

Role of regulatory dendritic cells in allergy and asthma

Omid Akbari and Dale T. Umetsu

Purpose of review

Dendritic cells are the most efficient inducers of all immune responses, and are capable of inducing either productive immunity or maintaining the state of tolerance to self-antigens and allergens. The present review summarizes the emerging literature on dendritic cells, with the emphasis on regulatory function of dendritic cells in allergy and asthma. In particular we summarize recent data regarding the relationship between dendritic cell subsets and Th1, Th2 and regulatory T (T_{Reg}) cells.

Recent findings

The diverse functions of dendritic cells have been attributed to distinct lineages of dendritic cells, which arise from common immature precursor cells that differentiate in response to specific maturation-inducing or local microenvironment conditions. These subsets induce different lineages of T cells such as Th1, Th2 and T_{Reg} cells, including Th1_{Reg} and Th2_{Reg} cells, which regulate allergic diseases and asthma.

Summary

Subsets of dendritic cells regulate the induction of a variety of T-cell subtypes, which suppress the development of allergy and asthma, thus providing antiinflammatory responses and protective immunity.

Keywords

airway hyperresponsiveness, asthma, CD8, dendritic cells, regulatory T cells

Curr Opin Allergy Clin Immunol 4:533–538. © 2004 Lippincott Williams & Wilkins.

Division of Immunology and Allergy, Department of Pediatrics, Stanford University, Stanford, California, USA

Correspondence to Dale T. Umetsu MD PhD, Division of Immunology and Allergy, Department of Pediatrics, 300 Pasteur Dr., Stanford University, Stanford, CA 94305-5208, USA

Tel: +1 650 723 5227; fax: +1 650 498 5560; e-mail: umetsu@stanford.edu

Current Opinion in Allergy and Clinical Immunology 2004, 4:533–538

Abbreviations

AHR	airway hyperreactivity
CLIP	MHC class II-associated invariant chain peptide
MHC	major histocompatibility complex
pDC	plasmacytoid dendritic cell
T _{Reg}	regulatory T cell
TSLP	thymic stromal lymphopoietin

© 2004 Lippincott Williams & Wilkins
1528-4050

Introduction

Dendritic cells represent a phenotypically heterogeneous and malleable population endowed with an important biologic function, namely, the presentation of antigen to both B and T lymphocytes [1,2]. Antigen presentation by dendritic cells can result in two opposite outcomes: productive immunity or tolerance to antigens and allergens. The fine regulation of these two distinct functions is not completely understood. For example, in lungs, the mucosal surfaces are continuously exposed to infectious agents as well as innocuous environmental antigens. Infectious microorganisms must be rapidly eliminated by the pulmonary immune system, while innocuous nonproliferating antigens must be cleared or tolerated in a manner that does not injure the host. Dendritic cells, therefore, must be capable of inducing active immunity, characterized by the development of subsets of effector and memory cells, as well as tolerance, characterized by anergy, the development of regulatory/suppressor cells or selection of autoreactive/allergen-reactive cells. The following article will review the spectrum of dendritic cells and subsets of regulatory T cells that have been shown to critically regulate the development of asthma and allergy.

Induction of Th2 cells and allergic disease by dendritic cells

In humans, Th2 cells are induced primarily by dendritic cells called DC2s [3,4]. Precursors of DC2s are called pDC2s or plasmacytoid dendritic cells, which produce large quantities of IFN- α/β [3,5,6]. Human pDC2s were recognized initially by their plasma-cell-like morphology and their unique surface phenotype (CD4⁺IL-3-receptor⁺CD11c⁺, negative for most other lineage markers). DC2s, which express few myeloid antigens, such as CD11b, CD11c, CD13, and CD33, depend on IL-3, but not granulocyte/macrophage colony-stimulating factor for their survival and maturation [6,7]. They have a low capacity for phagocytosis or macropinocytosis at all stages of their maturation.

In patients with both atopic and nonatopic asthma, Matsuda *et al.* [8] recently showed that the number of DC2s is markedly increased. This finding is of course consistent with the idea that Th2 cells and eosinophils are prominent features of the cellular infiltrate in the airway mucosa of patients with both atopic and nonatopic asthma. A recent investigation from Hagedorens *et al.* [9], however, compared dendritic cell populations in cord blood from children at risk for the development of atopy and found a reduction in

plasmacytoid (DC2) cells in atopic (asthmatic) children compared with healthy controls. The authors speculated that the decrease may be due to increased migration of DC2s to target organs. At this stage it is not clear why numbers of circulating DC2s might be reduced in children with asthma, but increased in adults with asthma, so there is a continuing need to examine dendritic cell function at various ages, both before and after allergic sensitization.

