

Update: the role of FoxP3 in allergic disease

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Current Opinion in Otolaryngology & Head and Neck Surgery 2008, 16:275–279

Purpose of review

T-regulatory cells play a key role in allergic and asthmatic inflammatory airway diseases. This review discusses the importance of a critical gene associated with T-regulatory cells. Forkhead box P3 is a forkhead-winged helix transcription factor gene involved in immune function in allergy and asthma.

Recent findings

Recently, many functions of forkhead box P3 and its influence on the immune system have been elucidated. T-regulatory cells that are CD4+CD25+ and express forkhead box P3, influence the development and expression of atopy and allergic response. The exact mechanisms are not yet delineated, but multiple recent studies provide greater understanding of the mechanism of forkhead box P3 and its influence on these T-regulatory cells.

Summary

Greater understanding of the molecular and immunological mechanisms underlying the T-regulatory cells and forkhead box P3 will permit the development of targeted treatment modalities to influence disease processes such as allergic rhinitis and bronchial asthma.

Keywords

allergic rhinitis, asthma, CD4+CD25+ T-regulatory cells, forkhead box P3

Curr Opin Otolaryngol Head Neck Surg 16:275–279
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1068-9508

Introduction

Allergic rhinitis and asthma are both expressions of inflammatory immune responses to environmental antigens. Allergic rhinitis and asthma affect 20 and 5% of the US population, respectively [1]. The activation of the immune system and the CD4+ T cells to effector T-helper cell subsets plays a major role in the development of allergic disorders. There are several subsets of T-helper cells (Table 1). The main subsets are T helper 1 (Th1), Th2, or the more recently described T-regulatory (Treg) cells [2–4]. Th1 cells characteristically interact with outside pathogens (bacteria, viruses) and secrete interleukin 2 (IL-2), IL-3, tumor necrosis factor alpha (TNF- α), and interferon gamma (IFN- γ). Th2 cells modulate B-cell production of immunoglobulins and humoral immunity. Th2 cells secrete IL-4, IL-5, IL-9, IL-10, and IL-13. IL-4 and IL-13 facilitate B-cell heavy-chain isotype switching from immunoglobulin G (IgG) to immunoglobulin E (IgE) production, with subsequent release of IL-5. IL-5 encourages eosinophilic inflammation, facilitating the allergic response and airway hyperresponsiveness. The IgE produced in response to allergens populates mast cells and basophils. Later exposure to the same allergen permits release of pro-

inflammatory molecules, such as histamine. The IL-5-facilitated eosinophilic inflammation creates the nasal symptoms and airway inflammation characteristic of allergic rhinitis and asthma [5,6]. Allergic rhinitis and asthma are associated with an abundance of Th2 cell response [7[•],8[•]]. The exact genetic mechanisms of these disease processes remain unknown, but recent research involving the role of the forkhead box P3 (FoxP3) gene has helped to increase our understanding. FoxP3 is a member of the forkhead-winged helix family of transcription regulators located on chromosome Xp11.23.

We will first review details of the Treg class of T cells, and then discuss their role in allergic rhinitis and asthma.

CD4+CD25+FoxP3+ T-regulatory cells

These Treg cells are crucial in developing self-tolerance. They assist suppression of autoreactive T cells and peripheral dendritic cells, downregulating the proinflammatory responses of both Th1 and Th2 cells. They also prevent transition from the early activation stage to differentiated Th2 state, limiting airway allergic inflammation and halting excessive Th2 responses to allergic antigens [9]. CD4+CD25+FoxP3+ Treg cells are naturally

Table 1 The subsets of T cells with their phenotype and products

Major T-cell populations		
Population	Phenotype	Cytokines
Th1	CD3+CD4+	IFN- γ , TNF- α
Th2	CD3+CD4+	IL-4, IL-5, IL-13
Th17	CD3+CD4+	IL-17, TNF- α
Treg	CD3+CD4+	
Naturally occurring	CD3+CD4+CD25+FoxP3+	FoxP3
Tr1	CD3+CD4+	Mainly IL-10
Th3	CD3+CD4+	Mainly TGF- β
Cytotoxic T cells	CD3+CD8+	IFN- γ , TNF- α

FoxP3, forkhead box P3; IFN- γ , interferon gamma; IL-4, interleukin 4; TGF- β , transforming growth factor beta; Th1, T helper 1; TNF- α , tumor necrosis factor alpha; Treg, T regulatory; Tr1, T regulatory 1.

occurring, thymus-derived, and usually represent 5–10% of the peripheral CD4+ T cells.

