Published in final edited form as:

Nat Immunol. 2010 December ; 11(12): 1077–1078. doi:10.1038/ni1210-1077.

Regulatory ripples

Yasmine Belkaid and

Mucosal Immunology Unit, Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA

WanJun Chen

Mucosal Immunology Unit, National Institutes of Dental and Craniofacial Research, National Institutes of Health, Bethesda, Maryland, USA

Yasmine Belkaid: ybelkaid@niaid.nih.gov

Abstract

Regulatory T cells come in many different forms depending on their mode of action or developmental origin. Data now show that interleukin 35, an immunomodulatory cytokine secreted by regulatory T cells, and interleukin 10 induce so-called ‘iT_R35 cells’, which may have an important role in the phenomenon of infectious tolerance.

The maintenance of host integrity relies on the constant resetting of tissue homeostasis by regulatory networks. One cardinal feature of this regulation is associated with the ability of lymphocytes with constitutive or induced regulatory properties to accumulate at the disrupted site and limit tissue damage. In this issue of *Nature Immunology*, a paper by Vignali and colleagues describes a newly identified population of induced CD4⁺ regulatory T cells (T_{reg} cells), called ‘iT_R35 cells’, with a highly distinctive phenotype and potent suppressive functions¹.

The idea of populations of cells with regulatory properties has taken center stage over the past few years. CD4⁺ T_{reg} cells in particular have an essential role in maintaining peripheral immune tolerance as well as in preventing autoimmunity and chronic inflammation. Several types of T_{reg} cells have been described on the basis of their origin, generation and mechanism of action. In a simplistic manner, these cells can be categorized as endogenous T_{reg} cells (nT_{reg} cells), represented by thymus-derived cells that express the transcription factor Foxp3, and inducible T_{reg} cells (iT_{reg} cells), such as interleukin 10 (IL-10)-producing Tr1 cells² or Foxp3⁺ T cells induced in the periphery via many different mechanisms^{3,4}. Although the precise mechanisms by which these cells function to maintain the delicate balance between immunity and tolerance remain poorly understood, it is presumed that ‘collaboration’ and crosstalk among these various T_{reg} cell populations are required for the integrated control of immune responses (Fig. 1).

Particular attention has been given to nT_{reg} cells as a critical mediators of peripheral tolerance. Although abundant experimental and clinical evidence supports the idea of a role for nT_{reg} cells in immune homeostasis, much remains to be understood about their mechanism of action, origin and connection with other T_{reg} cell subsets. In particular, what has remained unclear is how such a defined population could control the diverse immunologic landscapes of the host not only under steady-state conditions but also in the face of diverse insults. The beginning of an explanation was provided by studies demonstrating that the ability of T_{reg} cells to control immunologically polarized settings can be associated with their acquisition of specific transcription factors linked to effector T cell lineages, such as T-bet and IRF4 (refs. 5,6). Such a phenomenon would endow T_{reg} cells with defined homing, survival and regulatory properties and therefore allow them to ‘tune’ their suppressive capacity to suit specific settings.

A complementary explanation may be associated with the ‘passing of the torch’ of the T_{reg} cell phenotype to other cell subsets and the establishment of regulatory networks. This idea of ‘infectious tolerance’ proposes that regulatory function is not a property solely of specialized cells but is instead an ability that can be transferred to other cell subsets that themselves then become partners in the regulatory process⁷. Thus, regulation can target and be carried on by other lymphocyte populations—a well-described process in the context of transplantation tolerance⁸. In addition to allowing the propagation of regulation from a small number of nT_{reg} cells, another advantage would be that the induced regulation could be shaped by the endogenous features of the targeted site. This would trigger a regulatory response suitable to a given environment. The underlying mechanisms of such a phenomenon have remained incompletely understood but are believed to occur via diverse processes involving cell contact and/or the release of soluble factors. In this context, it has been suggested that nT_{reg} cells could mediate infectious tolerance by converting naive CD4⁺ T cells into iT_{reg} cells in a TGF- β dependent manner⁹. Dendritic cells are also probably central to this process. Indeed, nT_{reg} cells can manipulate antigen-presenting cells toward a tolerogenic phenotype; these in turn induce new populations of T_{reg} cells¹⁰. Because of the complexity of each microenvironment encountered by T_{reg} cells, the mediators of these responses are probably numerous and involve a large number of cytokines.

IL-35 is a heterodimeric cytokine consisting of an EBI3 subunit plus the p35 subunit of IL-12 (ref. 10). The introduction of IL-35 into the regulatory network came from a study proposing that this cytokine contributes to the ability of mouse nT_{reg} cells to mediate their regulatory functions¹¹. Vignali and colleagues now add another member to the expanding family of T_{reg} cells and propose that nT_{reg} cell-mediated suppression induces, via the concerted action of IL-10 and IL-35, a population of T_{reg} cells characterized by their production of IL-35, which they call ‘iT_R35 cells’¹. Notably, these cells are phenotypically and functionally distinct from other populations of T_{reg} cells described thus far in that they do not express Foxp3 and they mediate immunosuppression via IL-35 and seemingly independently of IL-10, TGF- β , the immunomodulatory receptor CTLA-4 or any other known T_{reg} cell-associated suppressive molecule. Although it seems that human nT_{reg} cells do not express IL-35 (ref. 12), naive human CD4⁺ T cells can be induced to develop into iT_R35 cells in the presence of IL-35 (ref. 1) or virus-exposed DCs¹³.

