

Targeting Dendritic Cells in Allergen Immunotherapy

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Dendritic cells (DCs) as gatekeepers of our immune system are located at the border zones of the body's internal environment. DCs play a major role in antigen presentation and T-cell priming and are therefore crucial in determining the nature of emerging immune responses. DCs have a paradigmatic role in the immune system because they are strong inducers of (1) allergic–immunogenic reactions that lead to the development and maintenance of allergic diseases, and (2) anti-allergic, tolerogenic reactions that lead to the rapid dampening or complete inhibition of allergic immune responses [1,2].

An allergic reaction is defined as a hyper-reactivity toward normally non-immunogenic substances. The spectrum of these substances ranges from food allergens such as peanuts, egg, milk, soy, and codfish, to aeroallergens such as birch or grass pollen, house dust mites, and cat dander, to natural rubber latex and hymenoptera venom [3–5]. The most severe variant of allergic reactions is life-threatening anaphylactic shock, which is a sudden and severe allergic reaction that occurs within minutes after allergen exposure, progresses rapidly, and can lead to death within a couple of minutes. In the past decades, allergic/atopic diseases such as allergic rhinitis, allergic asthma, and atopic dermatitis have shown an increased incidence that has led to a decreased quality of life for affected individuals [6,7].

Therefore, several therapeutic strategies have been developed to calm the symptoms of allergic diseases. Because of their bivalent character and ability to take up antigens, DCs represent attractive targets for antiallergic treatment

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regimens [8]. Classical allergen immunotherapy represents one of the most recently established therapeutic strategies [9].

What do we know about the mode of action of allergen immunotherapy?

In general, therapeutic strategies used for treating allergic diseases can be subdivided into two major forms: (1) short-term therapeutic strategies that treat the acute symptoms of allergic diseases, and (2) long-term therapeutic strategies, such as allergen-specific immunotherapy, that have the goal of efficient long-term down-regulation of the reactivity toward specific allergens.

Allergen-specific immunotherapy has been shown to be efficient, especially for individuals who have allergic rhinitis or hymenoptera allergy [4,9]. In this treatment regimen, increasing doses of the allergen are applied subcutaneously or sublingually [10–12]. Within weeks an allergen-specific IgG response develops whereby newly formed allergen–IgG complexes are assumed to inhibit further allergen-mediated effector cell activation through IgE receptor/IgG receptor co-activation [9,13,14].

Nevertheless, little is known about the exact immunologic mechanism leading to the therapeutic response of immunotherapy. Recent data support antigen-

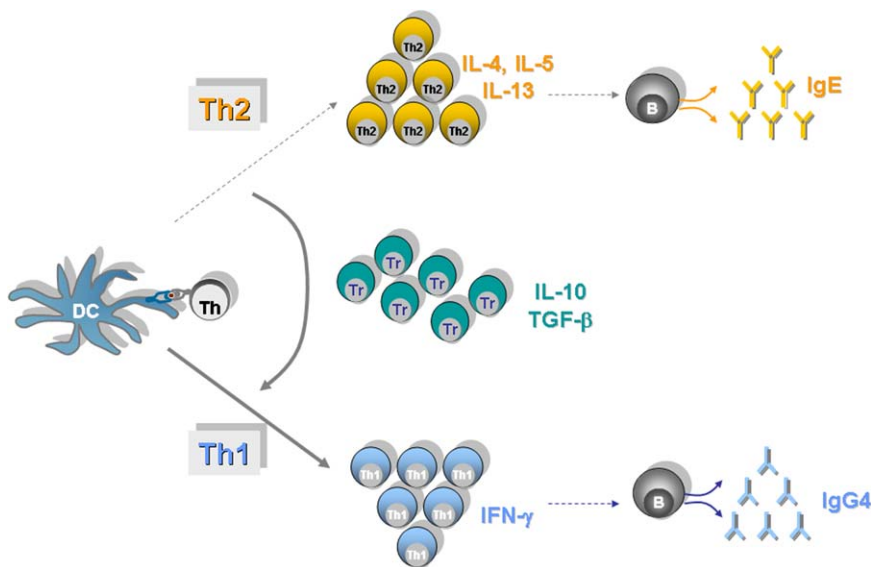


Fig. 1. Mechanisms of action of allergen immunotherapy. Allergen immunotherapy leads to a shift of Th2 immune responses predominated by IL-4-, IL-5-, and IL-13-producing T cells and IgE production by B cells to modified Th2 immune responses and Th1 immune responses in which IFN- γ -producing T cells prevail and B cells start to produce protective IgG4. In parallel, regulatory T cells with high IL-10 and TGF- β -producing properties are induced and might contribute to the mechanisms described.

specific tolerance induction as a leading immunologic mechanism in immunotherapy that inhibits concomitant early and late responses to allergenic substances. Immunotherapy accompanies increased B-cell production of inhibitory IgG subtypes such as IgG₂ and IgG₄, and an increase of allergen-specific IgA [9]. Furthermore, immunotherapy induces a shift from Th2-type immune responses, which predominate in allergic diseases and are characterized by high T-cell production of interleukin (IL)-4, IL-5, and IL-13, to Th1-type immune responses, which are characterized by high T-cell production of interferon (IFN)- γ [15]. In another recently discovered mechanism, immunotherapy induces IL-10 and transforming growth factor (TGF)- β production by T cells and enhances the suppressive activity of regulatory CD4⁺ CD25⁺ T-cell subtypes (Fig. 1) [16].

