

Regulatory T cells as a target for induction of immune tolerance in allergy

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Purpose of review

Reduced activity of regulatory T cells has recently been described in several diseases, including allergy. This concept of an alteration in the balance between the suppression and activation of harmful T helper type 2 immunity in allergy has important potential implications for strategies to prevent and control disease.

Recent findings

The past year has seen several important advances in analysing the determinants of this balance and models for inducing tolerance through regulatory T cells, including several different subtypes. These include the recognition that although T helper type 2 responses drive atopic sensitization, the expression of disease involves additional factors, and of a potential role for regulatory T cells in the development of neonatal tolerance. In addition to CD4⁺CD25⁺ regulatory T cells, experimental protocols for the induction of IL-10-producing, transforming growth factor beta and T helper type 1 regulatory T cells have been described in mouse models of airway disease. IL-6 and co-stimulation have been identified as potential determinants of the balance between the suppression and activation of allergic responses.

Summary

Different strategies for inducing regulatory T cells in animal models of allergic inflammation and an improved understanding of the factors accentuating or reducing suppression have identified important questions for future translational research.

Keywords

allergic disease, atopy, suppression

Abbreviations

GFP	green fluorescent protein
IDO	indoleamine 2,3 dioxygenase
TGF	transforming growth factor
Th	T helper
T_{reg}	regulatory T cell

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Introduction

Allergic diseases such as rhinitis, asthma and atopic dermatitis affect up to 15% of the population and their prevalence has increased. Despite effective anti-inflammatory medication, these diseases impact the quality of life of many patients, and there is a continued rate of deaths from asthma. Topical corticosteroids and other widely used drugs do not alter underlying sensitization, and although allergen immunotherapy offers disease modification and the potential to prevent progression, potential side effects limit its use.

There is general consensus that allergic inflammation is driven by the activation of T helper (Th) type 2 CD4⁺ T cells producing IL-4 and IL-13, which contributes to IgE production, mucus hypersecretion and airway hyper-responsiveness, and IL-5 that promotes eosinophilic inflammation [1]. With the description of regulatory T cells (T_{regs}) a hypothesis has emerged that the active suppression of inappropriate Th2 responses to allergens by both CD4⁺CD25⁺ T cells and IL-10-producing T_{regs} is either defective or is overcome in those who develop allergic disease. These interactions have been the subject of several recent reviews [2–4]. Much attention has been focused on determining the factors that drive the balance between active and suppressive immune responses to allergen, and how this balance might be manipulated for the treatment or prevention of allergic disease. Here we will consider publications from the past year that have added to our understanding of allergic disease and how T_{regs} might be exploited to induce tolerance.

The T helper type 2 hypothesis revisited

Although there is a considerable body of evidence linking Th2 responses to allergens to atopic sensitization and allergic disease, not all sensitized individuals develop symptoms [1]. A recent large immuno-epidemiological survey [5•] studied 172 children and related their peripheral blood T-cell responses to allergen stimulation

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with atopic sensitization, airway hyperresponsiveness and clinical symptoms of asthma (wheeze). Although atopy was associated with Th2 cytokine production, asthma symptoms were correlated with IL-5 production, and airway hyperresponsiveness with IFN- γ . These findings are in agreement with other studies of peripheral blood and may not reflect T-cell responses at the disease site. However, the large survey did reinforce the theory that although atopic sensitization is associated with Th2 responses, other factors, including Th1 cytokines, may be important for the clinical expression of disease. The regulation of the multiple and heterogeneous factors contributing to allergic disease should thus be considered when designing therapeutic strategies to induce tolerance.

The same group also followed up on their previous studies of neonatal sensitization to allergens with an elegant study of T-cell responses in umbilical cord blood [6•]. These data questioned previous reports that fetal allergen sensitization might occur, and showed that assumed recent thymic emigrant T cells were responsive to a number of neoantigens (including allergens) but not self-antigens. Furthermore, CD4⁺CD25⁺ T cells with regulatory function developed in these cultures, and the authors suggested that this might represent a normal braking mechanism leading to peripheral tolerance. The waning of specific IgE was associated with the loss of food allergy in children in a further report [7], and in an animal model tolerance was associated with the development of mucosal antigen-specific IgA responses. The balance of IgE and IgA or IgG4 responses to allergens seems to be an important theme in allergy versus tolerance and may be determined by the relative balance between Th2 cytokines and transforming growth factor (TGF)- β and IL-10 [2].

