ably have diminished elastin content. Since the rodent lung continues 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.

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

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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).

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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 deleted 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_R 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_R cells constitutively express CD25 (IL-2 receptor α chain) in the physiologic state. Indeed, removal of CD25$^+$CD4$^+$ T 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_R 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).

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Nonstandard abbreviations used: regulatory T (T_R); inflammatory bowel disease (IBD); T cell receptor (TCR).

FOXP3: master control gene for the development and function of natural CD4$^+$ T_R cells

There is now evidence not only for the presence of CD25$^+$CD4$^+$ T_R 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 depletion of CD25$^+$CD4$^+$ T_R cells (6). The causative gene, *FOXP3* (*Foxp3* in mice), which encodes a transcription repressor (7–10), is specifically expressed in CD25$^+$CD4$^+$ T cells in the thymus and periphery (11–13). Forced expression of the *Foxp3* gene can convert murine naive T cells to T_R cells that phenotypically and functionally resemble naturally arising CD25$^+$CD4$^+$ T_R cells

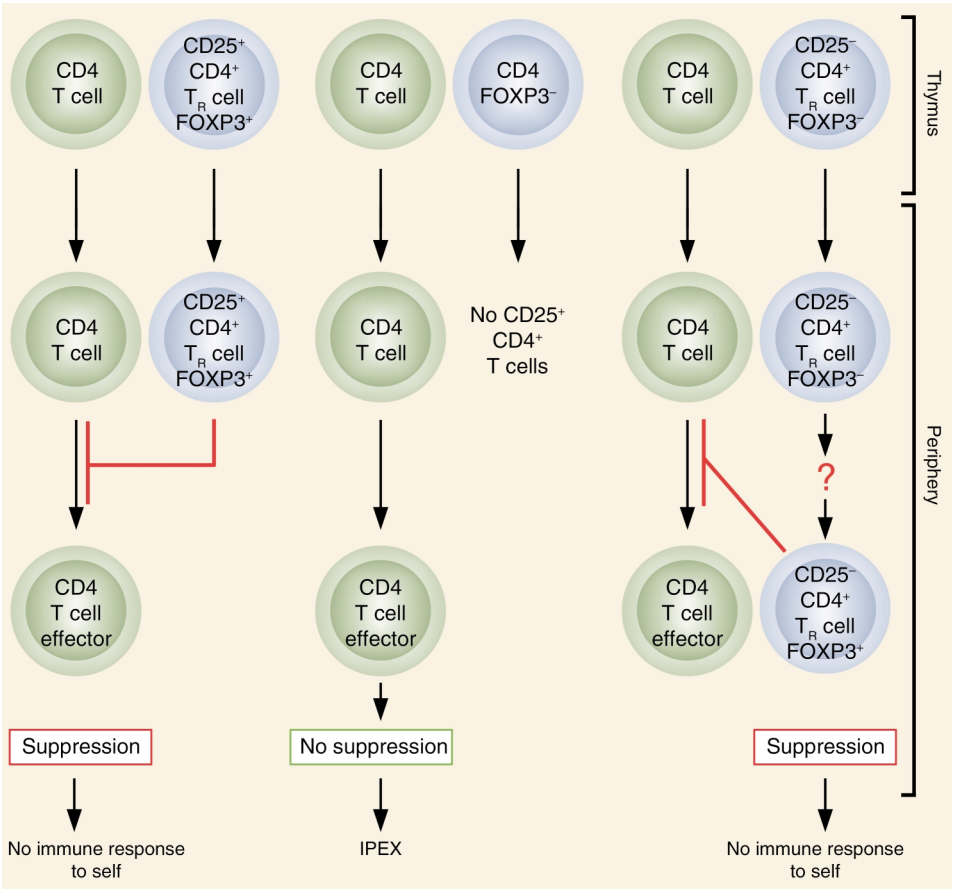

Figure 1
The normal thymus produces *FOXP3*-expressing $CD25^+CD4^+$ T_R cells. Some of the naive $CD25^-CD4^+$ T cells may also differentiate to *FOXP3*-expressing $CD25^+CD4^+$ T_R cells in the periphery. These T_R cells suppress the activation and expansion of self-reactive T cells that may cause autoimmune disease. Genetic defects of *FOXP3* cause IPEX due to developmental or functional defects of T_R cells. Adapted with permission from *Nature Immunology* (21).

(11, 12). 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 $CD25^+CD4^+$ T_R cells.

The origin and the developmental pathway of *FOXP3*-expressing T_R cells

The discovery of *FOXP3/Foxp3* as a specific and stable marker for natural T_R cells now makes it possible to determine the origin and the developmental pathway of T_R 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 $CD25^+CD4^+$ T_R 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 T_R 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 $CD25^+CD4^+$ T_R cells (Figure 1) (14). This interesting finding suggests two possibilities regarding the origin of $CD25^+CD4^+$ T_R cells. One is that naive T cells can differentiate to $CD25^+CD4^+$ T_R cells upon TCR stimulation, in a manner similar to that in which the expression of the transcription factors T-bet and GATA-3 instruct naive T cells to differentiate to Th1 and Th2 cells, respectively (15, 16). Another possibility is that some of the functionally mature T_R 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 $CD25^-$ T_R 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 T_R cells. Given the specific expression of *FOXP3* in T_R 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 $CD4^+$ T_R 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 T_R cells, further characterization of their developmental pathways will facilitate better control of pathologic as well as physiologic immune responses by expansion or reduction of T_R cell populations.

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Tales from the crypt

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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.

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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, with the discovery 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.

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Nonstandard abbreviations used: mitochondrial DNA (mtDNA); cytochrome *c* oxidase (COX); nuclear DNA (nDNA); succinate dehydrogenase (SDH).

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 respiratorily 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