

# Commentary

## T-cell-mediated control of autoimmunity

Don Mason

Sir William Dunn School of Pathology, Oxford, UK

**Correspondence:** Don Mason, Sir William Dunn School of Pathology, Oxford OX1 3RE, UK. Tel: +44 (0)1865 275 589; fax: +44 (0)1865 275 591; email: [Don.Mason@path.ox.ac.uk](mailto:Don.Mason@path.ox.ac.uk)

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### Abstract

Inflammatory responses provoked by pathogens are antigen-specific in their induction but are nonspecific in their effects. Consequently, they are potentially damaging to the host that produces them. In addition, the immune system can respond specifically to self antigens, thereby giving rise to autoimmune diseases. A number of regulatory mechanisms have evolved to prevent such adverse effects. One of these has been shown to depend on a particular subset of CD4<sup>+</sup> T cells that appears to have evolved specifically for this protective role. These cells are termed regulatory T cells. This review summarises what is known about them.

**Keywords:** autoimmunity, inflammation, regulation, T cells, thymus

### Introduction

The mammalian immune system has evolved a number of potent mechanisms to protect the individual from the wide range of pathogens that can infect it, but these effector mechanisms can often be damaging to the host, as well as to the pathogens that evoke them. For example, the tissue necrosis that accompanies the chronic inflammation of tuberculosis is caused not by the bacillus but by the immune response to it. Similarly, acute hypersensitivity reactions to otherwise innocuous sensitising agents may be unnecessary but life threatening, because of their effects on the respiratory system or cardiovascular system. Finally, there are a number of autoimmune diseases in which the immune system mounts a specific response against the tissues of the host.

Given these ample illustrations that the mammalian immune response is potentially lethal to the host, one may ask why are not all individuals equally susceptible to the types of diseases described? Currently, no comprehensive answer to this question can be given. Nonetheless, research in

immune homeostasis in the past 10 to 15 years has demonstrated the existence of a T-cell-mediated regulatory system that appears to have evolved specifically to prevent autoimmunity and that may play an equally vital role in moderating the immune response to foreign antigens.

### Evidence for regulatory T cells in the control of autoimmunity

It has been a widely held view that thymocytes with receptors for self antigens expressed in the thymus are purged from the developing T-cell repertoire by the process of clonal deletion. It was further accepted that tolerance to self antigens expressed exclusively in extrathymic sites was a consequence of either peripheral deletion of autoreactive T cells or the induction of nonresponsiveness (anergy) in these cells. However, these mechanisms were not compatible with the observation that rodents made relatively lymphopenic by a variety of experimental procedures developed a wide range of autoimmune diseases: gastritis, diabetes, thyroiditis, oophoritis, and hepatitis. Several methods of generating the lymphopenia resulted

in organ-specific autoimmunity: thymectomy in the first 3 days of life, adult thymectomy plus  $^{137}\text{Cs}$   $\gamma$  irradiation, partial restoration of T-cell numbers in genetically T-cell-deficient recipients, by the transfer of a limited number of T cells from normal congenic donors.

The key observation in all of these systems was that the development of disease could be prevented if the lymphopenic animals were given a particular subset of  $\text{CD4}^+$  peripheral T cells or  $\text{CD4}^+ \text{CD8}^-$  thymocytes from normal donors (reviewed [1–3]).

These experiments established three points:

1. Autoreactive T cells are to be found in normal, healthy animals that show no tendency to develop autoimmune disease.
2. These autoreactive T cells can be controlled by a defined subset of  $\text{CD4}^+$  T cells, now termed regulatory T cells, or Treg. Most of these cells express CD25, the IL-2R  $\alpha$  chain.
3. Treg are present in the thymus and in the periphery.

### The role of Treg in the control of immune responses to foreign antigens

Rodents made relatively T-cell-deficient in  $\text{CD25}^+ \text{CD4}^+$  T cells can develop severe inflammatory infiltrates in their lungs and an inflammation of the colon resembling ulcerative colitis [4,5]. Restoration of the deficiency in Treg in these rodents prevents these inflammatory diseases. It seems likely that, in both lungs and colon, the inflammation is induced by a dysregulated response to foreign antigens; germ-free mice do not get colitis [6]. While the specificity of the Treg that prevents these inflammatory diseases is not known, it is notable that the thymus is a potent source of these protective cells. These results may be interpreted in at least two ways. One interpretation is that Treg from the thymus provide a peripheral microenvironment for the induction of Treg that are specific for the foreign antigens causing the inflammation. An alternative interpretation is that the recognition of self antigens by Treg in the periphery moderates inflammatory responses by modifying the functions of antigen-presenting cells (see below) or by producing anti-inflammatory cytokines. Whichever mode of action proves to be the true one, it appears that Treg have not evolved solely to prevent autoimmunity, but also to control immune responses to foreign antigens. Indeed, a case might be made for maintaining that the latter role is their primary one and that subliminal autoimmunity in normal individuals serves the essential function of promoting the survival of Treg in the periphery.

