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Review

The role of IL-33/ST2L signals in the immune cells

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ABSTRACT

Interleukin (IL)-33 signals influence various immune cells during differentiation, immune responses and homeostasis. As discussed in this Review, IL-33 via TI/ST2L regulates the functions of immune cells including T cells, B cells, DCs, macrophages, mast cells, and innate lymphoid cells (ILCs). Stimulation with IL-33 is crucial for CD4+ T cell polarized into Th2 immunity and for the induction of Treg. CD8+ T cells can also express ST2L and IL-33 promotes features of effector CD8+ T cells. For macrophages and ILCs, ST2L presents on these cells and IL-33 induces Th2 cytokine production. IL-33 modulates adhesion, activation, maturation, and cytokine production by mast cells. ST2 is expressed in B1 and is important for differentiation of IL-10-producing B cells. Understanding the specific role of IL-33/ST2L in different immune cells will help to answer the remaining questions that are important for diseases pathologies and intervention strategies by targeting the IL-33/ST2L signals.

1. Introduction

Interleukin (IL)-33, as the most recently discovered IL-1 family member 11, is a dual-function cytokine that displays a nuclear factor and an "alarmin" released during cell injury. IL-33 is a ligand for a receptor complex consisting of two proteins: IL-1 receptor-related protein (IL-1RL1, ST2) and IL-1 receptor accessory protein (IL-1RAcP). IL-1RAcP is required for IL-33-induced signal transduction and in vivo effects, but is unable to directly bind to IL-33 or ST2 by itself [1]. Structurally, IL-33 binds to ST2 and forms suitable conformations to contact with IL-1RAcP [2]. Functionally, IL-1RAcP−/− mice treated with IL-33 fail to induce type 2 immune responses and IL-1RAcP can stabilize the ligated soluble IL-1R, allowing neutralization and sequestration of the cytokine in vivo [1,3].

ST2 has two forms: trans-membranes full-length form (ST2L) and soluble form (sST2). sST2 binds to IL-33 directly and acts as a decoy receptor to competing with membrane bound ST2L[4]. sST2 was described to be elevated in many diseases such as autoimmune diseases [5], asthma [6], idiopathic pulmonary fibrosis [7], myocardial infarction and heart failure [8]. IL-33 signals in cells are amplified through its interaction with a heterodimeric receptor consisting of membrane-bound ST2L and IL-1RAcP, leading to NF-κB and MAPK activation [9].

ST2L is expressed on many immune cells including macrophages [10], T cells particularly Th2 [11], mast cells [12], and innate lymphoid cells (ILCs) [13]. IL-33/ST2L signals are involved in the regulation of T cells and DCs differentiation, activation of macrophages and mast cells, promotion of Th2 cytokine production by ILCs [14–18]. It has been suggested that IL-33 is crucial for induction of Th2 cytokine such as IL-13, IL-5 to mediate Th2-type immune responses [19]. However, several evidences show that IL-33 can amplify both Th1 and Th2 responses [14,20]. A large number of evidences have supported its pathogenic role in arthritis [21], asthma [22], colitis [23], and acute kidney injury [24]. However, protective role for IL-33 has also been described in murine models of acute colitis [25,26], experimental autoimmune uveitis [27] and chronic cardiac rejection model [28].

The complex feature of IL-33 is seemingly opposing pro-inflammatory versus anti-inflammatory properties. To exhibit IL-33 complex features, IL-33 functions at different stages of an immune response and at different locations in the body. IL-33 is initially described as a proinflammatory cytokine to activate different cells of the innate immune system, but recent evidence suggests that IL-33 signalings are associated with regulatory T cell (Treg) and regulatory B cell (Breg) responses [26,29]. Furthermore, studies have indicated that both astrocytes and oligodendrocyte precursors in the brain express IL-33, which suggests that IL-33 may also play a role in the absence of an inflammatory response [30]. Thus, IL-33 expression seems to be associated with many

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cells, affirming its crucial role in the inflammatory diseases and cardiovascular diseases.