pDCs were discovered first in humans and only recently identified in mice. The murine pDCs are Gr-1⁺B220⁺CD19⁻, either CD4⁺ or CD8⁺, and localize within T-cell zones of lymph nodes. Freshly isolated CD11c⁺Gr-1⁺ cells express major histocompatibility complex (MHC) class II at low levels, display a plasmacytoid morphology, and survive poorly in culture [10]. Their survival is increased and they develop a dendritic cell-like morphology in IL-3 and CpG. Like human pDCs, these CD11c⁺Gr-1⁺ cells stimulate T-cell proliferation after activation with CpG and produce IFN- α after stimulation with influenza virus. These cells are reduced by 85% in the lymph nodes of L-selectin-deficient mice, and display a strain-specific variation in frequency, being fivefold increased in the lymph nodes of BALB/c relative to C57BL/6 mice, correlating with the increased propensity of BALB/c mice to develop Th2-dominated immune responses.

It is unclear whether (1) pDCs constitute a separate lineage [6], or (2) if they arise as a branch of the committed lymphoid lineage [11], or (3) by lineage conversion [12], or (4) if all dendritic cells arise from a common precursor cell [13]. Furthermore, it is not clear how DC2s differ from CD11c⁺CD8 α ⁻ dendritic cells (also previously known as 'myeloid' dendritic cells), which have also been shown to induce Th2 responses to soluble Ags [14,15]. pDCs differ from all other dendritic cell subsets with respect to expression of CIITA, a MHC class II regulator gene [16], in which pDCs rely strictly on the CIITA promoter pIII (also utilized by B cells), whereas macrophages and all other dendritic cells depend on pI. This suggests that pDCs are related to B cells and are distinct from other monocytes and dendritic cells. Shigematsu *et al.* [17], however, recently examined progenitors of pDCs and found that pDCs as well as conventional dendritic cells could be derived from both myeloid and lymphoid committed progenitors cells, but not from myeloid-erythroid progenitors or from pro-B cells. These studies suggest that pDCs have the same origin as conventional dendritic cell subsets, and that the function of dendritic cells is malleable and depends on how they differentiate.

Dendritic cells greatly influence the differentiation of CD4 cells towards Th2 by producing IL-10 but not IL-

12. IL-12 enhances IFN- γ production in T cells and natural killer cells and inhibits the development of IL-4 synthesis, while IL-10 inhibits dendritic cell production of IL-12, increases T-cell production of IL-4, or enhances the development of regulatory T cells, which can suppress allergic inflammation (see below). Dendritic cells respond to a variety of signals (e.g. immune complexes as well as IL-10) by reducing the production of IL-12p35, which allows increased Th2 responses to occur [18*]. A recent study showed that dendritic cells from children with allergic rhinitis, or allergic rhinitis with asthma, produced less IL-10 but comparable levels of IL-12 compared with healthy individuals [19], suggesting that IL-10 can function less as a Th2 cytokine but more as an agent that induces regulatory T cells, which may reduce the inflammatory effects of Th2 cells.

While IL-12 and IL-10 have significant effects on T-cell differentiation, other cytokines such as IL-18 and thymic stromal lymphopoietin (TSLP) play important roles by affecting dendritic cell function in allergy and asthma. IL-18 receptor (IL-18R) α and β chains were demonstrated by Kaser *et al.* [20] to be expressed on DC2 cells. pDC2s exposed to IL-18 skewed the development of Th cells toward Th1 development in coculture experiments of DC2s and allogeneic naive T cells. IL-18 is synergistic with IL-12, since IL-18 enhances IL-12R expression, and the IFN- γ enhancing effects of IL-18 are inhibited by neutralization of IL-12 p70. In 25% of allergic patients, the IFN- γ enhancing effects of IL-18 + IL-12 are impaired, which appears to result in enhanced Th2 cytokine production. The impairment in the induction of IFN- γ was completely restored by IL-2 + IL-18 [21], suggesting that IL-18 enhances IFN- γ production through an IL-12 and IL-2-dependent pathway. In contrast to IL-18, IL-6 was reported to play a role, via negative regulation of IL-12, in favoring of Th2 responses in lymph nodes draining the airway mucosa [22].

Another cytokine which has marked effects on Th2 cytokine production is TSLP. The human TSLP receptor, composed of an IL-7R α chain and a TSLP-specific receptor chain, is specifically expressed on CD11c⁺ dendritic cells. Interaction of TSLP with its receptor triggers activation of CD11c⁺ dendritic cells, and transforms dendritic cells such that they induce T cells to produce IL-4, IL-5, IL-13 but not IL-10, a profile that is prototypic of Th2 cells [23]. TSLP is highly expressed by keratinocytes from skin of patients with atopic dermatitis, and in human tonsil, suggesting that human TSLP may play a very important role in the induction of allergic inflammation in mucosal tissues [24].

