

The Role of Interleukin 10 in the Regulation of Allergic Immune Responses

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Key Words

Interleukin 10 · (Specific) Immunotherapy · Allergy · Anergy

Abstract

Several clinical studies and animal models have shown that Th2 lymphocytes play a key role in the pathophysiology of IgE-mediated allergic immune responses like allergic rhinitis and asthma or venom anaphylaxis. Classical specific immunotherapy (SIT) that has been proven to be clinically effective can serve as a role model for immunological changes that are associated with amelioration of allergic diseases. During SIT, the Th2-dominated immune response is modified towards a Th1 response leading to a decline in allergen-specific IgE and an increase in allergen-specific IgG production. Most importantly, however, production of the immunosuppressive/-regulatory cytokine interleukin 10 (IL-10) is also induced leading to T cell tolerance and prevention of tissue inflammation. In this article the role of IL-10-producing T cells in the regulation of allergic immune responses will be discussed.

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Introduction

Atopic allergic diseases, like allergic rhinitis and asthma, are T-cell-mediated disorders characterized by high serum IgE levels in most cases and eosinophilic airway inflammation. After allergen exposure, CD4⁺ T-helper cells are activated by antigen-presenting cells to produce Th2 cytokines such as IL-4, IL-5, IL-6, and IL-13, which are responsible for strong antibody responses including IgE synthesis by B lymphocytes, and for the growth and differentiation of eosinophils and mast cells. The release of histamine, leukotrienes and prostaglandins following cross-linking of allergen-specific IgE on the surface of mast cells and basophils induces the development of urticaria, edema, bronchial hyperreactivity, and even systemic anaphylaxis in the context of bee and wasp venom hypersensitivity [1–3]. Thus, inhibition of the Th2-dominated T cell response appears to be an attractive target for the treatment of the diseases described. A shift from Th2 to Th1 can be observed during specific immunotherapy (SIT), and also an induction of IL-10-producing T cells [4–7]. Another concept for the therapy of asthma may be the administration or endogenous induction of the anti-inflammatory cytokine IL-10 which was shown to inhibit the development of airway inflammation in a murine model of airway hyperreactivity [8–10]. Additionally, inhaled corticosteroids inhibit proinflammatory cytokines

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but partially enhance the production of IL-10 by alveolar macrophages from asthmatic patients, which may contribute to their beneficial effect in asthma [11]. Vaccination with allergen peptide- or DNA-pulsed dendritic cells (DC) may represent a third form of immunotherapy, as DC play an important role in induction of primary immune responses to aeroallergens in naive T lymphocytes [12–14]. This article summarizes the role of IL-10 in all of these therapeutic approaches indicating that IL-10 is one of the main regulators in allergic/atopic diseases.

Anti-Inflammatory and Anti-Allergic Properties of IL-10

IL-10 was first described as cytokine synthesis inhibiting factor generated by mouse Th2 cells which was able to suppress the proliferation especially of Th1 cells [reviewed in ref. 15]. However, IL-10 is not a Th2 cytokine since it is also produced by Th1 cells (at least in humans) and by other cell types including CD8⁺ T lymphocytes, monocytes/macrophages, B lymphocytes, mast cells, eosinophils, keratinocytes, and various tumor cells [15, 16]. Monocytes and B cells are the major source for human IL-10, which is released after stimulation with bacterial cell wall components, parasites, HIV or other viruses. The strong suppressive effects of IL-10 are due to the inhibition of the production of the proinflammatory cytokines IL-1 α , IL-1 β , IL-6, IL-8, IL-12, TNF- α , GM-CSF, and G-CSF by monocytes, and the downregulation of MHC class II molecules and costimulatory molecules on monocytes/macrophages and dendritic cells [17–19]. Furthermore, the production of the IL-1 receptor antagonist, which exerts anti-inflammatory properties on its own, is enhanced by IL-10 [20]. In vivo experiments with mice have shown that IL-10 inhibits delayed-type hypersensitivity, experimental autoimmune encephalomyelitis, and T-cell-mediated inflammatory bowel disease [21–24]. Besides the inhibition of mainly Th1-mediated inflammatory processes, IL-10 is also involved in the inhibition of Th2-driven allergic immune responses [9, 25, 26]. IL-10 mediates a monocyte-dependent inhibitory effect on IL-4 induced IgE and IgG₄ synthesis by human peripheral blood mononuclear cells (PBMC) and inhibits IgE-induced activation and cytokine production of human mast cells [27–29]. Additionally, IL-10 inhibits the production of IL-5 by human resting T cells and also directly decreases survival and cytokine, chemokine and mediator production by eosinophils and neutrophils [26, 30, 31]. Finally, IL-10 or IL-10-treated DC induce a long-term

