Tolerance to Allergens: How it Develops and How it Can be Induced

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ABSTRACT

The induction of immune tolerance and specific immune suppression are essential processes in the control of immune responses. Allergen immunotherapy induces early desensitization and peripheral T cell tolerance to allergens associated with development of Treg and Breg cells, and downregulation of several allergic and inflammatory aspects of effector subsets of T cells, B cells, basophils, mast cells and eosinophils. Similar molecular and cellular mechanisms have been observed in subcutaneous and sublingual AIT as well as natural tolerance to high doses of allergen exposure. In allergic disease, the balance between allergen-specific Treg and disease-promoting T helper 2 cells (Th2) appears to be decisive in the development of an allergic versus a non-disease promoting or “healthy” immune response against allergen. Treg specific for common environmental allergens represent the dominant subset in healthy individuals arguing for a state of natural tolerance to allergen in these individuals. In contrast, there is a high frequency of allergen-specific Th2 cells in allergic individuals. Treg function appears to be impaired in active allergic disease. For example, induction of IL-10- and TGF-beta-producing Treg cells, IgG4 isotype blocking antibodies, and suppression of mast cells, basophils and eosinophils represent major components of a relatively normalized immune response after allergen-specific immunotherapy. Allergen-specific Treg and Breg cells orchestrate a general immune regulatory activity, which can be summarized as suppression of cytokines from inflammatory dendritic cells; suppression of effector Th1, Th2 and Th17 cells; suppression of allergen-specific IgE, and induction of IgG4; suppression of migration to tissues of mast cells, basophils, eosinophils and effector T cells. A detailed knowledge of the mechanisms of allergen immunotherapy is not only important in designing the prevention and treatment of allergic diseases, but may also find applications in the treatment of autoimmune diseases, organ transplantation, chronic infection and cancer.
Introduction

Allergen-specific immunotherapy (AIT) is effective in reducing symptoms of allergic asthma and rhinitis as well as venom-induced anaphylaxis. A key feature of AIT is to change the course of disease by altering the underlying pathology. Currently, two types of AIT are in clinical practice, subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT), and several novel AIT approaches are being evaluated in clinical trials. There is moderate-level evidence for the efficacy of SIT against atopic dermatitis, and SLIT for the treatment of allergic rhinitis and asthma provided by recent meta analyses. Dysregulated immune function plays an essential role in many IgE-mediated diseases including asthma, atopic dermatitis, allergic rhinitis, food allergy, venom allergy as well as autoimmune diseases, organ transplantation, tumors, chronic infections and successful pregnancy. Multiple mechanisms of immune regulation take place depending on the type, place, intensity, chronicity of the immune response, as well as antigens/allergens, adjuvants, cytokines or small molecules in the micromilieu. In addition, the type of the tissue response plays an essential role in the thresholds for inflammation versus tolerance.

The physiopathology of allergic diseases is complex and influenced by many factors, including genetic susceptibility, route of exposure, antigen/allergen dose, time of exposure, structural characteristics of the allergen/antigen, and co-exposure with stimulators of innate immune response, such as infections or commensal bacteria. Allergens enter the body via the respiratory tract, gut, conjunctiva, injured skin or insect stings, and most of the time the result is induction of tolerance as a natural mechanism. Immune tolerance to allergens is characterized by establishment of a long-term clinical tolerance. The mechanisms by which allergen tolerance is established in humans have been studied through various modes of AIT as well as the processes by which a healthy immune response develops during high dose of allergen exposure in beekeepers and cat owners. Although many mechanisms are not fully elucidated, they include changes in the characteristics of allergen-specific memory T and B cell responses, the production of specific antibody isotypes to skew the immune response towards no inflammation, as well as decreased activation, tissue migration and mediator release of mast cells, basophils and eosinophils. After the discovery of Th1 and Th2 cell subsets in 1986, during the last 27 years, it is well understood that there is reciprocal regulation between individual Th cell subsets, such as Th1, Th2, Th9, Th17, Th22, however, Treg cells play a major role in the suppression of effector T cell responses in different diseases.