Multiple mechanisms underlying how Treg cells suppress effector T cells have been recently delineated. Treg cells produce suppressive cytokines and cell-surface molecules, including transforming growth factor beta (TGF- β), IL-10, cytotoxic T-lymphocyte antigen 4 (CTLA-4), and programmed death 1 (PD-1). Treg cells can also inhibit effector T cells via a direct cell–cell contact mechanism to induce the apoptosis (to kill) of effector T cells. In addition, Treg cells crosstalk with antigen-presenting cells (APCs) to suppress T-cell activation.

FoxP3 is a specific marker expressed by these Treg cells. It is a ‘master switch’ gene for Treg cells. FoxP3 transcriptional regulator determines the levels and activity of CD4+CD25+ Treg cells. FoxP3 expression is closely related to autoimmunity, transplantation, and allergy. FoxP3 loss-of-function mutations have severe health consequences for humans. Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is a fatal condition with very high IgE levels, neonatal autoimmune diabetes, eosinophilia, and rampant allergic inflammation with eczema and severe food allergies. X-linked autoimmunity allergic dysregulation (XLAAD) syndrome is another disorder with related symptoms [10–12]. FoxP3 is a critical regulator of natural CD4+CD25+ Treg cell development and function.

Molecular examinations of human and murine Treg cells clarify how FoxP3 exerts its influence. As a nuclear protein, FoxP3 was first found to cooperate with the transcription factor, nuclear factor of activated T cell (NFAT), for the production of suppressive genes, such as CTLA-4 and TGF- β . Another transcription factor acute myeloid leukemia 1 (AML1)/Runt-related transcription factor 1 (Runx1) interacts physically with FoxP3. AML1/Runx1 is required in normal hematopoiesis and thymic T-cell development. It activates IL-2 and IFN- γ gene expression in CD4+ T cells. When FoxP3

physically interacts with AML1/Runx1, IL-2 and IFN- γ production is suppressed, and Treg cells are upregulated to exert suppressive mechanisms [13•]. More recently, the transcription factor activation protein 1 (AP-1) has been found as an interacting partner of FoxP3 and their interaction also inhibits IL-2 production by Treg cells. Other molecular physical interactions with FoxP3 are under investigation currently; however, they have not been elucidated.

Allergic rhinitis

Many recent studies have examined the role of FoxP3 and CD4+CD25+ Treg cells in allergic rhinitis and asthma. Most have found that atopic patients have less FoxP3 and CD4+CD25+ Treg cells, therefore, less suppressive activity by these Treg cells. This, in turn, leads to more inflammation and allergic rhinitis and asthma symptoms. Nonatopic patients do not develop allergic disease because their Treg cells efficiently suppress Th2 responses.

A study by Xu *et al.* [7••] compared nasal tissues and peripheral blood mononuclear cells (PBMCs) between adult patients with and without allergic rhinitis. Allergic rhinitis patients had significantly fewer FoxP3+ lymphocytes and decreased FoxP3 mRNA expression. After stimulation, the PBMCs had significantly increased IL-2 and IFN- γ levels in the allergic rhinitis group vs. control. This suggests that decreased FoxP3 expression causes fewer CD4+CD25+ Treg cells, and that the function of these cells is impaired. The increased levels of Th1 mediators IL-2 and IFN- γ in the allergic rhinitis group vs. controls supports evidence that impaired suppressive activity of CD4+CD25+ Treg cells is due to decreased numbers and expression of FoxP3. The authors interpret this to mean that Treg cells in allergic rhinitis patients not only permit proliferation of Th2 responses but also do a subpar job of their normal balancing suppression of Th1 cells.

Research presented by us at the 2007 American Academy of Otolaryngology: Allergy Annual Meeting [14•] examined the gene expression levels of FoxP3 in the nasal secretions of allergic vs. nonallergic patients. We demonstrated significantly decreased FoxP3 mRNA expression in nasal secretions from atopic vs. nonatopic patients, similar to the findings of Xu *et al.* As FoxP3 is a specific lineage molecule of CD4+CD25+FoxP3+ Treg cells, this decrease means fewer Treg cells. Reduced FoxP3 gene expression or impaired FoxP3 functions are potentially responsible for the development of allergic diseases in humans.

