

Inhibition of the allergic response by regulatory T cells

Philippe Stock^a, Rosemarie H. DeKruyff^b and Dale T. Umetsu^b

Purpose of review

Allergic diseases are caused by the overdevelopment of T-helper type 2 biased immune responses in susceptible individuals. A number of recent studies indicate that regulatory T cells play an important role in controlling such T-helper type 2 biased responses not only in animal models, but in humans as well, and these will be reviewed in this article.

Recent findings

A family of regulatory cells appears to be involved in regulating allergies. Both naturally occurring CD4⁺CD25⁺ regulatory T cells and inducible forms of antigen-specific regulatory T cells, both expressing the transcription factor foxp3, have been shown to inhibit the inappropriate immune responses involved in allergic diseases. Impaired expansion of natural or adaptive regulatory T cells is hypothesized to lead to the development of allergy, and treatment to induce allergen-specific regulatory T cells could provide curative therapies for allergy and asthma.

Summary

Allergen-specific regulatory T cells play an important role in controlling the development of allergy and asthma.

Keywords

airway hyperresponsiveness, allergy, asthma, regulatory cells, tolerance

Introduction

Immune tolerance to self or exogenous antigens/allergens is mediated by several mechanisms, including clonal deletion, anergy or immune suppression by regulatory T (T_{Reg}) cells. T_{Reg} cells mediate tolerance by preventing the activation and function of nonregulatory effector T cells. The study of T_{Reg} cells has advanced markedly over the last few years, driven by a few key findings and improvements in the technology for identifying and isolating T_{Reg} cells. Several subtypes of T_{Reg} cells have been described, including those that develop centrally in the thymus, specific for auto/self-antigens (also called natural CD25⁺ T_{Reg} cells) and those that develop in the periphery on exposure to exogenous antigen/allergens (also called adaptive T_{Reg} cells). Allergen-specific adaptive T_{Reg} cells are thought to play an important role in limiting immune responses to allergens and preventing allergic disease, but the precise relationship between natural and adaptive subsets of T_{Reg} cells is not yet certain.

Thymus-generated natural T_{Reg} cells

Natural T_{Reg} cells develop in the thymus and constitute 5–10% of the CD4⁺ T cells in the periphery in both mice and in humans. Natural T_{Reg} cells constitutively express the CD25 [interleukin (IL)-2 receptor] molecule, as well as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), a member of the immunoglobulin superfamily, glucocorticoid-induced tumor necrosis factor receptor (GITR), a member of the tumor necrosis factor-nerve growth factor receptor family of proteins, and the transcription factor Foxp3 [1•]. Although the expression of CD25 has been used in many studies to specifically identify natural T_{Reg} cells in naïve mice, the value of CD25 as a marker of T_{Reg} cells is limited, since CD25 is highly expressed (as is CTLA-4, and GITR) on activated CD4⁺ T cells, virtually eliminating the value of CD25 as a marker for T_{Reg} cells in settings of immune activation, particularly in humans. In contrast, the expression of Foxp3 is highly restricted to a subset of αβ T-cell receptor (TCR) cells, and irrespective of CD25 expression, expression correlates closely with suppressor activity [2••]. Studies in mice suggest that Foxp3, which binds to DNA, localizes to the nucleus and acts as a transcriptional repressor [3], functioning as a T_{Reg} cell lineage specification factor [4–6].

Natural T_{Reg} cells develop in the thymus, presumably through mechanisms that involve TCR–ligand interactions, as well as additional, poorly understood signals,

Curr Opin Allergy Clin Immunol 6:12–16. © 2006 Lippincott Williams & Wilkins.

^aDepartment of Pediatric Pneumology and Immunology, University Hospital Charité, Berlin, Germany and ^bDivision of Immunology, Children's Hospital Boston, Harvard Medical School, Boston, Massachusetts, USA

Correspondence to Dale T. Umetsu MD, PhD, Division of Immunology, Children's Hospital Boston, Harvard Medical School, Karp Laboratories, Rm 10127, One Blackfan Circle, Boston, MA 02115, USA

Tel: +1 617 919 2414; fax: +1 617 7300528;
e-mail: dale.umetsu@childrens.harvard.edu

