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·Review·

Research progress on interleukin-33 and its roles in the central nervous system

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Abstract: Interleukin-33 (IL-33), a newly recognized IL-1 family member, is expressed by various tissues and cells. Since it can combine with chromosomes, IL-33 is regarded as an intracellular transcription repressor. Upon proinflammatory stimulation, it is released as an extracellular cytokine to function as an alarmin to dangerous signals. The IL-33 receptor is a heterodimer complex composed of ST2 and the IL-1 receptor accessory protein, the latter being conserved in other IL-1 family members. The IL-33/ST2 signaling pathway plays critical roles in inflammatory and immune diseases, as well as in central nervous system (CNS) diseases. Recently, there has been an increasing focus on IL-33, particularly on its production and functions in the CNS. The present review mainly focuses on progress in research on IL-33, especially its roles in the CNS.

Keywords: interleukin-33; ST2; signaling; central nervous system

1 Introduction

Interleukin-33 (IL-33), a member of the IL-1 family, has attracted growing interests since being found in 2003. With a DNA-binding domain, IL-33 may act as a transcription repressor[1,2]. When cellular necrosis occurs, IL-33 is released and causes autocrine or paracrine inflammation[3,4]. By interacting with its heteromeric receptor composed of ST2 and the IL-1 receptor accessory protein (IL-1RAcp)[5,6], IL-33 plays roles in inflammation by amplifying T helper 1 (Th1)- or Th2-type immune responses[7-15]. IL-33 has been implicated in the modulation of many diseases[8,9,15-20], including arthritis, asthma, allergy, and cardiovascular and infectious diseases. Also, studies show that it exerts biologic functions via its target cells, including mast cells, basophils, eosinophils, macrophages, natural helper cells, dendritic cells, natural killer T (NKT) cells, and natural killer (NK) cells[7,11,20-23].

Currently, there is increasing focus on the production and function of IL-33 in the central nervous system (CNS), where it is expressed[20] and located in astrocytes[24]. Recently, studies have reported that IL-33 is associated with experimental autoimmune encephalomyelitis (EAE)[20] and Alzheimer's disease (AD)[25]. Therefore, IL-33 may play critical roles in CNS physiopathology and function as a mediator in proinflammatory conditions[24]. In the present review, the development of research on IL-33, especially its role in the CNS, is discussed.

2 IL-33 and its receptor

IL-33 was first found in 2003 and named "nuclear factor from high endothelial venules" for its interaction with nuclear chromatin in an intracrine manner[21]. In 2005, it was recognized as a specific extracellular ligand for ST2,

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and then was renamed IL-33, due to its β-trefoil structure, a conserved structure in IL-1 cytokines at the carboxyl terminus[7], through which IL-33 exerts its cytokine activity[26]. The human IL-33 gene is mapped to chromosome 9p24.1 and encodes a peptide of 270 amino acids. It is reported that full-length IL-$33_{1–270}$ is immature and can be activated by caspase-1 cleavage[7] at Asp178[3], rather than amino acids 112–270[7]. Recently, calpain was also found to mediate the processing of the full-length IL-33 *in vivo*[27]. Moreover, caspase-1-deficient mouse macrophages treated with a calpain inhibitor secrete IL-33 normally[28], indicating that the full-length IL-33 is active. However, the processing and secretion of IL-33 remain to be clarified.

The IL-33 receptor is a heterodimer composed of 2 parts: IL-33-bound ST2 and IL-1RAcp[5,6,29,30,31]. ST2, known as the receptor of IL-33, has 2 major isoforms: a transmembrane form (ST2 or ST2L) and a soluble form (sST2)[32]. ST2 acts as a functional component to induce IL-33 bioactivity. When combined with ST2L and IL-1RAcp, IL-33 exerts its biological activity through the IL-33/ST2 signaling pathway. In contrast, sST2 acts as a decoy receptor for IL-33[8-10].

More recently, IL-33 has been shown to bind with another member of the IL-1R family, the single Ig IL-1R-related molecule (SIGIRR)[33]. This molecule is named "IL-33R2"[34] and seems to be a negative mediator of IL-33[23,33,35,36].