It was recently shown that CD4+CD25+FoxP3+ Treg cells from human peripheral blood can be specific for

individual antigens. It is well known that CD4+CD25+ Treg cells participate in controlling autoimmunity by recognizing self-antigens [15–17]. Whether these cells could also recognize foreign antigens was not defined. Using the exogenous ubiquitous antigens Der p 1 (a house dust mite antigen) and the bacterial antigen streptokinase, Maggi *et al.* [18•] show there are CD4+CD25+FoxP3+ cells capable of recognizing specific exogenous ubiquitous antigens in both atopic and nonatopic individuals. These cells can suppress (in-vitro) effector T-helper cells specific for the same antigen, but have no activity against effector T cells specific for a different antigen. This leaves the question of whether these antigen-specific CD4+CD25+FoxP3+ Treg cells are actually thymus-derived, or whether they represent a new class of peripherally induced cells.

Asthma

A study by Hartl *et al.* [19••] investigated the role of Treg cells in childhood asthma. Levels of CD4+CD25+ Treg cells in peripheral blood and bronchoalveolar lavage fluid (BALF) of children with asthma or chronic cough or no lung disease were studied. CD4+CD25+ Treg cells were decreased in the BALF of children with asthma vs. those with cough or no lung disease. Furthermore, the CD4+CD25+ Treg cells in children without asthma suppressed proliferation and cytokine production by pulmonary Th2 cells, but the Treg cells from asthmatic children did not suppress these T cells. Inhaled corticosteroids restored this suppressive capacity. This is strong evidence that CD4+CD25+ Treg cell function is locally impaired in asthmatic children.

Another investigation found correlation among disease severity, FoxP3 expression, and number of CD4+CD25+ Treg cells [8•]. The number of CD4+CD25+ Treg cells and FoxP3 mRNA expression was compared in children with and without allergic rhinitis or asthma. Flow cytometry of peripheral blood samples showed that children with allergic disease had significantly fewer CD4+CD25+ Treg cells vs. controls, supporting previous literature findings [20–23]. There were, however, more CD4+CD25+ Treg cells in children with persistent allergic rhinitis and/or moderate-to-severe asthma vs. those with less-severe asthma. Additionally, FoxP3 mRNA expression was significantly increased in moderate-to-severe vs. mild asthma. The authors suggest that as disease severity worsens, increased FoxP3 expression and more suppressive CD4+CD25+ Treg cells result from ‘induced or adaptive Treg cells generated during an exacerbation of allergic inflammation as a consequence of an immune response’. Close examination of the patient population, however, reveals that about 15% of the patients with intermittent rhinitis or mild asthma took inhaled or oral steroids vs. about 52% of the perennial rhinitis or severe

asthma patients. Given the effect of inhaled corticosteroids in asthmatic children summarized in the preceding paragraph, we theorize that these increased Treg cells represent normalization after steroid treatment.

A recent mouse model study (Morgan) examines the role of histamine in asthma and its association with recruitment of CD4+CD25+FoxP3+ Treg cells. The fourth type of histamine receptor (H4R) is expressed primarily on splenocytes, thymus, dendritic cells, and lymphocytes. It is known to play a role in mast cell and eosinophil chemotaxis. Intratracheal delivery of an H4R agonist (4-methylhistamine) before antigen challenge inhibited development of airway resistance and inflammation by focused recruitment of CD4+CD25+ Treg cells. In-vitro assays showed that the H4R agonist stimulated T-cell migration, especially the CD4+CD25+ Treg cells, but did not induce FoxP3 expression. This suggests that a therapeutic approach may exist in allergic asthma for selective H4R stimulation yielding CD4+CD25+ Treg recruitment and decreased airway inflammation [24•].

In addition to decreased FoxP3 gene expression in patients with asthma, gene mutations that result in the loss of FoxP3 functions have also been suggested as one of the causes of asthma. For example, patients with IPEX syndrome have extremely high levels of IgE. However, these patients mostly die from profound autoimmune disease at young age due to the complete loss of FoxP3 functions. Interestingly, we have recently identified a point mutation in FoxP3 gene in an adult patient with both rhinitis and asthma. This mutation locates in a highly conserved region of FoxP3 which could potentially impair its function. Indeed, the inhibitory activity of FoxP3/R146W mutant was partially impaired [14•]. Therefore, the partial loss of FoxP3 functions due to gene mutations in some ‘minor’ regions of FoxP3 appears to be a novel mechanism for asthma development.