Current Opinion in Allergy and Clinical Immunology 2006, 6:12–16

Abbreviations

T _{Reg}	regulatory T cells
TCR	T-cell receptor
TGF-β	transforming growth factor β
Th2	T-helper type 2
TLR	toll-like receptor
TSLP	thymic stromal lymphopoietin
IL	interleukin

© 2006 Lippincott Williams & Wilkins
1528-4050

distinct from those required for nonregulatory T-cell selection [7]. The TCR repertoire and specificity of T_{Reg} cells are overlapping with those of nonregulatory T cells, and a large proportion of the TCRs of T_{Reg} cells are self reactive [8]. The process of positive selection in the thymus for T_{Reg} cells does not appear to involve the *Aire* gene, which induces the transcription in the thymic medullary epithelium of a large set of genes encoding tissue-specific proteins. Rather, *Aire* is thought to primarily induce clonal deletion of self-reactive thymocytes, and not positive selection of T_{Reg} cells [9•]. A factor, however, that may be critically involved in positive selection of natural T_{Reg} cells in the thymus is thymic stromal lymphopoietin (TSLP), which is highly expressed in Hassall's corpuscles in the thymic medulla, and which activates dendritic cells to induce thymocyte expression of Foxp3 [10••]. Whether this mechanism that results in the development of natural CD25⁺ T_{Reg} cells is also involved in the development of adaptive T_{Reg} cells is not known.

Natural CD25⁺ T_{Reg} cells in allergy

Several studies have examined the role of the CD4⁺CD25⁺ T-cell population in regulating allergic disease. In studies of cow's milk allergy, children who had outgrown cow's milk sensitivity had higher frequencies of circulating CD4⁺CD25⁺ T cells and decreased in-vitro proliferative responses to bovine β -lactoglobulin in peripheral blood mononuclear cells compared with children who maintained a clinically active allergy [11••]. CD4⁺CD25⁺ T cells may also suppress allergic responses to inhaled allergens (e.g. cat allergen or grass pollen), as CD25⁺ T cells from nonallergic donors, but not from allergic donors, suppressed proliferation and IL-5 secretion by their own allergen-stimulated CD4⁺CD25⁻ T cells [12•]. The loss in inhibitory activity of CD25⁺ T cells from allergic donors was most pronounced during symptomatic periods, when pollen counts were highest. Similarly, CD25⁺ T cells from both allergic and non-allergic individuals potently suppressed T-cell proliferation and T-helper type 2 (Th2) cytokine production in response to birch allergen outside of the pollen season. During the birch pollen season, however, CD25⁺ T cells from allergic patients, although not from nonallergic controls, were defective in downregulating birch pollen induced IL-13 and IL-5 production [13]. These studies suggest that the 'natural' CD25⁺ T-cell population includes T cells that recognize allergens, or possibly that activated antigen-specific 'adaptive' T_{Reg} cells expressing CD25 are present in this population. Alternatively, nonspecific suppressive activity of the natural CD25⁺ T-cell population can inhibit the development of atopic disease, but this suppressive activity is reduced in atopic individuals for various reasons, for example by exposure to superantigen [14]. In mice, natural CD25⁺ T cells have been shown to limit airway inflammation but not airway

hyperreactivity [15], consistent with the idea that CD25⁺ T cells are weak against allergen-specific responses because they are not allergen specific. Therefore, pre-activation of the CD25⁺ T cells by nonspecific signals appears to be required to obtain strong inhibition of allergic responses [16].

Exogenous antigen-specific adaptive T_{Reg} cells

While it is clear that natural T_{Reg} cells are positively selected in the thymus by encounter with self-antigens, it is likely that allergen-specific adaptive T_{Reg} cells develop after encounters with exogenous allergens (e.g. from food or plants), not in the thymus, but rather in the periphery. This suggests that adaptive T_{Reg} cells develop through pathways distinct from CD25⁺ natural T_{Reg} cells, presumably from nonregulatory T cell precursors. Alternatively, it is possible that adaptive T_{Reg} cells derive from the same dedicated T_{Reg} cell lineage as do natural T_{Reg} cells, possibly by differentiation in the thymus, but then expand in the periphery after encounters with allergens. Because adaptive T_{Reg} cells do not have clear-cut markers that make them easy to identify and isolate, the specific characteristics and pathways by which they develop are difficult to study. In human patients with the immune dysregulation, polyendocrinopathy, X-linked (IPEX) syndrome, who have mutations in the Foxp3 gene, the development of both severe autoimmune disease as well as food allergy and eczema suggests that regulatory T cells expressing Foxp3 play an important role both in regulating autoimmunity as well as in regulating allergic responses to exogenous allergens. Therefore, natural and adaptive T_{Reg} cells may be related by the expression of Foxp3. The development of allergy, therefore, may be due to insufficient development of allergen-specific T_{Reg} cells expressing Foxp3 in allergic individuals [17] (see below).

