Neurosci Bull October 1, 2011, 27(5): 351–357. http://www.neurosci.cn
DOI: 10.1007/s12264-011-1025-5

·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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Article ID: 1673-7067(2011)05-0351-07
Received date: 2011-05-30; Accepted date: 2011-07-06

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

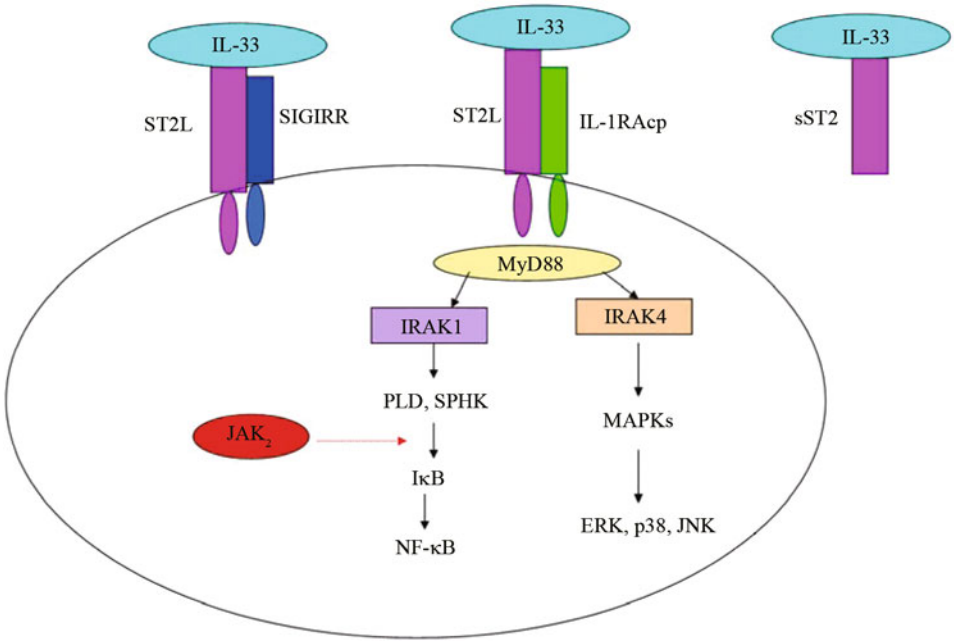

Fig. 1 Interleukin-33(IL-33)/ST2 signaling pathway. IL-33 is the ligand for ST2, which is composed of ST2L and IL-1R accessory protein (IL-1RAcp). The interaction of IL-33 with ST2 leads to the recruitment of the myeloid differentiation primary-response protein 88 (MyD88), IL-1R-associated kinase 1 (IRAK1) 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.

Acknowledgements: This work was supported by the National Natural Science Foundation of China (No. 31000495, 30970975, 30821002), Research Fund for the Doctoral Program of Higher Education of China (No. 20100071120046, 20100071120042) and the Fundamental Research Funds for the Central Universities and Young Scientist Foundation of Fudan University, China.

References:

[1] Carriere V, Roussel L, Ortega N, Lacorre DA, Americh L, Aguilar L, *et al*. IL-33, the IL-1-like cytokine ligand for ST2 receptor, is a chromatin-associated nuclear factor *in vivo*. Proc Natl Acad Sci U S A 2007, 104(1): 282–287.

[2] Moussion C, Ortega N, Girard JP. The IL-1-like cytokine IL-33 is constitutively expressed in the nucleus of endothelial cells and epithelial cells *in vivo*: a novel 'alarmin'? PLoS One 2008, 3(10): e3331.

[3] Cayrol C, Girard JP. The IL-1-like cytokine IL-33 is inactivated

after maturation by caspase-1. Proc Natl Acad Sci U S A 2009, 106(22): 9021–9026.

[4] Lüthi AU, Cullen SP, McNeela EA, Duriez PJ, Afonina IS, Sheridan C, *et al*. Suppression of interleukin-33 bioactivity through proteolysis by apoptotic caspases. Immunity 2009, 31(1): 84–98.