3 IL-33/ST2 signaling

The signaling pathway of IL-33/ST2 is shown in Fig. 1. IL-33 binds with the receptor complex containing ST2 and IL-1RAcp[6] and acts through the Toll/IL-1 receptor domain of IL-1RAcp[5], which is shared by other IL-1 family members such as IL-1R and IL-18R. This causes the recruitment of myeloid differentiation primary-response protein 88 (MyD88), IL-1R-associated kinase 1 (IRAK1) and

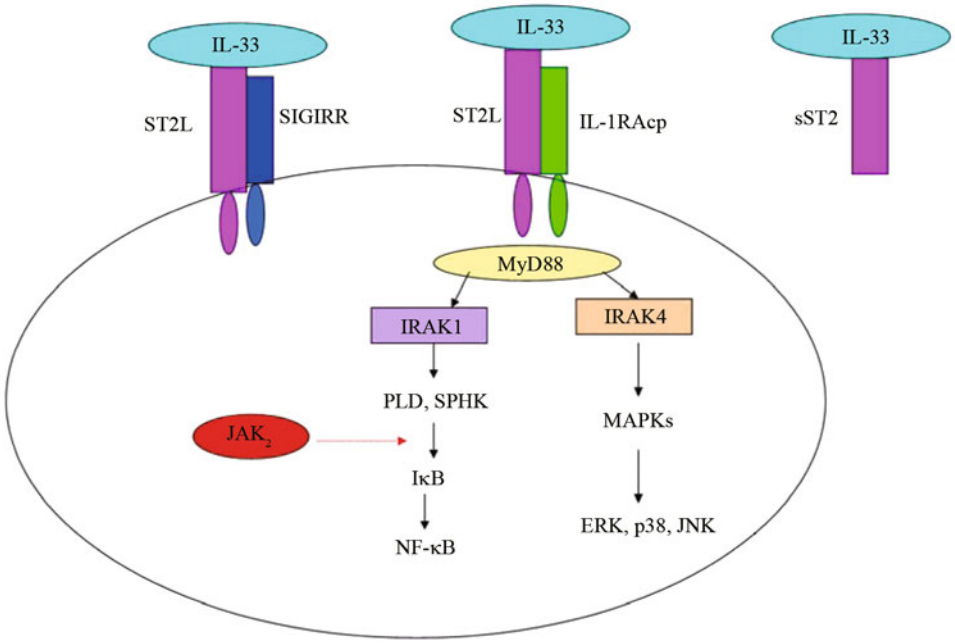

Fig. 1 Interleukin-33(IL-33)/ST2 signaling pathway. IL-33 is the ligand for ST2, which is composed of ST2L and IL-1R accessory protein (IL-1RAcp). The interaction of IL-33 with ST2 leads to the recruitment of the myeloid differentiation primary-response protein 88 (MyD88), IL-1R-associated kinase 1 (IRAK1) and IRAK4 to the receptor complex, which in turn results in the activation of NF-κB and mitogen-activated protein kinases (MAPKs). Contrast to ST2L, soluble ST2 (sST2) plays as a decoy receptor for IL-33. IL-33 can also combine with another receptor composed by ST2L and single Ig IL-1R-related molecule (SIGIRR), which seems as a negative mediator for IL-33. PLD: phospholipase D; SPHK: sphingosine kinase; ERK: extracellular signal-regulated kinase; JNK: JUN N-terminal kinase.

IRAK4 to the receptor complex[7]. Subsequently, transcription factors such as nuclear factor-κB (NF-κB) and mitogen-activated protein kinases (MAPKs) are activated[7,23].

In addition, Janus kinase 2 (JAK2) is a critical signal transducer in the NF-κB activation induced by IL-33[37]. JAK2 is activated rapidly and is also involved in IL-33-induced IκBα degradation. Furthermore, when JAK2 is inhibited or reduced, this signaling pathway is effectively inhibited, while the activation of ERK, JNK and p38 MAPK is unaffected[37].