IL-33 is an unconventional cytokine with important effects on the responseness of immune reaction. An understanding of how IL-33 expression is regulated in different immunes is important for the understanding of pathologies in different diseases. In this review, we discuss our current understanding of IL-33/ST2L expression and functions in different immune cells.

2. IL-33/ST2L in T cells

2.1. IL-33/ST2L in Th2 cells

Naïve CD4+ T cells are differentiated into helper cells by antigen stimulation in combination with certain cytokines. CD4+ T helper cells are present in at least four forms (Th1, Th2, Th17, and Treg cells) that shape and regulate the immune responses in separate ways [31]. Naive Th cells do not express ST2 on their surface; its expression is induced after contact with antigens on differentiated Th2 effector cells. ST2 is first described on Th2 cells, where its expression accompanies that of the Th2-type cytokines IL-4, IL-5, or IL-10, but not IFN-γ or IL-2 in vitro and ex vivo [11,32]. Antigen-specific ST2+ Th cells are the primary source of the Th2 cytokines IL-5 and IL-13 as compared with wild type ST2-Th cells or Th cells from ST2−/− mice [33]. Moreover, ST2 expression is slower than that of type 2 cytokine expression on Th2 cells in vitro, which indicates that ST2 expression is a late event during Th cell commitment to the Th2 phenotype and that signaling through ST2 specifically enhances Th2 effector function [32]. This is supported by the facts that expression of ST2 is not critical for the development of naive T cells toward a Th2 phenotype, but ST2−/− mice are significantly impaired in their ability to generate the Th2 cytokines IL-4 and IL-5 but not IFN-γ [34,35]. However, ST2 promotes Th2 cells activation. ST2+ cells represent the majority of Th cells with an increased expression of CD44 and CD25, and decreased expression CD62L [33]. This point to the presence of a specialized subset of activated Th2 cells.

It is currently not clear the exact molecular mechanisms required for the induction of ST2 by Th2. The regulation of ST2 expression by Th2 is thought to dependent on GATA3 [36]. Resting Th2 cells express little GATA3, which is increased by IL-33 and STAT5 activators such as IL-2, IL-7, and TSLP, in turn increasing ST2 from its low-level expression on resting Th2 cells [36]. ST2 expression is remarkably enhanced by IL-6, slightly enhanced by IL-1, TNF-α, and IL-5. Nevertheless, the induction of ST2 on Th2 cells is independent of cytokines such as IL-6, IL-4, IL-5, or IL-10 since it is also present in the respective cytokine-deficient mice [11,32].

IL-33 plays a role in the differentiation of typical and atypical Th2 cells. IL-33 induces differentiation of IL-5-positive IL-4-negative CD4+ T cells (IL-5+IL-4-Th cells) from naïve CD4+ T cells independently of IL-4, STAT6 and GATA3, which are important factors for the typical Th2 cell differentiation [37] (Fig. 1). IL-33 acts on ST2+ Th2 cells to induce production of IL-13, but not IL-4, in a TCR-independent, NF-κB, and p38-dependent manner [36]. These atypical Th2 cells fail to secrete IL-4. IL-33 also induces a significantly higher percentage of ST2+CD4+ cells, with elevated concentrations of IL-5, IL-4 and IL-13, but not IFN-γ and IL-17 [14,19,38] (Fig. 1). Mesenteric lymph node T cells stimulated with IL-33 have increased GATA3 expression, and show an IL-33 dose dependent increase in secreted Th2-type cytokines IL-4 and IL-5, whereas this effect is abolished by blocking IL-33 signaling [39]. As ST+ Th2 cells have higher responsiveness for IL-2 by increased CD25 expression [33], it provides better accessibility of the *il4* locus in Th2 cells and allow for enhanced production of IL-4, IL-5, and IL-13 mRNA. IL-4 and IL-13 can bind to the type 1 and/or type 2 IL-4 receptors and activate the STAT6 signaling pathways [40]. However, exogenous IL-33 induces a polarized type 2 cytokine response which is entirely MyD88 dependent but STAT6, IL-4 and IL-13 independent [41,42].

