

Regulatory Cells and the Control of Respiratory Infection

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The role of distinct CD4⁺ T-cell populations in regulating the nature and strength of immune responses is well documented, and has in the past principally focused on the mutual antagonism between Th1 and Th2 cells, which secrete interferon (IFN)- γ and interleukin (IL)-4, respectively. However, the recent identification of T cells that secrete high levels of IL-10 and/or transforming growth factor- β , but not IFN- γ or IL-4, called regulatory T (Tr) cells has prompted a paradigm shift in our understanding of the regulation of immune responses following infection. In this review, we focus on the role of antigen-specific Tr cells in the lungs following infection with various respiratory pathogens and discuss the targeting of Tr in the development of new therapies for immune-mediated diseases, such as allergy.

Introduction

The continual exposure to a large number of airborne pathogens within the respiratory tract presents the immune system with a relentless challenge. An appropriate immune response encompasses the ability to discriminate between self and non-self, and, importantly, differentiate between harmful and innocuous antigens. To protect the host, mechanisms must be in place to prevent deleterious reactions, such as immune responses to self-antigens leading to autoimmune diseases, immune response to food antigens in the intestine, or exaggerated immune responses to benign environmental antigens inhaled into the lungs. The existence of suppressor T cells and their role in the maintenance of immune homeostasis was first proposed in the early 1970s [1]. However, the field eventually floundered because these T cells could not be phenotyped, and attempts to clone the putative suppressor cells failed.

Following the re-discovery of suppressor T cells as regulatory T (Tr) cells in the mid-1990s, it is now fully accepted that distinct subtypes of CD4⁺ T cells, discriminated on the basis of phenotype or cytokine secretion, play a major role in the

maintenance of self tolerance, largely by their ability to suppress responses mediated by other populations of T cells. Several subsets of Tr cells with distinct phenotypes and distinct mechanisms of action have been described. These include naturally occurring CD4⁺CD25⁺ T cells, type 1 T regulatory (Tr1) cells, which secrete high levels of interleukin (IL)-10 but not IL-4 or interferon (IFN)- γ and Th3 cells, which secrete transforming growth factor (TGF)- β .

CD4⁺CD25⁺ natural Tr cells mature in the thymus, represent 5% to 10% of the peripheral CD4⁺ T-cell population, and have been shown to exhibit potent immunosuppressive activity both in vitro and in vivo [2]. Difficulties with CD25 (expressed on all activated T cells) as a marker lead to attempts to find alternative phenotypic markers for natural Tr cells. Thus, CD4⁺CD25⁺ Tr cells were further characterized by the constitutive expression of several other activation markers, including glucocorticoid-induced TNF receptor (GITR) [3], OX40 (CD134) [4], L-selectin (CD62L) [5], and CTLA-4 (CD152) [6]. However, the role these markers play (if any) in the suppressive abilities of CD4⁺CD25⁺ Tr cells remains poorly defined. Recently, the fork-head/winged helix transcription factor, Foxp3, has been proposed to be the “key to cell lineage” of naturally occurring Tr cells [7]. This transcription factor is thought to be critical in the development and function of CD4⁺CD25⁺ Tr cells, because both mice and humans deficient in a functional Foxp3 protein suffer from severe autoimmune disease symptoms [7,8].

Although the mechanism of suppression of natural Tr cells is not fully understood, it appears to be cell-contact mediated, involving CTLA-4, but a role for IL-10 and TGF- β has not been excluded [6,9,10]. Recent studies by Nakamura *et al.* [11] have suggested a possible role for membrane-bound TGF- β in mediating the suppressive abilities of murine CD4⁺CD25⁺ Tr cells. The suppressive capacity of human CD4⁺CD25⁺ thymocytes was blocked by a combination of monoclonal antibody (mAb) against CTLA-4 and membrane-bound TGF- β in vitro. However, CD4⁺CD25⁺ Tr cells isolated from TGF- β -deficient mice do not exhibit compromised suppressive activity. Furthermore, wild-type CD4⁺CD25⁺ Tr cells suppress CD25⁺ T cells expressing a dominant-negative TGF- β receptor [12].

In contrast with naturally occurring CD4⁺CD25⁺ Tr cells, Tr1 and Th3 cells are thought to acquire their suppressor activity through antigenic activation of CD4⁺CD25⁺ T

cells in the periphery. Inducible Tr cells exhibit variable expression of CD25 and other surface markers described for naturally occurring Tr cells [13••]. The suppressor activity of these Tr cells is cell-cell contact independent and is mediated primarily through the actions of the anti-inflammatory cytokines, IL-10 and TGF- β .

