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Regulatory T cells: Key Players in Tolerance and Autoimmunity

Talal Chatila

Division of Immunology, Allergy and Rheumatology, the Department of Pediatrics, The David Geffen School of Medicine at the University of California at Los Angeles, Los Angeles CA 90095-1752

Abstract

CD4⁺CD25⁺ natural regulatory T (nT_R) lymphocytes represent a separate, thymus derived T cell lineage that is essential to the maintenance of immunological tolerance in the host. The discovery of Foxp3 as a transcription factor essential to the differentiation of both nT_R and induced regulatory T cells (iT_R) ushered in detailed studies of the molecular mechanisms of T_R cell development, peripheral homeostasis and effector functions. In humans, loss of function mutations in genes that regulate T cell development and function, including *FOXP3*, *IL2RA* and *STAT5b*, have been associated with T_R cell deficiency or dysfunction and syndromes of autoimmunity and immune dysregulation, including neonatal type 1 diabetes and polyendocrinopathies. Augmentation of T_R cells by immunotherapy and pharmacologic agents is a promising strategy for the treatment of allergic and autoimmune diseases.

Introduction

Regulatory T (T_R) cells represent a distinct T cell lineage that plays a key role in tolerance to self-antigens and prevention of autoimmune diseases, as well as in the inappropriate immune responses involved in allergic diseases¹⁻³. 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) αβ⁺. T_R cells are anergic and do not produce IL-2 [reviewed in⁴]. 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 cells⁵⁻⁸. CD4⁺CD25⁺ T_R cells produce TGF-β and IL-10, two cytokines endowed with immunosuppressive functions and which play critical functions in T_R cell biology.

A majority of peripheral T_R cells are programmed in the thymus and are known as natural T_R (nT_R) cells³. 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. These recent advances made in elucidating those pathways are reviewed below.

Address correspondence to Talal A. Chatila at the Division of Immunology, Allergy and Rheumatology, Department of Pediatrics, The David Geffen School of Medicine at the University of California at Los Angeles, MDCC 12-430, 10833 Le Conte Avenue, Los Angeles, CA 90095-1752. Phone: 310-8256481; Fax: 310-8259832; Email: E-mail: tchatila@mednet.ucla.edu.

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Foxp3: a critical factor for T_R cell stability and function

While 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 is the forkhead-family transcription factor forkhead box p3, (Foxp3) which is indispensable to their suppressive activity, phenotype stability and survival in the periphery³.

Foxp3 was initially thought to function as a transcriptional repressor⁹. However, it has become clear that Foxp3 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 that mediates binding to specific DNA response elements. It 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 regulatory T 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 (T_{conv}) cells¹⁴.

nT_R versus iT_R and Tr-1 cells

Foxp3⁺ T_R cells are unique among the effector T cell subsets in being comprised of two developmentally distinct populations: nT_R cells, which develop in the thymus and adaptive or induced iT_R cells that 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 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 (Figure 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 cells counterparts (D. Haribhai, T.A. Chatila and C.B. Williams; unpublished observations). iT_R cells have been demonstrated to develop during induction of oral tolerance to an allergen and may play an important role in tolerance induction in immunotherapy^{19,20}. Their phenotype, however, 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 these adaptive iT_R cells²¹. 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-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 cells²². 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 play an essential role in down-regulating the inflammatory response triggered by the commensal flora²³⁻²⁵. 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 have implicated Tr-1 in mucosal tolerance, the precise contributions of Foxp3⁺ Tr cells and Foxp3⁻ Tr-1 cells to induced tolerance remains to be carefully analyzed with the newer analytical tools now available.

Breakdown of Tolerance and autoimmunity due to Foxp3 Deficiency

Loss of function mutations in the *Foxp3* gene underlie the lymphoproliferative disease of the Scurfy mouse and the homologous autoimmune lymphoproliferative disorder in man, termed Immune dysregulation Polyendocrinopathy Enteropathy –X linked syndrome (IPEX). In humans, loss of function *FOXP3* mutations result in the IPEX syndrome^{1,26}. The hallmark of IPEX is immune dysregulation due to the lack of functional Tr cells. It typically presents in a male infant with enteropathy, autoimmune endocrinopathy, immune-mediated cytopenias, and dermatitis. There is also allergic dysregulation that manifests in particular as food allergy, eosinophilia and elevated IgE levels^{27,28}. The autoimmune endocrinopathy is characterized by early onset type 1 diabetes, frequently beginning in the first year of life. Thyroiditis resulting in either hyper or hypothyroidism is also common. Some of the allergic dysregulation in IPEX results from the presence in circulation of Tr cell precursors that secrete large amounts of Th2 cytokines especially IL-4, while it is tempting to speculate that the food allergy is a manifestation of iT_R cell deficiency²⁹⁻³¹. *Foxp3* deficiency in mice, whether due to natural or induced mutations, gives rise to a fatal autoimmune and inflammatory disorder called Scurfy that has many of the features of IPEX³². In both mice and humans, female carriers are asymptomatic, consistent with X-linked recessive inheritance.

The immunopathology of Foxp3 deficiency results from unchecked T cell activation due to the lack of regulatory restraint by CD4⁺CD25⁺ Tr cells^{33,34}. That Foxp3 is essential for Tr cell function is supported by the observation that forced expression of Foxp3 in effector T cells endows them with regulatory properties and some, but not all, of the phenotypic markers of regulatory T cells^{35,36}. Also, Adoptive transfer of CD4⁺CD25⁺ Tr cells rescues Scurfy mice from disease, and Foxp3-transduced CD4⁺CD25⁻ T cells suppress wasting and colitis induced by the transfer of CD4⁺CD25⁻ T cells into RAG-deficient mice^{35,37}.

