IL-21 Signaling Sustains regulatory T cell Suppressive Functions to Dampen Th17-driven Experimental Autoimmune Encephalomyelitis

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Multiple sclerosis (MS) and its preclinical animal model called experimental autoimmune encephalomyelitis (EAE) are the chronic demyelinating disease of the 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 and γ-interferon (IFN-γ) contributing to the progression of EAE, whereas regulatory T cells (Tregs) are crucial to counteract the effector functions of those T cells. Previous studies indicated that cytokine signals are crucial to the differentiation and functional specialization of Tregs. Thus, these effector Tregs have suppressive ability to inhibit different types of effector T cells during inflammation. Recent reports have identified that RAR-related orphan receptor γt (RORγt)-expressing Tregs in both the gut and CNS preferentially mitigate inflammation driven by effector T cells. IL-21, a pleiotropic cytokine, stimulates potentially pathogenic and non-pathogenic responses in CD4 T cells. A previous study has demonstrated that co-transfer of wild-type effector T cells with Tregs from mice subjected to IL-21R blockade results in more severe EAE compared to Tregs from control mice. These data imply that IL-21 signaling plays an important role for modulating Tregs homeostasis in EAE. Moreover, IL-21 can induce the expression of Blimp-1 and c-Maf in CD4 T cells, and these two factors are known to be necessary for IL-10 production by Tregs. Our previous study demonstrated that IL-21 induces RORγt, IL-10 and c-Maf expression in Tregs. However, it is still unclear whether IL-21 influences RORγt expression and Treg suppressive function through c-Maf during EAE development.

First, we aim to investigate the potential role of IL-21 signaling in Tregs during EAE development, we adoptively transferred either $MOG_{35–55}$–reactive TCR transgenic (2D2) CD4 T cells alone or together with either WT Treg or *Il21r*$^{-/-}$ Treg into *Rag1*$^{-/-}$ mice. We found that *Rag1*$^{-/-}$ mice receiving 2D2 CD4 T cells alone or in combination with *Il21r*$^{-/-}$ Tregs exhibited an earlier onset of the disease and more severe symptoms compared to mice receiving WT Tregs. To further examine whether IL-21 signaling affects suppressive function or cytokine production in Tregs through c-Maf, we generated T cell-specific c-Maf Tg/*Il21r*$^{-/-}$ mice, and adoptively transfer 2D2 CD4 T cells alone or co-transferred with WT Tregs, *Il21r*$^{-/-}$ Tregs or c-Maf Tg/*Il21r*$^{-/-}$ Tregs into *Rag1*$^{-/-}$ mice to determine whether IL-21 may influence Treg suppressive function through c-Maf during EAE development. Our findings may suggest that IL-21 signaling in Tregs possibly through induction of c-Maf to prevent EAE disease progression.