Tr1 cells were first characterized in murine models of inflammatory bowel disease as efficient suppressors of antigen-specific immune responses. T cells from ovalbumin (OVA) T cell receptor–transgenic mice, repeatedly stimulated with OVA and IL-10, differentiated into Tr1 cells in vitro [14]. These Tr1 cells produced IL-10 and low to moderate levels of IL-5 and TGF- β , but little or no IL-2, IL-4, or IFN- γ . Naïve CD4⁺ T cells can be manipulated in vitro to generate homogenous populations of IL-10–producing Tr1 cells [15]. The ability of Tr1 cells to suppress proliferative responses has been demonstrated by co-culture of naïve CD4⁺ T cells and Tr1 cells in the presence of allogenic antigen-presenting cells (APCs) [14]. Similarly, Tr1 clones specific for filamentous hemagglutinin (FHA) from *Bordetella pertussis* suppress proliferation and cytokine production by a Th1 clone against an unrelated antigen—influenza virus hemagglutinin [16].

Th3 cells were originally identified in mice after oral tolerance induction to myelin basic protein (MBP) for their ability to suppress MBP-specific encephalomyelitis (EAE) in vivo in a TGF- β –dependent manner, as suppression was abrogated by injection of anti-TGF- β Ab [17,18]. Th3 cells provide help for IgA production and have suppressive properties for both Th1 and Th2 cells [19]. Furthermore, because TGF- β is broadly expressed and acts on multiple cell types, TGF- β –secreting Th3 cells probably have a major role in many aspects of immune regulation and homeostasis [20].

Dendritic cells (DC) play a key role in the initiation and regulation of T cell–dependent immune responses. Much of their significance lies in their role as the pivotal cell in linking the innate and adaptive immune system. It has been suggested that plasmacytoid DC selectively promote the induction of Th1 cells, whereas myeloid DC favor the induction of Th2 cells. However, it has been suggested that the activation status of the DC, rather than the lineage, determines its ability to selectively promote T-cell subtypes [15,21]. A key process in directing naïve T cells to differentiate into effector Th1 or Th2 cells is the induction of DC maturation through pathogen recognition receptors (PRRs). Many Toll-like receptor ligands, such as lipopolysaccharide (LPS), cytosine phosphate guanosine (CpG) motifs in bacterial DNA, and viral double-stranded (ds)RNA have been shown to promote IL-12 production, and to activate DC that promote the differentiation of Th1 cells [22,23]. In contrast, products of helminth parasites, yeast hyphae, and cholera toxin (CT) activate DC, which directs the induction of Th2 cells [23–25]. Because regulatory Tr1 and Th3 cells arise from naïve or resting CD4⁺ T cells in the periphery, it was highly conceivable that DCs activated with an appropriate stimulus, such as certain

pathogen-derived molecules, could selectively promote the induction of Tr cells. Indeed, certain pathogen-derived molecules, including FHA and adenylate cyclase toxin (CyaA) from *B. pertussis*, non-structural protein (NS) 4 from hepatitis C virus, and CT have been shown to promote the induction of Tr1 cells, through their interaction with DCs or other innate cells, such as macrophages [13••,26,27].

Induction of Tr Cells by Respiratory Pathogens *Mycobacterium tuberculosis*

It is estimated that one third of the world's population is infected with *Mycobacterium tuberculosis*, the bacterium that causes tuberculosis (TB) [28]. TB infection is a significant cause of morbidity worldwide. Most individuals infected with TB develop delayed-type hypersensitivity (DTH) response 2 to 3 weeks after infection [29]. An intradermal injection against purified protein derivative (PPD) from *M. tuberculosis* is used to screen for TB infection. However, the absence of skin reactivity to PPD has been described in immunocompetent individuals with active TB infection [30]. T-cell proliferation in response to PPD, as well as nonspecific mitogens, has been shown to be significantly impaired in anergic patients and is associated with high levels of IL-10–producing T cells in the peripheral blood [30]. Studies in IL-10 transgenic mice demonstrate that increased susceptibility to reactivation tuberculosis and suppression of protective Th1 responses is strongly influenced by the expression of IL-10 in the chronic phase of infection [31]. A recent study, using a model of OVA-induced eosinophilic airway inflammation, demonstrated that another strain of mycobacterium, *M. vaccae*, had suppressive activity on airway eosinophilia [32]. Treatment of mice with killed *M. vaccae* suspension (SRP299) gives rise to allergen-specific CD4⁺CD45RB^{low} Tr cells, which confer protection against airway epithelium damage. The regulatory activity of CD4⁺ T cells from SRP299-treated mice was highly potent, and cell numbers as low as 0.25×10^6 cells significantly suppressed allergen-induced eosinophilic inflammation. This study also demonstrated that SRP299-induced Tr cells reduced other pathophysiologic readouts, such as bronchial hyperresponsiveness (BHR). Therefore, Tr cells generated by certain mycobacteria or their products may provide a valuable therapeutic strategy for allergic diseases.