Why are dendritic cells attractive targets for allergen immunotherapy?

DCs are located at the interface of the body and the environment, such as the skin, respiratory tract, and mucosal sites [2]. Therefore, DCs are easily accessible for immunotherapeutic substances applied through subcutaneous injections or administered to mucosal surfaces such as the sublingual or intranasal mucous membranes. Obviously, DCs not only are one of the first cell types to come in contact with naturally occurring allergens in patients who have allergic diseases but also gain early access to allergenic compounds applied for therapeutic purposes through immunotherapy. As another attractive feature, DCs are capable of taking up allergens and presenting these allergens to antigen-specific T cells [17]. Thus, DCs prime T cells into activating proallergic or suppressive, anti-allergic T-cell subtypes [18]. Most importantly, DCs in the skin and oral and nasal mucosa of patients who have allergic diseases have been shown to bear the high-affinity IgE receptor (Fc ϵ RI) in high amounts on their cell surface [19–21]. As a characteristic feature of individuals who have allergies, the Fc ϵ RI on DCs is occupied partly by IgE molecules, and the pattern of allergen-specific IgE molecules bound to the cell surface of DCs might comply with the sensitization pattern of these patients [20,22].

DCs are capable of taking up allergens through Fc ϵ RI-bound IgE molecules, internalizing these allergens and presenting the processed allergen peptides to T cells after migrating to the peripheral lymphoid organs [23]. Presumably, allergens applied for the purpose of immunotherapy are also taken up by DCs and presented to T cells. Furthermore, variations in the maturation stage and grade of activation of DCs, the composition of DC subtypes at the different sites of the body, and the dosage of allergens applied, in combination with many other currently unidentified factors, critically modulate the nature of the immune response induced by DCs through immunotherapy [24].

One of the most striking properties of DCs in the context of immunotherapy is their bivalent character: DCs are paradigmatic players in the allergic cascade that on one hand are able to mediate immunogenic reactions leading to aller-

gic inflammation and on the other hand are capable of inducing antiallergic, tolerogenic immune responses [25].

Which tolerogenic properties of dendritic cells might be relevant in allergen immunotherapy?

Different studies provide evidence that DCs are critically involved in the induction of tolerance against allergens, which is a major mode of action of immunotherapy. However, the detailed mechanisms converting DCs into tolerogenic DCs in immunotherapy are far from being known. Although increasing insights into the biology of DCs show that these cells may have a critical involvement in the mechanism contributing to the therapeutic response to immunotherapy, most hypotheses concerning the role of DCs as facilitators of immunotherapy remain speculative. Therefore, experimental data acquired from ex vivo—mechanisms isolated DCs under subcutaneous and sublingual immunotherapy are needed to support these assumptions.

One of the most important mechanisms in this context might be enhanced IL-10 production mirrored by increased local IL-10 levels and IL-10 serum levels of patients undergoing immunotherapy, because IL-10 is known to enforce phenotypic and functional properties of regulatory DCs by creating regulatory DC subtypes [26,27]. IL-10, for instance, reduces the stimulatory capacity of DC toward T cells and modulates the maturation stage of differentiating DCs, keeping them in an immature stage [18,28]. As a secondary phenomenon, IL-10 induces several tolerogenic properties of DCs, such as increased expression of inhibitory Fc γ RIIB or increased immunoglobulin-like transcript receptors ILT2, ILT3, ILT4, and ILT5 [29], which are known to suppress T-cell responses while down-regulating the expression of costimulatory molecules [28].

Looking closer at the immunologic synapse between DCs and T cells, several studies show that the down-regulatory effect of DCs on T cells occurs partially in a cell contact—dependent manner and is mediated by second signals transferred by way of surface molecule interactions between these cells [30].

In this context, in vitro experiments show that the expansion of regulatory T cells is dependent on B7 costimulation and coinhibition by way of DCs [30]. Within the family of B7 costimulatory molecules on DCs, the costimulatory molecules CD80 and CD86 are well characterized and mediate signals through CD28 and CD152/cutaneous-lymphocyte antigen (CTLA)-4 to T cells. As certain types of opponents, the surface molecules B7-H1, B7-H2, B7-H3, B7-H4, and B7-DC belong to the coinhibitory B7 molecule family expressed by DCs [30,31]. One approach cross-linked the coinhibitory molecule B7-DC on DCs, resulting in diminished allergen responsiveness in a mouse model and indicating a critical role of these molecules in allergen-specific tolerance induction [32]. Moreover, another recently described member of the B7 family, the inducible costimulator ligand (B7-H2/ICOS-L), has been shown to be involved in the induction of regulatory T cells [33]. In a mouse model, the interaction of inducible costi-

mulator (ICOS) on T cells and ICOS-L/B7-H2 on pulmonary DCs led to the development of IL-10-producing regulatory T cells that inhibit airway hyper-reactivity, which is a cardinal feature of asthma [34–36]. However, whether B7 molecules expressed by DCs might be relevant for the induction of regulatory T cells in immunotherapy is unclear.

