Maturation of effector regulatory T cells

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Regulatory T cells adopt specialized differentiation programs controlled by transcription factors. The transcription factors Blimp-1 and IRF4 are now shown to be pivotal in the maturation of effector regulatory T cells.

The balance between naturally occurring regulatory T cells (T_{reg} cells) and effector T cells is crucial for the maintenance of immune self-tolerance and homeostasis. There is accumulating evidence that natural T_{reg} cells, which specifically express the transcription factor Foxp3, are heterogeneous in their differentiation stages, tissue localization and expression of effector molecules of suppression[1]. This functional diversity of T_{reg} cells is driven by specific transcription factors distinct from Foxp3 (refs. 2,3). The transcriptional repressor Blimp-1 (PRDM1) has a pivotal role in the terminal differentiation of B cells. Possible functions for Blimp-1 in T cells are now under investigation. In this issue of *Nature Immunology*, Cretney and colleagues focus on the possible involvement of Blimp-1 and the transcription factor IRF4 in the differentiation of natural T_{reg} cells[4]. They demonstrate that the expression of Blimp-1 and IRF4 defines a differentiation pathway that leads to the acquisition of a particular T_{reg} cell effector function.

Blimp-1 regulates a variety of genes to induce the differentiation of many various cell types. Blimp-1 typically represses its target genes and functions as a 'master regulator' of the terminal differentiation of B cells into antibody-secreting plasma cells[5]. It has been reported that Blimp1 also has roles in maintaining the homeostasis of effector T cells[6], in the specification of primordial germ cells in mice and as a tumor suppressor in germinal center–derived B cells. Genome-wide chromatin-immunoprecipitation and microarray analyses have also shown that the gene encoding Blimp-1 (*Prdm1*) is a target of Foxp3 in T_{reg} cells[7].

The IRF family of transcription factors includes ten members that contribute to various aspects of innate and adaptive immunity. IRF4, which is expressed in macrophages, dendritic cells and lymphocytes, downregulates Toll-like receptor signaling and is indispensable for the differentiation of T helper type 2 effector cells. Foxp3 directly regulates *Irf4* expression, then IRF4 and Foxp3 directly regulate *Prdm1* expression in T_{reg} cells (**Fig. 1**).

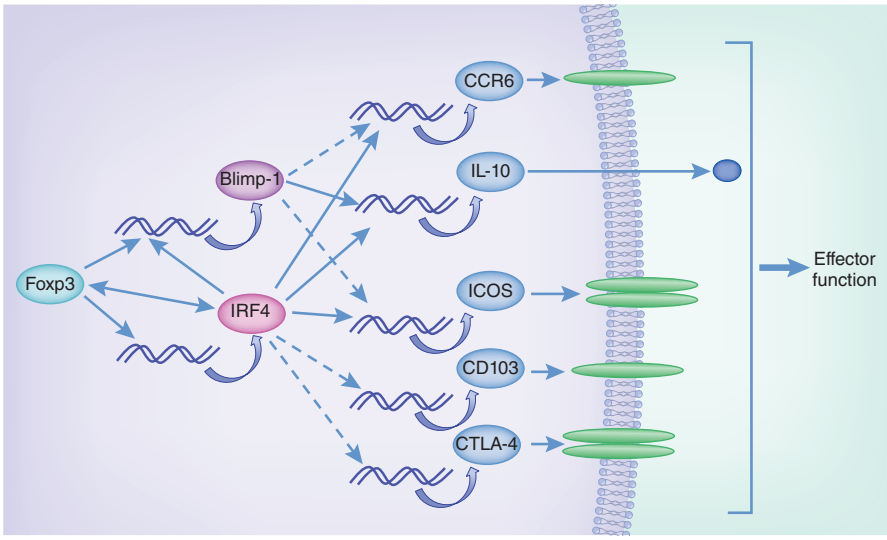

Figure 1 Control of the effector function of T_{reg} cells by transcription factors. Foxp3 directly or indirectly controls the expression of molecules responsible for conferring suppressive function to T_{reg} cells. Foxp3 directly regulates the expression of Blimp-1 and IRF4, which in turn upregulate Blimp-1 expression. IRF4 also associates with Foxp3, and the resulting molecular complex controls the expression of Foxp3 target genes. Blimp-1 and IRF4 regulate a variety of genes, some of which encode molecules that contribute to the effector function of T_{reg} cells. Solid lines in arrows indicate direct regulation, with experimental confirmation.

