Soluble CTLA-4 predominantly produced by Treg cells inhibits type 1 inflammation without hindering type 2 immunity for facilitating inflammation resolution

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Abstract

CTLA-4, which can bind to CD80/86, exists in two forms: membrane-bound (mCTLA-4) and soluble (sCTLA-4). The immunological role of sCTLA-4 in vivo remains poorly understood. In this study, we show that effector regulatory T cells (Tregs) predominantly produce sCTLA-4 at the cellular and population level among various immune cells under basal and inflammatory conditions, although TCR stimulation transiently reduces sCTLA-4 expression. Mice deficient in sCTLA-4 production exhibit spontaneous activation of Th1, Th17, Tfh and Tc1 cells, autoantibody and IgE production, M1-like macrophage polarization with age, and impaired wound healing. Conversely, sCTLA-4-intact but mCTLA-4-deficient mice develop severe autoimmunity but show longer survival compared to double-deficient mice, with predominant activation and differentiation of Th2 cells, M2-like macrophages and eosinophils. Consistently, recombinant sCTLA-4 inhibits in vitro differentiation of naive T cells into Th1 cells through CD80/CD86 blockade on antigen presenting cells, but does not affect Th2 differentiation. Furthermore, sCTLA-4-intact but mCTLA-4-deficient Tregs effectively inhibit Th1-mediated experimental colitis in contrast to double-deficient Tregs, and sCTLA-4 suppresses IFNγ-mediated anti-tumor T cell immunity. These findings highlight the critical role of sCTLA-4 in Tregs during chronic inflammation, where it controls type 1 immunity and allows type 2 immunity to dominate, facilitating resolution of inflammation. In addition, our results suggest potential therapeutic applications of sCTLA-4 in the treatment of autoimmune diseases and the enhancement of tissue repair by modulating immune responses.