Allergic diseases are complex disorders with several disease variants due to different underlying cellular and molecular mechanisms. Although there are several clinically relevant phenotypes for rhinitis, asthma, atopic dermatitis and even urticaria, these phenotypes do not necessarily give any insight into the pathomechanisms that underpin the diseases. An important unmet need in AIT is the identification
and validation of biomarkers that are predictive of clinical response. It is now thought that some clinical trials may have been unsuccessful in the past, because they were performed without attempting to classify AIT patients into subgroups that are defined by a distinct pathophysiology, namely ‘endotypes’. It seems essential to select AIT responder cases from the big pool of patients with asthma, allergic rhinitis and even atopic dermatitis. The definition of an AIT responsive endotype of allergic diseases and relevant biomarkers is urgently needed for patient selection, maybe also even for the selection of the type of vaccine or route of application.

**Mechanisms of allergen-specific immunotherapy**

Cellular and molecular events that take place during the course of AIT can be classified in four groups (Figure 1). Although there is significant variation between donors and protocols, decreases in mast cell and basophil activity and degranulation and the tendency for systemic anaphylaxis starts to take place within hours when natural allergens are used. The second group of events are generation of allergen-specific Treg and Breg cells and suppression of allergen-specific effector T cell subsets. The third group of events are regulation of antibody isotypes demonstrating early increase in specific IgE, which later decreases and early and continuous increase in specific IgG4. The forth group of events take place after several months with decreases in tissue mast cells and eosinophils and release of their mediators. It is accompanied with decrease in type I skin test reactivity. Multiple cell types in the blood and affected organs show changes and contribute to allergen-specific immune tolerance development (Table 1). All of these events are discussed below with a special focus on Treg and Breg cells and their suppressive functions. Although many mechanisms have been elucidated, AIT represents one of the most front research areas for better understanding of antigen-specific immune responses and immune tolerance development in humans, there still remains a lot to be investigated.

**Rapid desensitization of mast cells and basophils by allergens**

Several mechanisms have been proposed to explain why mast cells and basophils become unresponsive to environmental proteins even in the presence of specific IgE. Notably, after the first injection of AIT, very early decreases in the susceptibility of mast cells and basophils to degranulation and in systemic anaphylaxis can be observed, even though all the treated individuals have high quantities of specific IgE. This effect occurs when three dimensional structure-intact allergens are used. Although the underlying molecular pathways remain to be elucidated, this effect seems similar to the one observed when these two immune cell types are rapidly desensitized in anaphylactic reactions to drugs. Anaphylaxis is associated with the release of inflammatory mediators from both mast cells and basophils, and successful hyposensitization alters the magnitude of mediator release. The release of
these inflammatory mediators in low quantities, below the required dose for systemic anaphylaxis, may affect the subsequent threshold of activation of mast cells and basophils. 20, 21 The investigation of histamine receptors (HR) expression on basophils of patients undergoing venom immunotherapy (VIT) demonstrated that selective suppression of basophils mediated by H2R might be highly relevant for the very early induction of allergen tolerance and the so-called desensitization effect of VIT. Rapid upregulation of H2R within the first 6 hours of the build-up phase of VIT was observed. H2R strongly suppressed FcεRI-induced activation and mediator release of basophils, including histamine and sulfidoleukotrienes, as well as cytokine production in vitro. 22

