Genetic and epigenetic control of regulatory T cell development

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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, some Treg-associated genes are activated without Foxp3 in Treg lineage cells developing in the thymus; ectopic Foxp3 expression in conventional T cells fails 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 and parallel processes, *i.e.*, the expression of Foxp3 and the establishment of Treg-type CpG hypomethylation. Both are induced mainly by TCR stimulation. The demethylation begins with TCR stimulation in the thymus and continues to proceed in the periphery, and can be fully established in *Foxp3-null* Tregs that expressed *Foxp3*-driven reporter protein but not Foxp3 protein itself. Naïve T cells accumulate Treg-like CpG demethylation only when they are chronically and continuously stimulated *in vivo*. Importantly, Foxp3 expression or Treg-type CpG hypomethylation alone is insufficient, but both are required to induce full Treg phenotype and function. 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 programs explains how Treg cell fate and functional stability (or plasticity) is determined at the molecular level. It can be exploited to control immune responses via targeting Treg generation in the thymus and the periphery.