Regulatory T cells and allergic disease

The concept has arisen that a contributing factor to atopy (IgE sensitization to allergens) may be a lack of the adequate suppression of inappropriate Th2 responses by both CD4⁺CD25⁺ and IL-10-producing T_{regs} [2,3]. Further support for this came from the observations of Grindebacke *et al.* [8•], who confirmed the importance of seasonal allergen exposure in a study demonstrating the diminished suppression of birch allergen-stimulated IL-5 and IL-13 production by CD4⁺CD25⁺ T cells during the pollen season. There was no difference between suppression by CD4⁺CD25⁺ T cells from non-allergic and birch-allergic donors out of season, nor was there any difference in season in allergen-driven proliferation or IFN- γ production. The mechanism of the effect of allergen exposure is unclear, but one report demonstrated increased plasma IL-10 and kynurenine in asymptomatic sensitized individuals during the pollen season [9]. IL-10 can suppress T-cell responses and kynurenine is

an end-product of indoleamine 2,3 dioxygenase (IDO) activity, which is suppressive of T-cell function, partly through the induction of apoptosis [10]. A report examining CD4⁺CD25⁺ T-cell function in asthma found no difference in the ability to suppress anti-CD3, anti-CD28-stimulated Th2 cytokine production between cells from asthmatic and non-asthmatic individuals [11], confirming earlier observations [12]. There thus does not appear to be a generalized defect in CD4⁺CD25⁺ T_{Reg} function in asthma, in contrast to reports from autoimmune disease patients [13,14].

The emerging possibility is therefore that allergic sensitization (or atopy) may result partly from a lack of appropriate T_{reg} activity. Allergen exposure seems to tip the balance further away from suppression and towards active Th2 immunity, and this effect seems to be short lived, resolving after seasonal exposure in bee keepers, for example [15]. Atopic sensitization still does not generally lead to disease, and the mechanisms preventing the suppression of Th2 responses that are broken in allergic asthma, rhinitis and atopic dermatitis remain to be resolved but may relate partly to differences in the innate response [9] or antibody response to allergen exposure. Interestingly, eosinophils were also shown to have suppressive activity through IDO activity [16], although in this case there was preferential suppression of Th1 cells but not Th2 clones, so that eosinophilic inflammation might actually amplify Th2 responses to allergen. Further work is needed on the bidirectional interplay between granulocytes or structural cells and T cells and dendritic cells.

Regulatory T-cell biology: the importance of FoxP3

Although numerous examples of T_{reg} function have been described *in vivo* in mice, and in human cells *in vitro*, the mechanism of suppression by CD4⁺CD25⁺ T cells remains uncertain. A role for the immunosuppressive cytokines IL-10 and TGF- β is demonstrated in most, but not all, in-vivo mouse models. A major advance was the association of regulatory function with the activity of the forkhead transcription factor, FoxP3 [17]. FoxP3 was shown to interact with nuclear factor of activated T cells and nuclear factor kappa B to prevent gene activation by these transcription factors [18]; this trans-repression is presumably important in switching off inflammatory cytokine expression by regulatory T cells, although IFN- γ -producing FoxP3⁺ cells were recently described (see below).

An elegant paper by Fontenot *et al.* [19••] defined the biology of FoxP3 using a number of different transgenic mouse models. A green fluorescent protein (GFP) FoxP3 construct allowed the demonstration that FoxP3 expression was restricted to $\alpha\beta$ T-cell receptor T cells (mostly

CD4), and this expression correlated closely with regulatory function for both CD25-positive and CD25-negative T cells. CD25^{lo}FoxP3 GFP-expressing T cells formed up to 50% of FoxP3-expressing T cells in tissue. Furthermore, the generation of FoxP3GFP-OT-II T-cell receptor transgenic mice on a RAG 1-deficient background allowed the demonstration that FoxP3 did not play a role in limiting effector cell function, and that 'adaptive' FoxP3-expressing T cells were not generated during acute immune responses [19^{••}]. The same group defined an important role for TGF- β 1 in the maintenance of suppressor function in CD4⁺CD25⁺ T cells by sustaining FoxP3 expression [20], and responsiveness to TGF- β was shown to be important in regulation in TGF-receptor knockout mice [21]. However, other groups published data from an analysis of human T cells that suggested that FoxP3 expression might arise *de novo* in activated CD25-negative T cells [21,22]. It is possible that such cells expand from the human equivalent of the CD25^{lo}FoxP3 population defined by Fontenot *et al.* [19^{••}]. More recently, FoxP3 expressing CD4⁺CD25⁺ T_{regs} in inflamed synovium were identified as CD27⁺ [23]. Understanding the factors that derive and expand FoxP3-expressing cells, as well as their tissue trafficking, will be important if the cell type is to be exploited for therapy.