Table 1. The roles of different cells in the development of allergen tolerance

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>T cells</td>
<td>Decreased allergen-induced proliferation (PBMC)</td>
</tr>
<tr>
<td></td>
<td>Induction of allergen-specific Tr1 cells (PBMC and nose in allergic rhinitis)</td>
</tr>
<tr>
<td></td>
<td>Increased FOXP3 expression (PBMC, T cells)</td>
</tr>
<tr>
<td></td>
<td>Increased secretion of IL-10 and TGF-beta (PBMC and nose in allergic rhinitis)</td>
</tr>
<tr>
<td></td>
<td>Suppression of Th2 cells and cytokines (PBMC)</td>
</tr>
<tr>
<td>B cells</td>
<td>Induction of allergen-specific IL-10-secreting Br1 cells</td>
</tr>
<tr>
<td></td>
<td>Early increased late decreased specific IgE production (serum)</td>
</tr>
<tr>
<td></td>
<td>Increased specific IgG4 production (serum)</td>
</tr>
<tr>
<td></td>
<td>Increased specific IgA production (serum)</td>
</tr>
<tr>
<td></td>
<td>Suppressed IgE-facilitated antigen presentation (blood and cell lines)</td>
</tr>
<tr>
<td>Dendritic cells</td>
<td>Suppressed IgE-facilitated antigen presentation (blood)</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>Reduction of tissue numbers (allergic rhinitis)</td>
</tr>
<tr>
<td></td>
<td>Decrease in mediator release (nose and blood)</td>
</tr>
<tr>
<td>Mast cells</td>
<td>Reduction of tissue numbers (allergic rhinitis)</td>
</tr>
<tr>
<td></td>
<td>Decrease in mediator release (allergic rhinitis)</td>
</tr>
<tr>
<td></td>
<td>Decrease in proinflammatory cytokine production (allergic rhinitis)</td>
</tr>
<tr>
<td>Basophils</td>
<td>Decrease in mediator release (blood)</td>
</tr>
<tr>
<td></td>
<td>Decrease in proinflammatory cytokine production (blood)</td>
</tr>
<tr>
<td></td>
<td>Increased HR2 with suppressive effects on degranulation and cytokine production (blood)</td>
</tr>
</tbody>
</table>
T and B regulatory cells in allergen-specific immunotherapy

It is now generally appreciated that peripheral T cell tolerance is essential for a normal immune response and successful immunotherapy of allergic disorders (Figure 2). Although multiple factors contribute, the tolerant state of specific cells essentially results from increased IL-10 secretion. Suppressing capacity for allergen/antigen-stimulated T cells is particularly confined to IL-10, but not its other family members, such as IL-19, IL-20, IL-22, IL-24 and IL-26. IL-10 particularly originates from activated and antigen-specific Treg and Breg cell populations and increases during AIT and natural allergen exposure. High IL-10-producing Treg and Breg cell subsets are called Tregulator1 (Tr1) and Br1 cells, respectively. Allergen-specific CD4+ T cells that predominantly produce IFN-gamma, IL-4 and IL-10 and represent Th1, Th2 and Tr1-like cells, respectively. Healthy and allergic individuals exhibit all three subsets, but in different proportions. In healthy individuals, IL-10-secreting Tr1 or IL-10-Treg cells are the dominant subset against common environmental allergens, whereas in allergic individuals allergen-specific IL-4-secreting T cells (Th2-like) exist in high frequency. Therefore, a change in the dominant subset may lead to either the development of allergy or its reversal. Peripheral tolerance to allergens involves multiple suppressive factors such as IL-10, TGF-beta, cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed death-1 (PD-1).

Figure 1. Immunologic changes during the course of allergen-SIT. Although it shows differences
between protocols and routes of administration a similar profile is observed. Changes in ultra rush protocols of venom-AIT appear relatively early and show more intense effects compared to SLIT for pollen allergens. Starting with the first injection, decreases in mast cell and basophil activity, degranulation and tendency for systemic anaphylaxis degranulation takes place within the first hours. This is followed by generation of allergen-specific Treg and Breg cells and suppression of allergen-specific Th1 and Th2 cells. Specific IgE shows an early increase and decreases relatively late. These events are in parallel to increases of IgG4 that continuously increases as long as the treatment continues. After several months, the allergen-specific IgE/IgG4 ratio decreases. After a few months, decreases in tissue mast cells and eosinophils and release of their mediators and skin late phase response occurs. A significant decrease in type I skin test reactivity is also observed relatively late in the course.

