



Regulatory T cells and COPD

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ABSTRACT

While the innate immune system has long been implicated in the pathogenesis of COPD, a role for the acquired immune system is less well studied. The increasing recognition that COPD shares features with autoimmune disease has led to interest in a potential role for regulatory T cells, which are intimately involved in the control of autoimmunity. The suggestion that regulatory T cell numbers are increased in patients with COPD may indicate their dysfunction or resistance to suppression by target cells. Investigation of regulatory T cells may therefore be of importance in understanding the inflammation and tissue damage that occurs in patients with COPD who cease smoking.

INTRODUCTION

The role of autoimmunity in the pathogenesis of COPD is increasingly recognised. While tobacco smoking is the main risk factor for COPD, not all smokers develop the disease. In addition, inflammation persists in patients with COPD after they stop smoking, suggesting an on-going self-perpetuating immune process that continues after the initial stimulus of tobacco smoke has been removed.¹ Regulatory T cells (Tregs) are a subset of CD4 T cells that play a major role in controlling autoimmune responses, and studies showing increased numbers of CD4 cells in the lungs of patients with COPD have led to investigation of a potential role for Tregs in the pathogenesis of the disease.¹

PREVENTING AUTOIMMUNITY

The central problem confronting the adaptive immune system (T and B cells) is how to generate lymphocytes with enough specific receptors to recognise all conceivable foreign antigens. The solution to this problem involves random rearrangements of gene segments encoding either the T cell receptor (TCR), in the case of T cells, or immunoglobulin for B cells. This generates huge diversity, but initiates a second problem: how to prevent these receptors from recognising self tissues and causing autoimmunity. In T cells, this problem is addressed during their development in the thymus and perhaps more critically by regulation in the periphery.

Within the thymus, the T cell progenitors receive coordinated signals resulting in random rearrangement and selection of the TCR. The end result is the generation of naïve CD8 and naïve CD4 T cells, which exit into the circulation expressing a wide array of TCRs. In general, thymocytes with TCR rearrangements capable of self-reactivity are deleted by a process of negative selection; however, it is clear that the T cell repertoire is not entirely

purged of self-specificities, and there is a lifelong need for regulation of T cell responses in the periphery.

In this regard, a specialised population of Tregs identified by their expression of the transcription factor, forkhead box P3 (Foxp3), emerge from the thymus with naturally suppressive functions.^{1,2} The importance of both Foxp3 (and therefore Tregs) to immune tolerance is amply demonstrated in mice and humans that lack functional Foxp3 and develop a variety of profound autoimmune symptoms. Tregs are therefore critical for controlling otherwise self-reactive T cells in our bodies. Accordingly, in many inflammatory diseases, the balance between Tregs and effector T cells may be crucial.

While Tregs are able to act as regulatory cells immediately on leaving the thymus, naïve CD4 T cells can also, under appropriate conditions, be converted into adaptive Tregs. Other T cells with regulatory capacity have also been described that express regulatory cytokines such as interleukin (IL)-10 and transforming growth factor β .² Together this illustrates the general concept that the immune system has multiple mechanisms dedicated to controlling immune responses that are a continuous threat to our own bodies. Moreover, the ability to stimulate the differentiation of Tregs on demand is an area of great therapeutic relevance and active research.

The hallmark of natural Tregs in the resting immune system is the expression of high levels of the surface marker, CD25. Rather inconveniently, this cannot be reliably used to identify Tregs, since CD25 is also expressed on activated effector T cells, making identification in inflamed tissues difficult. The most widely accepted marker of natural Tregs is therefore the expression of FoxP3, which is essential for their development, function and homeostasis.² However, since Foxp3 is an intracellular protein, it is not possible to use this for functional studies on live cells isolated from patients. However, Foxp3-expressing cells have been shown to be reliably identified by a combination of high CD25 expression in combination with low level expression of CD127. This 25^{hi}127^{low} phenotype appears to be effective in isolating cells with regulatory function.²

HOW DO TREGS WORK?

