Naturally arising CD4+ regulatory T cells, which engage in the maintenance of immunologic self-tolerance, specifically express FOXP3, which encodes a transcription-repressor protein. Genetic defects in FOXP3 cause IPEX, an X-linked autoimmune/inflammatory syndrome. With FOXP3 as a specific marker for regulatory CD4+ T cells in humans, it is now possible to determine their origin and developmental pathway.
ably have diminished elastin content. Since the rodents lungs continue to develop until two months after birth, one wonders whether Eln+/– lungs undergo structural reorganization when exposed to postnatal transmural pressure and what the consequences of such reorganization might be on pulmonary function.


The origin of **FOXP3**-expressing CD4+ regulatory T cells: thymus or periphery

Shimon Sakaguchi

Department of Experimental Pathology, Institute for Frontier Medical Sciences, Kyoto University, Kyoto, Japan

Laboratory for Immunopathology, RIKEN Research Center for Allergy and Immunology, Yokohama, Japan

Naturally arising CD4+ regulatory T cells, which engage in the maintenance of immunologic self-tolerance, specifically express FOXP3, which encodes a transcription repressor protein. Genetic defects in FOXP3 cause IPEX, an X-linked autoimmune/inflammatory syndrome. With FOXP3 as a specific marker for regulatory CD4+ T cells in humans, it is now possible to determine their origin and developmental pathway (see the related article beginning on page 1437).


The immune system discriminates between self and non-self, maintaining immunologic self-tolerance (i.e., unresponsiveness to self-constituents). It is known that potentially hazardous self-reactive T and B cells are clonally delet

ed at immature stages of their development or inactivated upon encounter with self-antigens in the periphery. There is now accumulating evidence that, in addition to these passive mechanisms of self-tolerance, a population of CD4+ T cells, called regulatory T cells (T<sub>R</sub> cells), engage in the maintenance of peripheral self-tolerance by actively suppressing the activation and expansion of self-reactive T cells (1–3). The majority, if not all, of such naturally occurring CD4+ T<sub>R</sub> cells constitutively express CD25 (IL-2 receptor α chain) in the physiologic state. Indeed, removal of CD25+CD4+ T<sub>R</sub> cells, which constitute 5–10% of CD4+ T cells in rodents and humans, leads to spontaneous development of various autoimmune diseases in otherwise normal mice (4). The removal of CD25+CD4+ T<sub>R</sub> cells also triggers excessive or misdirected immune responses to microbial antigens, causing immunopathology, such as inflammatory bowel disease (IBD), due to hyper-reaction of the remaining T cells to commensal bacteria in the intestine (3).

**FOXP3**: master control gene for the development and function of natural CD4+ T<sub>R</sub> cells

There is now evidence not only for the presence of CD25+CD4+ T<sub>R</sub> cells in humans but also for their essential roles in controlling autoimmunity, immunopathology, and allergy in human diseases (5). This is best illustrated by IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome), a rare monogenic disease of male children that is accompanied by autoimmune disease (such as type 1 diabetes), IBD, and severe allergy similar to those produced in mice by deletion of CD25+CD4+ T<sub>R</sub> cells (6). The causative gene, FOXP3 (Foxp3 in mice), which encodes a transcription repressor (7–10), is specifically expressed in CD25+CD4+ T<sub>R</sub> cells in the thymus and periphery (11–13). Forced expression of the Foxp3 gene can convert murine naive T cells to T<sub>R</sub> cells that phenotypically and functionally resemble naturally arising CD25+CD4+ T<sub>R</sub> cells
Furthermore, inoculation of CD25⁺CD4⁺ T cells prepared from normal mice can prevent autoimmune disease in Foxp3-defective mice (12). These findings collectively indicate that FOXP3 is a master control gene for the development and function of natural CD25⁺CD4⁺ TR cells.