Similar to T helper cells, B cells can be classified into subsets according to the cytokines that they produce. One functional B cell subset, regulatory B cells (Bregs), has recently been shown to contribute to the maintenance of the fine equilibrium required for tolerance. Breg cells control the excessive inflammatory responses through IL-10, which inhibits proinflammatory cytokines and supports regulatory T cell differentiation. As observed in Tr1 cells, recently highly purified IL-10-secreting Breg cells (Br1) were phenotypically and functionally characterized. B cells specific for the major bee venom allergen phospholipase A2 (PLA) were isolated from beekeepers, who displayed tolerance to bee venom antigens and allergic patients before and after AIT. Human IL-10+ Br1 cells expressed high surface CD25 and CD71 and low CD73 levels. Sorting of CD73-CD25+CD71+ B cells allowed enrichment of human Br1 cells, which produced high levels of IL-10 and potently suppressed antigen-specific CD4+ T-cell proliferation. Apparently, T and B cell subsets, which are becoming predominant during AIT and natural antigen exposure, represent the Tr1 or IL-10-Treg cells and Br1 or IL-10-Breg cells in humans. Although there is limited data on recently demonstrated Br1 cells, there is substantial evidence on the role of Tr1 cells and allergen tolerance.

The investigation of human high dose allergen exposure models has also provided important insights into the nature of Treg responses in tolerance. In non-allergic bee keepers and cat owners, Treg cells specific for the major allergens present in bee venom and cat saliva represent the major T cell subset in healthy individuals. These Treg cells utilize numerous suppressive mechanisms, including the involvement of IL-10, TGF-beta, cytotoxic T lymphocyte antigen 4 (CTLA4) and programmed death 1 (PD1).
Figure 2. Role of Treg and Breg cells in the suppression of allergic inflammation. The balance between Th2 cells and Treg cells is decisive for the development or suppression of allergic inflammation. Treg cells and their cytokines suppress Th2 type immune responses and contribute to the control of allergic diseases in several major ways. Red arrows indicate the regulatory and suppressive effects of Treg cells, which exert their regulatory functions directly or indirectly on B cells by inducing IgG4 and IgA and suppressing IgE; on vascular endothelium by suppressing Th2 cell homing to tissues; on mast cells, basophils and eosinophils via direct and indirect suppressive effects; and on directly and indirectly suppression of epithelial cell activation and proinflammatory properties. In addition, B reg cells also suppress effector T cells and contribute to IgG4 synthesis.

Allergen immunotherapy and Treg and Breg cells influence allergen-specific antibody responses

Natural exposure to a relevant allergen is often associated with an increase in the IgE synthesis. Similarly, AIT often induces a transient increase in serum specific IgE followed by gradual decrease over months or years of continued treatment. \(^{34-36}\) In pollen-sensitive patients, desensitization prevents elevation of the serum specific IgE titer during the pollen season. \(^{37, 38}\) However, the changes in IgE levels cannot account for the diminished responsiveness to specific allergen due to AIT, since the decrease in serum IgE is late, relatively small, and poorly correlated with clinical improvement after AIT.

Research focused on the subclasses of IgG antibodies, especially IgG4, suggests that the allergen can be captured, before reaching the effector cell-bound IgE, and thus preventing activation of mast cells and basophils. Data from several studies indicated that increases in specific IgG4 levels accompanied clinical improvement. \(^{39, 40}\) With venom allergy, the rise of anti-venom IgG correlates, at
least at the onset of desensitization, with protection achieved by the treatment.\textsuperscript{41, 42} Blocking antibodies seem to inhibit allergen-induced release of inflammatory mediators from basophils and mast cells, IgE-facilitated allergen presentation to T cells, and allergen-induced boost of memory IgE production during high allergen exposure in pollen season. Grass pollen immunotherapy induces allergen-specific, IL-10-associated “protective” IgG4 responses.\textsuperscript{43} These studies demonstrated an association between IgG4-dependent blocking of IgE binding to B cells. However, IgG4 antibodies can be viewed as having the ability to modulate the immune response to allergen and thus the potential to influence the clinical response to allergen. In a study using well defined recombinant allergen mixtures, all treated subjects developed strong allergen specific IgG1 and IgG4 antibody responses.\textsuperscript{44} Some patients were not showing IgE and IgG4 against Phl p 5 at the start of AIT, but developed strong IgG4 antibody responses to that particular allergen without induction of any IgE, supporting the immune tolerance-inducing role of AIT.