Antigen-specific adaptive T_{Reg} cells have been induced in a number of experimental conditions. For example, the induction of tolerance by intravenous or oral administration of antigen resulted in the development of (adaptive) antigen-specific (CD25⁺) T_{Reg} cells [18], or suppressive Th3 cells [19], although Foxp3 expression was not examined in these studies. In addition, administration of peptide subcutaneously [20] or subcutaneously with osmotic pumps [21••], or of antigen into the respiratory tract [22,23••], or of antigen with the adjuvant heat-killed *Listeria monocytogenes* [24••] induced the development of antigen-specific T_{Reg} cells that expressed Foxp3. Some of these T_{Reg} cells expressed IL-10 [22], while others expressed transforming growth factor β (TGF- β) [23••], or both IL-10 and interferon γ (IFN- γ) [24••]. In particular, the IL-10 producing T_{Reg} cells (which expressed GATA-3, master regulator for Th2

polarization, and FoxP3), the IL-10 and IFN- γ producing T_{Reg} cells (which expressed T-bet and Foxp3) [22,24^{••}], and the TGF- β -producing T_{Regs} (which expressed Foxp3) [23^{••}] all had potent inhibitory activity, and blocked the development of airway hyperresponsiveness (AHR) in murine models of asthma. Thus, several types of adaptive T_{Reg} cells that express Foxp3 and that may be related to natural T_{Reg} cells can inhibit the development of Th2-driven inflammation.

Antigen-specific adaptive T_{Reg} cells expressing Foxp3 may also be related to T_R1 cells, which develop *in vitro* in the presence of IL-10 [25], or in the presence of vitamin D₃ and dexamethasone [26]. T_R1 cells, however, do not express Foxp3 [27], and treatment of mice with corticosteroids prevents the development of antigen-specific T_{Reg} cells [28], suggesting that corticosteroid therapy has the potential to worsen allergic diseases. In-vitro treatment with corticosteroids can induce Foxp3 expression in nonregulatory human T cells, but only twofold [29], and can enhance IL-10 production, but also only twofold [30], and the suppressor activity of such Foxp3⁺, IL-10⁺ T cells is modest. Additional mechanisms have been shown to increase Foxp3 expression in T cells, for example exposure to TGF- β [31,32], or by blockade of IL-6R [33], but the precise role of such Foxp3⁺ cells *in vivo* is not clear. Nor is it clear if the expression of Foxp3 is due to the expansion of a small population of Foxp3⁺ T cells that might contaminate the population, or due to a true conversion of nonregulatory T cells into T_{Reg} cells. The induction of T_{Reg} cells in the periphery is unlikely to involve TSLP, which induces Foxp3 expression in T_{Reg} cells in the thymus [10^{••}], since expression of TSLP in the lungs or the skin results in the development of allergic airway inflammation [34] and atopic dermatitis [35], respectively. Although meticulous analysis of mouse T cells *in vitro* and *in vivo* shows no upregulation of Foxp3 after activation of nonregulatory T cells [2^{••},36], under certain circumstances naïve CD25 cells, presumably those without regulatory cell activity, develop into allergen-specific adaptive T_{Reg} cells producing Foxp3 on encounter with allergen outside of the thymus. The precise mechanisms by which this occurs in the periphery, however, remain to be elucidated.

