

Reciprocal relationship between CD4+, Fox-P3+ T-reg and proinflammatory Th17 cells

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Upon activation, T cells undergo distinct developmental pathways, attaining specialized properties and effector functions. T-helper (T_H) cells are traditionally thought to differentiate into T_H1 and T_H2 cell subsets. Recently, a subset of interleukin (IL)-17-producing T cells (T_H17) distinct from T_H1 or T_H2 cells has been described and shown to have a crucial role in the induction of autoimmune tissue injury. In contrast, CD4⁺CD25⁺, Fox-P3⁺ regulatory T cells (T-regs) inhibit autoimmunity and protect against tissue inflammation. TGF-β1 is a critical differentiation factor for the generation of T-regs and using Foxp3-GFP “knock-in” mice we show that IL-6, an acute phase protein induced during inflammation, completely inhibits the generation of Foxp3⁺ T-reg cells induced by TGF-β1. Instead IL-6 and TGF-β1 induces differentiation of proinflammatory Th17 cells from naïve T cells. Consistent with these observations, immunization of inducible TGF-β1 transgenic mice with myelin antigens in complete Freund's adjuvant induces a severe and lethal experimental autoimmune encephalomyelitis (EAE) with massive production of IL-17. Our data suggests a reciprocal relationship in the generation of pathogenic (Th-IL-17) T cells that induce autoimmunity and regulatory (Foxp3⁺) T cells that inhibit autoimmune tissue injury. Differentiating Th17 cells produce IL-21 and IL-21 acts as the amplification factor for further differentiation of Th17 cells. At this stage differentiating Th17 cells express IL-23R and IL-23 now acts to further maintain and stabilize Th17 cells. Thus we believe there are three distinct steps in Th17 differentiation: Induction, Amplification and Stabilization and loss of any of the cytokines (TGF-β, IL-6, IL-21 or IL-23) in the pathway will mediate a defect in Th17 generation.

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