IL-33: A Cytokine that Acts as an Alarm Signal in Innate Immune Responses

Gao Jianhua, Cao Hua, Wang Chuan, Fang Yihu

Department of Basic Medicine, Jiangxi Medical College, Jiangxi Shangrao, 334000, China

Keywords: IL-33; cytokine; ST2 receptor; Immunological reaction

Abstract: Interleukin-33 (IL-33) is a member of the interleukin-1 family (IL-1F), which is constitutively expressed in normal tissues and rapidly released under cell injury or stress, acting as a alarm signal.IL-33 binds to the IL-1 family orphan receptor T1/ST2, this complex and the IL-1 receptor accessory protein IL-1RAcP act as co-receptors to mediate signaling through the NF-κB and MAPK pathways, and plays an important role in the innate immunity. IL-33 is a bifunctional protein that acts as a pro-inflammatory cytokine and a cellular nuclear factor with transcriptional regulatory properties. The IL-33 gene is located on the short arm 9p24.1 of chromosome 9, and contains eight exons, which are more than 42 kb in length and can produce two transcripts IL-33a and IL-33b mRNA, but they encode the same protein. The propeptide product contains two cleavage sites, which can be regulated by enzymatic hydrolysis. After apoptosis, caspase inactivates IL-33, whereas in the pathological (necrotic) cell death process, the IL-33 activity is greatly enhanced by inflammatory protease hydrolysis to rapidly activate the immune system to protect body tissues.

1. Introduction

Interleukin-33 (IL-33), also known as IL-1F11, belongs to the interleukin-1 family (IL-1F) according to the structural homology of cytokines. It is usually released by damaged or necrotic barrier cells (endothelial cells and epithelial cells) and serves as a warning signal [1]. IL-33 is similar to IL-1 and IL-18 in cytokine source mechanism, receptor structure and signal transduction pathway. Like IL-1 beta and IL-18, IL-33 first produces a full-length 30 kDa propeptide product, which is cut by cysteine protease to produce 18 kDa mature IL-33 with higher activity under pathological conditions such as tissue damage. Its precursor has been described as nuclear factor-high endothelial microvenous (NF-HEV) nuclear protein, encapsulating the protein. A nuclear localization sequence (NLS) and a helix-corner-helix DNA binding domain similar to the homologous domain bind to chromatin through the interaction of histone H2A-H2B. Nuclear localization is the basic characteristic of IL-33 and is essential for the regulation of cytokine activity. IL-33 is a bifunctional protein that acts as a pro-inflammatory cytokine and a cellular nuclear factor with transcriptional regulatory properties. The precursor also exerts unique biological activity independent of caspase cleavage and cell surface receptor binding [2]. IL-33 binds to the IL-1 family orphan receptor T1/ST2 and stimulates helper T cell 2 (Th2) and mast cell responses, plays an important role in innate and adaptive immunity, contributes to tissue homeostasis and to the environment. The pressure response, T1/ST2 receptor is highly expressed on Th2 lymphocytes, mast cells and epithelial cells, and therefore can also be used as a selective marker for these cells.

2. Gene and expression profile of IL-33

IL-33 gene is located on chromosome 9 short arm 9p24.1. It contains eight exons with a length of more than 42 kb. The single nucleotide polymorphism sequence associated with asthma susceptibility is located in intron 1 region (Figure 1). It can produce two transcripts, IL-33a and IL-33b, but they encode the same protein. The propeptide products contain two evolutionary conserved structures: nuclear domain and IL-1-like cytokine domain. The two conserved domains are the cleavage sites of cystatin and inflammatory protease, and are separated by the central domains [3].

  DOI: 10.25236/ibmc.2019.014

The length of human IL33 is 2.7 kb, encoding 270 residues, corresponding to the full-length protein of 30 kDa. Phylogenetic analysis showed that IL-33 protein in mammals was evolutionarily conserved, and human and mouse IL-33 had 52% identity at the amino acid level. Analysis of cDNA libraries by RTqPCR revealed that IL-33 mRNA is widely expressed in many tissues, and smooth muscle cells (SMC) and bronchial epithelial cells of various tissues of human tissues show constitutive expression of IL-33 mRNA in primary lung or dermis. In fibroblasts and keratinocytes, IL-33 gene expression can also be induced by activation with TNF-α and IL-1β. Similarly, high levels of IL- can be found in the stomach, lung, spinal cord, brain and skin of mice. 33 mRNA [4].

