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Review Article

Implications for Interleukin-33 in solid organ transplantation

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ABSTRACT

Interleukin(IL)-33 is a member of the IL-1 cytokine family that has been attributed T helper (Th) type 2 immunity-promoting capacity. However, new studies indicate that IL-33 is a multifunctional protein that acts as transcriptional/signaling repressor, functions as an alarmin alerting the immune system to necrosis, as well as serves as a cytokine that targets cells expressing ST2, the IL-33 receptor. Interestingly, IL-33 is also emerging as a pleiotropic cytokine. Depending on the innate or adaptive immune cells targeted by IL-33, it can not only promote type 2, but also IFN-γ dominated type 1 immunity. In addition, IL-33 expands regulatory T cells. In this review, we assimilate the current knowledge of IL-33 immunobiology and discuss how IL-33 may mediate such diverse roles in the immune response to pathogens and development of immune-mediated pathologies. The function of IL-33 in shaping alloimmune responses to transplanted organs is poorly explored, but a particularly beneficial role of IL-33 in experimental heart transplant models is summarized. Finally, given the implication of IL-33 in pathologies of the lung and intestine, we discuss how IL-33 may contribute to the comparatively poor outcomes following transplantation of these two organs.

1. Introduction

1.1. Standing out in the IL-1 cytokine superfamily

Presently, there are 11 identified Interleukin-1 (IL-1) cytokine superfamily members (IL-1α, -1β, IL-1 receptor antagonist (IL-1Ra), IL-18, IL-33, and IL-1F5-IL-1F10) that most likely arose from duplication of a common ancestral gene [1]. As such, IL-1 family members share general structural similarities in their cytokine domain, particularly a 12-stranded β-trefoil structure. Yet the IL-1 family has diverged into a group of fascinating molecules with pleiotropic, and often disparate, impacts on local and systemic responses to tissue injury and infection [1,2]. IL-1 superfamily cytokines are expressed or induced in both stromal cells, such as endothelium, epithelium, and keratinocytes, in addition to innate immune cells. Upon their secretion, the agonistic IL-1 family members (IL-1α, -1β, -18, -33, IL-1F6, -1F8, and -1F9) signal through receptors closely related to Toll-like receptors (TLR; [3]). Thus, IL-1 family members can induce pro-inflammatory innate cell responses similar to those promoted by TLR ligands. Subsets of T cells also express IL-1 receptors and IL-1 cytokines directly modulate their proliferation, polarization, and immunoregulatory function [1]. In total, IL-1 cytokines are both potent pro-inflammatory mediators of innate immune immunity and important controllers of adaptive immune cell functions.

Given their profound and often feed-forward pro-inflammatory functions, IL-1 cytokines are regulated at several levels to protect against unrestrained inflammation. The importance of this control is exemplified in multiple incapacitating inherited inflammatory diseases that arise due to IL-1β overproduction or lack of IL-1Ra [1]. Accordingly, most IL-1 cytokines are only expressed at low levels and require local stress or pro-inflammatory stimuli for large-scale transcriptional and translational induction [1]. IL-1α, -1β, -18, and -33 are initially generated as signal sequence-lacking pro-cytokines that require processing to bioactive or secreted forms by proteases, whose activities are also precisely controlled [2]. In addition, the

Abbreviations: APC, antigen presenting cell; BAL, bronchoalveolar lavage; CBM, chromatin-binding motiff; CAV, chronic allograft vasculopathy; DC, dendritic cells; DC-SIGN, DC-specific intercellular adhesion molecule-3-grabbing non-integrin; DSA, donor specific antibodies; Foxp3, forkhead box P3; HEV, high endothelial venules; HTH, helix-turn-helix; HTx, heart transplantation; i.p., intraperitoneal; I/R, ischemia/reperfusion; IFN, interferon; Ig, immunoglobulin; IL, interleukin; IL-1Ra, IL-1 receptor antagonist; IL-1RAcP, IL-1R accessory protein; IL1RL1, IL-1 receptor-like 1; ILC2, type 2 innate lymphoid cell; IRAK, IL-1 receptor-associated kinase; IS, immunosuppression; ITx, intestinal transplantation; IVIG, intravenous immunoglobulin; LTx, lung transplantation; MDSC, myeloid-derived suppressor cells; mu, murine; NH, natural helper cell; NF-HEV, nuclear factor from HEV; NLS, nuclear localization signal; RA, rheumatoid arthritis; sST2, soluble ST2; TCR, T cell receptor; Th, helper T cell; TIR, Toll-IL-1R; TLR, Toll-like receptor; TNF, tumor necrosis factor; Treg, regulatory T cell.