The controlled expansion or generation of new populations of T_{reg} cells has raised tremendous interest because of its therapeutic potential. However, the enthusiasm for using these cells has been tempered by the observation that in the face of inflammation, T_{reg} cells can lose their regulatory properties and in some cases acquire an effector phenotype¹⁴. One intriguing feature of the iT_R35 cells described by Vignali and colleagues is their apparent stability and efficiency *in vivo*. For example, these cells are as efficient as nT_{reg} cells at restoring immune homeostasis and preventing autoimmunity in *Foxp3*^{-/-} mice, controlling T cell proliferation in a lymphopenic setting and limiting the pathogenesis during experimental colitis. This would suggest that the ‘guilt by association’ of these T_{reg} cells could represent a safer and broadly effective therapeutic strategy for promoting regulation *in vivo*. The physiological relevance of this efficiency and stability *in vivo* remains unclear, but it could be speculated that iT_R35 cells, through their ability to produce IL-35, could in turn perpetuate regulation by inducing other populations of T_{reg} cells—in other words, infectious tolerance. However, both chains of IL-35 are much more abundant in T cells from various tumors, and transfer of iT_R35 cells promotes tumor development¹. Because of the potentially detrimental role of IL-35, assessing how far this rippling regulatory effect could go and identifying the factors able to constrain the spreading of regulation is critical. Nevertheless, one striking feature of IL-35 is its instability. This trait renders its generation *in vitro* challenging and has raised some controversy about the physiological existence of this molecule as a heterodimeric cytokine. However, the lability of IL-35 could in fact represent an inherent safety feature in that this constrains its effect to the targeted sites. Another surprising aspect of T_{reg} cells induced in the presence of IL-35 is the finding that they are apparently distinguished solely by the upregulation of both chains of this cytokine. This unusual and highly defined transcriptional profile clearly deserves further exploration. Furthermore, given this unusual phenotype, it remains unclear if these cells can be truthfully described as an actual subset, and indeed the authors of this study make no such claim¹.

As the cascade of events triggered by the introduction of a defined population of T_{reg} cells is linked to the microenvironment in which they are encountered, the participants and mediators of infectious tolerance are probably numerous. Furthermore, in many cases the mechanisms of action of the triggering population are probably distinct from the induced ones. Thus, much remains to be learned to grasp regulation in an integrated manner and devise appropriate therapeutic strategies aimed at the induction or limitation of regulatory pathways.

References

1. Collison LW, et al. Nat. Immunol. 2010; 11:1093–1101. [PubMed: 20953201]
2. Roncarolo MG, et al. Immunol. Rev. 2006; 212:28–50. [PubMed: 16903904]
3. Chen W, et al. J. Exp. Med. 2003; 198:1875–1886. [PubMed: 14676299]
4. Sun CM, et al. J. Exp. Med. 2007; 204:1775–1785. [PubMed: 17620362]
5. Koch MA, et al. Nature Immunology. 2009; 10:1–7. [PubMed: 19088730]
6. Zheng Y, et al. Nature. 2009; 458:351–356. [PubMed: 19182775]
7. Qin S, et al. Science. 1993; 259:974–977. [PubMed: 8094901]
8. Waldmann H, Adams E, Fairchild P, Cobbold S. Immunol. Rev. 2006; 212:301–313. [PubMed: 16903922]
9. Andersson J, et al. J. Exp. Med. 2008; 205:1975–1981. [PubMed: 18710931]

10. Niedbala W, et al. Eur. J. Immunol. 2007; 37:3021–3029. [PubMed: 17874423]
11. Collison LW, et al. Nature. 2007; 450:566–569. [PubMed: 18033300]
12. Bardel E, Larousserie F, Charlot-Rabiega P, Coulomb-L'Hermine A, Devergne O. J. Immunol. 2008; 181:6898–6905. [PubMed: 18981109]
13. Seyerl M, et al. Eur. J. Immunol. 2010; 40:321–329. [PubMed: 19950173]
14. Oldenhove G, et al. Immunity. 2009; 31:772–786. [PubMed: 19896394]

Figure 1. Regulatory networks

Foxp3⁺ nT_{reg} cells can control effector responses via various mechanisms, including the release of cytokines such as IL-10, TGF-β and IL-35 or cell surface molecules such as CD39 and CTLA-4. Molecules able to induce T_{reg} cells, such as regulatory cytokines (IL-10 or TGF-β) or metabolites (retinoic acid), can also be produced by other cell subsets from the surrounding microenvironment. These molecules can contribute to the induction of a new population of T_{reg} cells, such as iT_{reg} cells, Tr1 cells or iT_{R35} cells. These cells in turn directly or indirectly contribute to the expansion of the regulatory network by inducing new populations of T_{reg} cells via the process of infectious tolerance. In particular, iT_{R35} cells, through their ability to release IL-35, may be able to induce a new population of iT_{R35} cells. Foxp3⁺ nT_{reg} cells and iT_{reg} cells can also manipulate antigen-presenting cells in a way that renders these cells less efficient at inducing a new population of effector cells or reactivating them. Nrp-1, neuropilin 1; Lag3, lymphocyte-activation gene 3.