Blimp-1 is expressed in a defined subset of effector and memory T cells of both the $CD4^+$ lineage and $CD8^+$ lineage[8]. Blimp-1-deficient T cells produce more interleukin 2 (IL-2) and interferon-γ and less IL-10 and IL-4 than wild-type T cells do. Mice with T cell–specific deletion of *Prdm1* develop severe colitis, but it has remained unclear how the absence of Blimp-1 in T cells elicits this disease. To address this issue, Cretney and colleagues now examine the effects of Blimp-1 deficiency on T_{reg} cell function[4], as T_{reg} cells express Blimp-1 and are able to suppress the development of colitis. They show that Blimp-1 expression is confined to IL-10-producing T_{reg} cells with an effector phenotype and that Blimp-1-deficient T_{reg} cells fail to secrete IL-10, which indicates that Blimp-1 is essential for the ability of T_{reg} cells to produce IL-10. Analysis of mixed–bone marrow chimeras shows that Blimp-1-deficient T_{reg} cells are overrepresented in Peyer's patches, gastrointestinal epithelium and bronchoalveolar fluid relative to their competing wild-type T_{reg} competitors. In addition, both wild-type and Blimp-1-deficient T_{reg} cells are efficiently recruited to the lung after infection with influenza virus, but only wild-type T_{reg} cells upregulate expression of the inducible costimulator ICOS, whereas Blimp-1-deficient T_{reg} cells fail to do so. These results collectively suggest that Blimp-1 is required for the maturation of effector T_{reg} cells.

As IL-2 has a key role in the survival and function of T_{reg} cells and can induce *Prdm1* expression in conventional $CD4^+$ T cells, the authors attempt to determine whether IL-2 signaling modulates *Prdm1* expression in T_{reg} cells *in vivo*. They observe more Blimp-1-expressing T_{reg} cells in mice given injections of complexes of IL-2 and antibody to IL-2, which augments IL-2 signaling and results in more T_{reg} cells. They find a similarly larger fraction of Blimp-1-expressing T_{reg} cells after repeated injection of agonistic antibody to the costimulatory molecule CD40, which activates antigen-presenting cells to secrete proinflammatory cytokines. These data indicate that IL-2 and proinflammatory cytokines can induce Blimp-1 expression in natural T_{reg} cells.

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The transcription factors IRF4 and T-bet are well known for their functions in the polarization and functional diversification of $CD4^+$ helper T cells. Given the finding that the Blimp-1^+ T_{reg} population has high expression of both IRF4 and T-bet, the authors next attempt to determine whether IRF4 and/or T-bet are/is necessary for the generation of Blimp-1^+ effector T_{reg} cells. Analysis of mice deficient in T-bet shows that T-bet is not essential for the differentiation of Blimp-1-expressing $ICOS^+$ effector T_{reg} cells. In contrast, mice deficient in IRF4 show a striking absence of Blimp-1^+ T_{reg} cells. IRF4-deficient T_{reg} cells fail to differentiate into effector T_{reg} cells, lack expression of Blimp-1, ICOS and IL-10 and are severely impaired in their expression of activation markers and molecules required for the homing of T_{reg} cells, such as CD62L, CD103 and CCR6, and for suppressive function, such as CTLA-4. These findings are consistent with published reports proposing that IRF4 expression endows T_{reg} cells with the ability to suppress T helper type 2 responses[3].