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stimuli inducing cytokine production also trigger expression of negative regulators of the IL-1 family cytokines or IL-1R/TLR family members. These include IL-1Ra, that stifles IL-1 activity by blocking IL-1α/β binding to the IL-1R1, as well as soluble, agonistic decoy receptors (i.e. IL-18-binding protein).

IL-33 was the 11th identified IL-1 family member (IL-1F11) discovered by computational sequence database searches for unidentified IL-1 family members [4]. IL-33 was subsequently identified as the ligand of the orphan receptor, ST2 [4], a member of the IL-1R/TIR family possessing a high degree of sequence similarity with the IL-1R [5]. In this review, we describe how IL-33 has emerged, since these early studies, as a unique and multifunctional member of the IL-1 family with suggested cytokine, alarmin, and transcriptional regulatory functions. We also discuss the important immunoregulatory role that we propose IL-33 may play in transplantation. This discussion is based on accumulating clinical and experimental evidence for IL-33 regulation of other disease processes and initial examination of IL-33 in heart transplantation.

2. Current understanding of the immunobiology of IL-33

2.1. Expression and distribution

The human IL-33 gene is located on chromosome 9, while its mouse counterpart is localized on chromosome 19 [4]. Thus, like IL-18, which is found on chromosome 11 in the human and 9 in the mouse, IL-33 has diverged from all other IL-1 family cytokine members, which in both the human and mouse, are located on chromosome 2 [1]. Recent studies have characterized two distinct murine mRNA transcripts, *IL33a* and *IL33b*, that are generated from alternative promoters and have different 5′untranslated regions, yet they code for an identical IL-33 proteins following alternative splicing [6,7]. Although there may be some tissue-specific and stimulus-dependent differences [6], *IL-33a* appears to be the dominate form [6,7].

Expression of IL-33 RNA and protein has been confirmed in many tissue and cell types [8]. However in humans, the highest constitutive levels of IL-33 protein are observed in fibroblastic reticular, epithelial, and endothelial cells [9,10]. IL-33 is particularly expressed in the high endothelial venules (HEVs), where it was first identified [11]. Using IL-33-β-galactosidase reporter mice, it was demonstrated that a quiescent mice constitutively expresses IL-33 in epithelial cells and α smooth muscle actin$^+$ fibroblastic reticular cells, but not endothelial cells [12]. Thus, some species-specific differences in IL-33 expression may exist. These data are consistent with related examinations of murine tissue that found IL-33 expression typically in the central nervous system, stomach, eye, lymphoid organs, skin, and lung [6,13,14]. Other studies have suggested expression in the kidney, pancreas, and heart [4]. Human tissue constitutive expression of IL-33 is widespread, with IL-33 found in the same locations as in mice, as well as being prominent in the epithelial and endothelial cells of most organs and tissues [9].

Pro-inflammatory stimuli, such as TLR ligands [6,15], cytokines (IL-3 and IL-4 [16]; tumor necrosis factor (TNF)-α and IL-1β [15,17]), virus and bacterial infections [7,13] greatly augment IL-33 expression in the above tissues and cells. Relatedly, administration of the TLR4 ligand, bacterial lipopolysaccharide, also induces IL-33 expression in the liver [6,12] and murine endothelial cells [12]. Tissue pathology is often associated with increases in IL-33. Rheumatoid arthritis (RA) patients display significant synovial IL-33 [17]. Likewise, hypertrophic cardiomyopathy is associated with profound increases of IL-33 in cardiac fibroblasts [18]. Atherosclerosis is also associated with augmented IL-33 expression in vascular tissues [19] and allergens drive IL-33 expression in the conjunctiva of the eye [14].