4 Target cells and functions

4.1 Target cells Constitutively, IL-33 is expressed in the stomach, lung, skin, lymph nodes, spleen, pancreas, kidney, heart, and brain[7]. It is expressed by endothelial[2,7,21,38], epithelial[1] and smooth muscle cells[6,22]. IL-33 is also induced in activated macrophages[7], fibroblasts and keratinocytes stimulated by tumor necrosis factor-α (TNF-α) and IL-1β[7], in astrocytes exposed to lipopolysaccharide (LPS) and adenosine triphosphate[20], and in adipocytes stimulated by TNF-α[23]. It is reported that IL-33 amplifies both Th1- and Th2-type responses by acting on human basophils, allergen-reactive Th2 cells, NKT and NK cells[11]. As in basophils, eosinophil adhesion is enhanced by IL-33[39]. Besides, the degranulation of mast cells sensitized by free IgE is directly activated by IL-33[22].

In the CNS, IL-33 and ST2 are also expressed by various cells[7,40]. A feedback loop has been suggested, in which glia are stimulated by the toll-like receptor to release IL-33[20], while IL-33 in turn induces the secretion of proinflammatory factors by glia.

4.2 Functions When tissues are injured during trauma or infection, necrotic cells release endogenous proinflammatory factors termed "damage-associated molecular patterns" (DAMPs or alarmin), which promote immune responses and induce local or systemic inflammation. IL-33 is suggested as a DAMP molecule and a crucial amplifier of innate immunity[10]. Similar to the high-mobility group box 1 (HMGB1) protein which is known as a DAMP, IL-33 may also act as a transcription repressor by combining with the H2A-H2B dimer at the nucleosomal surface[1,41]. Like its secretion and processing, the functions of IL-33 need to be clarified.

IL-33 exerts its functions via its target cells and plays different roles in diseases. IL-33 exacerbates antigen-induced arthritis by acting on mast cells[15]. Administration of IL-33 exacerbates experimental asthma and induces features of asthma in animal models[10,42,43]. The levels of IL-33 expression are substantially increased in the blood of patients during anaphylactic shock and in the inflamed skin of patients with atopic dermatitis[22]. In contrast, IL-33 plays protective roles in other diseases. For instance, atherosclerosis in mice with cardiovascular disease is attenuated by IL-33 and exacerbated by sST2[12].

5 Roles of IL-33 in the CNS

5.1 IL-33 expression in the CNS IL-33 is expressed at high levels in the spinal cord and brain[7]. A recent study[24] showed that both mRNA and protein of IL-33 are expressed by brain endothelial cells and astrocytes but not by cortical neurons or microglia. Astrocytes, the non-hematopoietic epithelial-like cells in the CNS, are known to express the whole IL-33 receptor (ST2L and IL-1RAcp)[5,7,20,24,44]. Similar to astrocytes, microglia, the macrophage-like cells in the CNS, also express both components of the IL-33 receptor[24], suggesting that astrocytes and microglia may be the primary responders to IL-33. ST2 has been found not only in T cells especially Th2 cells[8,45], but also in the brain[46]. ST2L and sST2 are both expressed in astrocytes and microglia, while in brain endothelial cells, only sST2 is expressed[24]. Another study has demonstrated that ST2 is expressed in astrocytes but not in neurons or microglia[44]. Unlike ST2, IL-1RAcp is expressed not only by endothelial cells in the CNS, but also by neurons, astrocytes and microglia[24].

Studies have shown that LPS and double-stranded RNA enhance IL-33 mRNA expression in astrocytes[20, 24], but they induce no change in endothelial cells[24]. Microglia treated with IL-33 proliferate significantly and release proinflammatory cytokines and chemokines such as IL-1β, TNF-α and chemokine (C-C motif) ligand 2[24]. Besides, remarkable enhancement of microglial phagocytosis

occurs[24].