IL-10 and tolerance in allergy and asthma

Until recently, the development of allergic diseases was thought to be due to an imbalance between allergen-specific Th1 and Th2 cells. The importance of T_{Reg} cells, however, suggests that allergy is due rather to an imbalance between allergen-specific T_{Reg} cells and Th2 cells. In allergic individuals, there is an increase in the frequency of IL-4-secreting, allergen-specific T cells, and a reduction in the frequency of IL-10-secreting, allergen-specific T_{Reg} cells compared with nonallergic individuals

[37^{••}]. This is consistent with the cytokine profiles observed in a large cohort of allergic and nonallergic children, in which increased IL-4, IL-5 and IL-13 was associated with allergy, and IL-10 was associated with negative allergy skin tests [38]. The lack of allergen-specific tolerance (and limited development of T_{Reg} cells) in allergic individuals has been hypothesized to be related to improved hygiene in industrialized countries, possibly due to reduced infections, alterations in commensal microflora in the intestinal tract and reduced toll-like receptor (TLR) signaling [39]. This idea is consistent with the observation that oral tolerance cannot be induced in germ-free mice [40]. Furthermore, elimination of commensal intestinal microflora and TLR signaling with broad spectrum antibiotics also prevented oral tolerance from developing, enhanced allergic sensitization [41], and resulted in susceptibility to intestinal inflammation [42^{••}]. These observations suggest that TLR signaling by commensal bacteria under normal steady-state conditions is required for maintenance of intestinal epithelial homeostasis, and possibly for the induction of some forms of T_{Reg} cells.

Allergen-specific immunotherapies for allergic diseases

If allergic disease is due to a lack of allergen-specific T_{Reg} cells, then effective therapies for allergy should induce the development of T_{Reg} cells producing cytokines such as IL-10 [43[•]]. Although treatment using recombinant IL-10 itself is well tolerated, IL-10 has both inflammatory as well as noninflammatory effects, and when administered as a pharmaceutical agent may exacerbate allergic disease [44]. Therefore, delivery of IL-10 by allergen-specific T_{Reg} cells, induced with allergen immunotherapy, is a more attractive approach that has the potential to cure patients with allergy and asthma. Allergen immunotherapy involves the subcutaneous, sublingual or intranasal application of increasing doses of specific allergen extract and is highly effective in patients with immunoglobulin E (IgE)-mediated diseases, such as allergic rhinitis, asthma and venom anaphylaxis [45–47]. Traditional allergen-desensitization immunotherapy, which has been in use for almost a century now [46,47], may be effective for the treatment of allergy because it induces the development of T_{Reg} cells. Thus, successful allergen immunotherapy is associated with a decrease in an allergen-specific Th2 response and the induction of allergen-induced IL-10-secreting T_{Reg} cells [48–51].

Because traditional immunotherapy is associated with significant adverse side effects, including anaphylaxis and death, and because sustained benefit requires prolonged administration over a period of several years, improved and more efficient immunotherapy regimens have been studied recently. First, the use of purer

allergen preparations, including recombinant allergen proteins, may increase the safety and specificity of immunotherapy, as well as improve the diagnosis of specific allergy [52]. This strategy is dependent on a clear understanding of the important allergenic epitopes that induce T_{Reg} cells. Second, to limit the allergenicity of whole allergens, investigators have examined peptide-based allergen preparations, which do not bind IgE and therefore do not activate mast cells, but which reduce both Th1 and Th2-cytokine synthesis, while increasing levels of IL-10 [53,54]. The beneficial effects of peptide immunotherapy, however, appear not to depend on enhancing the development of $CD4^+CD25^+ T_{Reg}$ cells [55]. A third strategy, which may improve the safety of allergen immunotherapy, is to administer anti-IgE-monoclonal antibody omalizumab with allergen immunotherapy [56,57]. Such a combination may improve the rapidity by which immunotherapy induces T_{Reg} cells.

A fourth strategy to improve the efficiency by which immunotherapy induces T_{Reg} cells is to use adjuvants. For example, treatment of mice with mycobacterium-induced allergen-specific T_{Reg} cells producing IL-10 and TGF- β protected against airway inflammation [58]. Similarly, the use of just one dose of heat-killed *L. monocytogenes* as adjuvant induced allergen-specific T_{Reg} cells producing IFN- γ and IL-10, which protected against airway inflammation and AHR in mice [24^{••}], and against food allergy in dogs [59]. The combination of IFN- γ and IL-10 produced by the T_{Reg} cells may be particularly effective in reducing allergic inflammation [60]. The adjuvant closest to clinical application in man is immunostimulatory CpG motifs, which are present in bacterial DNA but suppressed in vertebrates, and which activate TLR9 [61]. Trials in humans showed that CpG allergen (ragweed) possesses greatly reduced allergenicity, and early reports of the clinical efficacy are highly encouraging [62,63]. Because the beneficial effects of the CpG-allergen conjugates appear to last well beyond the treatment period (which generally includes only six injections), it is likely that the CpG-allergen conjugates induce some form of T_{Reg} cells, which may produce IL-10 and IFN- γ , although this has not been formally studied. In any case, adjuvants such as CpG or heat-killed *Listeria* appear to greatly enhance the efficiency and efficacy of allergen immunotherapy to provide safe and long-lasting control of allergic diseases.