Other factors that may enhance the capacity of dendritic cells to induce Th2 responses include the expression by dendritic cells of molecules such as MHC class II-

associated invariant chain peptide (CLIP), and of 'jagged', which induces specific Notch signaling pathways. Mature dendritic cells selectively express CLIP, on their surface, which appears to favor polarization of autologous naive T cells toward Th2 [25••]. This is consistent with the fact that H2-DM-deficient mice, which have a CLIP^{hi} phenotype on their mature dendritic cells, and generate considerably more Th2 cells than Th1 cells. Notch proteins also regulate the Th1/Th2 cell fate. The Notch pathways have been known to regulate a broad spectrum of cell fate decisions and differentiation processes during fetal and postnatal development [26]. Notch proteins have been found to be expressed on mature T cells, and its ligands, jagged and delta, have been found to be expressed on activated antigen presenting cells and dendritic cells. Jagged expression is induced by certain Th2-activating stimuli such as cholera toxin and prostaglandin E₂, and results in Notch signaling that specifically induces Th2 IL-4 and IL-5 production, independent of the IL-4 receptor pathway [27]. In contrast, delta signaling induces T cells to produce IFN- γ , but not IL-4 or IL-5. Thus, production of IL-10 but not IL-12 in dendritic cells, and expression of specific cell surface molecules such as CLIP, jagged but not delta, allow DC2s to induce Th2 responses.

Induction of Th1 cells by dendritic cells

DC1s produce large quantities of IL-12 and selectively enhance the differentiation of naive T cells into Th1 cells. Blood monocytes, termed pDC1, are commonly used as precursor cells for generating human DC1s in culture. In the presence of granulocyte/macrophage colony-stimulating factor and IL-4, DC1s are generated within 6 days with little or no proliferation, but in the presence of macrophage colony-stimulating factor, monocytes differentiate into macrophages [5,28–30]. The Th2 cytokine IL-4 enhances DC1 maturation and kills pDC2, an effect potentiated by IL-10 but blocked by CD40 ligand and IFN- γ . This negative feedback loop from the mature Th2 cells may selectively inhibit vigorous Th2 responses and enhance Th1 responses by regulating survival of dendritic cell subsets [5]. Like human DC1, mouse CD8 α ⁺ dendritic cell subsets, previously known as 'lymphoid' dendritic cells, promote differentiation of naive T cells into Th1 effector cells [14,15,31]. Dendritic cells have also been subdivided on the basis of the relative expression of the myeloid-related marker CD11b. About half of the splenic CD11b^{dull} population are CD8 α ⁺ dendritic cells [15,32], which are the major dendritic cell subset that produces IL-12, particularly after cross-linking of CD40 [33–35].

Although Th1 cells can limit the development of Th2 cells, effector Th1 cells cannot counterbalance the function of effector Th2 cells. In fact, Th1 cells that

enter mucosal tissues exacerbate inflammation codominantly with Th2 cells [36,37], and are likely to cause tissue damage. Thus, because both Th1 and Th2 cells are proinflammatory, other mechanisms exist to down-regulate inflammation in the respiratory mucosa and skin. These mechanisms include tolerance mediated by anergy, clonal deletion and the development of regulatory T (T_{Reg}) cells.

Induction of regulatory T cells by dendritic cells

Dendritic cells induce the development not only of Th1 and Th2 cells but also of T_{Reg} cells. The term T_{Reg} cell refers to cells that actively control or suppress the function of other cells, generally in an inhibitory fashion. T_{Reg} cells appear to control the development of autoimmune disease and transplant rejection, and may also play a critical role in controlling the expression of asthma and allergy. The specific mechanisms by which these T_{Reg} cells function, or the specific characteristics of these cells, are still being investigated. T_{Reg} cells have been studied primarily in the context of tolerance to self-antigens. However, tolerance is also important in the peripheral immune system, in terms of immune responses to antigens or allergens encountered in the respiratory and intestinal tracts. Normally, these sites are continuously exposed to a wide variety of environmental, nonreplicating, nonpathogenic antigens, which generally induce tolerance or hyporesponsiveness rather than active immunity. For example, exposure to cats or dogs in the first year of life reduces subsequent risk of allergic sensitization to multiple allergens [38,39]. Other studies have shown that children growing up on farms, particularly those with direct contact with animals, were less likely to be allergic than children growing up in urban environments [40,41], possibly due to exposure to allergens in the presence of endotoxin [42]. In any case, tolerance to environmental allergens encountered at mucosal surfaces such as the lungs or intestinal tract could be mediated by the development of T_{Reg} cells [31], or alternatively by clonal deletion or anergy in allergen-specific cells. It appears that in allergic individuals, antigen-specific T_{Reg} cells that produce IL-10 are present in much lower frequencies than are present in nonallergic individuals [43••], whereas allergen-specific Th1 cells are present in allergic and nonallergic individuals at equivalent frequencies. These observations strongly suggest that IL-10 producing antigen-specific T_{Reg} cells, rather than Th1 cells, prevent the development of symptoms in nonallergic individuals.