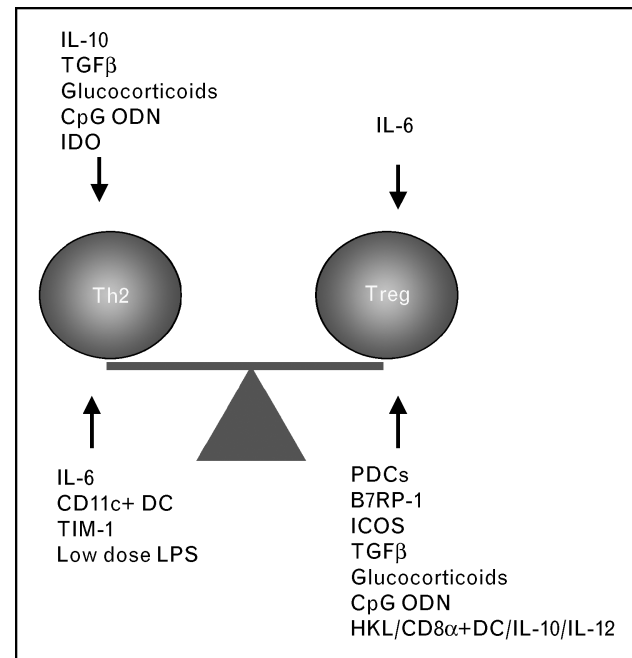
Determinants of active T helper type 2 responses versus tolerance in the airway

If the expression of allergic disease results from an imbalance between the activation and suppression of Th2 responses, it will be important to define the factors driving each of these outcomes to allergen challenge; potential factors are summarized in Fig. 1. A number of reports have recently defined potential determinants in mouse models, both of Th2 sensitization and airway challenge, and of tolerance induced by intranasal antigen administration.

Cells, cytokines and co-stimulation in T helper type 2-dependent airway inflammation

Dendritic cells play a pivotal role in primary antigen sensitization, but their role in maintaining airway inflammation is less certain. Van Rijt *et al.* [24[•]] showed that the depletion of CD11c⁺ cells from the airway in CD11c diphtheria toxin receptor transgenic mice by the inhalation of diphtheria toxin before inhaled challenge of sensitized mice abrogated airway hyperresponsiveness, eosinophilic inflammation and airway Th2 cytokine expression. Piggott *et al.* [25] have previously shown a requirement for low-dose lipopolysaccharide in airway Th2 responses and went on to report that lung dendritic cells (unlike dendritic cells derived from other sites) mediate this effect via MyD88-dependent signalling pathways.

Figure 1. Determinants of the balance between T helper type 2 and regulatory T-cell responses to allergen exposure.



T helper (Th) type 2 responses are accentuated by IL-6, antigen presentation via CD11c-positive dendritic cells (DCs), TIM-1 co-stimulation and low-dose lipopolysaccharide (LPS) exposure, whereas IL-10, transforming growth factor beta (TGF- β), glucocorticoids, CpG oligodeoxynucleotides (ODN) and indoleamine 2,3 dioxygenase (IDO) activity all suppress Th2 cytokine expression. Regulatory T-cell (T_{reg}) numbers or function is increased by TGF- β (partly through sustaining FoxP3 expression), B7RP-1 and ICOS co-stimulation, plasmacytoid dendritic cells in the airway, glucocorticoids (which increase FoxP3 expression), CpG oligodeoxynucleotides (ODN) (increase IDO activity), and heat-killed *Listeria* (HKL). IL-6 reduces the expansion of CD4⁺CD25⁺ regulatory T cells. PDC, Plasmacytoid dendritic cell.

CD8 T cells have been suggested to play potential suppressive roles, but can also express type 2 cytokines both in mice and human airways. Stock *et al.* [26] showed that CD8 depletion before Th2 sensitization increased IgE responses and subsequent airway inflammation and airway hyperresponsiveness upon airway challenge in mice, whereas the depletion of CD8 T cells after sensitization had no effect. CD8 T cells may thus regulate the development of IgE responses, but at least in this model do not appear to suppress airway inflammation.

An intriguing role for IL-6 in determining airway Th2 effector and T_{reg} function was described by Doganci *et al.* [27^{••}]. IL-6 can act either via membrane-anchored IL-6R α chain associated with gp130 or by binding to soluble IL-6R, which then associates with gp130 on the cell membrane. The blockade of sIL-6R in the airway inhibited Th2 responses to inhaled antigen in sensitized mice, whereas the blockade of mIL-6R induced the expansion of FoxP3⁺ CD4⁺CD25⁺ T_{regs}. Increased

sIL-6R was detected in bronchoalveolar lavage fluid from asthmatic patients compared with non-asthmatic individuals, and this was further increased after allergen inhalation challenge. These data suggest that the inhibition of IL-6 might be a useful therapeutic approach in allergic asthma [27••].