The origin and the developmental pathway of FOXP3-expressing Tᵦ cells

The discovery of FOXP3/Foxp3 as a specific and stable marker for natural Tᵦ cells now makes it possible to determine the origin and the developmental pathway of Tᵦ cells in humans, as reported by Walker et al. in this issue of the JCI (14). It has been shown, mainly in rodents, that the normal thymus continuously produces CD25⁺CD4⁺ Tᵦ cells as a functionally mature T cell subpopulation that recognizes a broad repertoire of self- and non-self antigens, and that abrogation of the thymic production of Tᵦ cells leads to the development of autoimmune disease (1–3). Walker et al. (14) show that CD25⁺CD4⁺ T cells in the peripheral blood lymphocytes express FOXP3 and are capable of suppressing the activation and expansion of other T cells in vitro, as shown in rodents (11–13). Furthermore, they show that, in contrast with murine Foxp3 expression, activation of CD25⁻CD4⁺ T cells by T cell receptor (TCR) stimulation induces FOXP3 expression, and that FOXP3-expressing T cells derived from CD25⁻CD4⁺ T cells are equally as suppressive as natural CD25⁺CD4⁺ Tᵦ cells (Figure 1) (14). This interesting finding suggests two possibilities regarding the origin of CD25⁺CD4⁺ TR cells. One is that naive T cells can differentiate to CD25⁺CD4⁺ TR cells upon TCR stimulation, in a manner similar to that in which the expression of the transcription factors T-bet and GATA-3 instruct naïve T cells to differentiate to Th1 and Th2 cells, respectively (15, 16). Another possibility is that some of the functionally mature Tᵦ cells produced by the thymus are CD25⁺ or lose CD25 expression with retention of their suppressive function, as has been shown in rodents (17–19). Such CD25⁻ Tᵦ cells may become CD25⁺ upon activation, especially when other T cells respond to antigen stimulation, and IL-2 secreted by them may trigger the expansion of Tᵦ cells. Given the specific expression of FOXP3 in Tᵦ cells whether they are of thymic or peripheral origin, it remains to be determined whether other T cells with regulatory functions, such as IL-10-secreting Tr1 or TGF-β-secreting Th3 cells, may also express FOXP3 (20).

Besides self-tolerance and autoimmunity, evidence is now accumulating that natural CD4⁺ TR cells actively engage in negative control of a broad spectrum of immune responses to quasi-self or non-self antigens, as in tumor immunity, organ transplantation, allergy, and microbial immunity (1–3). With FOXP3 as a useful tool for investigating Tᵦ cells, further characterization of their developmental pathways will facilitate better control of pathologic as well as physiologic immune responses by expansion or reduction of Tᵦ cell populations.

Tales from the crypt

Eric A. Schon

Department of Neurology and Department of Genetics and Development, Columbia University, New York, New York, USA

Intestinal colonic crypts are derived from a stem cell population located at the base of each crypt. A new analysis of mitochondrial function and of the rates of mitochondrial DNA (mtDNA) mutation in individual crypts shows that mtDNA mutations arise in stem cells — and at a surprisingly high frequency (see the related article beginning on page 1351). Because crypts turn over extremely rapidly (about once per week), somatic mtDNA mutations can “take over the system” and even become homoplasmic, in a manner similar to what has been shown to occur in tumors.


Stem cells are the progenitors of specific cell lineages that become the body’s organs and tissues during embryonic development. After birth, however, stem cells continue to play an equally important role in tissue maintenance, as they are called upon to repopulate cells that turn over constantly. Hematopoietic stem cells were among the earliest identified exemplars of this role, but stem cells exist even in long-lived tissues — for example, muscle “satellite” cells — and, result in the last few years of stem cell lineages in brain and heart, our whole view of the idea of a “terminally differentiated” tissue has undergone a complete overhaul.

Mitochondrial dysfunction in stem cells

Mitochondria are semiautonomous organelles that are present in essentially all cells of the body. They contain their own DNA (mtDNA) and are the seat of a number of important housekeeping functions. Foremost among these is the production of energy via the respiratory chain and oxidative phosphorylation, an intricate system composed of five complexes and two electron carriers (Figure 1a). The mtDNA (Figure 1b), a tiny 16.6 kb maternally inherited circular genome present in multiple copies in each organelle (there are about 10,000 mtDNAs in a typical cell), encodes 2 rRNAs, 22 tRNAs, and only 13 polypeptides, all of which are subunits of the respiratory complexes. In the last 15 years, mutations in mtDNA, all of which impair oxidative energy metabolism, have been found to cause a wide spectrum of disorders (1). In these patients, the mutations are typically heteroplasmic; that is, mutated mtDNAs coexist with wild-type mtDNAs in varying proportions, resulting in a mosaic pattern of respirationally competent and incompetent cells. Respiratorily deficient cells must typically contain at least 80% mutated mtDNA to initiate dysfunction.

Heteroplasmic populations of mtDNA mutations can also arise randomly in somatic cells and can accumulate at low levels in individual cells during the course of normal aging (2). Even more intriguingly, somatic mtDNA mutations arise and are amplified in solid tumors, such as colon cancers (3), although a causative