IL-21 signaling shapes CD4 T cell pathogenicity by modulating GM-CSF production to ameliorate experimental autoimmune encephalomyelitis

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Abstract:

Experimental autoimmune encephalomyelitis (EAE) is a T-cell-mediated mouse-based multiple sclerosis (MS) which is an inflammatory demyelinating disease caused by destruction of central nervous system (CNS). During the development of EAE, peripheral CD4 T cells infiltrate into CNS and secrete effector cytokines such as interleukin (IL)-17, gamma-interferon (IFN-γ) and granulocyte-macrophage colony-stimulating factor (GM-CSF) to contribute their pathogenicity, whereas anti-inflammatory cytokine IL-10 to counter-regulate the disease. Interleukin (IL)-21 is a pleiotropic cytokine and drives proinflammatory IL-17A, GM-CSF or anti-inflammatory IL-10 productions from CD4 T cells. Although IL-21 is critical for the development of autoimmune diseases, the role of IL21 in EAE is still controversial. Our data demonstrated that IL-21 receptor deficient CD4 T cells displayed higher GM-CSF and lower IL-17A production compared to wild-type CD4 T cells. To investigate the pathogenic role of IL-21R deficient CD4 T cells in EAE, we adoptively transferred either 2D2/*Il21r*$^{+/+}$ or 2D2/*Il21r*$^{-/-}$ CD4 T cells into *Rag1* KO mice. *Rag1* KO mice receiving 2D2/*Il21r*$^{-/-}$ CD4 T cells exhibited earlier disease onset and greater disease severity than recipients receiving 2D2/*Il21r*$^{+/+}$ CD4 T cells. Moreover, the population of GM-CSF-producing CD4 T cells in CNS was significantly augmented in mice that received 2D2/*Il21r*$^{-/-}$ CD4 T cells compared to those mice received 2D2/*Il21r*$^{+/+}$ CD4 T cells. These results indicated that IL-21R signaling in CD4 T cells is indispensable for modulating their pathogenicity in a MOG Ag–driven manner. Based on our RNA-Seq data that *Prdm1* and *Maf* expression was downregulated in *Il21r*$^{-/-}$ CD4 T cells, we evaluated the potential role of Blimp-1 or c-Maf to suppress GM-CSF production by generating T cell-specific Blimp-1 transgenic (Tg)/ 2D2/*Il21r*$^{-/-}$ or c-Maf Tg/2D2/*Il21r*$^{-/-}$ mice. Either Blimp-1 or c-Maf overexpression in 2D2/*Il21r*$^{-/-}$ CD4 T cells decreased population and expression level of GM-CSF-producing CD4 T cells and attenuated EAE disease severity in these transgenic 2D2/*Il21r*$^{-/-}$ mice. Our findings suggested that IL-21R signaling in CD4 T cells repressed GM-CSF production possibly through induction of either Blimp-1 or c-Maf to modulate T cell pathogenicity and attenuate EAE disease progression.