T_{Reg} cells can be divided into those that develop centrally in the thymus and are specific for autoantigens (natural CD25⁺ T_{Reg} cells) and those that develop in the periphery on exposure to exogenous antigen (adaptive T_{Reg} cells). The dendritic cells that activate natural

CD25⁺ T_{Reg} cells are not fully known, and those that activate/induce adaptive T_{Reg} cells are only now being identified (see below). Patients with a syndrome known as XLAAD or IPEX, due to mutations in the transcription factor *Foxp3*, specifically lack CD25⁺ T_{Reg} cells, and develop severe eczema, elevated IgE levels, eosinophilia and food allergy [44]. It is very likely that these patients lack both natural CD25⁺ and adaptive T_{Reg} cells, and that both natural CD25⁺ and adaptive T_{Reg} cells are related, although adaptive T_{Reg} cells might be more important in controlling the development of allergic disease and asthma.

Induction of adaptive T_{Reg} cells

For many years, it was thought that immature dendritic cells, expressing low levels of costimulatory molecules, were the major dendritic cells responsible for the induction of adaptive T_{Reg} cells [45,46]. These immature dendritic cells take up self-antigen without becoming activated and induce anergy in T cells. Although the anergic T cells may have regulatory activity, more recent studies indicate that mature rather than immature dendritic cell types, expressing high levels of costimulatory molecules, actively induce the development of T_{Reg} cells that have potent inhibitory/regulatory activity. These dendritic cells include pDCs, CD8 α ⁻ dendritic cells, as well as CD8 α ⁺ dendritic cells.

Several years ago, pDCs were observed to be capable of inducing T_{Reg} cells [47]. These CD11c^{low}CD45RB^{high} pDCs display a plasmacytoid morphology, are present in the spleen and lymph nodes of normal mice and are significantly enriched in the spleens of IL-10 Tg mice. These pDCs secrete high levels of IL-10 after activation, and when pulsed with Ag specifically induce T_{Reg} cell development and tolerance. However, in the lung, both CD8 α ⁻ (myeloid) as well as pDCs take up inhaled antigen, and both have been shown to be capable of inducing the development of tolerance to antigen [48,49•]. The CD8 α ⁻ dendritic cells appear in the bronchial lymph nodes of mice exposed to respiratory antigen, produce IL-10 transiently, and induce the development of T_{Reg} cells via an ICOS–ICOS-L dependent pathway [48]. Adoptive transfer of CD8 α ⁻ dendritic cells producing IL-10 from tolerized mice inhibited the development of airway hyperreactivity (AHR), and induced the development of antigen-specific T_{Reg} cells.

Alternatively, depletion of pDCs rather than CD8 α ⁻ dendritic cells prior to respiratory exposure to antigen led to IgE production associated with airway inflammation (AHR was not examined), and Th2 cell cytokine production. When cultured *in vitro*, the pDCs suppressed the generation of effector T cells induced by CD8 α ⁻ dendritic cells. Furthermore, adoptive transfer of pDCs before sensitization prevented respiratory disease

in this murine asthma model [49•]. Thus, CD8 α ⁻ dendritic cells (from the bronchial lymph nodes) as well as pDCs (in the lung parenchyma) play important roles in the protection against the development of respiratory inflammatory responses to inhaled allergens.

While CD8 α ⁻ dendritic cells induce T_{Reg} cells, CD8 α ⁺ dendritic cells have also been shown to induce T_{Reg} cells that prevent respiratory inflammation [50,51,52••]. Recently, Stock *et al.* [52••] showed that immunization with bacterial products (heat-killed *Listeria monocytogenes*) as adjuvant activated CD8 α ⁺ dendritic cells producing both IL-10 and IL-12 to induce the development of a novel T_{Reg} cell, which potently inhibited the development of airway inflammation and AHR. These T_{Reg} cells produced both IFN- γ and IL-10, expressed *foxp3* (the master T_{Reg} cell transcription factor [53]) as well as *T-bet* (the master Th1 transcription factor). The combination of expression of T-bet and *foxp3* and induction by CD8 α ⁺ dendritic cells suggested the term Th1_{Reg} for these regulatory cells [52••]. In contrast, T_{Reg} cells induced by respiratory CD8 α ⁻ dendritic cells, and which develop through an IL-4 intermediate stage, expressed IL-10, *foxp3* and Gata-3 (the master Th2 transcription factor), warranting the term Th2_{Reg} cells [31,52••]. Thus, T_{Reg} cells can be classified into at least two subgroups, termed Th1_{Reg} and Th2_{Reg} cells based upon their cytokine secretion patterns, signaling pathways and requirement of distinct types of dendritic cells. Both Th1_{Reg} and Th2_{Reg} cells can inhibit the development of Th2-driven AHR, and inflammation.