Is the high-affinity receptor for IgE (FcεRI) on dendritic cells a key structure in allergen immunotherapy?

The detection of FcεRI on antigen-presenting DC has brought new insights into the distribution and function of this immunoglobulin receptor. FcεRI has been shown to be expressed in a trimeric form, consisting of the IgE-binding α-chain and the γ-chain dimer responsible for signal transduction, in antigen-presenting cells such as monocytes, Langerhans cells (LCs), and other DC subtypes [19].

The function of FcεRI on DCs is still not elucidated in detail, but FcεRI on DCs is known to play opposing roles. On one hand, FcεRI on DCs such as LCs and inflammatory dendritic epidermal cells (IDECs) in the epidermis of atopic dermatitis is involved in the induction of proinflammatory cytokine production and recruitment of more inflammatory cells to the skin [37]. Thus, FcεRI-bearing DCs in the skin perpetuate the allergic inflammation. In contrast, recent published data suggest that FcεRI is also involved in tolerogenic processes [38]. In this context, on ligation of FcεRI on monocytes and DCs, FcεRI has been shown to trigger production of the anti-inflammatory cytokine IL-10 [39]. Furthermore, this production of IL-10 endogenously induces the generation of DCs with a lower stimulatory capacity toward T cells [39]. Consequently, increased IL-10 production of DCs after FcεRI-mediated allergen challenge under immunotherapy might be another putative mechanism in which DCs might contribute not only to the increased IL-10 levels observable in patients undergoing immunotherapy but also to the overbalance of tolerogenic immune responses after allergen application under immunotherapy. As another tolerogenic mechanism that might be relevant in immunotherapy, FcεRI engagement of monocytes induces the overexpression of indoleamine 2,3-dioxygenase (IDO), the immunosuppressive enzyme involved in the catabolism of the essential amino acid tryptophan to kynurenine and other potentially toxic metabolites [40–43]. Induction of IDO and prevention of the activation of CD4⁺ T cells has been shown to be mediated through CTLA-4 activation in *in vitro* studies [42,43].

Conversely, contact and activation of T cells by way of IDO-expressing DCs increases the CTLA-4 expression and regulatory capacities of T cells [42,43]. Presumably, the tolerogenic properties of FcεRI-bearing DCs might be encouraged through repeated allergen challenge and FcεRI activation of DCs under immunotherapy, leading to an increase in IDO-expressing tolerogenic DCs, and allergen-specific tolerance perpetuated by regulatory T cells as another putative mechanism of immunotherapy [43,44].

How do the different routes of allergen immunotherapy target dendritic cells?

The classical and most established model for immunotherapy is the subcutaneous immunotherapy for insect sting allergy. In addition, subcutaneous immunotherapy has been used for treating several other allergic sensitizations, such as birch pollen or grass pollen allergy in individuals who have single sensitizations but also allergy to house dust mites and other aeroallergens. Although the mechanisms contributing to the shift from a high reactivity toward allergens to a state of unresponsiveness and tolerance are not completely elucidated, an immune response shift from Th2 to Th1 and a predominant IL-10 production by regulatory T cells of the Tr1 type and T-cell anergy combined with lower allergen-specific IgE and increase of allergen-specific IgG have been shown to be crucial for the process of tolerance induction underlying the therapeutic effect of subcutaneous immunotherapy [9,45–49]. Little information about changes at the local sites of subcutaneous allergen application [50,51] or the DC phenotype and function under immunotherapy exists to confirm that DCs have a key role as natural silencers in subcutaneous immunotherapy.

Apparently the route through which an allergen enters the body affects the nature of the resulting immune responses. One reason is the unique composition of the micromilieu at different sites of the body. In comparison to the classical routes of allergen application in immunotherapy, through compartments such as the skin, the mucosal sites such as the oral mucosa have been shown to represent immunoprivileged compartments that are somewhat capable of maintaining a state of immunologic unresponsiveness to subsequent allergen challenge under physiologic conditions [52]. This effect might be achieved through induction of regulatory T cells with suppressive properties, anergy, or deletion of immunoresponsive cells [52]. Therefore, immunotherapeutic strategies that use alternative routes of application, through immunoprivileged organs such as the oral mucosa, have recently gained increasing interest and hold promise as alternative modes of immunotherapy that may help increase safety by decreasing the risk for anaphylactic side reactions. The key cells perpetuating the state of tolerance in the oral mucosa are believed to be DCs. Their dampening function on the immune response is achieved partially through their expression of coinhibitory IgG receptors such as Fc γ RIIB observed in murine models [53]. Signaling through these receptors after coactivation of Fc ϵ RI and Fc γ RIIB induces intracellular signaling through immunoreceptor tyrosine-based inhibition motifs and inhibits the outcome of an allergic immune response by antagonizing the activation signals mediated through immunoreceptor tyrosine-based activation motifs of Fc ϵ RI [14,54].