### The tissue distribution and characterisation of Treg

In the periphery, Treg are present in lymph node, spleen, thoracic duct lymph, and blood. In both rats and mice,

they have the phenotype of memory cells, as judged by the low-molecular-mass isoform of CD45 that they express. The majority, but not all, are  $\text{CD25}^+$  [2,3,7]. In view of the memory phenotype of these peripheral cells, it was surprising to find that the thymus is a rich source of Treg [8]. However, these cells also express CD25 and are found among the mature  $\text{CD4}^+$  subset of thymocytes that expresses L-selectin; they are not peripheral cells that have returned to the thymus from the periphery. These findings showed that, in addition to its well recognised role in the positive and negative selection of thymocytes, the thymus has a *third* function, that of generating Treg [9].

### The mode of action of Treg and their antigen specificity

Treg isolated from the thymus, or from peripheral lymphoid tissue, can inhibit *in vitro* T-cell activation induced either by specific antigen or by the T-cell mitogens concanavalin A (Con A) and phytohaemagglutinin (PHA). However, they cannot prevent activation induced by the combination of calcium ionophore and phorbol esters nor by cross-linking of the T-cell receptor by plate-bound anti-CD3 monoclonal antibody. Further, the inhibition by Treg of mitogen-induced activation requires that these cells make cognate interactions with the T cells that they are inhibiting and with the antigen-presenting cells that are essential for T-cell mitogens to function. In contrast, it is not possible to abrogate this inhibition by adding anti-cytokine antibodies to the T-cell cultures [10,11]. These results suggest that Treg mediate their inhibitory effects by interfering directly with the stimulatory function of dendritic cells and there is experimental evidence that this is so [12–14]. The interaction of Treg with dendritic cells results in the downregulation of expression of the costimulatory molecules CD80 and CD86, which play an essential role in the activation of naïve T cells [14]. Further, Treg that prevent organ-specific autoimmunity and inflammatory bowel disease in mice constitutively express CTLA-4, which is a ligand for both CD80 and CD86 [15–17]. It is not yet known whether the interaction between CTLA-4 on Treg and its ligands on dendritic cells is directly responsible for the downregulation of ligand expression. However, antibodies to CTLA-4 *in vitro* and *in vivo* abrogate the inhibitory action of Treg [15–17].

These results contrast with those from *in vivo* tests of the function of Treg, where there is clear evidence for a role for anti-inflammatory cytokines. Neutralising antibodies, to IL-4 and transforming growth factor (TGF)- $\beta$ , prevent Treg from protecting rats from lymphopenia-induced autoimmune thyroiditis [18], and in mice, IL-10 and TGF- $\beta$  have been shown to play an essential role in the prevention of inflammatory bowel disease by Treg [19,20]. Taken together, the results found *in vitro* and *in vivo* indicate that Treg have at least two modes of action.

## Antigen-specificity of Treg

Peripheral CD4<sup>+</sup> memory T cells from young adult rats that have had their thyroid glands ablated by exposure *in utero* to <sup>131</sup>I are not able to prevent autoimmune thyroiditis on transfer into syngeneic recipients made lymphopenic by adult thymectomy and <sup>137</sup>Cs  $\gamma$  irradiation. As described above, peripheral CD4<sup>+</sup> memory T cells from euthyroid donors are able to do so. This deficiency of protective capacity of Treg from athyroid animals appears specific for thyroid autoimmunity; Treg from these rats are perfectly able to protect rats from lymphopenia-induced diabetes. Significantly, thymocytes from athyroid rats function as effectively as those from euthyroid donors in preventing thyroiditis in lymphopenic recipients. It appears that the absence of a thyroid gland does not impair the intrathymic generation of Treg that can prevent autoimmune thyroiditis, but it does cause a failure of these cells to survive in the periphery [21].

It is difficult to account for these results other than by assuming that Treg specifically recognise the autoantigen that they are protecting.

## Conclusion

Regulatory T cells have been demonstrated in mouse, rat, and man [Stephens L and coworkers, paper submitted], but much remains to be learnt about their homeostasis and their site and mode of action. It seems likely that a relative deficiency of Treg is at least one cause of diseases that arise through inappropriate immune responses to self and foreign antigens. There is also a theoretical possibility, yet to be fully explored, that they inhibit protective immune responses to malignant cells. They are, therefore, of clinical interest for several reasons and they are currently being studied intensively.

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