Conclusion

The induction of allergen-specific regulatory T cells provides a local, allergen-driven inhibitory immune response, which allows a safe and long-lasting control of allergic diseases. Further understanding of the mechanisms involved to induce these cells is necessary to utilize them more efficiently in therapeutic strategies.

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 (p. 71).

- 1 Sakaguchi S. Naturally arising Foxp3-expressing $CD25^+CD4^+$ regulatory T cells in immunological tolerance to self and non-self. *Nat Immunol* 2005; 6:345–352.
This recent study nicely reviews the field of naturally arising regulatory T cells, and discusses the feasibility of those cells as potential therapeutic targets.
- 2 Fontenot JD, Rasmussen JP, Williams LM, *et al.* Regulatory T cell lineage specification by the forkhead transcription factor foxp3. *Immunity* 2005; 22:329–341.
This paper systematically analyzes Foxp3 expression in the mouse. The authors have generated mice harboring a GFP-Foxp3 fusion protein-reporter knockin allele and report that Foxp3 functions as a lineage specification marker for regulatory T cells.
- 3 Schubert L, Jeffery E, Zhang Y, *et al.* Scurfin (FOXP3) acts as a repressor of transcription and regulates T cell activation. *J Biol Chem* 2001; 276:37672–37679.
- 4 Fontenot JD, Gavin MA, Rudensky AY. Foxp3 programs the development and function of $CD4^+CD25^+$ regulatory T cells. *Nat Immunol* 2003; 4:330–336.
- 5 Hori S, Nomura T, Sakaguchi S. Control of regulatory T cell development by the transcription factor Foxp3. *Science* 2003; 299:1057–1061.
- 6 Fontenot JD, Rudensky AY. A well adapted regulatory contrivance: regulatory T cell development and the forkhead family transcription factor Foxp3. *Nat Immunol* 2005; 6:331–337.
- 7 van Santen H, Benoist C, Mathis D. Number of T reg cells that differentiate does not increase upon encounter of agonist ligand on thymic epithelial cells. *J Exp Med* 2004; 200:1221–1230.
- 8 Hsieh C, Liang Y, Tzgnik A, *et al.* Recognition of the peripheral self by naturally arising $CD25^+ CD4^+$ T cell receptors. *Immunity* 2004; 21:267–277.
- 9 Anderson M, Venanzi E, Chen Z, *et al.* The cellular mechanism of Aire control of T cell tolerance. *Immunity* 2005; 23:227–239.
The authors demonstrate that the cellular mechanism by which *Aire* exerts its tolerance-promoting function is not primarily positive selection of regulatory T cells, but rather negative selection of T effector cells.
- 10 Watanabe N, Wang Y, Lee H, *et al.* Hassall's corpuscles instruct dendritic cells to induce $CD4^+CD25^+$ regulatory T cells in human thymus. *Nature* 2005; 436:1181–1185.
This study demonstrates that TSLP is an important factor that results in the expression of Foxp3, and the development of T_{Reg} cells.
- 11 Karlsson MR, Rugtveit J, Brandtzaeg P. Allergen-responsive $CD4^+CD25^+$ regulatory T cells in children who have outgrown cow's milk allergy. *J Exp Med* 2004; 199:1679–1688.
This study provides data in humans and suggests that mucosal induction of tolerance against dietary antigens is associated with the development of $CD4^+CD25^+$ regulatory T cells.
- 12 Ling EM, Smith T, Nguyen XD, *et al.* Relation of $CD4^+CD25^+$ regulatory T-cell suppression of allergen-driven T-cell activation to atopic status and expression of allergic disease. *Lancet* 2004; 363:608–615.
The authors show that an imbalance between regulatory and effector T cells in allergic diseases may result from a deficiency in suppression by regulatory T cells in allergic individuals. $CD4^+CD25^+$ T cells from nonatopic donors suppressed proliferation and IL-5 production by their own allergen-stimulated $CD4^+CD25^-$ T cells. The capacity of $CD4^+CD25^+$ T cells from atopic donors to inhibit T-cell proliferation was significantly reduced.
- 13 Grindebacke H, Wing K, Andersson AC, *et al.* Defective suppression of Th2 cytokines by $CD4^+CD25^+$ regulatory T cells in birch allergies during birch pollen season. *Clin Exp Allergy* 2004; 34:1364–1372.
- 14 Ou LS, Goleva E, Hall C, Leung DY. T regulatory cells in atopic dermatitis and subversion of their activity by superantigens. *J Allergy Clin Immunol* 2004; 113:756–763.
- 15 Hadeiba H, Locksley R. Lung $CD25^+ CD4^+$ regulatory T cells suppress type 2 immune responses but not bronchial hyperreactivity. *J Immunol* 2003; 170:5502–5510.
- 16 Stassen M, Jonuleit H, Muller C, *et al.* Differential regulatory capacity of $CD25^+$ T regulatory cells and preactivated $CD25^+$ T regulatory cells on development, functional activation, and proliferation of Th2 cells. *J Immunol* 2004; 173:267–274.
- 17 Umetsu D, McIntire J, Macaubas C, *et al.* Asthma: an epidemic of dysregulated immunity. *Nat Immunol* 2002; 3:715–720.

