Immunol Res (2012) 52:89–99
DOI 10.1007/s12026-012-8283-9

IMMUNOLOGY IN SERBIA

IL-33/ST2 axis in inflammation and immunopathology

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Published online: 6 March 2012

Abstract Interleukin-33 (IL-33), a member of the IL-1 family of cytokines, binds to its plasma membrane receptor, heterodimeric complex consisted of membrane-bound ST2L and IL-1R accessory protein, inducing NFkB and MAPK activation. IL-33 exists as a nuclear precursor and may act as an alarmin, when it is released after cell damage or as negative regulator of NFκB gene transcription, when acts in an intracrine manner. ST2L is expressed on several immune cells: Th2 lymphocytes, NK, NKT and mast cells and on cells of myeloid lineage: monocytes, dendritic cells and granulocytes. IL-33/ST2 axis can promote both Th1 and Th2 immune responses depending on the type of activated cell and microenvironment and cytokine network in damaged tissue. We previously described and discuss here the important role of IL-33/ST2 axis in experimental models of type 1 diabetes, experimental autoimmune encephalomyelitis, fulminant hepatitis and breast cancer. We found that ST2 deletion enhance the development of T cell-mediated autoimmune disorders, EAE and diabetes mellitus type I. Disease development was accompanied by dominantly Th1/Th17 immune response but also higher IL-33 production, which suggest that IL-33 in receptor independent manner could promote the development of inflammatory autoreactive T cells. IL-33/ST2 axis has protective role in Con A hepatitis. ST2-deficient mice had more severe hepatitis with higher influx of inflammatory cells in liver and dominant Th1/Th17 systemic response. Pretreatment of mice with IL-33 prevented Con A-induced liver damage through prevention of apoptosis of hepatocytes and Th2 amplification. Deletion of IL-33/ST2 axis enhances cytotoxicity of NK cells, production of IFN-γ in these cells and systemic production of IFN-γ, IL-17 and TNF-α, which leads to attenuated tumor growth. IL-33 treatment of tumor-bearing mice suppresses activity of NK cells, dendritic cell maturation and enhances alternative activation of macrophages. In conclusion, we observed that IL-33 has attenuated anti-inflammatory effects in T cell-mediated responses and that both IL-33 and ST2 could be further explored as potential therapeutic targets in treatment of immune-mediated diseases.

Keywords IL-33/ST2 axis · Con A hepatitis · EAE · MLD-STZ diabetes · Mouse breast cancer

IL-33/ST2 axis

Interleukin-33 (IL-33) is a member of the IL-1 cytokine family, originally described as a nuclear protein in cerebral arteries [1] and later as NF-HEV, a nuclear factor expressed in human high endothelial venules in secondary lymphoid organs [2]. Recently, IL-33 was identified as the ligand for the orphan receptor, ST2 (IL-1RL1). ST2 molecule is a member of the IL-1 receptor family [3] that exists in two forms: a transmembrane full-length form (ST2L) and a soluble, secreted form (sST2) due to differential splicing of ST2 mRNA [4]. Soluble ST2 acts as a decoy receptor for IL-33 [5]. In normal conditions, the serum concentration of soluble ST2 is below the detectable level, but elevated level of ST2 has been reported in patients with autoimmune diseases [6], asthma [7], idiopathic pulmonary fibrosis [8], myocardial infarction and heart failure [9].

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