

### **Stabilization versus flexibility in T helper decisions**

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Many developmental lineage determination choices are induced by transient signals provided in a stereotypic manner within the environment of the embryo. By contrast, the direction of development taken by naïve CD4 T cells is strongly influenced by the environmental signals induced by pathogens interacting with the innate immune system. The cytokine signals as well as the transcription factors that generate Th1 or Th2 phenotypes of CD4 T cells have been characterized in great depth. However, Th1 and Th2 responses are not perfect mirror images, but show certain differences in behavior. In vitro, Th2 responses exhibit greater degree of stability compared to their Th1 counterpart. The intracellular transcription all circuitry underlying Th2 development involves a cell-intrinsic transcriptional autoactivation pathway that underlies this stability <sup>1</sup>, whereas a similar feedback pathway may be lacking in Th1 cells <sup>2</sup>. A second difference between Th1 and Th2 responses is the capacity to induce IFN- $\gamma$  from Th1 cells in an antigen-independent manner through the actions of the cytokines IL-12 and IL-18 <sup>3</sup>, which allowing them to generate a graded response more sensitive to the intensity of infection and inflammation .

Costimulation of naïve T cells for regulating early activation involves members of the CD28/B7 superfamily, and the actions for CD8-dependent costimulation have generally emphasized the impact on early priming events. Recently additional CD28-like and B7-like factors have been identified that play more significant roles during later stages of T cells development, particularly in the effector and/or contraction phases of the immune response. We have recently identified a new member of this family, BTLA, which is an inhibitory receptor expressed by lymphocytes, and which becomes selectively expressed on Th1 T cells following polarization. BTLA, upon phosphorylation of conserve tyrosine-based motifs, can interact with the SHP-1 and SHP-2 phosphatases. Mice deficient in BTLA expression show an increased susceptibility to specific antigen-induced EAE, but show only a moderate increase in spontaneous levels of antibody production and show no evidence so far of spontaneous autoimmune disease. Based on the similarity of BTLA with PD-1, and the potential that the ligands for BTLA may include additional members of the B7 family, we suggest that PD-1 and BTLA exerts overlapping and partially redundant inhibitory effects on T cells.

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