In the context of allergen challenge, human oral mucosal LCs (oLCs) have recently been shown to display characteristic features, which differ in individuals who have allergies compared with those who do not [21,55]. In contrast to their counterparts in the skin, oLCs express higher levels of IgE-occupied Fc ϵ RI [21]. Furthermore, oLCs express higher levels of major histocompatibility complex I

and II molecules and costimulatory molecules such as CD80, CD86, or CD40 than do skin DCs and are therefore much more potent stimulators of T cells [21]. On the functional level, oLCs produce favorably anti-inflammatory cytokines such as TGF- β or IL-10 after allergen challenge in vitro, indicating their ability to induce tolerogenic mechanisms (Allam and Novak, unpublished data, 2005). These LCs express enhanced amounts of IgG receptors [21] and coinhibitory molecules such as B7-H1 and B7-H2 on their cell surface (Allam and Novak, unpublished data, 2005), which are responsible for the DC–T-cell contact-dependent induction of inhibitory regulatory T cells and the maintenance of peripheral tolerance toward allergens (Fig. 2). As another important feature that classifies them as tolerogenic DCs, oLCs induce high amounts of IL-10- and TGF- β -producing T cells after allergen challenge and secrete chemokines capable of recruiting regulatory T cells in vitro (see Fig. 2). Although oLCs express C-type lectins such as CD205, CD206, and CD209 in lower quantities on their cell surface than do LCs in the nasal mucosa [55], oLCs bear higher amounts of the lipopolysaccharide receptor CD14 on their cell surface compared with nasal

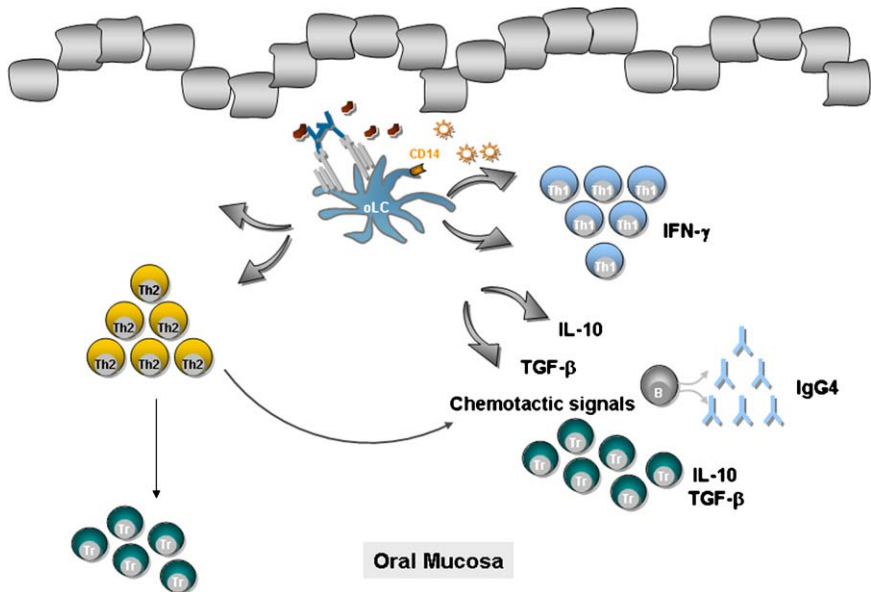


Fig. 2. Summary of the tolerogenic properties of oLCs as putative target cells of sublingual allergen immunotherapy. oLCs express high levels of Fc ϵ RI and the lipopolysaccharide receptor CD14 on their cell surface. Costimulation of Fc ϵ RI and CD14 might favor the priming of IFN- γ -producing T cells of the Th1 type. Fc ϵ RI allergen challenge induces IL-10 and TGF- β production by oLCs combined with the activation of IL-10 and TGF- β -producing regulatory T cells (Tr). Secondary signals mediated through inhibitory B7 molecules such as B7-H2 expressed in high amounts on oLCs might induce allergen-specific tolerance through regulatory T cells.

mucosal LCs or skin LCs (see Fig. 2) [55]. Because bacterial products are often used as adjuvants to boost immune responses of the Th1 type, the expression of CD14 on oLCs makes them attractive targets for adjuvants added to allergen preparations to increase therapeutic effects in immunotherapy.

Are dendritic cells attractive targets for adjuvants of allergen immunotherapy?