antigen-specific anergic state in human CD4⁺ and CD8⁺ T cells [32–34] and the differentiation of a regulatory T cell subset, which is characterized by high levels of IL-10 secretion and strong suppressive properties [35]. More recently, the same group has shown that such IL-10-producing T cells, which have been termed Tr1 cells due to their additional production of IFN- γ , can also inhibit Th2-specific responses in vivo indicating that regulatory cells play a fundamental role into preventing allergic disorders [36].

Induction of Regulatory IL-10-Producing T Cells during Immunotherapy

SIT has been shown to modify the course of allergic diseases inducing changes in serum immunoglobulin concentrations towards IgG and reducing the recruitment of inflammatory cells [4, 37, 38]. Immunotherapy decreases mast cell and eosinophil numbers in nasal lavage or bronchoalveolar fluid as well as infiltration of CD4⁺ T lymphocytes and eosinophils in cutaneous late-phase responses [39–41]. In vitro studies with human T cell lines and clones from peripheral blood have provided evidence that SIT influences allergen-specific T helper cells in particular. We and others have demonstrated that SIT – including insect venom immunotherapy (VIT) – induces a shift in the dominance of allergen-specific Th cells from Th2 (IL-4, IL-5) to Th1 (IFN- γ) [5–7, 42, 43]. These changes in cytokine production appear also to be the reason for the subsequent shift in allergen-specific Ig production from IgE towards IgG₄, as IgE and IgG₄ responses are conversely regulated by IL-4 and IFN- γ [44].

Despite the observation that SIT induces a shift of the allergen-specific immune response from a Th2-dominated to a Th1-dominated response, successful SIT is not characterized by enhanced tissue inflammation. The reason is that SIT also leads to a strong inhibition of the allergic immune response due to induction of anergy in allergen-specific T cells and also due to induction of IL-10-producing T cells. Induction of IL-10-producing T cells has been first described by us in VIT. One week after initiation of VIT, according to a rush protocol, we observed a strong increase in IL-10 production at the protein level after 48 h of stimulation of PBMC with the respective venom as well as at the mRNA level in freshly isolated PBMC [7, 45].

In our investigation, CD4⁺ T cells were the main source of allergen-induced IL-10 production at this early time point [7]. The induction of increased IL-10 produc-

tion after initiation of VIT was also observed by Akdis et al. [46], who found a substantial production of IL-10 also by B cells and monocytes at later time points. Additionally, these authors demonstrated that neutralization of IL-10 in PBMC fully reconstituted the proliferative T cell and cytokine responses which had been inhibited due to blocking the CD28 costimulatory signal in T cells and that addition of exogenous IL-10 to B cell cultures from patients allergic to bee venom inhibited the production of phospholipase-A₂-specific IgE, but enhanced the production of IgG4 [46–48]. In our study, blocking of IL-10 by monoclonal antibodies also restored the proliferative response of PBMC to the respective venom, but not the allergen-induced IL-4 production, while the allergen-induced IFN- γ production was further increased [7]. Thus, the induction of IL-10-producing regulatory T cells during VIT appears to prevent inflammatory responses that might otherwise result from enhanced Th1 responses.