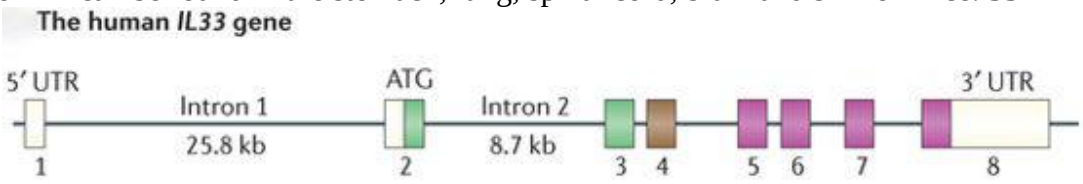

Figure 1 Human IL-33 gene structure map

3. IL-33 receptor complex

Identification of the binding sites of two receptors ST2 in IL-33 (Figure 2), identification of acidic residues Glu148 and Asp149 at position 1, and formation of specific salt bridges with basic residues of ST2 Role, site 2 Glu165 residues play a key role in high affinity binding. IL-33 binds to orphan IL-1 receptor ST2, and this complex and IL-1 receptor accessory protein IL-1RAcP act as co-receptors to mediate signaling through NF-κB and MAPK pathways, IRAK, IRAK4, MyD88 The recruitment of TRAF6 to ST2 ultimately led to activation of NF-κB and MAP kinase [4, 5] (Figure 3).

ST2 is a member of the IL-1 receptor family with transmembrane (ST2L) and soluble (sST2) isoforms, both of which have the same sequence in the extracellular region, except that sST2 has 9 amino acids at the C-terminus. Soluble ST2 (sST2) is an antagonistic receptor of IL-33. It can act as an inhibitor of IL-33 by binding to IL-33 in cell microenvironment. Soluble IL-1 RAcP can enhance the inhibition of sST2. The elevated serum sST2 concentration in patients with various diseases associated with abnormal Th2 response (including systemic lupus erythematosus and asthma) also indicates the inhibitory effect of receptor sST2 on IL-33. In mice, L-33 can induce the expression of IL-4, IL-5 and IL-13, and lead to severe pathological changes of lung and digestive tract. It further proves that IL-33 can be used as Th2 cells in vitro and in vivo [6].