The answer to this critical question is the subject of intensive research. A number of mechanisms involving direct cell contact or indirect cytokine release have been suggested, and it seems likely that there is no single mechanism.² More probably Tregs work by generating a multicomponent



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suppressive environment in which it is difficult for activated T cells to thrive. However, some essential mechanisms used by Tregs have been identified such as those that act via the protein, cytotoxic T-lymphocyte antigen 4 (CTLA4), which is known to be critical in maintaining self-tolerance. Accordingly, mice containing CTLA4-deficient Tregs suffer generalised autoimmunity and die at ~6–7 weeks of age, establishing a non-redundant role for CTLA4.³ Interestingly, CTLA4 is an inhibitory receptor that binds via the same ligands as a key T cell activating protein, CD28. Recent data from our laboratory have indicated that CTLA4 may work by physically removing the CD28 ligands (CD80 and CD86) from antigen-presenting cells.⁴ Thus, interaction between Tregs and dendritic cells via CTLA4 inhibits effector T cell activation by controlling the levels of stimulatory ligands.^{2,3} While it is clear that other mechanisms (eg, IL-10) are also important to Treg function, CTLA4 appears to be one of the more dominant mechanisms for systemic tolerance. Interestingly, it is possible that IL-10 and CTLA4 may target the same pathway in that both can affect the expression of costimulatory molecules, CD80 and CD86, which are upregulated by inflammatory cytokines on dendritic cells and macrophages. Thus it is possible that CTLA4 and IL-10 work in concert to reduce the costimulatory function of antigen-presenting cells. Conversely, in inflammatory diseases, these same costimulatory molecules are highly upregulated by pathogen recognition and inflammatory cytokines, thereby potentially antagonising or over-riding suppression via these mechanisms.

Other mechanisms involved in immune suppression include the consumption of cytokines such as IL-2 by Tregs or the degradation of important factors for T cell proliferation such as tryptophan (via indoleamine 2,3-dioxygenase in the antigen-presenting cells) or adenosine generation via the CD39/73 pathways.² Taking these facts together, an emerging concept in T cell regulation is the setting up of a local immunosuppressive environment that inhibits the metabolic fitness of effector T cell responses (figure 1).

ROLE OF TREGS IN COPD

In COPD, there is evidence of involvement of both the innate and acquired immune system, with increased numbers of macrophages, neutrophils and lymphocytes present in the lungs of patients with the disease.¹ Increased levels of both CD8 and CD4 T cells have been found in the lungs of patients with COPD compared with controls.¹ Contrary to expectations, increased numbers of Tregs have been found in patients with acute exacerbations of COPD and in the lung of patients with emphysema, suggesting that these cells may not be effective in controlling inflammation in these patients. Interestingly, an increase in Tregs is often observed in the tissues of autoimmune conditions, suggesting that they may be elevated in an attempt to control local inflammation. Several studies investigating Tregs in COPD have identified increased CD4+CD25+ cells, but have not examined FoxP3 expression, making it difficult to be sure whether this is an increase in Tregs or activated T cells.^{5,6}

