Regulatory T Cells: Key Players in Tolerance and Autoimmunity

Talal A. Chatila, MD, MSc

KEYWORDS

• Regulatory T cells • Foxp3 • Tolerance
• Autoimmunity • IPEX • CD25

Regulatory T (T_R) cells represent a distinct T-cell lineage that has a key role in tolerance to self-antigens and the prevention of autoimmune disease, as well as the inappropriate immune responses involved in allergic disease.[1–3] T_R cells are characterized by a set of phenotypic and functional attributes that distinguish them from conventional T cells. They are predominantly $CD4^+CD25^+$, T-cell receptor (TCR) ab^+. T_R cells are anergic and do not produce interleukin-2 (IL-2).[4] When activated, they suppress the proliferation and cytokine production of conventional $CD4^+CD25^-$ T cells as well as that of $CD8^+$ T cells and established Th1 and Th2 cells.[5–8] $CD4^+CD25^+$ T_R cells produce transforming growth factor beta (TGF-β) and IL-10, two cytokines endowed with immunosuppressive functions that have critical functions in T_R cell biology.

Most peripheral T_R cells are programmed in the thymus and are known as natural T_R (nT_R) cells.[3] Other T_R cells known as induced or adaptive (iT_R) cells are derived de novo from a naïve $CD4^+$ precursor pool in peripheral lymphoid tissues following antigenic stimulation in the presence of TGF-β and IL-2. Intense effort has gone into defining the molecular events that guide T_R cells through development and lineage commitment, and those that enable the acquisition and maintenance of T_R cell phenotypic and functional attributes. The recent advances made in elucidating those pathways are reviewed herein.

FOXP3: A CRITICAL FACTOR FOR T_R CELL STABILITY AND FUNCTION

Although T_R cells are characterized by the expression of a distinctive combination of surface antigens including CD25, CTLA-4, and GITR, the cardinal hallmark of a T_R cell

Work for this article was supported by National Institutes of Health grants R01AI065617 and R21AI80002.
Division of Immunology, Allergy and Rheumatology, Department of Pediatrics, The David Geffen School of Medicine, University of California, MDCC 12-430, 10833 Le Conte Avenue, Los Angeles, CA 90095-1752, USA
E-mail address: tchatila@mednet.ucla.edu

Endocrinol Metab Clin N Am 38 (2009) 265–272
doi:10.1016/j.ecl.2009.01.002 **endo.theclinics.com**
0889-8529/09/$ – see front matter

is the forkhead family transcription factor forkhead box p3 (Foxp3), which is indispensable to their suppressive activity, phenotype stability, and survival in the periphery.[3]

Foxp3 was initially thought to function as a transcriptional repressor[9]; however, it has become clear that it may function as either a transcriptional activator or repressor depending on the context.[10,11] The transcriptional functions of Foxp3 are enabled by the capacity of its different domains to interact with distinct sets of regulatory proteins to form large macromolecular transcriptional complexes. An N-terminal domain mediates transcriptional activation and repression; zinc finger and leucine zipper domains mediate homo- and hetero-oligomerization of Foxp3 with related members of the Foxp family; and a carboxyl terminal forkhead domain mediates binding to specific DNA response elements. Foxp3 also includes residues that contribute to the physical association of Foxp3 with other transcription factors, including the nuclear factor of activated T cells (NFAT) and Runx1/AML1, both of which contribute to the transcriptional program and suppressive functions of T_R cells.[12,13] An isoform of Foxp3 is expressed that lacks an N-terminal domain 33 amino acid peptide that is encoded by exon 2. This isoform is ineffective in conferring regulatory function upon expression in conventional T cells (T_{conv}).[14]

nT_R VERSUS iT_R AND TR-1 CELLS

$Foxp3^+$ T_R cells are unique among the effector T-cell subsets in that they are comprised of two developmentally distinct populations—nT_R cells, which develop in the thymus, and adaptive or induced iT_R cells, which are induced de novo in the periphery from T_{conv} cells. The two populations display a close affinity in their regulatory function and phenotype but are not identical. The phenotypic and genetic attributes of nT_R cells are "hard-wired," with most them persisting even in the absence of Foxp3. This persistence is a reflection of an irreversible commitment to the T_R cell lineage that occurs in the course of thymic selection and maturation of nT_R cells. In contrast, iT_R cells are "plastic," developing upon antigenic stimulation of T_{conv} cells in the presence of TGF-β and IL-2 (**Fig. 1**).[15–18] Foxp3, whose expression in iT_R cells is induced by the action of TGF-β and T-cell receptor signaling, is required for the suppressive functions of iT_R cells, similar to the situation of their nT_R cell counterparts (D. Haribhai, T.A. Chatila, and C.B. Williams, unpublished observations, 2009). iT_R cells have been demonstrated to develop during induction of oral tolerance to an allergen and may have an important role in tolerance induction in immunotherapy[19,20]; however, their phenotype is less stable than that of nT_R cells. Whereas the Foxp3 locus is stably hypomethylated in nT_R cells, it is weakly so in adaptive iT_R cells.[21] The suppressive function and Foxp3 expression levels of the latter may accordingly decline over time.

In addition to the $Foxp3^+$ iT_R cells, another class of T_R cells is the $Foxp3^-IL\text{-}10^+$ T regulatory type 1 (Tr-1) cells, derived by the ex vivo activation of naïve $CD4^+$ T cells in the presence of IL-10 or by IL-10–conditioned dendritic cells.[22] Previous studies attempting to track these cells in vivo have been impeded by the lack of clear markers that could distinguish Tr-1 cells from $Foxp3^+$ nT_R and iT_R cells, which also express IL-10, especially after activation. Recent studies have overcome this limitation by using IL-10 locus-tagged mice, revealing $Foxp3^-$ Tr-1–like cells to be particularly abundant in the small and large intestine, where they have an essential role in down-regulating the inflammatory response triggered by the commensal flora.[23–25] $Foxp3^-$ Tr-1–like cells share with $Foxp3^+$ iT_R cells a requirement for TGF-β for their in vivo differentiation, but it remains unclear whether Tr-1 cells branch off from a common differentiation pathway with $Foxp3^+$ iT_R cells or arise by a separate pathway. Whereas earlier studies