Influence of IL-10 on Effector Cells during VIT

Besides the observed changes in cytokine expression by allergen-specific T cells, VIT also reduces the histamine and sulfido-leukotriene release of mast cells and basophils [49, 50]. This reduced reactivity of effector cells is partially due to the induction of IL-10 (and IFN- γ) during VIT, as neutralization of IL-10 and IFN- γ restored the release after the initiation of VIT, while the addition of exogenous IL-10 and IFN- γ leads to a reduction of the release before VIT [49]. As already mentioned, IL-10 also exerts anti-allergic properties by decreasing the expression of CD40 in eosinophils leading to an enhanced apoptosis of these cells [51]. Consistent with these findings a decreased production of IL-10 mRNA was found in purified T cells from asthmatic patients compared to healthy controls, while after multiple bee stings hyperimmune beekeepers showed an enhanced intracytoplasmic IL-10 content of CD4+CD25+ T cells and monocytes [46, 52]. However, there are also reports describing an enhanced production of IL-10 in atopic dermatitis or in the gut mucosa of asthmatic patients which was discussed to counterbalance the effect of proinflammatory cytokines mitigating their inflammatory reaction [53, 54]. Additionally, in a murine model of asthma IL-10 inhibited eosinophilia and Th2 cytokine production, but augmented airway reactivity to methacholine [55]. Another study stated that IL-10-deficient mice developed a pulmonary inflammatory response but not airway hyperresponsiveness, which was restored after reconstitution of these mice with IL-10 [56].

Therefore, the direct application of IL-10 may be problematic, especially in asthmatics.

Induction of Allergen-Specific Hyporesponsiveness of T Cells by IL-10-Treated Dendritic Cells

Dendritic cells (DC), which are located in an immature state in peripheral organs at the site of the antigen entry, are the most potent antigen-presenting cells due to their capacity to induce primary immune responses in naive T lymphocytes [reviewed in ref. 12]. After antigen capture they are activated to migrate to the draining lymph nodes, where they present processed peptide on MHC molecules to naive T cells and induce a polarized Th1 or Th2 type response. It has been proposed that distinct DC lineages control the initiation of Th1 versus Th2 immune responses [57, 58]. However, factors of the microenvironment also determine the type of immune response induced. For example, the presence of IFN- γ during DC maturation promotes the development of IL-12-producing DC with Th1-driving capacity while PGE₂ primes for a low IL-12 production ability and a Th2-driving capacity [59–61]. Thus, DC also play an important role in the induction of Th2-mediated immune responses in allergic diseases [reviewed in ref. 13]. In this respect we and others have shown that allergen-pulsed DC are able to induce Th2 responses in naive and memory T helper cells from atopic individuals [13, 60–63]. DC modified in vitro can shift an allergen-specific immune response towards a Th1 response and may represent a new form of immunotherapy. For this purpose the development of culture conditions to generate DC in large numbers from peripheral blood monocytes or CD34+ precursors in vitro was very helpful [64, 65].

Maturation of DC in the presence of IL-10 inhibits their terminal differentiation characterized by a decreased expression of MHC class II molecules, several costimulatory and adhesion molecules including the DC-specific marker CD83 and induces their function towards tolerance induction, especially of Th1 cells [33, 66]. However, we were able to demonstrate that IL-10-treated DC also inhibit allergen-specific Th2 cells, while DC pretreated with another anti-inflammatory agent, hydrocortisone, only inhibit Th1 but not Th2 cells [67]. The IL-10-DC-mediated inhibition was long-lasting and stable as cytokine production remained low at least among the naive T cell population even after restimulation with regularly matured DC. The inhibitory effects of IL-10- or

HC-treated DC were not due to enhanced apoptosis of allergen-specific T cells but to functional hyporesponsiveness, as the addition of exogenous IL-2 restored all cytokine responses [67].

Concluding Remarks

Taken together, IL-10 plays an important role in the regulation and prevention of inflammatory immune responses including eosinophilic airway inflammation.

Therefore, the induction of IL-10-producing regulatory T cells as it occurs during SIT or IL-10-treated DC may be useful new therapeutic tools for the downregulation of allergic responses.