The study published in this issue demonstrates potential roles for Blimp-1 and IRF4 in the differentiation and maturation of effector T_{reg} cells[4], yet important questions remain unanswered. For example, given the marginal effects of Blimp-1 deficiency on T_{reg} cell function, what specific function does Blimp-1 have in the differentiation of effector T_{reg} cells? Is there any interaction between Blimp-1 and other transcription factors involved in the T_{reg} cell–specific transcriptional regulation of cell activation, suppressive function, production of cytokines (such as IL-10) and homing to inflammation sites? Given that T_{reg} cell–specific transcriptional control is mediated by a large molecular complex containing Foxp3 and other transcription factors, chromatin-remodeling factors and coregulators, the combination or balance of these factors may be critical for determining T_{reg} cell development and function. It will be useful to delineate any possible cross-talk between Blimp-1 and other transcription factors, including IRF4, in the differentiation and function of effector T_{reg} cells. In addition, as Blimp-1 is broadly expressed in various lineages of lymphoid cells, which functions of Blimp-1 are common for the differentiation of various types of lymphocytes, including plasma cells and effector or memory T cells, need to be determined.

Finally, another important finding in this study is the sequential effect of transcription factors on the differentiation of effector T_{reg} cells. It has been shown that several transcription factors, including Runx1, NFAT, Foxo, Eos and Foxp3, interactively control T_{reg} development and function. Runx1 binds to Foxp3 in T_{reg} cells and contributes to Foxp3-mediated transcriptional regulation[9]. Foxo1 and Foxo3, which bind to the *Foxp3* locus and control the activity of the *Foxp3* promoter, are critical in specifying the T_{reg} cell lineage[10]. NFAT and Eos, whose expression is independent of Foxp3 in T_{reg} cells, contribute to the Foxp3-dependent transcriptional regulation via direct binding to Foxp3 (refs. 11,12). Blimp-1 and IRF4, whose expression is controlled by Foxp3, are required for the maturation of the effector T_{reg} cells. Moreover, IRF4 directly regulates *Prdm1* expression and associates with Foxp3. Thus, the results in this study provide the opportunity to further explore the transcription factor–dependent sequential development of T_{reg} cells and also elucidate how particular transcription factors act together in an immune network.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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Defeating sepsis by misleading MyD88

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Helminth parasites are adept at dampening immunity. New data showing that intracellular degradative pathways are manipulated have important implications for therapy.

Antigen-presenting cells (APCs) such as macrophages and dendritic cells are the watchdogs of the immune system that raise the first alarm in the event of pathogen invasion or tissue trauma. They express an array of extracellular and intracellular receptors, including Toll-like receptors (TLRs) and Nod-like receptors, which detect pathogen-associated molecular patterns and initiate the production of inflammatory cytokines in the host[1]. Additional C-type lectin receptors recognize critical carbohydrate structures on pathogens and self antigens[2]. TLRs and C-type lectin receptors are also important in determining responses to damage-associated molecular pattern signals from dying cells. In response to this battery of detectors, pathogens have evolved multifarious means of evading, defusing and even misdirecting the intracellular response to pathogen-associated molecular patterns, as shown by Puneet *et al.* in an important new study in this issue of *Nature Immunology*[3].

Pathogen-associated molecular patterns such as microbial lipoprotein, lipopolysaccharide (LPS), viral double-stranded RNA or unmethylated bacterial DNA activate TLRs and associated adaptor molecules such as MyD88 and TRIF (**Fig. 1a**). These molecules trigger a protein kinase–mediated cascade that leads to the expression of genes encoding characteristic inflammatory effectors. Thus, recognition of bacterial LPS by TLR4 activates APCs and induces key proinflammatory cytokines such as interleukin 12, tumor necrosis factor and interleukin 1β, which results in a strongly biased T helper type 1 phenotype of T cells responding to such dendritic cells (DCs) during antigen presentation.

In many infectious settings, pathogens and their products disrupt normal APC function in response to infection[4]. Although this process can be beneficial for the pathogen, it can also affect the ability of the APC to react in the presence of an unrelated pathogen or inflammatory condition. This is particularly true in the case of helminth infection, during which parasitized hosts frequently have a diminished

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