

Function of Natural and Induced Regulatory T Cells in Peripheral Tolerance

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CD4⁺CD25⁺ regulatory T (T_R) cells are crucial to the maintenance of peripheral tolerance. In addition to natural regulatory T (nT_R) lymphocytes, representing a distinct thymus-derived lineage that is critically dependent on the transcription factor Foxp3 for its differentiation, a second subset of Foxp3⁺ regulatory T cells is induced de novo from conventional CD4⁺Foxp3⁻ T cells upon antigenic stimulation in the presence of TGF-beta and IL-2. Similar to nT_R cells, induced (iT_R) cells are also dependent on Foxp3 expression for their suppressor function. The two populations are molecularly and functionally distinct, with both being required for the complete rescue of the autoimmune inflammatory disease induced by Foxp3 deficiency and to achieve full tolerance in experimental colitis. Concurrent MyD88 deficiency dissociates Foxp3 deficiency into two disease components, one that is MyD88-dependent, involving inflammation at the mucosal surfaces in the skin, gut and lungs, and another that is MyD88-independent, manifesting as unrestrained systemic lympho and myeloproliferation. Thus a fundamental function of T_R cells is to regulate innate immune response pathways triggered by the microbial flora at the mucosal interface. Whether the different components of the autoimmune inflammatory disease caused by Foxp3 deficiency reflect specialized functions of nT_R and iT_R cells is the subject of ongoing investigation.

Supported by a National Institutes of Health grants AI080002 (T.A.C.) and AI47154 (C.B.W.).

References:

1. Haribhai D, Lin W, Relland LR, Truong N, Williams CB, Chatila TA. Regulatory T Cells Dynamically Control the Primary Immune Response to Foreign Antigen. *J. Immunol.* 178(5):2961-72 (2007).
2. Lin W, Haribhai D, Relland LR, Truong N, Williams CB, Chatila TA. Regulatory T cell Development in the Absence of a Functional Foxp3 Protein. *Nat. Immunol.* 8(4):359-68 (2007).
3. Haribhai D, Lin W, Edwards B, Ziegelbauer J, Salzman NH, Carlson MR, Chatila TA, Williams CB. A Central Role for Induced Regulatory T Cells in Tolerance Induction in Experimental Colitis. *J. Immunol.* (in press).