[5] Ali S, Huber M, Kollewe C, Bischoff SC, Falk W, Martin MU. IL-1 receptor accessory protein is essential for IL-33-induced activation of T lymphocytes and mast cells. Proc Natl Acad Sci U S A 2007, 104(47): 18660–18665.

[6] Chackerian AA, Oldham ER, Murphy EE, Schmitz J, Pflanz S, Kastelein RA. IL-1 receptor accessory protein and ST2 comprise the IL-33 receptor complex. J Immunol 2007, 179(4): 2551–2555.

[7] Schmitz J, Owyang A, Oldham E, Song Y, Murphy E, McClanahan TK, *et al*. IL-33, an interleukin-1-like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines. Immunity 2005, 23(5): 479–490.

[8] Xu D, Chan WL, Leung BP, Huang F, Wheeler R, Piedrafita D, *et al*. Selective expression of a stable cell surface molecule on type 2 but not type 1 helper T cells. J Exp Med 1998, 187(5): 787–794.

[9] Sanada S, Hakuno D, Higgins LJ, Schreiter ER, McKenzie AN, Lee RT. IL-33 and ST2 comprise a critical biomechanically induced and cardioprotective signaling system. J Clin Invest 2007, 117(6): 1538–1549.

[10] Kurowska-Stolarska, Kewin MP, Murphy G, Russo RC, Stolarski B, Garcia CC, *et al*. IL-33 induces antigen-specific IL-5$^+$ T cells and promotes allergic-induced airway inflammation independent of IL-4. J Immunol 2008, 181(7): 4780–4790.

[11] Smithgall MD, Comeau MR, Yoon BR, Kaufman D, Armitage R, Smith DE. IL-33 amplifies both Th1- and Th2-type responses through its activity on human basophils, allergen-reactive Th2 cells, iNKT and NK cells. Int Immunol 2008, 20(8): 1019–1030.

[12] Miller AM, Xu D, Asquith DL, Denby L, Li Y, Sattar N, *et al*. IL-33 reduces the development of atherosclerosis. J Exp Med 2008, 205(2): 339–346.

[13] Verri WA Jr, Guerrero AT, Fukada SY, Valerio DA, Cunha TM, Xu D, *et al*. IL-33 mediates antigen-induced cutaneous and articular hypernociception in mice. Proc Natl Acad Sci U S A 2008, 105(7): 2723–2728.

[14] Leung BP, Xu D, Culshaw S, McInnes IB, Liew FY. A novel therapy of murine collagen-induced arthritis with soluble T1/ST2. J Immunol 2004, 173(1): 145–150.

[15] Xu D, Jiang HR, Kewin P, Li Y, Mu R, Fraser AR, *et al*. IL-33 exacerbates antigen-induced arthritis by activating mast cells. Proc Natl Acad Sci U S A 2008, 105(31): 10913–10918.

[16] Humphreys NE, Xu D, Hepworth MR, Liew FY, Grencis RK. IL-33–a potent inducer of adaptive immunity to intestinal nematodes. J Immunol 2008, 180(4): 2443–2449.

[17] Walzl G, Matthews S, Kendall S, Gutierrez-Ramos JC, Coyle AJ, Openshaw PJ, *et al.* Inhibition of T1/ST2 during respiratory syncytial virus infection prevents T helper cell type 2 (Th2)- but not Th1-driven immunopathology. J Exp Med 2001, 193(7): 785–792.

[18] Préfontaine D, Lajoie-Kadoch S, Foley S, Audusseau S, Olivenstein R, Halayko AJ, *et al.* Increased expression of IL-33 in severe asthma: evidence of expression by airway smooth muscle cells. J Immunol 2009, 183(8): 5094–5103.

[19] Weinberg EO, Shimpo M, Hurwitz S, Tominaga S, Rouleau JL, Lee RT. Identification of serum soluble ST2 receptor as a novel heart failure biomarker. Circulation 2003, 107(5): 721–726.

[20] Hudson CA, Christophi GP, Gruber RC, Wilmore JR, Lawrence DA, Massa PT. Induction of IL-33 expression and activity in central nervous system glia. J Leukoc Biol 2008, 84(3): 631–643.