Since several studies proved that the therapeutic effect of immunotherapy accompanies a shift of Th2 toward modified Th2 or Th1 responses, immunotherapy strategies have been developed to coadminister adjuvants with a high capacity to trigger Th1 immune responses and transfer the immune response from innate to adaptive immunity. Most of these adjuvants are bacterial products, such as monophosphoryl lipid A (MPL) or synthetic oligonucleotides containing unmethylated CpG dinucleotides [56,57]. Structures belonging to innate immunity, such as the pattern recognition receptors expressed by DCs, play a key role as target structures for these strategies. Some of these adjuvants have been shown to modulate the maturation stage, phenotype, and stimulatory capacity of targeted DCs toward T cells in vitro [58–60]. Under immunotherapy, these adjuvants might bind to phylogenically conserved transmembrane proteins expressed by DCs, such as Toll-like receptor 9 binding to the adjuvant CpG or the lipopolysaccharide receptor CD14 binding to the adjuvant MPL [59,61–65], and force a rapid shift of Th2 to Th1 immune responses to increase the therapeutic benefit of immunotherapy.

How does anti-IgE treatment target dendritic cells?

An alternative approach to allergen immunotherapy is to reduce the amount of IgE molecules in the sera of the patients, using anti-IgE antibodies to reduce the number of allergen-specific IgE molecules bound to FcεRI on DCs. These strategies have the goal of preventing the earliest steps of allergic reactions by reducing the frequency of IgE–FcεRI receptor interaction. In summary, treatment with anti-IgE antibodies results in a significant reduction of free IgE molecules in the sera of individuals who have allergies [66]. Because the amount of IgE receptors expressed on the cell surface of DCs correlates with the IgE serum levels, the therapeutic reduction of IgE in the sera of the patients accompanies a decrease of the amount of FcεRI expressed on DCs [66]. This down-regulation of FcεRI expressed on DCs reduces the probability of IgE–FcεRI-binding to effector cells of allergic diseases. Anti-IgE treatment has been shown to reduce the total number of myeloid CD11c⁺ DCs in the peripheral blood of patients treated during the grass pollen season [67]. The advantage of this strategy is that any type of IgE molecule can be targeted. The disadvantage is that although the efficacy of anti-

IgE antibodies has been proven in different clinical studies [66,68], the application of this treatment regimen is limited to a concomitant long-term therapy and can not be used for the treatment of acute allergic reactions.

Summary

What are the future perspectives for dendritic cells as targets for antiallergic treatment strategies?

In summary, DCs play a paradigmatic role in our immune system and are therefore attractive targets of allergy immunotherapeutic strategies, which take advantage of the capability of DCs to act as natural silencers of allergic diseases [24,69,70]. The outstanding features qualifying DCs as target cells for allergen immunotherapy include their accessibility for immunotherapy preparations because of their localization at the border zones of the immune system, their capability to selectively take up allergens by way of IgE receptors on their cell surface, and the expression of a broad spectrum of inhibitory receptors on their cell surface, in combination with a high number of expressed surface structures appropriate for adjuvants of allergen immunotherapy. Furthermore, their capacity to induce exclusively allergic immune responses of the late type after Fc ϵ RI-receptor allergen challenge favors DCs as safe targets for allergen immunotherapy. Therefore, using DCs as a route for allergen immunotherapy represents a clever way to use physiologic methods of allergen challenge without increased risk for unwanted anaphylactic side effects.

Future approaches will be aimed at optimizing the routes of allergen immunotherapy, specifically focusing on DC subtypes with a high tolerogenic potential, such as DCs located in the oral mucosa; adjustment of the optimal allergen dosage and frequency of application in combination with the optimal choice of adjuvants; and use of allergen–adjuvant combinations [71].

Approaches that target DCs directly will be further established, such as the administration of B7-DC cross-linking antibodies, which have been used successfully in treating allergic hyper-responsiveness in animal models [32], or the use of chimeric fusion proteins [72] to concomitantly challenge activating Fc ϵ RI and inhibitory Fc γ RIIB receptors, which have already been shown to display inhibitory effects on human DCs [73] in vitro. Other approaches targeting DCs will include different vaccination strategies that use genetically modified allergen derivatives or allergen hybrid molecules [74–76] to lower the risk for anaphylactic side reactions while increasing the efficacy of these treatment strategies. However, future studies will have to focus on the phenotypic and functional changes of DCs under immunotherapy to close the gap of knowledge about the exact role of DCs in immunotherapy. These studies might help to finally prove the hypothesis of DCs as efficient silencers and promising candidate cells for immunotherapy.