The therapeutic potentials of T-regulatory cells in allergic rhinitis and asthma

Given the facts that CD4+CD25+FoxP3+ Treg cells suppress allergic responses and that decreases in Treg cell populations are one of the major causes of allergic diseases, upregulation of Treg cell populations holds great therapeutic potential in the treatment of these diseases. Indeed, although the precise mechanisms of allergen-specific immunotherapy are not well defined, upregulation of FoxP3+ Treg cells has been found in treated patients [25]. Van Hove *et al.* [26•] also found in a mouse model that sustained allergen exposure after sensitization ultimately resulted in disappearance of allergic airway inflammation. This is apparently an active immune-mediated tolerance through suppressive mechanisms. Compared with mice with acute eosinophilic

inflammation showing upregulation of CD4+CD25+ Treg cells and FoxP3 expression as protective measures, the 'allergic' mice subjected to chronic allergen stimulation and subsequent tolerance displayed a decrease in the percentage of CD4+CD25+ Treg cells. The immune mechanisms involved in disease inhibition with acute eosinophilic airway inflammation may differ from anti-inflammatory mechanisms activated after the acute phase. Direct induction of membrane-bound TGF- β and FoxP3 gene expression by CD4+ T cells by inhaled allergen is likely one mechanism of Treg cell upregulation during immunotherapy [27]. In addition, allergens can induce Treg cells by educating dendritic cells, as Wu *et al.* [28] recently showed by demonstrating that allergen-modified dendritic cells promote allergen-specific Treg cell differentiation.

IL-6 is a proinflammatory cytokine found in the airways of asthmatic mice. One study found that local antibody blockade of membrane-bound IL-6R signaling transduction results in a decrease of inflammatory cells through apoptosis in the asthmatic mouse airway. Additionally, anti-IL-6 antibody in the airway of the asthmatic mice suppressed signal transducer and activator of transcription 3 (STAT-3) activation and potentiated lung CD4+CD25- T-effector cell apoptosis by inducing FoxP3 expression and CD4+CD25+ Treg cells [29]. This finding may translate and represent a future target receptor, IL-6R, as a treatment for asthma in humans.

Yet to be clinically tested in humans, adoptive transfer of Treg cells has great promise to inhibit airway inflammation in mice. However, difficulties are still to be overcome for in-vitro expansion of functional human Treg cells because of their anergic nature. Notably, it has been demonstrated that both mouse and human naïve CD4+CD25- T cells can be 'converted' to CD4+CD25+FoxP3+ Treg cells [30]. Adoptive transfer of these Treg cells, which have been polarized from their own CD4+CD25- T cells, back to patients with allergic disease, could be an ideal therapeutic approach.

As the molecular mechanisms of these interactions are further delineated, further potential points of therapeutic intervention will undoubtedly be identified.

Conclusion

FoxP3 gene and its upregulation of CD4+CD25+ Treg cells are critical in the dampening of allergic response. However, the exact interactions and immunological mechanism of the role of Treg cells still need to be elucidated. Recent studies in the past year have provided important advances in our understanding of this area:

- (1) In nonatopic patients, both antigen-independent and antigen-specific Treg cells suppress Th2 (and possibly Th1) expression.
- (2) CD4+CD25+FoxP3+ Treg cells are lacking in number or function in allergic rhinitis and asthma.
- (3) FoxP3 expression is decreased in allergic rhinitis and asthma.
- (4) Inhaled or oral steroid treatment may reverse the CD4+CD25+FoxP3+ Treg cell dysfunction and scarcity in allergic rhinitis and asthma.
- (5) Mouse studies suggest that several interrelated receptors may act as therapeutic targets that indirectly affect the expression and amount of FoxP3 and CD4+CD25+ Treg cells. These may provide clues to the working mechanisms of allergy immunotherapy.

Numerous research groups are currently working on further elucidation of the role of FoxP3 transcription factor and CD4+CD25+ Treg cells in allergic disease and asthma. This will allow more precise identification of their roles of these factors in allergic rhinitis and asthma, and ultimately provide opportunities for targeted therapeutic treatment modalities for these disease processes in humans.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 299–300).

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