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References

- Wills-Karp M: Immunologic basis of antigen-induced airway hyperresponsiveness. *Annu Rev Immunol* 1999;17:255–281.
- Yssel H, Groux H: Characterization of T cell subpopulations involved in the pathogenesis of asthma and allergic diseases. *Int Arch Allergy Immunol* 2000;121:10–18.
- Muller UR: New developments in the diagnosis and treatment of hymenoptera venom allergy. *Int Arch Allergy Immunol* 2001;124:447–453.
- Malling HJ: Immunotherapy as an effective tool in allergy treatment. *Allergy* 1998;53:461–472.
- Secrist H, Chelen CJ, Wen Y, Marshall JD, Umetsu DT: Allergen immunotherapy decreases interleukin 4 production in CD4+ T cells from allergic individuals. *J Exp Med* 1993;178:2123–2130.
- Jutel M, Pichler WJ, Skrbic D, Urwyler A, Dahinden C, Muller UR: Bee venom immunotherapy results in decrease of IL-4 and IL-5 and increase of IFN-gamma secretion in specific allergen-stimulated T cell cultures. *J Immunol* 1995;154:4187–4194.
- Bellinghausen I, Metz G, Enk AH, Christmann S, Knop J, Saloga J: Insect venom immunotherapy induces interleukin-10 production and a Th2-to-Th1 shift, and changes surface marker expression in venom-allergic subjects. *Eur J Immunol* 1997;27:1131–1139.
- Stämpfli MR, Cwiartka M, Gajewska BU, Alvarez D, Ritz SA, Inman MD, et al: Interleukin-10 gene transfer to the airways regulates allergic mucosal sensitization in mice. *Am J Respir Cell Mol Biol* 1999;21:586–596.
- Tournoy KG, Kips JC, Pauwels RA: Endogenous interleukin-10 suppresses allergen-induced airway inflammation and nonspecific airway responsiveness. *Clin Exp Allergy* 2000;30:775–783.
- Koulis A, Robinson DS: The anti-inflammatory effects of interleukin-10 in allergic disease. *Clin Exp Allergy* 2000;30:747–750.
- John M, Lim S, Seybold J, Jose P, Robichaud A, O'Connor B, et al: Inhaled corticosteroids increase interleukin-10 but reduce macrophage inflammatory protein-1alpha, granulocyte-macrophage colony-stimulating factor, and interferon-gamma release from alveolar macrophages in asthma. *Am J Respir Crit Care Med* 1998;157:256–262.
- Banchereau J, Briere F, Caux C, Davoust J, Lebecque S, Liu YJ, et al: Immunobiology of dendritic cells. *Annu Rev Immunol* 2000;18:767–811.
- Lambrecht BN: The dendritic cell in allergic airway diseases: A new player to the game. *Clin Exp Allergy* 2001;31:206–218.
- Spiegelberg HL, Orozco EM, Roman M, Raz E: DNA immunization: A novel approach to allergen-specific immunotherapy. *Allergy* 1997;52:964–970.
- Moore KW, O'Garra A, de Waal Malefyt R, Vieira P, Mosmann TR: Interleukin-10. *Annu Rev Immunol* 1993;11:165–190.
- Del Prete G, De Carli M, Almerigogna F, Giudizi MG, Biagiotti R, Romagnani S: Human IL-10 is produced by both type 1 helper (Th1) and type 2 helper (Th2) T cell clones and inhibits their antigen-specific proliferation and cytokine production. *J Immunol* 1993;150:353–360.