- 18 Thorstenson K, Khoruts A. Generation of anergic and potentially immunoregulatory CD25+CD4 T cells in vivo after induction of peripheral tolerance with intravenous or oral antigen. *J Immunol* 2001; 167:188–195.
- 19 Chen Y, Kuchroo VK, Inobe J, *et al.* Regulatory T cell clones induced by oral tolerance: suppression of autoimmune encephalomyelitis. *Science* 1994; 265:1237–1240.
- 20 Bynoe MS, Evans JT, Viret C, *et al.* Epicutaneous immunization with autoantigenic peptides induces T suppressor cells that prevent experimental allergic encephalomyelitis. *Immunity* 2003; 19:317–328.
- 21 Apostolou I, Von Boehmer H. In vivo instruction of suppressor commitment in naive T cells. *J Exp Med* 2004; 199:1401–1408.
Describes antigen-specific T_{Reg} cells that develop in response to antigen exposure, presumably from nonregulatory T cells.
- 22 Akbari O, Freeman GJ, Meyer EH, *et al.* Antigen-specific regulatory T cells develop via the ICOS–ICOS-Ligand pathway and inhibit allergen-induced airway hyperreactivity. *Nat Med* 2002; 8:1024–1032.
- 23 Ostroukhova M, Seguin-Devaux C, Oriss TB, *et al.* Tolerance induced by inhaled antigen involves CD4(+) T cells expressing membrane-bound TGF-beta and FOXP3. *J Clin Invest* 2004; 114:28–38.
Describes antigen-specific T_{Reg} cells that develop in response to antigen exposure, presumably from nonregulatory T cells.
- 24 Stock P, Akbari O, Berry G, *et al.* Induction of T helper type 1-like regulatory cells that express Foxp3 and protect against airway hyper-reactivity. *Nat Immunol* 2004; 5:1149–1156.
Describes antigen-specific T_{Reg} cells that develop in response to antigen exposure, presumably from nonregulatory T cells.
- 25 Groux H, O'Garra A, Bigler M, *et al.* A CD4+ T-cell subset inhibits antigen-specific T-cell responses and prevents colitis. *Nature* 1997; 389:737–742.
- 26 Barrat FJ, Cua DJ, Boonstra A, *et al.* In vitro generation of interleukin 10-producing regulatory CD4(+) T cells is induced by immunosuppressive drugs and inhibited by T helper type 1 (Th1)- and Th2-inducing cytokines. *J Exp Med* 2002; 195:603–616.
- 27 Vieira PL, Christensen JR, Minaee S, *et al.* IL-10-secreting regulatory T cells do not express Foxp3 but have comparable regulatory function to naturally occurring CD4+CD25+ regulatory T cells. *J Immunol* 2004; 172:5986–5993.
- 28 Stock P, Akbari O, DeKruyff R, Umetsu D. Respiratory tolerance is inhibited by the administration of corticosteroids. *J Immunol* (in press).
- 29 Karagiannidis C, Akdis M, Holopainen P, *et al.* Glucocorticoids upregulate FOXP3 expression and regulatory T cells in asthma. *J Allergy Clin Immunol* 2004; 114:1425–1433.
- 30 Dao Nguyen X, Robinson DS. Fluticasone propionate increases CD4CD25 T regulatory cell suppression of allergen-stimulated CD4CD25 T cells by an IL-10-dependent mechanism. *J Allergy Clin Immunol* 2004; 114:296–301.
- 31 Chen W, Jin W, Hardegen N, *et al.* Conversion of peripheral CD4+CD25–naive T cells to CD4+CD25+ regulatory T cells by TGF-beta induction of transcription factor Foxp3. *J Exp Med* 2003; 198:1875–1886.