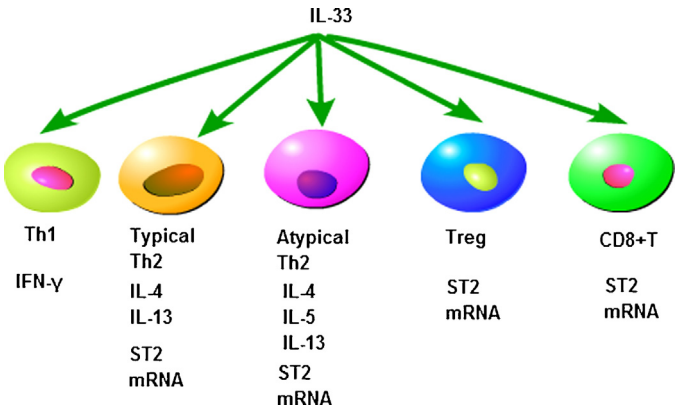

Fig. 1. IL-33 in the T cells. ST2L is expressed by Th2, Tregs and CD8+ T cells, but not by Th1 cells in response to different stimuli. IL-33 plays a role in the differentiation of typical and atypical Th2 cells, they secrete IL-5, IL-13 or IL-4, IL-5, IL-13, respectively. IL-33 leads to a significant increase in the frequency and total number of Treg cells. IL-33 can activate CD8+ T cells by increasing CD69. IL-33 also can promote Th1-type cytokine IFN-γ production to induce Th1 type 1 immunity.

In addition to CD4+ Th2 cells, it has been show that IL-33 promotes Th1-type cytokine IFN-γ production to induce Th1 type 1 immunity [14] (Fig. 1). IL-33 stimulation of Th1 cultures results in increased IFN-γ and IL-13 production concurrent with reduced IL-10 gene transcription and secretion [14]. The earlier findings report that Th1 cells fail to express ST2L even when cultured with various immunological stimuli such as ConA, IL-2, IL-4, IFN-γ, or with anti-IFN-γ or anti-IL-4 antibodies [43,44]. However, ST2L weakly and transiently expresses on the surface of Th1 cells after incubation with IL-5 or anti-CD3 antibody [44]. Further evidence confirms that mRNA expression of *ST2L* is found in Th1 cultures, indicating that Th1 cells have the potential to express ST2L on the cell surface [14]. However, it is not clear which regulatory factors influence ST2L expression on Th1 cells.

2.2. IL-33/ST2L in CD8+ T cells

Besides its expression on effector cells of Th2 immune response and roles in innate Th1 type immune responses, IL-33/ST2L also plays a role in adaptive Th1 type immune response. Recent studies have revealed that IL-33 can activate CD8+ T cells by increasing CD69 [45]. NF-κB signaling pathway is involved in the IL-33-mediated activation of CD8+ T cells [45]. CD8+ T cells can also express ST2L and respond to IL-33 (Fig. 1). The ST2 mRNA is not expressed in naïve CD8+ T cells and can be induced in CD8+ T cells cultured in Tc0 and Tc17 conditions [46]. Expression of ST2 in Tc1 cells is dependent on T-bet, a master Th1/Tc1 transcription factor [46]. IL-33 synergizes with TCR, IL-12 signaling, or both to drive IFN-γ reduction in Tc1 cells and promote features of effector CD8+ T cells [46]. In mice with lymphocytic choriomeningitis virus (LCMV) infection, up to 20% of activated antigen (Ag)-specific CD8+ T cells expressed ST2 [47]. However, CD8+ T cells sensitized in poly(I:C)-pretreated mice fail to fully up-regulate ST2L, which leads to impaired T-cell receptor independent responses to IL-33 [48].

2.3. IL-33/ST2L in Treg cells

Treg cells are dependent on the production of IL-33 by other cells because, unlike activated Th1 cells, Treg cells do not produce IL-33