The development of allergy and asthma may be due to an aberrant development of Th2 cells rather than T_{Reg} cells in allergic individuals [54]. The specific mechanisms by which dendritic cells induce T_{Reg} cells rather than Th2 responses are not known, but are likely to involve specific costimulatory molecules. These costimulatory molecules expressed by dendritic cells include OX40L, ICOSL and PD-L1/PD-L2. The function of a dendritic cell is not immutably fixed, but is influenced by the maturation state of the dendritic cells, which determines the expression of specific costimulatory molecules. OX40L, a member of the tumor necrosis factor family of receptors, is expressed on dendritic cells and binds to its ligand, OX40, on T cells. In OX40-deficient mice, goblet cell hyperplasia, mucus production, eosinophilia, IgE production, Th2 cytokine production and AHR are inhibited, illustrating the importance of the OX40–OX40L pathway in the development of Th2 responses [55,56]. ICOSL is a member of the B7 family, and binds to ICOS, a member of the CD28 family. ICOS is expressed on recently activated T cells, and preferentially on Th2 cells. Costimulation of T cells through ICOS results in enhanced production of IL-4, IL-5 and IL-10 [57], and ICOS-deficient mice have

reduced IgE production, reduced Th2 cytokine production, and reduced AHR [58,59]. However, the ICOS–ICOSL pathway is also required in the development of respiratory tolerance and the function of Th2_{Reg} cells, and blockade of this pathway prevents the development of tolerance [48,60**]. PD-L1 and PD-L2 are also members of the B7 family and are expressed on dendritic cells as well as on lung epithelial cells after allergen challenge. Both PD-L1 and PD-L2 bind to PD-L1 (programmed death), which is a member of the CD28/CTLA-4 family. PD-L1 has been shown to regulate the development of peripheral tolerance [57]. Treatment of mice with a blocking anti-PD-L2 mAb at the time of allergen challenge, but not at the time of sensitization, significantly increased AHR, airway eosinophilia, production of IL-5 and IL-13, and decreased IFN- γ production in the lungs and draining lymph node cells [61]. Consistent with this, an agonistic PD-L2 cross-linking antibody reduced lung inflammation and AHR in a mouse model of allergic airway disease. The suppressive effect on AHR was dependent on cross-linking of PD-L2 on dendritic cells, which increased IL-12 production in a Stat4 dependent manner, reduced Th2 cytokine production and increased IL-10 production [62], indicating that the PD-L2–PD-L1 pathway critically regulates allergic asthma. These studies indicate that expression of costimulatory molecules by dendritic cells can influence whether tolerance or Th2 responses develop in allergen-specific T cells.

Conclusion

Dendritic cells control the development of productive immunity and tolerance to self-antigens and allergens, thus regulating the development of allergic disease and asthma. Subsets of dendritic cells exist with distinct functions, but the relationship between these subsets and the mechanisms by which these dendritic cells induce immunity versus tolerance are not fully known. One mechanism by which dendritic cells regulate tolerance is the induction of a variety of distinct T_{Reg} cell types, which actively suppress the development of allergy and asthma, providing antiinflammatory responses and protective immunity. Better understanding of the factors determining development and function of dendritic cells will be a prerequisite to the future design of improved strategies for prevention and treatment of allergic diseases and asthma.