The inhibitory co-stimulator molecules CTLA-4 and PD1 have been linked to CD4⁺CD25⁺ T_{reg} function. In a mouse model of airway inflammation, the expression of PD-1 and PD-L2 was increased but a PD-L2-Fc activating protein actually accentuated airway inflammation when given *in vivo*, despite suppressive activity *in vitro* [28], emphasizing that regulation depends on multiple cell interactions.

Inhaled antigen exposure has been shown to induce tolerance in a number of experimental protocols. Repeated low-dose antigen exposure in mice induced a FoxP3⁺ CD4 subset of suppressive T cells with surface-associated TGF- β [29•]. In contrast, high-dose intranasal antigen-induced tolerance acts through IL-10 production by dendritic cells and the induction of IL-10-producing T_{regs}. Stock *et al.* [30•] described a further T_{reg} population induced by the co-administration of heat-killed listeria at the time of ovalbumin sensitization in a mouse model. This led to the development of FoxP3 and T-bet messenger RNA-positive T_{reg} that produced both IL-10 and IFN- γ . This was dependent on CD8 α -positive dendritic cells and their production of both IL-10 and IL-12 [30•]. In contrast, T_{reg} induced via high-dose inhaled antigen were described as FoxP3 and GATA3 mRNA-positive, but did not express mRNA for T-bet. It will be important to determine how these models relate to the development of tolerance to airborne allergens in humans.

Several reports have examined the determinants of high-dose inhaled tolerance in mice; this was shown to depend on plasmacytoid dendritic cells [31•], and B7RP-1 co-stimulation (in addition to the previous definition of a role for the inducible costimulator) [32]. Furthermore, TIM-4 interaction with TIM-1 was shown to activate Th2 cells, and an agonist TIM-1 antibody could prevent airway tolerance and potentiate airway Th2 responses [33•, 34•]. This pathway may be an important determinant of the activation/suppression balance in allergic disease as an atopy-associated gene encodes TIM-1.

The route of antigen exposure may be important. It has previously been suggested that epicutaneous sensitization might be important for the development of peanut allergy [35], and Strid *et al.* [36] showed that epicutaneous exposure could prevent and partly reverse existing oral tolerance induction to peanut allergen in a mouse model, with subsequent amplification of Th2 responses.

Tipping the balance: how can tolerance be promoted?

Clearly, understanding T_{reg} biology and the induction of tolerance in mouse models is of interest, but how can we translate this information to therapy? Glucocorticosteroids are the most widely used anti-inflammatory treatment for allergic diseases. They inhibit Th2 cytokine expression, induce IL-10-producing T_{regs} [3], and increase CD4⁺CD25⁺ T-cell suppression of allergen-driven T-cell responses *in vitro* by increasing IL-10 production [37]. Furthermore, these drugs increased FoxP3, both *in vitro* and in asthmatic patients treated with either inhaled or oral steroids [38•].

Allergen immunotherapy has also been associated with the activation of IL-10 production from CD4⁺CD25⁺ T cells [2], and these observations were supported by the observation of increased numbers of IL-10-expressing CD4⁺CD25⁺ T cells in the peripheral blood of patients treated with house-dust mite extract immunotherapy, although functional suppression by these cells was not confirmed [39]. Interestingly, immunotherapy using T-cell epitope peptides of cat allergen decreased blood CD4 cell responses to cat allergen, but did not alter suppression by CD4⁺CD25⁺ T cells [40]. As this therapy reduces allergen responsiveness, increases IL-10 production, and was shown to induce a suppressive population of CD4 T cells [41•], this raises the possibility of the induction of non-CD25-positive IL-10-producing T_{regs}, analogous of those described for peptide treatment in mice [42]. There is much current interest in the use of adjuvants to increase the efficacy of allergen immunotherapy to improve safety and simplify dosing. One approach is to co-administer Toll receptor ligands such as bacterial DNA sequences rich in CpG repeats (TLR9 ligand). As TLR9 ligation induces dendritic cell production of IFN- α , this might be expected to deviate the immune response towards a Th1 pattern, and this was suggested by the analysis of allergen responses of blood T cells in patients treated with allergen-CpG conjugate [43]. Interestingly, in a mouse model CpG induced pulmonary IDO activity to inhibit Th2 inflammation, raising the possibility of the regulatory activity of such treatment, or indeed natural exposure to bacterial products [44•].

Conclusion

The past year has seen an expansion in the understanding of T_{reg} biology and murine models of tolerance in allergic sensitization and airway inflammation. The challenge is now to relate these findings to clinical allergic disease, and to the development of prevention and treatment strategies. One important point will be to distinguish between factors driving atopic sensitization and those leading to allergic disease.

References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 580–581).

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