Review Article

Potential Therapeutic Aspects of Alarmin Cytokine Interleukin 33 or Its Inhibitors in Various Diseases

Muhammad Imran Arshad, PhD[1,2,3,4]; Hilal Ahmad Khan, MBBS[4]; Gregory Noel, PhD[1,2,3]; Claire Piquet-Pellorce, PhD[1,2,3]; and Michel Samson, PhD[1,2,3]

[1]Institut National de la Santé et de la Recherche Médicale (Inserm), Institut de Recherche Santé Environnement Travail (IRSET), Rennes, France; [2]Université de Rennes 1, Rennes, France; [3]Structure Fédérative BioSit UMS 3480 CNRS-US18 Inserm, Rennes, France; and [4]Institute of Microbiology, University of Agriculture, Faisalabad, Pakistan

ABSTRACT

Purpose: The purpose of this review was to examine the comprehensively accumulated data regarding potential therapeutic aspects of exogenous administration of interleukin 33 (IL-33) or its antagonists in allergic, cancerous, infectious, and inflammatory diseases.

Methods: A selected review was undertaken of publications that examined the protective and exacerbating effects of IL-33 or its inhibitors in different diseases. Mechanisms of action are summarized to examine the putative role of IL-33 in various diseases.

Findings: IL-33 promoted antibacterial, antiviral, anti-inflammatory, and vaccine adjuvant functions. However, in T_H2-biased respiratory, allergic, parasitic, and inflammatory conditions, IL-33 exhibited disease-sensitizing effects. The alarmin cytokine IL-33 induced protective effects in diseases via recruitment of regulatory T cells; antiviral $CD8^+$ cells, natural killer cells, γδ T cells, and nuocytes; antibacterial and antifungal neutrophils or macrophages; vaccine-associated B/T cells; and inhibition of nuclear factor–κB–mediated gene transcription. In contrast, IL-33 exacerbated the disease process by increasing T_H2 cytokines, IgE and eosinophilic immune responses, and inhibition of leukocyte recruitment in various diseases.

Implications: The protective or exacerbated aspects of use of IL-33 or its inhibitors are dependent on the type of infection or inflammatory condition, duration of disease (acute or chronic), organ involved, cytokine microenvironment, dose or kinetics of IL-33, and genetic predisposition. The alarmin cytokine IL-33 acts at cellular, molecular, and transcriptional levels to mediate pluripotent functions in various diseases and has potential therapeutic value to mitigate the disease process. (*Clin Ther*. 2016;38:1000–1016)

Key words: diseases, IL-33, immunity, therapeutic aspects.

INTRODUCTION

The alarmins or danger signals are defined as the class of molecules that alert the immune system to circumvent the invading antigens in the host. The term *alarmin* was first described in 2005[1] as a class of structurally diverse and pluripotent host proteins.[2] Defensins, eosinophil-derived neurotoxin, cathelicidins, interleukin (IL) 1α, cytosolic calcium-binding proteins of the S100 family, heat-shock proteins, and HMGB1 protein were known to be the classic examples of alarmins.[1,3]