Bordetella pertussis

Induction of high levels of IL-10 and/or TGF- β by innate cells following infection has been reported for a large number of pathogens. In certain cases, specific pathogen-derived immunoregulatory molecules have been identified that stimulate IL-10 from macrophages and/or DC. *B. pertussis*, the etiologic agent of whooping cough, causes a severe and protracted respiratory disease, often complicated by secondary infections that can have a lethal outcome in young children. Recovery from infection in humans and mice is associated with the development of *B. pertussis*-specific Th1

cells [33,34]. However, antigen-specific Th1 immune responses in the lungs of infected mice are severely suppressed during the acute phase of infection [35]. The *B. pertussis* virulence factors, FHA and CyaA, have been shown to inhibit IL-12 and enhance IL-10 production from macrophages and DC and selectively stimulate the induction of IL-10 secreting Tr1 cells from naïve T cells. Furthermore, Tr1 clones specific for FHA have been generated at low frequency from the lungs of acutely infected mice, but could not be generated from the spleens of infected or convalescent mice or the lungs of naïve mice [13••]. These findings suggest that certain pathogens have developed strategies to exploit Tr cells to counteract protective immune responses and, thereby, prolong their survival in the host.

Although the induction of Tr cells following infection in many cases promotes bacterial persistence, it is important to note that pathogen-specific Tr cells are not exclusively detrimental for the host. One beneficial role for regulatory cells maybe in controlling exaggerated inflammatory immune responses. This has been illustrated by infection of TLR4-deficient mice with the respiratory pathogen *B. pertussis*. Innate and adaptive IL-10 is defective in response to *B. pertussis* in TLR4-defective mice. During the acute phase of infection, Th1 responses were shown to be enhanced, and IL-10-producing T cells significantly reduced in TLR4-deficient mice. Furthermore, this was associated with enhanced inflammatory cytokine production, cellular infiltration, and severe pathologic changes in the lungs of the TLR4-deficient mice [36••]. These findings suggest that ligation of conserved pathogen molecules on specific pathogen recognition receptors promotes the induction of Tr cells that prevents immunopathology. As such, the differentiation of Tr cells may represent a protective strategy adopted by the host to limit collateral damage mediated by excessive pathogen-stimulated inflammatory responses.

Pneumocystis carinii

Pneumocystis carinii (PC) is an opportunistic pulmonary pathogen that can cause life-threatening pneumonia in immunocompromised individuals, such as AIDS patients. Although an indispensable role for CD4⁺ T cells in bacterial clearance is well established [37], it has also been suggested that, under certain circumstances, CD4⁺ T cell-mediated inflammatory responses contribute significantly to PC pneumonia pathogenesis [38]. Recent studies by Hori *et al.* [39••] have suggested an important role for CD4⁺CD25⁺ Tr cells in controlling excessive T cell-mediated inflammatory responses. Adoptive transfer of CD4⁺CD25⁺ T cells into PC-infected RAG2^{-/-} mice leads to a lethal pneumonia within 13 days post-transfer. In contrast, transfer of CD4⁺CD25⁻ Tr cells did not induce pneumonia and prevented the development of disease induced by CD4⁺CD25⁺ T cells. Furthermore, CD4⁺CD25⁻ T cells reduced PC load in the lungs whereas CD4⁺CD25⁺ Tr cells inhibited this immune response [39••]. The finding that CD4⁺CD25⁺ Tr cells inhibits both pulmonary inflammation and elimination of

the pathogen mediated by CD4⁺CD25⁻ T cells illustrates a dual role for Tr cells in infection, inhibiting both deleterious and protective aspects of an immune response.