5.2 IL-33 and AD Recently, it was reported that a polymorphism of the IL-33 gene is associated with the risk of AD[25]. IL-33 production is decreased in the brains of AD patients, and *in vitro* overexpression of IL-33 reduces β-amyloid peptide secretion. Hence, the IL-33 gene is recognized as a candidate gene for AD[25]. Another clinical report showed that genetic variants of IL-33 affect the susceptibility to late onset AD in a Han Chinese population[47]. Interestingly, IL-33 activates microglia and up-regulates their phagocytosis[24]. Since microglia phagocytose β-amyloid peptide in AD[48], this finding implies that IL-33 may have a neuroprotective effect in AD by reducing β-amyloid peptide secretion and activating microglia to increase its phagocytosis.

5.3 IL-33 and EAE In mice with EAE, increases in astrocytes in the spinal cord have been detected, and most express IL-33 in inflammatory lesions[24]. IL-33 mRNA expression can be induced by viral infection in the CNS, indicating that IL-33 may also participate in host defense[20]. These findings suggest that IL-33 may be neurotoxic in EAE.

5.4 IL-33 and subarachnoid hemorrhage IL-33 is also implicated in subarachnoid hemorrhage. ST2 expression is increased in cells in the cerebrospinal fluid from patients with subarachnoid hemorrhage, suggesting that ST2 may be related to the CNS inflammatory responses that follow this event[49]. The Dvs27 gene, which is highly active after experimental subarachnoid hemorrhage[50], encodes IL-33, hinting that IL-33 plays a pathogenic role in hypoxic and vascular damage in the CNS.

5.5 IL-33 and inflammatory pain IL-33 mRNA and protein are detected in the joints of mice with collagen-induced arthritis (CIA) and increase during the early phase of the disease[13]. In CIA mice, spinal astrocytes begin to increase on the 10th day after the onset of arthritis[51]. In addition, IL-33, like other IL-1 cytokines, induces inflammatory pain in the peripheral nervous system and mediates antigen-induced cutaneous and articular hypernociception in mice via the IL-33→TNF-α→IL-1β→IFN-γ→ET-1→PGE2 signaling cascade[13], suggesting a pivotal role for IL-33 in arthritic pain.

6 Conclusion

The cytokine IL-33 has attracted increasing attention since its identification, especially concerning its roles in inflammatory diseases, allergies and cardiovascular diseases. Currently, the main expression of IL-33 in the CNS and its relation with some CNS diseases, such as AD, EAE and inflammatory pain, are known. However, many questions remain unclear, including the exact means of secretion and processing of IL-33 in the CNS *in vivo*, as well as the molecular mechanism underlying the mediatory roles of IL-33 in CNS diseases. Furthermore, whether IL-33 is involved in other CNS diseases, such as Parkinson's disease, epilepsy and Huntington's disease, remains to be further investigated. Previous studies imply that IL-33 is a proinflammatory mediator by activating microglia and inducing inflammatory cytokines and chemokines, having neuroprotective or neurotoxic effects depending on the tissue conditions. Investigations on IL-33 will shed light on the pathogenesis of CNS diseases and provide critical clues for seeking new targets of clinical drug development.

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IL-33 及其在中枢神经系统中作用的研究进展

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摘要：白介素-33(interleukin-33, IL-33)是IL-1家族的新成员，在多种细胞和组织中表达。IL-33能与常染色体结合，因此被认为具有抑制核内转录的作用。当受到炎性刺激时，IL-33可作为危险信号的警报释放到细胞外发挥细胞因子的作用。IL-33的受体是由ST2和IL-1受体结合蛋白组成的异物二聚体，其中IL-1受体结合蛋白是所有白介素家族受体共有的部分。IL-33/ST2信号通路通过调节细胞因子的生成，不仅对炎症、免疫性疾病发挥关键作用，还参与了许多其他疾病如中枢神经系统疾病。近年来有关IL-33尤其是它在中枢神经系统中表达及功能的研究不断增多，本文对IL-33及其在中枢神经系统中的作用进行了综述。

关键词：白介素-33；ST2；信号转导；中枢神经系统