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The cytokine IL-33 is the 11th described member of the IL-1 family and is designated as IL-1F11. IL-33 was originally identified as *DVS27*, a gene that was up-regulated in vasospastic cerebral arteries after subarachnoid hemorrhage in canines,[4] and as a nuclear factor from high endothelial venules, which is expressed in endothelial cells nuclei.[5] In 2005, the *DVS27* gene was rediscovered as IL-33 by using computational tools on the basis of sequences that contained the 12 β-trefoil structure seen in IL-1/fibroblast growth factor–like proteins.[2] The cytokine IL-33 was described as an alarmin with a dual function protein that acts as a cytokine when released from cells and a nuclear factor–regulating gene transcription.[6] Once released from cells, the cytokine functions of IL-33 are mediated by interaction with its specific receptors, including ST2 (IL-1 receptor–like 1) and IL-1RAcP (IL-1 receptor accessory protein). The cellular sources of IL-33 include endothelial cells, epithelial cells, smooth muscle cells, keratinocytes, astrocytes, adipocytes, fibroblasts, hepatic and pancreatic stellate cells, monocytes, macrophages, and hepatocytes.[7–10] The target cells of IL-33 include B cells, T_H2 cells, $CD8^+$T cells, macrophages, dendritic cells, mast cells, basophils, and a recently identified population of innate lymphoid cells called nuocytes in different tissues, including lungs, gut, liver, spleen, or skin.[2,11–16] Extracellular IL-33 induces autocrine, paracrine, and juxtacrine actions that are important in autoimmune or inflammatory diseases, immune defense, and repair mechanisms.[16,17] The underlying signaling pathway of the IL-33/ST2 axis is dependent on activation of cytoplasmic TIR domain, such as MyD88 and the serine threonine kinases IRAK1, IRAK4, and TRAF6, leading to activation of nuclear factor–κB (NF-κB), AP-1, and mitogen-activated protein kinase (MAPK) pathways. The nuclear functions of IL-33 are associated with down-regulation of NF-κB–dependent gene transcription.[18] IL-33 was used as a promising mucosal vaccine adjuvant and induced protective immunity (i.e., primary and memory immune responses).[19]

The mouse *Il33* gene revealed the existence of two transcripts, IL-33a and IL-33b, with different 5'UTRs but coding for the same protein. The IL-33a and IL-33b mRNAs started with two different noncoding first exons, distant by 20 kb. A consensus TATA-like sequence was found 29 bp upstream of each of these transcription start sites, evidencing that IL-33a and IL-33b are transcribed from classic TATA box–containing promoters.[20] IL-33 was found to be synthesized as a 270–amino acid protein precursor containing an N-terminal nuclear localization sequence, a helix-turn helix motif, and a C-terminal region with structural homology to other IL-1 cytokines (IL-1α, IL-1β, and IL-18).[2,5] The human and mouse IL-33 shared a 55% homology at the amino acid level. The translated full-length IL-33 protein (30.7 kDa) was found to be a nuclear factor associated with heterochromatin *in vivo* and mitotic chromosomes in living cells, which possesses potent transcriptional-repressor properties.[6,21] The protective functions of IL-33 plausibly attributed to its binding to acidic pocket of a dimeric histone, H2A-H2B, on the surface of nucleosomes, resulting in suppression of gene transcription.[21,22] Accordingly, IL-33 interacts with transcription factor NF-κB (p65 subunit) and impaired its DNA binding, resulting in diminished NF-κB–dependent proinflammatory gene transcription.[18]

IL-33 was described as an alarmin in different pathologic conditions or infectious diseases,[23] and it induces multivalent functions, resulting in proinflammatory or anti-inflammatory effects in various conditions.[24] The full-length bioactive form of IL-33 was released during cell necrosis and act as an endogenous danger signal or alarmin.[6,25,26] It was found that apoptotic caspases cleave IL-33 and rendered it inactive or nonfunctional.[25,27] IL-33 was also cleaved by neutrophil elastase and cathepsin G, mast cell chymase enzyme, and calpain enzyme as previously described.[28–31] Recently, IL-33 was found to be associated with a form of cell death called necroptosis as inhibitors of necroptosis (necrostatin-1 and PJ34) down-regulated IL-33 expression in liver injury.[32] These studies described the activity of endogenous IL-33, but exogenous administration of IL-33 induced dual edge functions, depending on the immune pathology or organ involved.

Although IL-33 has been extensively studied in various diseases, a comprehensive review on therapeutic implications of IL-33 and its mechanism of action in different conditions remained obscure. Therefore, based on our and other published data, we summarized a review on the effect of therapeutic administration of IL-33 or blocking of IL-33/ST2 during infectious, allergic, and inflammatory diseases (Figure). The protective and exacerbating or sensitizing role of IL-33 administration in immunopathologic animal disease models and respective mechanism of action is elaborated comprehensively in this review.