Although IL-33 expression in quiescent cells is confined predominantly to stromal cells, pro-inflammatory stimuli has been reported to induce its expression in murine myeloid cells, particularly macrophages and conventional dendritic cells (DCs) [6–8]. Immunoglobulin (Ig) binding to FcεRI receptors on murine mast cells [20] or DC-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) on DC, macrophages, and monocytes induce the expression of IL-33 [21]. Careful examinations have found that ligation of TLR3 and 4, but not TLR2 or TLR9, can upregulate IL-33 mRNA expression [7]. However, IL-33 expression has not yet been described in human myeloid cells, suggesting that additional species-specific differences in IL-33 expression may exist.

Overall, IL-33 is abundantly expressed and rapidly induced in tissues that are continuously exposed to the external environment or line the vasculature. IL-33 expression therein, as well as possible upregulation of IL-33 in the innate myeloid cells that patrol these tissues, suggest a fundamental role for IL-33 in early immune responses to injury and infection. However, many of these studies, particularly those examining macrophages and DC, have only examined IL-33 message [7,21] and the functional role of IL-33 protein in these cells and tissues is only emerging, as discussed below.

2.2. Proteolytic processing and release

Database mining for distant IL-1 and fibroblast growth factor proteins lead to the discovery of IL-33 in 2005 [4]. Schmitz et al. originally described IL-33 in the human and mouse as 270 and 266 amino acid proteins, with respective calculated molecular weights of 30 and 29.9 kDa [4] (see Fig. 1). Human and mouse IL-33 are 55% identical at the amino acid level [4] and, like most IL-1 family members, IL-33 is expressed as a pro-cytokine lacking a classic signaling peptide to facilitate secretion in both species (Fig. 1). However, unlike IL-1β and IL-18, which both require protease processing to an active, cytokine-form, IL-33 is similar to IL-1α, with its full-length, "pro-cytokine" form possessing functional activity [1]. Any mechanisms by which IL-33 may be processed or released, however, are still emerging.

It was proposed initially that, like IL-1β and IL-18, IL-33 required cleavage by caspase-1 to be secreted as an 18-kDa, "mature" cytokine form, IL-33$_{112–270}$ [4]. However, subsequent studies revealed that, where full-length IL-33 is biologically active, caspase-1 does not process IL-33 and cleavage by caspase-3 or caspase-7 diminishes IL-33 activity [22–24]. Consequently, it appears that IL-33 is inactivated by caspases during apoptotic cell death, but is functional when released from necrotic cells [24]. These observations have led to classification of IL-33 as an alarmin, or an endogenous molecule that alerts the immune system to tissue damage [22]. The alarmin function of IL-33 is particularly implicated in effective CD8$^+$ T cell viral control (see below for more details).

Alternative mechanisms of IL-33 processing do appear to also exist. Neutrophil serine proteases cathepsin G and elastase were convincingly shown to cleave full-length human IL-33$_{1–270}$ and generate mature forms IL-33$_{95–270}$, IL-33$_{99–270}$, and IL-33$_{109–270}$ which display 10-fold increased biological activity compared to full-length IL-33 [25]. In vitro-translated murine IL-33$_{1–266}$ was similarly cleaved by these neutrophil proteases, generating bands that co-migrated with IL-33$_{102–266}$ and IL-33$_{109–266}$ proteins. In wild type, but not IL-33-deficient mice, bands corresponding to IL-33$_{102–266}$ and full-length IL-33$_{1–266}$ were found increased in bronchoalveolar lavage (BAL) fluid following oleic acid-induced acute lung injury [25]. These data suggest when activated neutrophils are recruited to injured lung tissue, they may proteolytically