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

- 1 Steinman RM. The dendritic cell system and its role in immunogenicity. *Annu Rev Immunol* 1991; 9:271–296.
- 2 Inaba M, Inaba K, Hosono M, *et al.* Distinct mechanisms of neonatal tolerance induced by dendritic cells and thymic B cells. *J Exp Med* 1991; 173:549–559.
- 3 Liu YJ, Kanzler H, Soumelis V, Gilliet M. Dendritic cell lineage, plasticity and cross-regulation. *Nat Immunol* 2001; 2:585–589.
- 4 Risoan M-C, Soumelis V, Kadowaki N, *et al.* Reciprocal control of T helper cell and dendritic cell differentiation. *Science* 1999; 283:1183–1186.
- 5 Risoan MC, Soumelis V, Kadowaki N, *et al.* Reciprocal control of T helper cell and dendritic cell differentiation. *Science* 1999; 283:1183–1186.
- 6 Grouard G, Risoan MC, Filgueira L, *et al.* The enigmatic plasmacytoid T cells develop into dendritic cells with interleukin (IL)-3 and CD40-ligand. *J Exp Med* 1997; 185:1101–1111.
- 7 Grouard G, Risoan M-C, Filgueira L, *et al.* The enigmatic plasmacytoid T cells develop into dendritic cells with interleukin (IL)-3 and CD40-ligand. *J Exp Med* 1997; 185:1101–1112.
- 8 Matsuda H, Suda T, Hashizume H, *et al.* Alteration of balance between myeloid dendritic cells and plasmacytoid dendritic cells in peripheral blood of patients with asthma. *Am J Respir Crit Care Med* 2002; 166:1050–1054.
- 9 Hagendorens MM, Ebo DG, Schuerwegh AJ, *et al.* Differences in circulating dendritic cell subtypes in cord blood and peripheral blood of healthy and allergic children. *Clin Exp Allergy* 2003; 33:633–639.
- 10 Nakano H, Yanagita M, Gunn MD. CD11c(+)B220(+)Gr-1(+) cells in mouse lymph nodes and spleen display characteristics of plasmacytoid dendritic cells. *J Exp Med* 2001; 194:1171–1178.
- 11 Corcoran L, Ferrero I, Vremec D, *et al.* The lymphoid past of mouse plasmacytoid cells and thymic dendritic cells. *J Immunol* 2003; 170:4926–4932.
- 12 Comeau MR, Van der Vuurst de Vries A-R, Maliszewski CR, Galibert L. CD123 plasmacytoid predendritic cells: progenitors undergoing cell fate conversion? *J Immunol* 2002; 169:75–83.
- 13 del Hoyo GM, Martin P, Vargas HH, *et al.* Characterization of a common precursor population for dendritic cells. *Nature* 2002; 415:1043–1047.
- 14 Maldonado-Lopez R, De Smedt T, Michel P, *et al.* CD8alpha+ and CD8alpha- subclasses of dendritic cells direct the development of distinct T helper cells in vivo. *J Exp Med* 1999; 189:587–592.
- 15 Pulendran B, Smith JL, Caspary G, *et al.* Distinct dendritic cell subsets differentially regulate the class of immune response in vivo. *Proc Natl Acad Sci U S A* 1999; 96:1036–1041.
- 16 LeibundGut-Landmann S, Waldburger J-M, e Sousa CR, *et al.* MHC class II expression is differentially regulated in plasmacytoid and conventional dendritic cells. *Nat Immunol* 2004; 5:899–908.
- 17 Shigematsu H, Reizis B, Iwasaki H, *et al.* Plasmacytoid dendritic cells activate lymphoid-specific genetic programs irrespective of their cellular origin. *Immunity* 2004; 21:43–53.
- 18 Anderson CF, Lucas M, Gutierrez-Kobeh L, *et al.* T cell biasing by activated dendritic cells. *J Immunol* 2004; 173:955–961.
- The authors demonstrated that dendritic cells respond to immune complexes by altering their cytokine production such as IL-12p70 to induce a Th2-like cytokine response in T cells. Furthermore, the mechanism by which dendritic cells altered their cytokine production in response to immune complexes was shown to be different from macrophages. Macrophages downregulated the transcription of both the p40 and p35 subunits of IL-12, whereas dendritic cells decreased only p35 expression.
- 19 Gentile DA, Schreiber R, Howe-Adams J, *et al.* Diminished dendritic cell interleukin 10 production in atopic children. *Ann Allergy Asthma Immunol* 2004; 92:538–544.
- 20 Kaser A, Kaser S, Kaneider NC, *et al.* Interleukin-18 attracts plasmacytoid dendritic cells (DC2s) and promotes Th1 induction by DC2s through IL-18 receptor expression. *Blood* 2004; 103:648–655.
- 21 El-Mezayen REH, Matsumoto T. In vitro responsiveness to IL-18 in combination with IL-12 or IL-2 by PBMC from patients with bronchial asthma and atopic dermatitis. *Clin Immunol* 2004; 111:61–68.
- 22 Dodge IL, Carr MW, Cernadas M, Brenner MB. IL-6 production by pulmonary dendritic cells impedes Th1 immune responses. *J Immunol* 2003; 170:4457–4464.
- 23 Watanabe N, Hanabuchi S, Soumelis V, *et al.* Human thymic stromal lymphopoietin promotes dendritic cell mediated CD4+ T cell homeostatic expansion. *Nat Immunol* 2004; 5:426–434.
- 24 Ge Q, Palliser D, Eisen HN, Chen J. Homeostatic T cell proliferation in a T cell-dendritic cell coculture system. *Proc Natl Acad Sci U S A* 2002; 99:2983–2988.