- de Waal Malefyt R, Haanen J, Spits H, Roncarolo MG, te Velde A, Figdor C, et al: Interleukin 10 (IL-10) and viral IL-10 strongly reduce antigen-specific human T cell proliferation by diminishing the antigen-presenting capacity of monocytes via downregulation of class II major histocompatibility complex expression. *J Exp Med* 1991;174:915–924.
- Willems F, Marchant A, Delville JP, Gerard C, Delvaux A, Velu T, et al: Interleukin-10 inhibits B7 and intercellular adhesion molecule-1 expression on human monocytes. *Eur J Immunol* 1994;24:1007–1009.
- de Waal Malefyt R, Abrams J, Bennett B, Figdor CG, de Vries JE: Interleukin 10 (IL-10) inhibits cytokine synthesis by human monocytes: An autoregulatory role of IL-10 produced by monocytes. *J Exp Med* 1991;174:1209–1220.
- Cassatella MA, Meda L, Gasperini S, Calzetti F, Bonora S: Interleukin 10 (IL-10) upregulates IL-1 receptor antagonist production from lipopolysaccharide-stimulated human polymorphonuclear leukocytes by delaying mRNA degradation. *J Exp Med* 1994;179:1695–1699.
- Enk AH, Saloga J, Becker D, Mohamadizadeh M, Knop J: Induction of hapten-specific tolerance by interleukin 10 in vivo. *J Exp Med* 1994;179:1397–1402.
- Li L, Elliott JF, Mosmann TR: IL-10 inhibits cytokine production, vascular leakage, and swelling during T helper 1 cell-induced delayed-type hypersensitivity. *J Immunol* 1994;153:3967–3978.
- Burkhart C, Liu GY, Anderton SM, Metzler B, Wraith DC: Peptide-induced T cell regulation of experimental autoimmune encephalomyelitis: A role for IL-10. *Int Immunol* 1999;11:1625–1634.
- Steidler L, Hans W, Schotte L, Neiryck S, Obermeier F, Falk W, et al: Treatment of murine colitis by *Lactococcus lactis* secreting interleukin-10. *Science* 2000;289:1352–1355.
- Borish L: IL-10: Evolving concepts. *J Allergy Clin Immunol* 1998;101:293–297.
- Pretolani M: Interleukin-10: An anti-inflammatory cytokine with therapeutic potential. *Clin Exp Allergy* 1999;29:1164–1171.
- Punnonen J, de Waal Malefyt R, van Vlasselaer P, Gauchat JF, de Vries JE: IL-10 and viral IL-10 prevent IL-4-induced IgE synthesis by inhibiting the accessory cell function of monocytes. *J Immunol* 1993;151:1280–1289.
- Arock M, Zuany Amorim C, Singer M, Benhamou M, Pretolani M: Interleukin-10 inhibits cytokine generation from mast cells. *Eur J Immunol* 1996;26:166–170.
- Royer B, Varadarajalou S, Saas P, Guillosson JJ, Kantelip JP, Arock M: Inhibition of IgE-induced activation of human mast cells by IL-10. *Clin Exp Allergy* 2001;31:694–704.
- Schandene L, Alonso Vega C, Willems F, Gerard C, Delvaux A, Velu T, et al: B7/CD28-dependent IL-5 production by human resting T cells is inhibited by IL-10. *J Immunol* 1994;152:4368–4374.