Foxp3 deficiency is permissive to the development in the thymus of Tr cell precursors that share many of the phenotypic and genetic attributes of Tr cells. However, unlike Foxp3-sufficient Tr cells, Foxp3-deficient Tr cell precursors fail to mediate suppression^{29,31}. Once in the periphery, they acquire the attributes of an activated cytotoxic cell phenotype. They express high levels of mRNA encoding granzymes, some killer cell markers and a mixed Th1 and Th2 cytokine profile. In particular, they secrete large amounts of IL-4 and other Th2 cytokines, which may account for much of the allergic dysregulation associated with Foxp3 deficiency^{27,29,31}. Circulating Foxp3-deficient Tr cell precursors also exhibit a high rate of apoptotic death, possibly due to suboptimal responses to growth factors such as IL-2. The continued requirement for Foxp3 expression to maintain the phenotype of mature Tr cell in the periphery was demonstrated in experiments in which the acute inactivation of the *Foxp3* locus rapidly lead to the loss of Tr cell regulatory function. Acute Foxp3 deficiency also alters the transcriptional program of Tr cells in a manner reminiscent of that of Foxp3-deficient Tr cell precursors³⁸.

Other Heritable disorders of Tr cells

IPEX like syndromes in humans and in mice also arise from mutations along the IL-2 signaling pathway, including loss of function mutations in IL-2 receptor alpha chain (CD25) and the IL-2-responsive transcription factor STAT5b, the latter with an associated phenotype of resistance to growth hormone³⁹⁻⁴¹. CD25 deficiency has been associated with early onset of type 1 diabetes in humans, consistent with the phenotype observed in IPEX syndrome due to Foxp3 mutations. More broadly, the CD25 and IL-2 gene loci have been associated with type

1 diabetes in humans (see chapter 3) and mice, respectively, indicating the essential function of this pathway in maintaining tolerance to islet β -cells (Figure 2) ^{42,43}.

T_R cell-directed therapies in autoimmunity

Manipulation of T_R cells is an attractive strategy for immunotherapy, as suggested by adoptive transfer of T_R cells to treat experimental autoimmune diseases ^{44,45}. Similar treatment strategies are now being developed in humans in whom it is envisaged that cellular therapy with antigen-specific T_R cells may allow the development of long-term immune modulation without the problem of general immunosuppression and systemic toxicity ^{46,47}. Other approaches include the derivation for therapeutic use of human cell lines that stably express ectopic Foxp3, which converts both naïve and antigen-specific memory CD4⁺ T cells into cells with T_R cell-like properties ⁴⁸. T_R cell therapy may also be rendered more effective by combining it with immunomodulatory drugs that spare T_R cells while targeting conventional T cells. One such drug is rapamycin, an inhibitor of the mTor pathway, which plays an important role in T cell proliferation and survival. The mTor pathway is relatively inactive in T_R cells, which employ an alternative IL-2 receptor-coupled STAT5 pathway to mediate cell growth and proliferation ^{49,50}. A second approach is to use histone deacetylase inhibitors, which promote the development of Foxp3⁺ iT_R cells ⁵¹.

Concluding remarks

Impressive progress has been made in elucidating molecular mechanisms underlying T_R cell development and differentiation. The stage is now set to tackle some important outstanding issues in the field. These include the nature of the molecular circuitry governing the early development of nT_R cells in the thymus, the mechanisms underlying suppressive function of T_R cells, the respective roles of nT_R and iT_R cells in dominant tolerance, and the nature of the molecular pathways mediating their non-redundant functions. The striking allergic dysregulation and food allergy associated with the IPEX syndrome indicates a fundamental role for T_R cells in tolerance to allergens, especially foods. Pharmacological interventions that aim to bolster T_R cell development and function, alone or together with immunotherapy, offer the potential for novel therapeutic strategies in the treatment of allergic and autoimmune diseases.

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Natural (thymus-derived) $CD4^+CD25^+$ T_R cells

Induced $CD4^+CD25^+$ T_R cells

IL-10 secreting Tr-1 cells

Figure 1.

Natural and induced T_R cell populations. **Upper panel:** natural (thymic) $CD4^+CD25^+$ T_R cells develop in the thymus, are exported to the periphery where they constitutively express $Foxp3$. **Middle panel.** $CD4^+CD25^-Foxp3^-$ cells can be induced to differentiate into $CD4^+CD25^+Foxp3^+$ induced T_R cells under special conditions including low antigen exposure, oral tolerance, and immunotherapy. Induction *in vitro* can be achieved by stimulation in the presence of TGF- β . **Lower panel.** IL-10 secreting Tr1 and related T_R are $Foxp3^-$ and are induced *in vivo* in a TGF- β -dependent manner, usually in the context of high antigenic exposure such as exists in the gastrointestinal tract and in chronic infection.

Figure 2.

Genetic lesions resulting in T_R cell deficiency/dysfunction and autoimmunity. **A.** Activation of effector T (T_{eff}) cells by antigen presenting cells (APC) triggers T_{eff} cell activation and IL-2 production. Signaling by the IL-2 /IL-2 receptor (IL-2R)/STAT5 pathway is essential for the competency of T_R cells and helps maintain high level expression of Foxp3. It enables the suppression by T_R cells of both APC and T_{eff} cell function. **X** denotes genetic defects associated with IPEX (Foxp3) and IPEX-like syndromes (IL-2Rα chain and STAT5b).