Interleukin 10 is a growth factor for a population of regulatory T cells


Abstract
Induction and maintenance of peripheral tolerance are important mechanisms to maintain the balance of the immune system. In addition to the deletion of T cells and their failure to respond in certain circumstances, active suppression mediated by T cells or T-cell factors has been proposed as a mechanism for maintaining peripheral tolerance. However, the inability to isolate and clone regulatory T cells involved in antigen-specific inhibition of immune responses has made it difficult to understand the mechanisms underlying such suppression. Here, we show that chronic activation of both human and murine CD4+ T cells in the presence of interleukin (IL)-10 gives rise to CD4+ T-cell clones with low proliferative capacity, producing high levels of IL-10, low levels of IL-2 and no IL-4. These antigen-specific T-cell clones suppress the proliferation of CD4+ T cells in response to antigen, and prevent colitis induced in SCID mice by pathogenic CD4+CD45RBhigh splenic T cells. Thus IL-10 drives the generation of a CD4+ T-cell subset, designated T regulatory cells 1 (Tr1), which suppresses antigen-specific immune responses and actively downregulates a pathological immune response in vivo.

Comment
A hallmark of the intestinal immune system is its ability to mount a rapid and potent effector response to pathogenic bacteria, viruses and parasites, while remaining tolerant to the vast array of luminal bacteria and ingested antigens. It is generally considered that the breakdown of this tolerance is of crucial importance in the development of inflammatory bowel disease (IBD) in humans. The mechanisms governing immune responsiveness and non-responsiveness in the intestine are not well understood; however, the recent finding that IBD develops in mice which lack particular T cell subsets (severe combined immunodeficient (SCID) mice restored with CD45RBhigh CD4+ T cells1,2 and T cell receptor-α chain deficient mice3), or in mice with targeted deletions of the interleukin (IL)-10 (IL-10KO)4 or IL-2 (IL-2KO)5 genes suggests that T cell subsets and cytokines play an active role in regulating potentially tissue damaging immune responses in the intestine. Although these models may seem complex and arcane to clinical gastroenterologists, several broad themes have emerged from these studies which may be of tremendous clinical importance.

The paper by Groux et al sheds some light on how IL-10 (generally thought of as an immunosuppressive cytokine) may act to regulate intestinal inflammation. The authors show that repetitive antigenic stimulations in vitro of human and murine CD4+ cells in the presence of IL-10 results in the generation of a T cell subset with low proliferative capacity which secretes high levels of IL-10 and interferon γ (IFN-γ) and has immune regulatory activities both in vitro and in vivo. These cells, which the authors term T regulatory 1 cells (Tr1), exhibit a cytokine profile distinct from previously described Th1, Th2 and Th0 subsets of CD4+ T cells.

A striking aspect of the paper, particularly with regard to regulation of intestinal inflammation, was the finding that colitis induced in SCID mice by transfer of CD45RBhigh CD4+ T cells could be prevented by co-transfer of murine Tr1 clones derived from CD4+ T cells which expressed a transgenic T cell receptor specific for a peptide of ovalbumin (OVA). Immune suppression depended on antigen induced activation of Tr1 cells in vivo as these cells only inhibited colitis in recipients which received OVA in their drinking water. Evidence to date suggests that colitis in this model is due to the development of a pathogenic Th1 response against components of the normal flora with excessive local production of IFN-γ and tumour necrosis factor, as is seen in patients with Crohn’s disease.6,7 How, then, do OVA-reactive Tr1 cells inhibit this tissue damaging response? The authors conclude that Tr1 cells are activated as a result of oral administration of OVA and secrete soluble mediators which suppress activation of pathogenic T cells (presumably responding to bacterial antigens) in the local environment by an antigen driven bystander suppression mechanism. Although this is an attractive hypothesis and fits with the in vitro described properties of these cells, no data are presented to support this view. Further experiments are required to identify where Tr1 cells are activated in vivo and precisely how they mediate their immune suppressive activities, particularly whether these activities are attributable entirely to the production of soluble immune suppressive molecules, such as IL-10 and transforming growth factor (TGF)-β, or involve cellular interactions between pathogenic and regulatory populations of T cells, either directly or via antigen presenting cells.

The functional properties of Tr1 cells resemble those of the regulatory T cells shown to be present among the CD45RBhigh CD4+ T cell subset from the spleen of normal mice. These cells, when co-transferred with CD45RBhigh CD4+ T cells to SCID mice, were able to inhibit the development of colitis by a mechanism that depended on TGF-β, but was independent of IL-4, suggesting that these cells also represented a subset of T cells functionally distinct from Th2 cells.8 IL-10, however, also plays an important role in the function of this population as CD45RBhigh CD4+ cells isolated from IL-10KO mice failed to inhibit colitis (Powrie et al, unpublished data). It seems likely that IBD, which develops spontaneously in IL-10KO mice, is partly a result of the absence of this population of regulatory T cells which act normally to inhibit the
development of inflammatory responses in the gut. It is possible that the Tr1 cells described by Groux et al represent an in vitro generated and enriched counterpart of these regulatory T cells which exist naturally within the CD4+ CD45RB\textsuperscript{low} population.

Numerous studies have documented the existence of T cell populations which are able to inhibit immune responses against a range of different antigens, including antigens of pathogenic micro-organisms, autoantigens and alloantigens. A major obstacle in characterising these cells has been the inability to cultivate these cells routinely in vitro. The finding that IL-10 is a growth factor for regulatory T cells is an important step forward in this field. It should now be possible to generate Tr1 cells against a wide variety of antigens and test their capacity to modulate primary as well as established antigen specific responses in vivo.

An obvious clinical extension of these studies would be to use cellular therapy with Tr1 cells as a treatment for inflammatory diseases. One of the problems in proposing immune therapy for the treatment of such diseases is that in most cases the antigen specificity of pathogenic T cells is not known, making it very difficult to design antigen specific immune therapies. However, use of Tr1 cells may circumvent this problem as they are able to inhibit inflammatory responses via a mechanism of bystander suppression. Tr1 cells could be generated in response to antigens known to be present in the target organ which are not necessarily the precise antigens that drive the pathogenic response (that is, insulin for insulin dependent diabetes, MBP for multiple sclerosis, and bacterial antigens for IBD). Antigen specific Tr1 cells should in theory home to the target organ and inhibit responses against both their specific antigen and other antigens present in the local environment. This approach, however, may not be practical as Tr1 cells do not proliferate well and it may be very difficult to grow enough of them. A more practical and no doubt more cost efficient alternative will be to develop pharmacological interventions which would induce the development of Tr1 cells in situ. One of these, IL-10 itself, is already in clinical trials for the treatment of IBD and it will be very interesting to determine whether there is evidence of increased numbers of Tr1 cells in the intestines of these patients.

Clearly, studies on Tr1 cells are at an embryonic stage and while offering some attractive avenues for potential therapeutic intervention, more information on the basic biology of these cells is required before considering clinical applications. Perhaps most importantly it will be essential to establish whether Tr1 cells themselves are capable of causing immune pathology as both IL-10\textsuperscript{+} and TGF-\beta\textsuperscript{+} can, under some circumstances, increase immune pathology.

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