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Deletion of IL-33R (ST2) Abrogates Resistance to EAE in BALB/C Mice by Enhancing Polarization of APC to Inflammatory Phenotype

Marija Milovanovic, Vladislav Volarevic, Biljana Ljujic, Gordana Radosavljevic, Ivan Jovanovic, Nebojsa Arsenijevic, Miodrag L. Lukic*

Center for Molecular Medicine and Stem Cell Research, Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia

Abstract

The administration of interleukin 33 and deletion of IL-33 receptor, ST2 molecule, affects the induction of autoimmunity in different experimental models of human autoimmune diseases. The aim of this study was to analyze the effect of ST2 deletion on the induction of experimental autoimmune encephalomyelitis (EAE) in resistant BALB/c mice. Mice were immunized with MOG_{35-55} peptide or disease was induced by passive transfer of encephalitogenic singenic cells and EAE was clinically and histologically evaluated. Expression of intracellular inflammatory cytokines, markers of activation and chemokine receptors on lymphoid tissue and CNS infiltrating mononuclear cells was analyzed by flow cytometry. We report here that deletion of $ST2^{-/-}$ molecule abrogates resistance of BALB/c mice to EAE induction based on clinical and histopathological findings. Brain and spinal cord infiltrates of $ST2^{-/-}$ mice had significantly higher number of $CD4^+$ T lymphocytes containing inflammatory cytokines compared to BALB/c WT mice. Adoptive transfer of $ST2^{-/-}$ primed lymphocytes induced clinical signs of the disease in $ST2^{-/-}$ as well as in WT mice. MOG_{35-55} restimulated $ST2^{-/-}$ $CD4^+$ cells as well as *ex vivo* analyzed lymph node cells had higher expression of T-bet and IL-17, IFN-γ, TNF-α and GM-CSF in comparison with WT $CD4^+$ cells. $ST2^{-/-}$ mice had higher percentages of $CD4^+$ cells expressing chemokine receptors important for migration to CNS in comparison with WT $CD4^+$ cells. Draining lymph nodes of $ST2^{-/-}$ mice contained higher percentage of $CD11c^+CD11b^+CD8^-$ cells containing inflammatory cytokines IL-6 and IL-12 with higher expression of activation markers. Transfer of $ST2^{-/-}$ but not WT dendritic cells induced EAE in MOG_{35-55} immunized WT mice. Our results indicate that ST2 deficiency attenuates inherent resistance of BALB/c mice to EAE induction by enhancing differentiation of proinflammatory antigen presenting cells and consecutive differentiation of encephalitogenic T cells in the draining lymph node rather than affecting their action in the target tissue.

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* E-mail: miodrag.lukic@medf.kg.ac.rs

Introduction

Multiple sclerosis is the inflammatory disease of the CNS, characterized by inflammatory lesions, demyelination and axonal loss [1]. Experimental autoimmune encephalomyelitis (EAE) is the experimental model of multiple sclerosis induced in susceptible animals by active immunization with myelin antigens mixed with adjuvant. T lymphocytes activated by encephalitogen in the periphery differentiate in inflammatory helper T cells able to pass blood-brain barrier where they recognize their cognate target antigen and initiate an inflammatory cascade leading to tissue damage. EAE also can be induced by passive transfer of myelin reactive population of $CD4^+$ T helper cells. However T helper differentiation toward inflammatory phenotype with encephalitogenic potential depends on the function of antigen presenting cells.

ST2 molecule is a member of the IL-1 receptor family [2] that exists in two forms: a transmembrane full length form (ST2L) or a soluble form (sST2) due to differential splicing of ST2 mRNA [3]. Soluble ST2 can serve as decoy receptor. Full length ST2 is expressed by many hematopoietic cells, monocytes, dendritic cells, macrophages NK and NKT cells, mast cells, and granulocytes and selectively by murine Th2 [4], and human Th2 cells [4]. ST2 is reported as a marker of effector Th2 cells that enhances Th2 response [5]. Natural ligand for ST2L (IL-33Rα-chain) is IL-33, a member of the IL-1 family of cytokines. IL-33 can act as classical cytokine that binds to ST2L and IL-1R accessory protein (IL-1RAp), activate NFkB and MAPK [6,7]. IL-33 can also stimulate innate type 2 immune cells, natural helper cells from adipose tissues and lung [8–10], nuocytes from mesenteric lymph nodes and spleen [9], and innate helper 2 cells from various tissues [11] to produce large amounts of IL-5, IL-6, IL-13 and GM-CSF [8,9]. IL-33 can enhance LPS mediated TNF and IL-6 production by macrophages [12,13] and induce IFN-γ production in iNKT and NK cells [14]. IL-33 was firstly described as important mediator of allergic diseases [15] and resistance to parasite infection [16]. IL-33 also has proinflammatory role in collagen induced arthritis [17,18] and ulcerative colitis and experimental Th1/Th2 driven enteritis [19] inducing production of IL-5, IL-6, and IL-17 in