[21] Baekkevold ES, Roussigné M, Yamanaka T, Johansen FE, Jahnsen FL, Amalric F, *et al*. Molecular characterization of NF-HEV, a nuclear factor preferentially expressed in human high endothelial venules. Am J Pathol 2003, 163(1): 69–79.

[22] Pushparaj PN, Tay HK, H'ng SC, Pitman N, Xu D, McKenzie A, *et al.* The cytokine interleukin-33 mediates anaphylactic shock. Proc Natl Acad Sci U S A 2009, 106(24): 9773–9778.

[23] Palmer G, Talabot-Ayer D, Lamacchia C, Toy D, Seemayer CA, Viatte S, *et al*. Inhibition of interleukin-33 signaling attenuates the severity of experimental arthritis. Arthritis Rheum 2009, 60(3): 738–749.

[24] Yasuoka S, Kawanokuchi J, Parajuli B, Jin S, Doi Y, Noda M, *et al*. Production and functions of IL-33 in the central nervous system. Brain Res 2011, 1385: 8–17.

[25] Chapuis J, Hot D, Hansmannel F, Kerdraon O, Ferreira S, Hubans C, *et al*. Transcriptomic and genetic studies identify IL-33 as a candidate gene for Alzheimer's disease. Mol Psychiatry 2009, 14(11): 1004–1016.

[26] Smith DE. IL-33: a tissue derived cytokine pathway involved in allergic inflammation and asthma. Clin Exp Allergy 2010, 40(2): 200–208.

[27] Hayakawa M, Hayakawa H, Matsuyama Y, Tamemoto H, Okazaki H, Tominaga S. Mature interleukin-33 is produced by calpain-mediated cleavage *in vivo*. Biochem Biophys Res Commun 2009, 387(1): 218–222.

[28] Ohno T, Oboki K, Kajiwara N, Morii E, Aozasa K, Flavell RA, *et al.* Caspase-1, caspase-8, and calpain are dispensable for IL-33 release by macrophages. J Immunol 2009, 183(12): 7890–7897.

[29] Towne JE, Garka KE, Renshaw BR, Virca GD, Sims JE. Interleukin (IL)-1F6, IL-1F8, and IL-1F9 signal through IL-1Rrp2 and IL-1RAcP to activate the pathway leading to NF-kappaB and MAPKs. J Biol Chem 2004, 279(14): 13677–13688.

[30] Palmer G, Lipsky BP, Smithgall MD, Meininger D, Siu S, Talabot-Ayer D, *et al*. The IL-1 receptor accessory protein (AcP) is required for IL-33 signaling and soluble AcP enhances the ability of soluble

ST2 to inhibit IL-33. Cytokine 2008, 42(3): 358–364.

[31] Cullinan EB, Kwee L, Nunes P, Shuster DJ, Ju G, McIntyre KW, *et al*. IL-1 receptor accessory protein is an essential component of the IL-1 receptor. J Immunol 1998, 161(10): 5614–5620.

[32] Iwahana H, Yanagisawa K, Ito-Kosaka A, Kuroiwa K, Tago K, Komatsu N, *et al.* Different promoter usage and multiple transcription initiation sites of the interleukin-1 receptor-related human ST2 gene in UT-7 and TM12 cells. Eur J Biochem 1999, 264(2): 397–406.

[33] Bulek K, Swaidani S, Qin J, Lu Y, Gulen MF, Herjan T, *et al*. The essential role of single Ig IL-1 receptor-related molecule/Toll IL-1R8 in regulation of Th2 immune response. J Immunol 2009, 182(5): 2601–2609.

[34] Oboki K, Ohno T, Kajiwara N, Saito H, Nakae S. IL-33 and IL-33 receptors in host defense and diseases. Allergol Int 2010, 59(2): 143–160.

[35] Garlanda C, Anders HJ, Mantovani A. TIR8/SIGIRR: an IL-1R/TLR family member with regulatory functions in inflammation and T cell polarization. Trends Immunol 2009, 30(9): 439–446.

[36] Garlanda C, Riva F, Polentarutti N, Buracchi C, Sironi M, De Bortoli M, *et al*. Intestinal inflammation in mice deficient in Tir8, an inhibitory member of the IL-1 receptor family. Proc Natl Acad Sci U S A 2004, 101(10): 3522–3526.