- 31 Takanashi S, Nonaka R, Xing Z, O'Byrne P, Dolovich J, Jordana M: Interleukin 10 inhibits lipopolysaccharide-induced survival and cytokine production by human peripheral blood eosinophils. *J Exp Med* 1994;180:711-715.
- 32 Groux H, Bigler M, de Vries JE, Roncarolo MG: Interleukin-10 induces a long-term antigen-specific anergic state in human CD4⁺ T cells [see comments]. *J Exp Med* 1996;184:19-29.
- 33 Steinbrink K, Wolfl M, Jonuleit H, Knop J, Enk AH: Induction of tolerance by IL-10-treated dendritic cells. *J Immunol* 1997;159:4772-4780.
- 34 Steinbrink K, Jonuleit H, Muller G, Schuler G, Knop J, Enk AH: Interleukin-10-treated human dendritic cells induce a melanoma-antigen-specific anergy in CD8(+) T cells resulting in a failure to lyse tumor cells. *Blood* 1999;93:1634-1642.
- 35 Groux H, O'Garra A, Bigler M, Rouleau M, Antonenko S, de Vries JE, et al: A CD4⁺ T-cell subset inhibits antigen-specific T-cell responses and prevents colitis. *Nature* 1997;389:737-742.
- 36 Cottrez F, Hurst SD, Coffman RL, Groux H: T regulatory cells 1 inhibit a Th2-specific response in vivo. *J Immunol* 2000;165:4848-4853.
- 37 Van Oosterhout AJ, Van Esch B, Hofman G, Hofstra CL, Van Ark I, Nijkamp FP, et al: Allergen immunotherapy inhibits airway eosinophilia and hyperresponsiveness associated with decreased IL-4 production by lymphocytes in a murine model of allergic asthma. *Am J Respir Cell Mol Biol* 1998;19:622-628.
- 38 Durham SR, Till SJ: Immunologic changes associated with allergen immunotherapy. *J Allergy Clin Immunol* 1998;102:157-164.
- 39 Durham SR, Varney V, Gaga M, Jacobson MR, Frew AJ, Kay AB: Immunotherapy suppresses T lymphocyte infiltration in the cutaneous late phase reaction. *J Allergy Clin Immunol* 1991;87:299.
- 40 Iliopoulos O, Proud D, Adkinson NF, Jr., Creticos PS, Norman PS, Kagey Sobotka A, et al: Effects of immunotherapy on the early, late, and rechallenge nasal reaction to provocation with allergen: Changes in inflammatory mediators and cells. *J Allergy Clin Immunol* 1991;87:855-866.
- 41 Durham SR, Ying S, Varney VA, Jacobson MR, Sudderick RM, Mackay IS, et al: Grass pollen immunotherapy inhibits allergen-induced infiltration of CD4⁺ T lymphocytes and eosinophils in the nasal mucosa and increases the number of cells expressing messenger RNA for interferon-gamma. *J Allergy Clin Immunol* 1996;97:1356-1365.
- 42 Akoum H, Tscopoulos A, Vorng H, Wallaert B, Dessaint JP, Joseph M, et al: Venom immunotherapy modulates interleukin-4 and interferon-gamma messenger RNA expression of peripheral T lymphocytes. *Immunology* 1996;87:593-598.
- 43 McHugh SM, Deighton J, Stewart AG, Lachmann PJ, Ewan PW: Bee venom immunotherapy induces a shift in cytokine responses from a TH-2 to a TH-1 dominant pattern: Comparison of rush and conventional immunotherapy. *Clin Exp Allergy* 1995;25:828-838.
- 44 Carballido JM, Carballido Perrig N, Oberli Schrammli A, Heusser CH, Blaser K: Regulation of IgE and IgG4 responses by allergen specific T-cell clones to bee venom phospholipase A₂ in vitro. *J Allergy Clin Immunol* 1994;93:758-767.
- 45 Bellinghausen I, Knop J, Saloga J: Role of interleukin 10-producing T cells in specific (allergen) immunotherapy. *Allergy Clin Immunol Int* 2000;12:20-25.
- 46 Akdis CA, Blesken T, Akdis M, Wüthrich B, Blaser K: Role of Interleukin 10 in specific immunotherapy. *J Clin Invest* 1998;102:98-106.
- 47 Joss A, Akdis M, Faith A, Blaser K, Akdis CA: IL-10 directly acts on T cells by specifically altering the CD28 co-stimulation pathway. *Eur J Immunol* 2000;30:1683-1690.
- 48 Akdis CA, Joss A, Akdis M, Blaser K: Mechanism of IL-10-induced T cell inactivation in allergic inflammation and normal response to allergens. *Int Arch Allergy Immunol* 2001;124:180-182.
- 49 Pierkes M, Bellinghausen I, Hultsch T, Metz G, Knop J, Saloga J: Decreased release of histamine and sulfido-leukotrienes by human peripheral blood leukocytes after wasp venom immunotherapy is partially due to induction of interleukin-10 and interferon-gamma production of T cells. *J Allergy Clin Immunol* 1999;103(2 pt 1):326-332.