References

- [1] Novak N, Allam JP, Betten H, et al. The role of antigen presenting cells at distinct anatomic sites: they accelerate and they slow down allergies. *Allergy* 2004;59:5–14.
- [2] Rossi M, Young JW. Human dendritic cells: potent antigen-presenting cells at the crossroads of innate and adaptive immunity. *J Immunol* 2005;175:1373–81.
- [3] Holt PG, Thomas WR. Sensitization to airborne environmental allergens: unresolved issues. *Nat Immunol* 2005;6:957–60.
- [4] Golden DB. Insect sting allergy and venom immunotherapy: a model and a mystery. *J Allergy Clin Immunol* 2005;115:439–47.
- [5] Sicherer SH, Leung DY. Advances in allergic skin disease, anaphylaxis, and hypersensitivity reactions to foods, drugs, and insects. *J Allergy Clin Immunol* 2005;116:153–63.
- [6] Kay AB. Allergy and allergic diseases. First of two parts. *N Engl J Med* 2001;344:30–7.
- [7] Kay AB. Allergy and allergic diseases. Second of two parts. *N Engl J Med* 2001;344:109–13.
- [8] Wallet MA, Sen P, Tisch R. Immunoregulation of dendritic cells. *Clin Med Res* 2005;3:166–75.
- [9] Till SJ, Francis JN, Nouri-Aria K, et al. Mechanisms of immunotherapy. *J Allergy Clin Immunol* 2004;113:1025–34.
- [10] Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases. A WHO position paper. *J Allergy Clin Immunol* 1998;102:558–62.
- [11] Lockey RF. “ARIA”: global guidelines and new forms of allergen immunotherapy. *J Allergy Clin Immunol* 2001;108:497–9.
- [12] Marogna M, Spadolini I, Massolo A, et al. Clinical, functional, and immunologic effects of sublingual immunotherapy in birch pollinosis: a 3-year randomized controlled study. *J Allergy Clin Immunol* 2005;115:1184–8.
- [13] Gehlhar K, Schlaak M, Becker W, et al. Monitoring allergen immunotherapy of pollen-allergic patients: the ratio of allergen-specific IgG4 to IgG1 correlates with clinical outcome. *Clin Exp Allergy* 1999;29:497–506.
- [14] Daron M, Latour S, Malbec O, et al. The same tyrosine-based inhibition motif, in the intracytoplasmic domain of Fc gamma RIIB, regulates negatively BCR-, TCR-, and FcR-dependent cell activation. *Immunity* 1995;3:635–46.
- [15] Jutel M, Pichler WJ, Skrbic D, et al. 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;154:4187–94.
- [16] Jutel M, Akdis M, Budak F, et al. IL-10 and TGF-beta cooperate in the regulatory T cell response to mucosal allergens in normal immunity and specific immunotherapy. *Eur J Immunol* 2003;33:1205–14.
- [17] Villadangos JA, Schnorrer P, Wilson NS. Control of MHC class II antigen presentation in dendritic cells: a balance between creative and destructive forces. *Immunol Rev* 2005;207:191–205.
- [18] Lutz MB, Schuler G. Immature, semi-mature and fully mature dendritic cells: which signals induce tolerance or immunity? *Trends Immunol* 2002;23:445–9.
- [19] Novak N, Tepel C, Koch S, et al. Evidence for a differential expression of the FcepsilonRIgamma chain in dendritic cells of atopic and nonatopic donors. *J Clin Invest* 2003;111:1047–56.
- [20] Novak N, Allam JP, Hagemann T, et al. Characterization of FcepsilonRI-bearing CD123 blood dendritic cell antigen-2 plasmacytoid dendritic cells in atopic dermatitis. *J Allergy Clin Immunol* 2004;114:364–70.
- [21] Allam JP, Novak N, Fuchs C, et al. Characterization of dendritic cells from human oral mucosa: a new Langerhans’ cell type with high constitutive FcepsilonRI expression. *J Allergy Clin Immunol* 2003;112:141–8.
- [22] Bieber T, de la Salle H, Wollenberg A, et al. Human epidermal Langerhans cells express the high affinity receptor for immunoglobulin e (fc epsilon ri). *J Exp Med* 1992;175:1285–90.
- [23] Novak N, Kraft S, Bieber T. Unraveling the mission of FcepsilonRI on antigen-presenting cells. *J Allergy Clin Immunol* 2003;111:38–44.

