

Regulatory CD4 T cells

Alexander Rudensky

HHMI and University of Washington School of Medicine, Seattle, WA, USA

Abstract

Recent studies have strongly suggested that regulatory T cells are essential for the maintenance of self-tolerance. In 1995, a major subset of naturally arising regulatory T cells has been identified as CD25⁺CD4⁺ T cells and has become since a focus of intense investigations. In addition to the control of autoimmunity, these cells have been implicated in the regulation of immune responses and inflammation in the course of some infections. Despite growing realization of the functional significance of this subset of T cells in the immune homeostasis, molecular mechanisms governing the function of CD25⁺ CD4⁺ T cells are poorly understood. Our analysis of genes differentially expressed in CD25⁺ CD4⁺ vs. CD25⁻ CD4⁺ T cells revealed the forkhead transcription factor *Foxp3* as specifically expressed in CD25⁺ CD4⁺ regulatory T cells. We further found that the lethal lymphoproliferative autoimmune syndrome observed in *Foxp3*-mutant mice results from a CD25⁺ CD4⁺ regulatory T cell deficiency and not from a cell-intrinsic defect in control of activation or expansion of CD25⁻ CD4⁺ T cells. Further analysis of a *Foxp3* reporter gene expression knocked into the *Foxp3* locus revealed that *Foxp3* expression is limited exclusively to a subset of α/β T cells in the thymus and in the periphery including both CD25⁺ and CD25⁻ T cells. We find expression of *Foxp3* in regulatory T cell precursors the thymus is dependent upon increased avidity interactions of TCR with self-peptide MHC class II complexes in combination with a second unknown signal. Thus, regulation of immune homeostasis by *Foxp3* expressing regulatory T cells seems to be induced in response to thymic generation of a cohort of T cells with self-reactive TCR. In aggregate, our results demonstrate that *Foxp3* serves as a regulatory T cell lineage specification factor and defines the genetic mechanism of dominant tolerance. Failure of dominant tolerance due to *Foxp3* deficiency results in fatal autoimmune disorders in mice and humans.