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Regulatory T cell development requires two independent events: TCR stimulation-induced epigenetic changes and Foxp3 expression

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Abstract

Regulatory T cells (Tregs) engage in the maintenance of immunological self-tolerance and homeostasis by suppressing aberrant or excessive immune responses harmful to the host. The transcription factor Foxp3 specifically expressed in Tregs crucially controls their development. Yet, Foxp3 expression per se is not sufficient to establish full Treg phenotype and function. For example, ectopic Foxp3 expression in conventional T cells failed to induce two-third of Treg signature genes; and T cell receptor (TCR) stimulation can induce transient Foxp3 expression in naive T cells, but not suppressive activity, in humans. Here we show that the establishment of Treg-type whole gene expression profile, the formation of Treg-signature proteins, and the acquisition of suppressive activity is achieved by the combination of two independent processes, *i.e.*, the expression of Foxp3 and the establishment of Treg-type CpG hypomethylation. Both are induced by TCR stimulation. The demethylation began with TCR stimulation in the thymus and continued to proceed in the periphery, and could be fully established in *Foxp3-null* Tregs that expressed *Foxp3*-driven reporter protein but not Foxp3 protein itself. In addition, the hypomethylation was induced partially in conventional T cells chronically activated by antigens, and fully in developing Tregs reactive with thymic self-ligands. Importantly, Foxp3 expression or Treg-type CpG hypomethylation alone was insufficient, but both were required to induce Treg-type gene expression, lineage stability, and full suppressive activity. Thus, those T cells in which the two events have concurrently occurred are developmentally set into the Treg lineage. This model of Treg development with distinct contribution of Foxp3 and TCR-induced epigenetic changes explains how Treg cell fate and functional stability (or plasticity) is determined at the molecular level, and can be exploited to generate functionally stable Tregs.