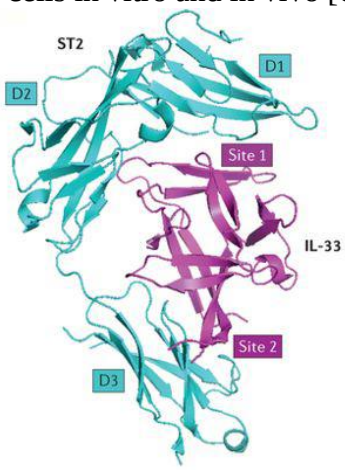

Figure 2 IL-33 binding site to ST2

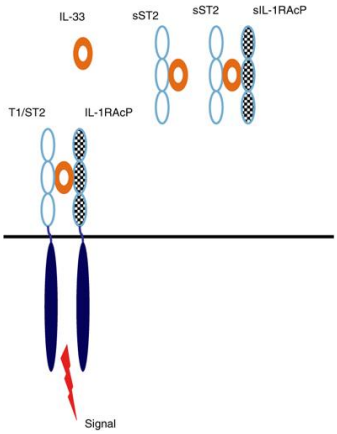

Figure 3 the binding mode of IL-33 and ST2/sST2

4. Regulation of IL-33 Secretion and Activity

The constitutive expression of IL-33 in normal tissues can be released at any time as a tissue-derived nuclear alarm. To "warn" ILC2 and other immune cells, IL-33 does not contain signal sequence, so it is not secreted like conventional cytokines. After tissue damage and cell death (or cell stress), such as exposure to allergens, viruses or parasites, IL-33 is fully bioactive. It is released outside the cell as an endogenous danger signal or a nuclear alarm to alert the immune system of damaged tissue. After release, IL-33 responds by activating various types of immune cells, including mast cells and ILC2, which secrete large amounts of IL-5 and IL-13. Studies have shown that IL-33 is in the process of damage to the central nervous system (CNS). Rapid release of damaged oligodendrocytes in the cerebrospinal fluid, promoting immune cell recruitment and tissue repair, and after programmed cell death (apoptosis), caspase inactivates IL-33 to avoid excessive immune system Reaction [7]

Although full-length IL-33 is active, IL-33 cytokine activity can be increased or inhibited in vivo by proteolytic hydrolysis. IL-33 contains a caspase-binding motif and a cleavage site for caspase and inflammatory proteases, which can be processed into shorter "more active" mature forms by inflammatory proteases (Cathepsin G, elastase). Neutrophil serine proteases, cathepsin G and elastase have been found to process full-length IL-33 into mature forms containing IL-1 like cytokine domains (IL-3395-270, IL-3399-270 and IL- 33109-270), the biological activity is greatly increased (1 to 10 times) compared with the full-length protein [8]. At the same time, IL-33 contains the common site of cystatin-3 cleavage, which can hydrolyze to produce two kinds of inactive products in the process of apoptosis, so as to avoid activating the immune system after the death of physiologically programmed (apoptotic) cells. On the contrary, in the process of pathological (necrotic) cell death, IL-33 activity is greatly increased by hydrolysis of inflammatory proteinase in vivo to activate the immune system to protect organism tissues [9].

5. The important role of IL-33 in innate immunity, inflammation and allergy

IL-33 acts as an "alarm" signal in innate immunity, inflammation and allergic reactions, and initiates myeloid differentiation factor 88 (MyD88) dependence by binding to the ST2 / IL-1RAcP receptor complex expressed in target cells. The signaling pathway activates innate lymphoid cells ILC2s, mast cells, basophils, eosinophils, Th2 cells, and NK cells to participate in immune responses [10]. In a mouse experiment, IL-33 rapidly proliferated and produced a large amount of IL-13 in mice infected with worms, resulting in goblet cell proliferation and worm excretion in the intestine, while IL-33 deficient mice failed. Clear the worm [11]. Infection with nematodes or intranasal chitin experiments also confirmed that endogenous IL-33 is important for pulmonary eosinophilic inflammation and IL-5 production by ILC2s [12]. IL-33 also participates in the body's response to virus infection. After influenza virus infection, IL-33/ST2 can activate lung ILC2 independently of adaptive immune mediated signal transduction to restore the integrity of

respiratory epithelial cells. In addition, parainfluenza virus infection of IL-33 deficient mice also leads to excessive mucus production and chronic lung disease [13].

Recent studies have shown that the response of ILC2s to IL-33 is controlled by transcription factor-dependent growth factor GFI1 expressed by its surface receptor ST2 [14]. Although ILC2 does not express antigen receptors, it can recognize IL-33 secreted by infected tissues and produce anti-infective effects, which can be used to induce allergic inflammation shortly after exposure to allergens or parasites or viruses. The key role of endogenous IL-33 in allergic inflammation was confirmed by the use of IL-33 deficient mice. IL-33 is also a potent stimulator of skin ILC2, a reduction in skin inflammation in a mouse model lacking IL-33 signaling, and the presence of ILC2s in nasal polyps in patients with chronic sinusitis and in skin lesions of patients with atopic dermatitis. Encoding IL-33 and ST2/IL1RL1 in several genome-wide association studies of thousands of patients of different races and forms of asthma (associated with blood eosinophils, early childhood asthma with severe acute attacks, etc.) The gene has been identified as a major susceptibility locus for human asthma, and the potent activity of IL-33 on ILC2s and the critical role these cells play in causing allergic airway inflammation may explain the IL-33/ST2 pathway in human asthma [15].