- 50 Jutel M, Muller UR, Fricker M, Rihs S, Pichler WJ, Dahinden C: Influence of bee venom immunotherapy on degranulation and leukotriene generation in human blood basophils (see comments). *Clin Exp Allergy* 1996;26:1112-1118.
- 51 Ohkawara Y, Lim KG, Xing Z, Glibetic M, Nakano K, Dolovich J, et al: CD40 expression by human peripheral blood eosinophils. *J Clin Invest* 1996;97:1761-1766.
- 52 Koning H, Neijens HJ, Baert MR, Oranje AP, Savelkoul HF: T cells subsets and cytokines in allergic and non-allergic children. II. Analysis and IL-5 and IL-10 mRNA expression and protein production. *Cytokine* 1997;9:427-436.
- 53 Ohmen JD, Hanifin JM, Nickoloff BJ, Rea TH, Wyzykowski R, Kim J, et al: Overexpression of IL-10 in atopic dermatitis. Contrasting cytokine patterns with delayed-type hypersensitivity reactions. *J Immunol* 1995;154:1956-1963.
- 54 Lamblin C, Desreumaux P, Colombel JF, Tonnel AB, Wallaert B: Overexpression of IL-10 mRNA in gut mucosa of patients with allergic asthma. *J Allergy Clin Immunol* 2001;107:739-741.
- 55 van Scott M, Justice JP, Bradfield JF, Enright E, Sigounas A, Sur S: IL-10 reduces Th2 cytokine production and eosinophilia but augments airway reactivity in allergic mice. *Am J Physiol Lung Cell Mol Physiol* 2000;278:L667-L674.
- 56 Makela MJ, Kanehiro A, Borish L, Dakhama A, Loader J, Joetham A, et al: IL-10 is necessary for the expression of airway hyperresponsiveness but not pulmonary inflammation after allergic sensitization. *Proc Natl Acad Sci USA* 2000;97:6007-6012.
- 57 Risoan MC, Soumelis V, Kadowaki N, Grouard G, Briere F, de Waal Malefyt R, et al: Reciprocal control of T helper cell and dendritic cell differentiation (see comments). *Science* 1999;283:1183-1186.
- 58 Pulendran B, Smith JL, Caspary G, Brasel K, Pettit D, Maraskovsky E, et al: Distinct dendritic cell subsets differentially regulate the class of immune response in vivo. *Proc Natl Acad Sci USA* 1999;96:1036-1041.
- 59 Kapsenberg ML, Hilkens CM, Wierenga EA, Kalinski P: The paradigm of type 1 and type 2 antigen-presenting cells. Implications for atopic allergy. *Clin Exp Allergy* 1999;29 (suppl 2):33-36.
- 60 Kalinski P, Hilkens CM, Snijsers A, Snijsdewint FG, Kapsenberg ML: IL-12-deficient dendritic cells, generated in the presence of prostaglandin E₂, promote type 2 cytokine production in maturing human naive T helper cells. *J Immunol* 1997;159:28-35.
- 61 Vieira PL, de Jong EC, Wierenga EA, Kapsenberg ML, Kalinski P: Development of Th1-inducing capacity in myeloid dendritic cells requires environmental instruction. *J Immunol* 2000;164:4507-4512.
- 62 Bellinghausen I, Brand U, Knop J, Saloga J: Comparison of allergen-stimulated dendritic cells from atopic and nonatopic donors dissecting their effect on autologous naive and memory T helper cells of such donors. *J Allergy Clin Immunol* 2000;105:988-996.
- 63 Stumbles PA, Thomas JA, Pimm CL, Lee PT, Venaille TJ, Proksch S, et al: Resting respiratory tract dendritic cells preferentially stimulate T helper cell type 2 (Th2) responses and require obligatory cytokine signals for induction of Th1 immunity. *J Exp Med* 1998;188:2019-2031.
- 64 Romani N, Reider D, Heuer M, Ebner S, Kampgen E, Eibl B, et al: Generation of mature dendritic cells from human blood. An improved method with special regard to clinical applicability. *J Immunol Methods* 1996;196:137-151.
- 65 Jonuleit H, Kuhn U, Muller G, Steinbrink K, Paragnik L, Schmitt E, et al: Pro-inflammatory cytokines and prostaglandins induce maturation of potent immunostimulatory dendritic cells under fetal calf serum-free conditions. *Eur J Immunol* 1997;27:3135-3142.
- 66 Caux C, Massacrier C, Vanbervliet B, Barthelémy C, Liu YJ, Banchereau J: Interleukin 10 inhibits T cell alloreactivity induced by human dendritic cells. *Int Immunol* 1994;6:1177-1185.
- 67 Bellinghausen I, Brand U, Steinbrink K, Enk AH, Knop J, Saloga J: Inhibition of human allergic T cell responses by interleukin-10-treated dendritic cells: Differences from hydrocortisone-treated dendritic cells. *J Allergy Clin Immunol* 2001;108:242-249.

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