- 25 Rohn TA, Boes M, Wolters D, *et al.* Upregulation of the CLIP self peptide on mature dendritic cells antagonizes T helper type 1 polarization. *Nat Immunol* 2004; 5:909–918.
More than 200 individual MHC class II-associated peptides were found on human dendritic cells and mature dendritic cells were shown to selectively upregulate the self-peptide CLIP. The increased representation of CLIP-MHC class II complexes favored polarization of autologous naive T cells toward the nonpolarized and Th2 phenotype. Thus, the self-peptide CLIP on dendritic cells qualifies as an endogenous regulator in priming of Th cells by antagonizing the polarization toward the Th1 phenotype.
- 26 Radtke F, Wilson A, Mancini S, MacDonald H. Notch regulation of lymphocyte development and function. *Nat Immunol* 2004; 5:247–253.
- 27 Amson D, Blander J, Lee G, *et al.* Instruction of distinct CD4 T helper cell fates by different notch ligands on antigen-presenting cells. *Cell* 2004; 117:515–526.
- 28 Sallusto F, Lanzavecchia A. Efficient presentation of soluble antigen by cultured human dendritic cells is maintained by granulocyte/macrophage colony-stimulating factor plus interleukin 4 and downregulated by tumor necrosis factor alpha. *J Exp Med* 1994; 179:1109–1118.
- 29 Bender A, Sapp M, Schuler G, *et al.* Improved methods for the generation of dendritic cells from nonproliferating progenitors in human blood. *J Immunol Methods* 1996; 196:121–135.
- 30 Romani N, Gruner S, Brang D, *et al.* Proliferating dendritic cell progenitors in human blood. *J Exp Med* 1994; 180:83–93.
- 31 Akbari O, DeKruyff RH, Umetsu DT. Pulmonary dendritic cells secreting IL-10 mediate T cell tolerance induced by respiratory exposure to antigen. *Nat Immunol* 2001; 2:725–731.
- 32 Maraskovsky E, Brasel K, Teepe M, *et al.* Dramatic increase in the numbers of functionally mature dendritic cells in Flt3 ligand-treated mice: multiple dendritic cell subpopulations identified. *J Exp Med* 1996; 184:1953–1962.
- 33 Belz GT, Behrens GM, Smith CM, *et al.* The CD8alpha(+) dendritic cell is responsible for inducing peripheral self-tolerance to tissue-associated antigens. *J Exp Med* 2002; 196:1099–1104.
- 34 Liu K, Iyoda T, Saternus M, *et al.* Immune tolerance after delivery of dying cells to dendritic cells in situ. *J Exp Med* 2002; 196:1091–1097.
- 35 Grohmann U, Fallarino F, Bianchi R, *et al.* IL-6 inhibits the tolerogenic function of CD8 alpha+ dendritic cells expressing indoleamine 2,3-dioxygenase. *J Immunol* 2001; 167:708–714.
- 36 Hansen G, Berry G, DeKruyff RH, Umetsu DT. Allergen-specific Th1 cells fail to counterbalance Th2 cell-induced airway hyperreactivity but cause severe airway inflammation. *J Clin Invest* 1999; 103:175–183.
- 37 Randolph DA, Carruthers CJ, Szabo SJ, *et al.* Modulation of airway inflammation by passive transfer of allergen-specific Th1 and Th2 cells in a mouse model of asthma. *J Immunol* 1999; 162:2375–2383.
- 38 Platts-Mills T, Vaughan J, Squillace S, *et al.* Sensitisation, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study. *Lancet* 2001; 357:752–756.
- 39 Ownby D, Johnson C, Peterson E. Exposure to dogs and cats in the first year of life and risk of allergic sensitization at 6 to 7 years of age. *JAMA* 2002; 288:963–972.
- 40 Braun-Fahrlander C, Gassner M, Grize L, *et al.* Prevalence of hay fever and allergic sensitization in farmer's children and their peers living in the same rural community. SCARPOL team. Swiss Study on Childhood Allergy and Respiratory Symptoms with Respect to Air Pollution. *Clin Exp Allergy* 1999; 29:28–34.
- 41 Riedler J, Braun-Fahrlander C, Eder W, *et al.* Exposure to farming in early life and development of asthma and allergy: a cross-sectional survey. *Lancet* 2001; 358:1129–1133.
- 42 Braun-Fahrlander C, Riedler J, Herz U, *et al.* Environmental exposure to endotoxin and its relation to asthma in school-age children. *N Engl J Med* 2002; 347:869–877.
- 43 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.
Immune response to allergens in health and disease is shown to be the result of a balance between allergen-specific Th1 and Th2 cells. While Th1 cells use multiple suppressive mechanisms, IL-10 and transforming growth factor- β as secreted cytokines, and cytotoxic T-lymphocyte antigen 4 and programmed death 1 as surface molecules, healthy and allergic individuals exhibit all three allergen-specific subsets in different proportions, indicating that a change in the dominant subset may lead to allergy development or recovery. Blocking the suppressor activity of Th1 cells or increasing Th2 cell frequency was found to enhance allergen-specific Th2 cell activation *ex vivo*.