6. Conclusion

IL-33 is a nuclear cytokine from the IL-1 family, originally described as NF-HEV, constitutively expressed in various tissues such as barrier tissues and lymphoid organs, and is cell-derived under cell damage or cellular stress. A rapid release alarm (alarm signal) that acts to activate NF-κB and MAPK kinase by binding to its specific major receptor ST2 and the co-receptor IL-1 receptor helper protein (IL-1RAcP), polarized T Cells produce TH2-associated cytokines that induce the production of IL-4, IL-5 and IL-13, with pleiotropic activity in host defenses and innate and adaptive immune responses in disease. Although these important advances have been made since it was identified and named in 2005, many problems remain to be solved. A better understanding of the release, mode of action and regulation of IL-33 has important guiding significance for the development of therapies for asthma and other inflammatory diseases through IL-33/ST2 pathway.

Acknowledgement

Funded by the Natural Science Foundation of Jiangxi Province Project No.: 20161BAB205281.

References

[1] Cayrol C, Girard J P.IL-33: an alarmin cytokine with crucial roles in innate immunity, inflammation and allergy [J].Current opinion in immunology, 2014, 31:31-37.

[2] Carriere V, Roussel L, Ortega N, et al.IL-33, the IL-1-like cytokine ligand for ST2 receptor, is a chromatin-associated nuclear factor in vivo [J].Proceedings of the National Academy of Sciences, 2007, 104(1): 282-287.

[3] Talabot‐Ayer D,Calo N,Vigne S,et al.The mouse interleukin (Il) 33 gene is expressed in a cell type‐and stimulus‐dependent manner from two alternative promoters [J].Journal of leukocyte biology,2012, 91(1):119-125.

[4] Liew F Y, Girard J P, Turnquist H R. Interleukin-33 in health and disease [J].Nature Reviews Immunology, 2016, 16(11):676-689.

[5] Schmitz J, Owyang A, Oldham E, 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 [J].Immunity, 2005,23(5):479-490.

[6] Hayakawa H, Hayakawa M, Kume A, et al. Soluble ST2 blocks interleukin-33 signaling in allergic airway inflammation [J].Journal of Biological Chemistry,2007,282(36):26369-26380.

[7] Gadani S P,Walsh J T, Smirnov I, et al.The glia-derived alarmin IL-33 orchestrates the immune response and promotes recovery following CNS injury [J].Neuron,2015,85(4):703-709.

[8] Lefrançais E, Roga S, Gautier V, et al.IL-33 is processed into mature bioactive forms by neutrophil elastase and cathepsin G [J].Proceedings of the National Academy of Sciences, 2012, 109(5):1673-1678.

[9] Lüthi A U, Cullen S P, McNeela E A, et al. Suppression of interleukin-33 bioactivity through proteolysis by apoptotic caspases[J].Immunity,2009,31(1):84-98.

[10] Garlanda C, Dinarello C A, Mantovani A. The interleukin-1 family: back to the future [J]. Immunity, 2013, 39(6):1003-1018.

[11] Price A E, Liang H E, Sullivan B M, et al. Systemically dispersed innate IL-13–expressing cells in type 2 immunity [J]. Proceedings of the National Academy of Sciences, 2010, 107(25):11489-11494.

[12] Van Dyken S J, Mohapatra A, Nussbaum J C, et al. Chitin activates parallel immune modules that direct distinct inflammatory responses via innate lymphoid type 2 andγδT cells [J].Immunity, 2014,40(3):414-424.

[13] Byers D E, Alexander-Brett J, Patel A C, et al. Long-term IL-33–producing epithelial progenitor cells in chronic obstructive lung disease [J].The Journal of clinical investigation, 2013, 123(9):3967-3982.

[14] Spooner C J, Lesch J, Yan D, et al. Specification of type 2 innate lymphocytes by the transcriptional determinant Gfi1[J].Nature immunology,2013,14(12):1229－1236.

[15] Bønnelykke K, Sleiman P, Nielsen K, et al. A genome-wide association study identifies CDHR3 as a susceptibility locus for early childhood asthma with severe exacerbations [J].Nature genetics, 2014, 46(1):51－55.