[37] Funakoshi-Tago M, Tago K, Sato Y, Tominaga S, Kasahara T. JAK2 is an important signal transducer in IL-33-induced NF-κB activation. Cell Signal 2011, 23(2): 363–370.

[38] Küchler AM, Pollheimer J, Balogh J, Sponheim J, Manley L, Sorensen DR, *et al*. Nuclear interleukin-33 is generally expressed in resting endothelium but rapidly lost upon angiogenic or proinflammatory activation. Am J Pathol 2008, 173(4): 1229–1242.

[39] Suzukawa M, Koketsu R, Iikura M, Nakae S, Matsumoto K, Nagase H, *et al*. Interleukin-33 enhances adhesion, CD11b expression and survival in human eosinophils. Lab Invest 2008, 88(11): 1245–1253.

[40] Haga Y, Yanagisawa K, Ohto-Ozaki H, Tominaga S, Masuzawa T, Iwahana H. The effect of ST2 gene product on anchorage-independent growth of a glioblastoma cell line, T98G. Eur J Biochem 2003, 270(1): 163–170.

[41] Roussel L, Erard M, Cayrol C, Girard JP. Molecular mimicry between IL-33 and KSHV for attachment to chromatin through the H2A-H2B acidic pocket. EMBO Rep 2008, 9(10): 1006–1012.

[42] Kondo Y, Yoshimoto T, Yasuda K, Futatsugi-Yumikura S, Morimoto M, Hayashi N, *et al*. Administration of IL-33 induces airway hyperresponsiveness and goblet cell hyperplasia in the lungs in the absence of adaptive immune system. Int Immunol 2008, 20(6): 791–800.

[43] Kurowska-Stolarska M, Stolarski B, Kewin P, Murphy G, Corrigan CJ, Ying S, *et al*. IL-33 amplifies the polarization of alternatively activated macrophages that contribute to airway inflammation. J Immunol 2009, 183(10): 6469–6477.

[44] Andre R, Lerouet D, Kimber I, Pinteaux E, Rothwell NJ. Regulation of expression of the novel IL-1 receptor family members in the mouse brain. J Neurochem 2005, 95(2): 324–330.

[45] Löhning M, Stroehmann A, Coyle AJ, Grogan JL, Lin S, Gutierrez-Ramos JC, *et al*. T1/ST2 is preferentially expressed on murine Th2 cells, independent of interleukin 4, interleukin 5, and interleukin 10, and important for Th2 effector function. Proc Natl Acad Sci U S A 1998, 95(12): 6930–6935.

[46] Kumar S, Tzimas MN, Griswold DE, Young PR. Expression of ST2, an interleukin-1 receptor homologue, is induced by proinflammatory stimuli. Biochem Biophys Res Commun 1997, 235(3): 474–478.

[47] Yu JT, Song JH, Wang ND, Wu ZC, Zhang Q, Zhang N, *et al*. Implication of IL-33 gene polymorphism in Chinese patients with Alzheimer's disease. Neurobiol Aging 2010. [Epub ahead of print]

[48] Lee CY, Landreth GE. The role of microglia in amyloid clearance from the AD brain. J Neural Transm 2010, 117(8): 949–960.

[49] Kanda M, Ohto-Ozaki H, Kuroiwa K, Tominaga S, Watanabe E, Iwahana H. Elevation of ST2 protein levels in cerebrospinal fluid following subarachnoid hemorrhage. Acta Neurol Scand 2006, 113(5): 327–333.

[50] Onda H, Kasuya H, Takakura K, Hori T, Imaizumi T, Takeuchi T, *et al*. Identification of genes differentially expressed in canine vasospastic cerebral arteries after subarachnoid hemorrhage. J Cereb Blood Flow Metab 1999, 19(11): 1279–1288.

[51] Inglis JJ, Notley CA, Essex D, Wilson AW, Feldmann M, Anand P, *et al.* Collagen-induced arthritis as a model of hyperalgesia: functional and cellular analysis of the analgesic actions of tumor necrosis factor blockade. Arthritis Rheum 2007, 56(12): 4015–4023.

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