Genetic and epigenetic basis of Treg cell development and function

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Naturally arising CD25+CD4+ regulatory T cells (Tregs), which specifically express the transcription factor Foxp3, are engaged in the maintenance of immunological self-tolerance and immune homeostasis by suppressing aberrant or excessive immune responses, such as autoimmune disease and allergy. Key issues for understanding immunological functions of natural CD25+Foxp3+CD4+ Tregs include: how they develop in the thymus and the periphery, how they suppress immune responses, and how their functional and lineage stability is established and maintained.

Foxp3 is essential for the development of Tregs, yet its expression is insufficient for establishing the Treg cell lineage. We have recently shown that Treg development is achieved by the combination of two independent processes, *i.e.*, the expression of Foxp3 and the establishment of Treg-specific CpG hypomethylation pattern. Both are induced by TCR stimulation. The Treg-type CpG hypomethylation begins in the thymus and continues to proceed in the periphery, and can be fully established without Foxp3. The hypomethylation is required for Foxp3+ T cells to acquire 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 cell lineage. This model explains how Treg cell fate and plasticity is controlled, and can be exploited to generate functionally stable Tregs.

How these findings can be exploited in clinical settings will be discussed.