- 44 Gambineri E, Torgerson TR, Ochs HD. Immune dysregulation, polyendocrinopathy, enteropathy, and X-linked inheritance (IPEX), a syndrome of systemic autoimmunity caused by mutations of FOXP3, a critical regulator of T-cell homeostasis. *Curr Opin Rheumatol* 2003; 15:430–435.
- 45 Steinman RM, Hawiger D, Nussenzweig MC. Tolerogenic dendritic cells. *Annu Rev Immunol* 2003; 21:685–711.
- 46 Jonuleit H, Schmitt E, Schuler G, *et al.* Induction of interleukin 10-producing, nonproliferating CD4(+) T cells with regulatory properties by repetitive stimulation with allogeneic immature human dendritic cells. *J Exp Med* 2000; 192:1213–1222.
- 47 Wakkach A, Fournier N, Brun V, *et al.* Characterization of dendritic cells that induce tolerance and T regulatory 1 cell differentiation in vivo. *Immunity* 2003; 18:605–617.
- 48 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.
- 49 de Heer HJ, Hammad H, Soullie T, *et al.* Essential role of lung plasmacytoid dendritic cells in preventing asthmatic reactions to harmless inhaled antigen. *J Exp Med* 2004; 200:89–98.
pDCs were shown to provide intrinsic protection against inflammatory responses to harmless antigens in lungs. Depletion of pDCs during inhalation of normally inert antigen led to airway eosinophilia and asthma. Furthermore, adoptive transfer of pDCs before sensitization prevented disease in a mouse asthma model.
- 50 Suss G, Shortman K. A subclass of dendritic cells kills CD4 T cells via Fas/Fas-ligand-induced apoptosis. *J Exp Med* 1996; 183:1789–1796.
- 51 Kronin V, Wu L, Gong S, *et al.* DEC-205 as a marker of dendritic cells with regulatory effects on CD8 T cell responses. *Int Immunol* 2000; 12:731–735.
- 52 Stock P, Akbari O, Berry G, *et al.* Induction of T helper type 1-like regulatory cells that express Foxp3 and protect against airway hyperreactivity. *Nat Immunol* 2004 [Epub ahead of print].
The authors developed a novel adaptive T_{Reg} cell type *in vivo* from naive CD4+ CD25– T cells. These antigen-specific T_{Reg} cells produced both IL-10 and IFN- γ , were induced by CD8 α + dendritic cells, and potentially inhibited the development of allergen-induced airway hyperreactivity. Furthermore, these T_{Reg} cells were shown to express foxp3, as well as T-bet. The expression of IFN- γ and T-bet, and their induction by CD8 α + dendritic cells, indicates that these T_{Reg} cells are related to Th1 cells.
- 53 Hori S, Nomura T, Sakaguchi S. Control of regulatory T cell development by the transcription factor Foxp3. *Science* 2003; 299:1057–1061.
- 54 Umetsu D, McIntire J, Macaubas C, *et al.* Asthma: an epidemic of dysregulated immunity. *Nat Immunol* 2002; 3:715–720.
- 55 Jember A, Zuberi R, Liu F, Croft M. Development of allergic inflammation in a murine model of asthma is dependent on the costimulatory receptor OX40. *J Exp Med* 2001; 193:387–392.
- 56 Salek-Ardakani S, Song J, Halteman B, *et al.* OX40 (CD134) controls memory T helper 2 cells that drive lung inflammation. *J Exp Med* 2003; 198:315–324.
- 57 Sharpe AH, Freeman GJ. The B7-CD28 superfamily. *Nat Rev Immunol* 2002; 2:116–126.
- 58 McAdam AJ, Greenwald RJ, Levin MA, *et al.* ICOS is critical for CD40-mediated antibody class switching. *Nature* 2001; 409:102–105.
- 59 Coyle A, Gutierrez-Ramos J. The role of ICOS and other costimulatory molecules in allergy and asthma. *Springer Semin Immunopathol* 2004; 25:349–359.
- 60 Herman A, Freeman G, Mathis D, Benoist C. CD4+CD25+ T regulatory cells dependent on ICOS promote regulation of effector cells in the prediabetic lesion. *J Exp Med* 2004; 199:1479–1489.
The authors demonstrated that T_{Reg} cells in the pancreatic lesion express Foxp3, produce high levels of IL-10 and ICOS. Blockade of ICOS rapidly converts early insulinitis to diabetes, which disrupts the balance of T_{eff}s and Tregs and promotes a very broad shift in the expression of the T regulatory-specific profile.
- 61 Matsumoto K, Inoue H, Nakano T, *et al.* B7-DC regulates asthmatic response by an IFN- γ -dependent mechanism. *J Immunol* 2004; 172:2530–2541.
- 62 Radhakrishnan S, Iijima K, Kobayashi T, *et al.* Blockade of allergic airway inflammation following systemic treatment with a B7-dendritic cell (PD-L2) cross-linking human antibody. *J Immunol* 2004; 173:1360–1365.