- 32 Zheng SG, Wang JH, Gray JD, *et al.* Natural and induced CD4+CD25+ cells educate CD4+CD25– cells to develop suppressive activity: the role of IL-2, TGF-beta, and IL-10. *J Immunol* 2004; 172:5213–5221.
- 33 Doganci A, Eigenbrod T, Krug N, *et al.* The IL-6R alpha chain controls lung CD4+CD25+ Treg development and function during allergic airway inflammation in vivo. *J Clin Invest* 2005; 115:313–325.
- 34 Zhou B, Comeau MR, Smedt TD, *et al.* Thymic stromal lymphopoietin as a key initiator of allergic airway inflammation in mice. *Nat Immunol* (in press).
- 35 Yoo J, Omori M, Gyarmati D, *et al.* Spontaneous atopic dermatitis in mice expressing an inducible thymic stromal lymphopoietin transgene specifically in the skin. *J Exp Med* 2005; 202:541–549.
- 36 Yagi H, Nomura T, Nakamura K, *et al.* Crucial role of FOXP3 in the development and function of human CD25+CD4+ regulatory T cells. *Int Immunol* 2004; 16:1643–1656.
- 37 Akdis M, Verhagen J, Taylor A, *et al.* Immune responses in healthy and allergic individuals are characterized by a fine balance between allergen-specific T regulatory 1 and T helper 2 cells. *J Exp Med* 2004; 199:1567–1575.
This is the first study to associate a reduced frequency of regulatory T cells to allergic diseases in humans. Atopic individuals displayed a lower frequency of IL-10-producing T-reg cells than nonatopic controls.
- 38 Heaton T, Rowe J, Turner S, *et al.* An immunoepidemiological approach to asthma: identification of in-vitro T-cell response patterns associated with different wheezing phenotypes in children. *Lancet* 2005; 365:142–149.
- 39 Prioult G, Nagler-Anderson C. Mucosal immunity and allergic responses: lack of regulation and/or lack of microbial stimulation? *Immunol Rev* 2005; 206:204–218.
- 40 Sudo N, Sawamura S, Tanaka K, *et al.* The requirement of intestinal bacterial flora for the development of an IgE production system fully susceptible to oral tolerance induction. *J Immunol* 1997; 159:1739–1745.
- 41 Smith DW, Nagler-Anderson C. Preventing intolerance: the induction of nonresponsiveness to dietary and microbial antigens in the intestinal mucosa. *J Immunol* 2005; 174:3851–3857.
- 42 Rakoff-Nahoum S, Paglino J, Eslami-Varzaneh F, *et al.* Recognition of commensal microflora by toll-like receptors is required for intestinal homeostasis. *Cell* 2004; 118:229–241.
This is an important study indicating that commensal bacteria signaling through TLRs can provide antiinflammatory signals in the gastrointestinal tract.
- 43 Hawrylowicz CM, O'Garra A. Potential role of interleukin-10-secreting regulatory T cells in allergy and asthma. *Nat Rev Immunol* 2005; 5:271–283.
This is a well written summary of the recent findings in the field of adaptive regulatory T cells and their potential therapeutic capacities for the treatment of allergy and asthma.
- 44 Asadullah K, Sterry W, Volk HD. Interleukin-10 therapy: review of a new approach. *Pharmacol Rev* 2003; 55:241–269.
- 45 Wilson DR, Lima MT, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. *Allergy* 2005; 60:4–12.
- 46 Bousquet J, Lockey R, Malling HJ, *et al.* Allergen immunotherapy: therapeutic vaccines for allergic diseases. *Ann Allergy Asthma Immunol* 1998; 81:401–405.
