial cells suggests a mechanism whereby the respiratory tract can generate a “danger signal” that drives a subsequent Th2 immune response, arguably the initial trigger of asthma. This would likely occur in response to an insult from an infection (viral or bacterial) or from the environment (allergen or pollutant), or a combination of both that results in necrosis of the epithelial cell layer.

Released IL-33 would then be available to interact with various cells of the immune system. Simultaneously, fibroblasts secrete soluble ST2 that serves to dampen inflammation and return the system to a nonresponsive state. In the absence of this response or in the presence of a sufficiently robust inflammatory signal that overwhelms this response, IL-33 activates mast cells in the tissue, leading to production and release of proinflammatory cytokines, chemokines, and lipid mediators. Simultaneously, resident DCs are activated by IL-33 and promote naïve CD4⁺ T cells (including nuocytes) to produce IL-5 and IL-13. Previously differentiated Th2 cells would also be directly recruited to the site of inflammation via the chemotactic effects of IL-33. The combination of IL-33, secreted IL-5, and chemokines released from the mast cells recruits circulating eosinophils into the lungs that are triggered to release their own proinflammatory mediators. The result is a vicious cycle of inflammation fanning further inflammation, which if unchecked establishes a chronic inflammatory state in the lungs. In part, this would explain why current attempts to inhibit IL-4 and IL-5 with targeted therapies have failed, as they do not address the primary driver of the inflammatory response.

Conclusions

In targeting a mediator with the aim of accomplishing disease modification or prevention, the goal is to find a target that is a central regulator of immunologic activity. IL-33 is poised to be such a molecule in asthma and allergic diseases, as it is among the earliest-released signaling molecules and can orchestrate the recruitment of the cells responsible for disease. Unregulated IL-33 activity results in activation of Th2 cells, mast cells, DCs, eosinophils, and basophils, ultimately leading to increased expression of mediators that define the disease. As such, IL-33 is an attractive candidate for therapeutic intervention, either with soluble receptors targeting the lung or small molecule inhibitors that could act systemically. Whereas other therapies blocking various components of the down-stream immune response in asthma have failed, it is hoped that with IL-33 being a central regulator of the inflammatory response, blockade of this molecule will deliver on the promise of immune modulation.

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Fig. 1.

Damage to the epithelial cell layer results in necrosis and release of interleukin (IL)-33. IL-33 can act on many cell types, resulting in the maturation and migration of these cells and release of proinflammatory factors at the site of injury. Soluble ST2 (sST2) from the underlying fibroblasts can bind IL-33 and dampen the immune response and prevent onset of or lead to resolution of inflammation. Left unchecked, continual production of IL-33 results in the chronic allergic inflammation characteristic of asthma. *GM-CSF* granulocyte-macrophage colony-stimulating factor; *Th2* T-helper type 2