- [24] Rutella S, Lemoli RM. Regulatory T cells and tolerogenic dendritic cells: from basic biology to clinical applications. *Immunol Lett* 2004;94:11–26.
- [25] Steinman RM. The control of immunity and tolerance by dendritic cell. *Pathol Biol (Paris)* 2003;51:59–60.
- [26] Jonuleit H, Schmitt E. The regulatory T cell family: distinct subsets and their interrelations. *J Immunol* 2003;171:6323–7.
- [27] Roncarolo MG, Levings MK, Traversari C. Differentiation of T regulatory cells by immature dendritic cells. *J Exp Med* 2001;193:F5–9.
- [28] Mosmann TR. Regulation of immune responses by t cells with different cytokine secretion phenotypes: role of a new cytokine, cytokine synthesis inhibitory factor (il10). *Int Arch Allergy Appl Immunol* 1991;94:110–5.
- [29] Velten FW, Duperrier K, Bohlender J, et al. A gene signature of inhibitory MHC receptors identifies a BDCA3(+) subset of IL-10-induced dendritic cells with reduced allostimulatory capacity in vitro. *Eur J Immunol* 2004;34:2800–11.
- [30] Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. *Annu Rev Immunol* 2005;23: 515–48.
- [31] Yamazaki S, Iyoda T, Tarbell K, et al. Direct expansion of functional CD25+ CD4+ regulatory T cells by antigen-processing dendritic cells. *J Exp Med* 2003;198:235–47.
- [32] 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;173:1360–5.
- [33] Bellinghausen I, Klostermann B, Bottcher I, et al. Importance of the inducible costimulator molecule for the induction of allergic immune responses and its decreased expression on T helper cells after venom immunotherapy. *Immunology* 2004;112:80–6.
- [34] 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;8:1024–32.
- [35] 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;5:1149–56.
- [36] Witsch EJ, Peiser M, Hutloff A, et al. ICOS and CD28 reversely regulate IL-10 on re-activation of human effector T cells with mature dendritic cells. *Eur J Immunol* 2002;32:2680–6.
- [37] Novak N, Valenta R, Bohle B, et al. FcepsilonRI engagement of Langerhans cell-like dendritic cells and inflammatory dendritic epidermal cell-like dendritic cells induces chemotactic signals and different T-cell phenotypes in vitro. *J Allergy Clin Immunol* 2004;113:949–57.
- [38] Novak N, Kraft S, Bieber T. IgE receptors. *Curr Opin Immunol* 2001;13:721–6.
- [39] Novak N, Bieber T, Katoh N. Engagement of fcepsilonRI on human monocytes induces the production of il-10 and prevents their differentiation in dendritic cells. *J Immunol* 2001;67: 797–804.
- [40] Von Bubnoff D, Matz H, Frahnert C, et al. Fc epsilon RI induces the tryptophan degradation pathway involved in regulating T cell responses. *J Immunol* 2002;169:1810–6.
- [41] Mellor A. Indoleamine 2,3 dioxygenase and regulation of T cell immunity. *Biochem Biophys Res Commun* 2005;338(1):20–4.
- [42] Boasso A, Herbeuval JP, Hardy AW, et al. Regulation of indoleamine 2,3-dioxygenase and tryptophanyl-tRNA-synthetase by CTLA-4-Fc in human CD4+ T cells. *Blood* 2005;105: 1574–81.
- [43] Munn DH, Sharma MD, Lee JR, et al. Potential regulatory function of human dendritic cells expressing indoleamine 2,3-dioxygenase. *Science* 2002;297:1867–70.
- [44] Boasso A, Herbeuval JP, Hardy AW, et al. Regulation of indoleamine 2,3-dioxygenase and tryptophanyl-tRNA-synthetase by CTLA-4-Fc in human CD4+ T cells. *Blood* 2005;105: 1574–81.
- [45] Akdis CA, Blaser K. IL-10-induced anergy in peripheral T cell and reactivation by micro-environmental cytokines: two key steps in specific immunotherapy. *FASEB J* 1999;13:603–9.
- [46] Akdis CA, Blesken T, Akdis M, et al. Role of interleukin 10 in specific immunotherapy. *J Clin Invest* 1998;102:98–106.

