IL-21R signaling is critical for induction of spontaneous experimental autoimmune encephalomyelitis.

Abstract:
IL-17-producing CD4+ T cells (Th17 cells) have well-described pathogenic roles in tissue inflammation and autoimmune diseases, such as experimental autoimmune encephalomyelitis (EAE); however, the involvement of IL-21 in these processes has remained controversial. While IL-21 is an essential autocrine amplification factor for differentiation of Th17 cells, the loss of IL-21 or IL-21 receptor (IL-21R) does not protect mice from actively induced EAE. Here, we utilized a transgenic EAE mouse model, in which T and B cells overexpress receptors for myelin oligodendrocyte glycoprotein (MOG) (referred to as 2D2xTH mice), and demonstrated that IL-21 is critical for the development of a variant form of spontaneous EAE in these animals. Il21r deletion in 2D2xTH mice reduced the incidence and severity of spontaneous EAE, which was associated with a defect in Th17 cell generation. Moreover, IL-21R deficiency limited IL-23R expression on Th17 cells and inhibited expression of key molecules involved in the generation of pathogenic Th17 cells. Conversely, loss of IL-23R in 2D2xTH mice resulted in complete resistance to the development of spontaneous EAE. Our data identify a previously unappreciated role for IL-21 in EAE and reveal that IL-21-mediated signaling supports generation and stabilization of pathogenic Th17 cells and development of spontaneous autoimmunity.