Implications for allergy

Although it has been demonstrated that Th2 as well as Tr1 cells secrete IL-10, an important distinction between these two cell types is that Tr1 cells do not secrete IL-4. Despite the fact that they express the CD4 marker, normally associated with helper function, Tr1 cells do not appear to act as classic T helper cells. It has also been reported that certain Tr1 cells can suppress Th2 responses [40] and may, therefore, have implications for our understanding and treatment of allergic diseases. The theory that allergic inflammation may result from reduced cross-regulation by Th1-inducing pathogens may need to be revisited in light of the observation that numerous viral and bacterial species and almost all parasites may induce Tr cells. One recent study has demonstrated that the suppressive effect of *M. vaccae* on eosinophilic airway inflammation in OVA-primed mice is related to the induction of pathogen-specific Tr cells [32]. In addition, studies examining the relationship between allergies and parasitic infections have demonstrated that children with chronic helminth infection have reduced allergic responses to the house dust mite [41]. These studies support the proposition that the induction of Tr cells by both respiratory and systemic pathogens may play an important role in the protective effect of infections on the generation of allergic disorders [42]. Furthermore, identification of specific immunomodulatory molecules, such as FHA from *B. pertussis*, that promote the development of Tr cells *in vivo*, may provide us with novel immunotherapeutic drugs for the prevention and treatment of autoimmune diseases and allergy (Fig. 1).

Conclusions

Autoimmune diseases and asthma are still a major cause of morbidity and mortality in humans worldwide. For the most part, treatment of these disorders is heavily reliant on immunosuppressive drugs, which can lack specificity or have serious side effects. Approaches based on understanding the immunology of the disease and designing interventions that inhibit aberrant immune responses have considerable potential in the development of new therapeutics. As reviewed in this article, several respiratory pathogens have evolved strategies to prevent the host from eliminating them by inducing Tr cells that subvert protective immune responses. A novel approach for the treatment of allergy based on immunomodulation may be to exploit the immunomodulatory function of these pathogens and their products. Furthermore, as Tr cells are thought to be more prevalent at mucosal surfaces, immunization with pathogen-derived immunomodulators via the nasal route may favor the induction of Tr cells capable of suppressing allergen-specific Th2 cells at the local site of inflammation. However, although manipulation of the Tr cell to effector T cell ratio *in vivo* may have considerable

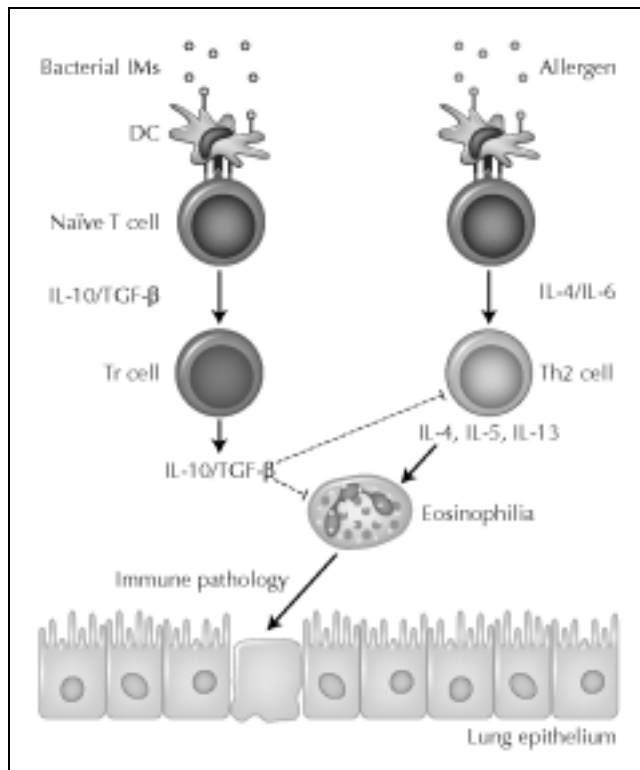


Figure 1. Role of Tr cells in the prevention of allergic disorders. When allergens enter the lung, they bind to immature dendritic cells (DC), which, following maturation, promote the differentiation of Th2 cells. The expansion of Th2 cells, enhanced IL-4 and IL-5 production, and subsequent extravasation of eosinophils from the vasculature leads to immune-mediated pathology and damage to the lung epithelium. However, exposure to or immunization with bacterial immunomodulators (ILMs) capable of promoting the differentiation of Tr cells may help to reduce these aberrant inflammatory responses by suppressing both the induction and/or expansion of reactive Th2 cells and, thus, facilitating the attenuation of allergen-mediated disorders. IL—interleukin; TGF—transforming growth factor; Tr—regulatory T cell.

potential for the prevention and treatment of allergic disorders, identification and purification of safe but effective specific immunomodulatory proteins from these pathogens is required before their therapeutic potential can be realized.

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