- 47 Norman PS. Immunotherapy: 1999–2004. *J Allergy Clin Immunol* 2004; 113:1013–1023; quiz 1024.
- 48 Till SJ, Francis JN, Nouri-Aria K, Durham SR. Mechanisms of immunotherapy. *J Allergy Clin Immunol* 2004; 113:1025–1034; quiz 1035.
- 49 Faith A, Richards DF, Verhoef A, *et al.* Impaired secretion of interleukin-4 and interleukin-13 by allergen-specific T cells correlates with defective nuclear expression of NF-AT2 and jun B: relevance to immunotherapy. *Clin Exp Allergy* 2003; 33:1209–1215.
- 50 Francis J, Till S, Durham S. Induction of IL-10+CD4+CD25+ T cells by grass pollen immunotherapy. *J Allergy Clin Immunol* 2003; 111:1255–1261.
- 51 Nouri-Aria KT, Wachholz PA, Francis JN, *et al.* Grass pollen immunotherapy induces mucosal and peripheral IL-10 responses and blocking IgG activity. *J Immunol* 2004; 172:3252–3259.
- 52 Valenta R, Ball T, Focke M, *et al.* Immunotherapy of allergic disease. *Adv Immunol* 2004; 82:105–153.
- 53 Oldfield WL, Larche M, Kay AB. Effect of T-cell peptides derived from Fel d 1 on allergic reactions and cytokine production in patients sensitive to cats: a randomised controlled trial. *Lancet* 2002; 360:47–53.
- 54 Fellrath JM, Kettner A, Dufour N, *et al.* Allergen-specific T-cell tolerance induction with allergen-derived long synthetic peptides: results of a phase I trial. *J Allergy Clin Immunol* 2003; 111:854–861.
- 55 Smith TR, Alexander C, Kay AB, *et al.* Cat allergen peptide immunotherapy reduces CD4(+) T cell responses to cat allergen but does not alter suppression by CD4(+) CD25(+) T cells: a double-blind placebo-controlled study. *Allergy* 2004; 59:1097–1101.
- 56 Kuehr J, Brauburger J, Zielen S, *et al.* Efficacy of combination treatment with anti-IgE plus specific immunotherapy in polysensitized children and adolescents with seasonal allergic rhinitis. *J Allergy Clin Immunol* 2002; 109:274–280.
- 57 Rolinck-Werninghaus C, Hamelmann E, Keil T, *et al.* The co-seasonal application of anti-IgE after preseasonal specific immunotherapy decreases ocular and nasal symptom scores and rescue medication use in grass pollen allergic children. *Allergy* 2004; 59:973–979.
- 58 Zuany-Amorim C, Sawicka E, Manlius C, *et al.* Suppression of airway eosinophilia by killed Mycobacterium vaccae-induced allergen-specific regulatory T-cells. *Nat Med* 2002; 8:8625–8629.
- 59 Frick O, Teuber S, Buchanan B, *et al.* Allergen immunotherapy with heat-killed *Listeria monocytogenes* (HKL) alleviates peanut and food-induced anaphylaxis in dogs. *Allergy* 2005; 60:243–250.
- 60 Trinchieri G. Regulatory role of T cells producing both interferon gamma and interleukin 10 in persistent infection. *J Exp Med* 2001; 194:F53–F57.
- 61 Akira S, Takeda K. Toll-like receptor signalling. *Nat Rev Immunol* 2004; 4:499–511.
- 62 Simons FE, Shikishima Y, Van Nest G, *et al.* Selective immune redirection in humans with ragweed allergy by injecting Amb a 1 linked to immunostimulatory DNA. *J Allergy Clin Immunol* 2004; 113:1144–1151.
- 63 Tulic MK, Fiset PO, Christodoulou P, *et al.* Amb a 1-immunostimulatory oligodeoxynucleotide conjugate immunotherapy decreases the nasal inflammatory response. *J Allergy Clin Immunol* 2004; 113:235–241.