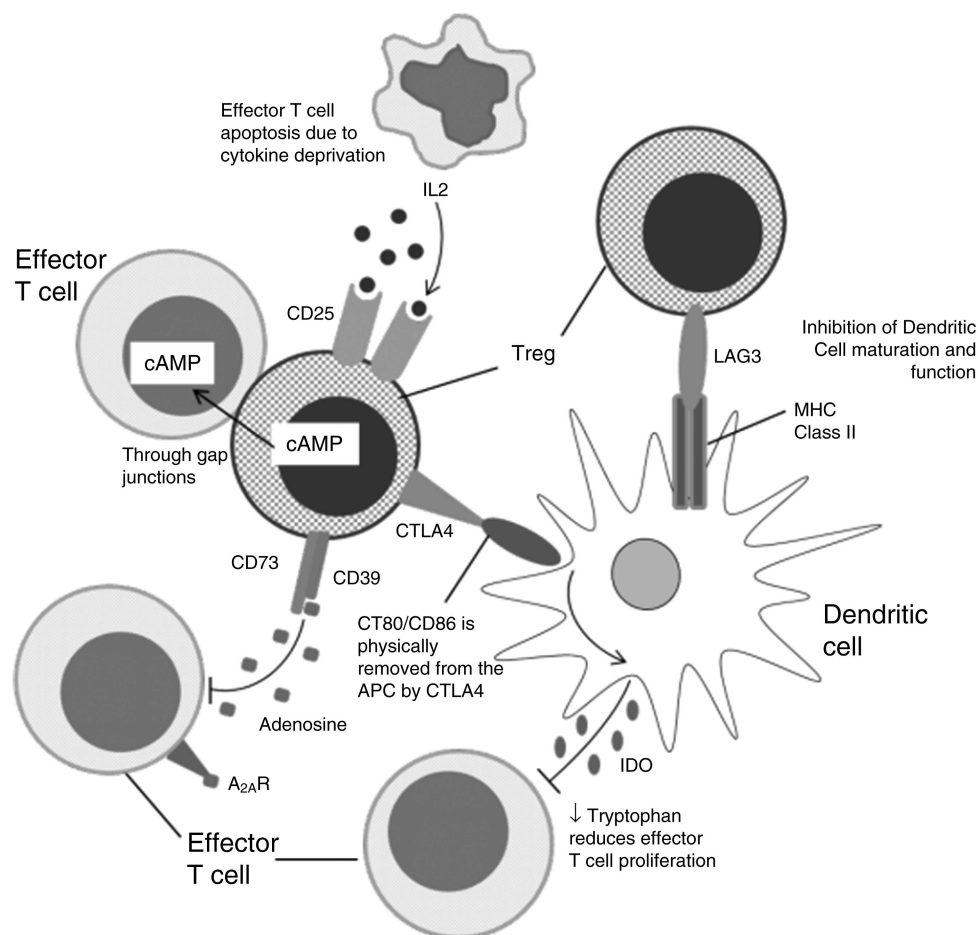


Figure 1 Mechanisms used by T regulatory cells (Tregs). Tregs use a variety of mechanisms to control self-reactive T cells, including direct effects on effector T cells and indirect effects via antigen-presenting cells (APCs). It is likely that different suppressive mechanisms are important in different biological settings. CTLA4, cytotoxic T-lymphocyte antigen 4; IDO, indoleamine 2,3-dioxygenase; MHC, major histocompatibility complex.

A more recent study suggested that the majority of CD4+CD25+ cells in the airways in patients with COPD do not express FoxP3 and may be activated T cells rather than regulatory cells.⁶ Interestingly, levels of FoxP3+ cells have been found to correlate with pack-year history in patients with COPD, and smokers who do not have COPD have also been found to have increased numbers of CD4+CD25+FoxP3+ Tregs in the large airways.¹ In addition, one study has also found higher numbers of Tregs in lymphoid follicles in the lung and postulated that Tregs in the patient with COPD may be adaptive Tregs. While the link between smoking and Tregs is as yet unclear, it is interesting to reflect that smoke contains dioxins, which are ligands for the aryl hydrocarbon receptor, which has intriguing effects on Treg/Th17 balance as well as possibly influencing the tissues themselves.

CONCLUSIONS

Tregs act to control immune responses via a variety of mechanisms including direct cell contact and release of cytokines. The counterintuitive finding of increased levels of Tregs in patients with COPD suggests possible dysfunction of the regulatory cell,

resulting in increased tissue damage in response to inflammation caused by cigarette smoke. However, investigation of these cells in COPD is still in its early stages, and greater clarification on the number and function of these cells, both locally and systemically, is required if Tregs are to be considered therapeutic targets in COPD.

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