- [47] Bellinghausen I, Metz G, Enk AH, et al. 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;27:1131–9.
- [48] Nasser SM, Ying S, Meng Q, et al. Interleukin-10 levels increase in cutaneous biopsies of patients undergoing wasp venom immunotherapy. *Eur J Immunol* 2001;31:3704–13.
- [49] 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;172:3252–9.
- [50] Eberlein-Konig B, Jung C, Rakoski J, et al. Immunohistochemical investigation of the cellular infiltrates at the sites of allergoid-induced late-phase cutaneous reactions associated with pollen allergen-specific immunotherapy. *Clin Exp Allergy* 1999;29:1641–7.
- [51] Jung CM, Funk A, Rakoski J, et al. Immunohistochemical analysis of late local skin reactions during rush venom immunotherapy. *Allergy* 1997;52:717–26.
- [52] Kelsall BL, Leon F. Involvement of intestinal dendritic cells in oral tolerance, immunity to pathogens, and inflammatory bowel disease. *Immunol Rev* 2005;206:132–48.
- [53] Samsom JN, van Berkel LA, van Helvoort JM, et al. Fc gamma RIIB regulates nasal and oral tolerance: a role for dendritic cells. *J Immunol* 2005;174:5279–87.
- [54] Kopley CL, Cambier JC, Morel PA, et al. Negative regulation of FcepsilonRI signaling by FcgammaRII costimulation in human blood basophils. *J Allergy Clin Immunol* 2000;106:337–48.
- [55] Allam JP, Niederhagen B, Büchler M, et al. Comparative analysis of nasal and oral mucosal myeloid Dendritic Cells. *Allergy* 2006;61:166–72.
- [56] Freytag LC, Clements JD. Mucosal adjuvants. *Vaccine* 2005;23:1804–13.
- [57] Jain S, Yap WT, Irvine DJ. Synthesis of protein-loaded hydrogel particles in an aqueous two-phase system for coincident antigen and CpG oligonucleotide delivery to antigen-presenting cells. *Biomacromolecules* 2005;6:2590–600.
- [58] Kuchtey J, Chefalo PJ, Gray RC, et al. Enhancement of dendritic cell antigen cross-presentation by CpG DNA involves type I IFN and stabilization of class I MHC mRNA. *J Immunol* 2005;175:2244–51.
- [59] Ismaili J, Rennesson J, Aksoy E, et al. Monophosphoryl lipid A activates both human dendritic cells and T cells. *J Immunol* 2002;168:926–32.
- [60] De BG, Moulin V, Pajak B, et al. The adjuvant monophosphoryl lipid A increases the function of antigen-presenting cells. *Int Immunol* 2000;12:807–15.
- [61] Mothes N, Heinzkill M, Drachenberg KJ, et al. Allergen-specific immunotherapy with a monophosphoryl lipid A-adjuvanted vaccine: reduced seasonally boosted immunoglobulin E production and inhibition of basophil histamine release by therapy-induced blocking antibodies. *Clin Exp Allergy* 2003;33:1198–208.
- [62] Bohle B, Jahn-Schmid B, Maurer D, et al. Oligodeoxynucleotides containing CpG motifs induce IL-12, IL-18 and IFN-gamma production in cells from allergic individuals and inhibit IgE synthesis in vitro. *Eur J Immunol* 1999;29:2344–53.
- [63] Tighe H, Takabayashi K, Schwartz D, et al. Conjugation of immunostimulatory DNA to the short ragweed allergen amb a 1 enhances its immunogenicity and reduces its allergenicity. *J Allergy Clin Immunol* 2000;106:124–34.
- [64] Marshall JD, Abtahi S, Eiden JJ, et al. Immunostimulatory sequence DNA linked to the Amb a 1 allergen promotes T(H)1 cytokine expression while downregulating T(H)2 cytokine expression in PBMCs from human patients with ragweed allergy. *J Allergy Clin Immunol* 2001;108:191–7.
- [65] Tulic MK, Fiset PO, Christodoulopoulos P, et al. Amb a 1-immunostimulatory oligodeoxynucleotide conjugate immunotherapy decreases the nasal inflammatory response. *J Allergy Clin Immunol* 2004;113:235–41.
- [66] Milgrom H, Fick Jr RB, Su JQ, et al. Treatment of allergic asthma with monoclonal anti-IgE antibody. rhuMAB-E25 Study Group. *N Engl J Med* 1999;341:1966–73.
- [67] Feuchtinger T, Bartz H, von BA, et al. Treatment with omalizumab normalizes the number of myeloid dendritic cells during the grass pollen season. *J Allergy Clin Immunol* 2003;111:428–30.
- [68] Leung DY, Sampson HA, Yunginger JW, et al. Effect of anti-IgE therapy in patients with peanut allergy. *N Engl J Med* 2003;348:986–93.

- [69] Hackstein H, Thomson AW. Dendritic cells: emerging pharmacological targets of immunosuppressive drugs. *Nat Rev Immunol* 2004;4:24–34.
- [70] O'Neill DW, Adams S, Bhardwaj N. Manipulating dendritic cell biology for the active immunotherapy of cancer. *Blood* 2004;104:2235–46.
- [71] Marcucci F, Sensi L, Di CG, et al. Dose dependence of immunological response to sublingual immunotherapy. *Allergy* 2005;60:952–6.
- [72] Zhu D, Kepley CL, Zhang K, et al. A chimeric human-cat fusion protein blocks cat-induced allergy. *Nat Med* 2005;11:446–9.
- [73] Kepley CL, Zhang K, Zhu D, et al. FcepsilonRI-FcgammaRII coaggregation inhibits IL-16 production from human Langerhans-like dendritic cells. *Clin Immunol* 2003;108:89–94.
- [74] Linhart B, Hartl A, Jahn-Schmid B, et al. A hybrid molecule resembling the epitope spectrum of grass pollen for allergy vaccination. *J Allergy Clin Immunol* 2005;115:1010–6.
- [75] Hufnagl K, Winkler B, Focke M, et al. Intranasal tolerance induction with polypeptides derived from 3 noncross-reactive major aeroallergens prevents allergic polysensitization in mice. *J Allergy Clin Immunol* 2005;116:370–6.
- [76] Reisinger J, Horak F, Pauli G, et al. Allergen-specific nasal IgG antibodies induced by vaccination with genetically modified allergens are associated with reduced nasal allergen sensitivity. *J Allergy Clin Immunol* 2005;116:347–54.