IL-10 that is induced in Tr1 and Br1 cells and increasingly secreted during AIT appears to counter-regulate antigen-specific IgE and IgG4 antibody synthesis.\textsuperscript{24-26, 28} Recently, it was demonstrated in bee venom model that IgG4 production was selectively confined to human Br1 cells. B cells specific for the major bee venom allergen phospholipase A2 isolated from nonallergic beekeepers show increased expression of IL-10 and IgG4. Furthermore, the frequency of IL-10+ PLA-specific B cells increased in allergic patients receiving allergen-specific immunotherapy. Apparently, IL-10 potently suppresses both total and allergen-specific IgE and simultaneously increases IgG4 production.\textsuperscript{26} Thus, IL-10 not only generates tolerance in T cells; it also regulates specific isotype formation and skews the specific response from an IgE- to an IgG4-dominated phenotype.

**Suppression of late phase responses of effector cells during AIT**

Long-term AIT is associated with significant reduction of the immediate response to allergen provocation and the late phase reaction (LPR) in the nasal and bronchial mucosa or the skin. The mechanism of LPR is different from mast cell-mediated immediate reaction and involves the recruitment, activation and persistence of eosinophils and activation of T cells at the sites of allergen exposure. The immunopathologic changes in the mucosal tissues of subjects chronically exposed to inhalant allergens resemble those seen during the LPR. Since LPR is associated with increased bronchial and nasal hyperresponsiveness and mimics the pathologic condition of chronic allergic inflammation, it has been postulated that the effect of AIT on the LPR is relevant to its clinical efficacy.\textsuperscript{45}

Successful AIT results in an increase of allergen concentration necessary to induce immediate or LPR in the target tissue and in decreased responses to nonspecific stimulation. Bronchial, nasal, and conjunctival hyperreactivity to nonspecific stimuli, which seems to reflect underlying mucosal
inflammation, decrease after AIT and correlate with clinical improvement.\cite{46, 47} During birch pollen AIT, reduced plasma levels of eosinophil cationic protein (ECP), a marker of eosinophil activation, and chemotactic factors for eosinophils and neutrophils correlate with decreased bronchial hyperreactivity and clinical improvement.\cite{46} AIT also inhibits the seasonal increase in eosinophil priming.\cite{48} After grass pollen AIT, decreased eosinophil and mast cell infiltration in nasal and bronchial mucosa correlate with an anti-inflammatory effect. In addition, plasma concentrations and in vitro production of endothelin-1 (a bronchoconstrictor and proinflammatory peptide) are significantly decreased in asthmatic children after 2 years of immunotherapy with mite extract.\cite{49, 50} In addition, mast cell and basophil suppression require T cell cytokines for priming, survival and activity, which are not efficiently provided by suppressed Th2 cells and activated Treg cells.\cite{51, 52} Peripheral T cell tolerance to allergens, which is characterized by functional inactivation of the cell to antigen encounter, can overcome both acute and chronic events in allergic reactions. AIT efficiently modulates the thresholds for mast cell and basophil activation and decreases immunoglobulin E-mediated histamine release.\cite{53, 54} In addition, IL-10 reduces proinflammatory cytokine release from mast cells.\cite{55} IL-10 down regulates eosinophil function and activity and suppresses IL-5 production by human resting Th0 and Th2 cells.\cite{56} Moreover, IL-10 inhibits endogenous GM-CSF production and CD40 expression by activated eosinophils and enhances eosinophil cell death.\cite{57}

**T regulatory and B regulatory cells and other cells of immune regulation**

More than 30 years ago, it was postulated that CD8+ suppressor cells limit ongoing immune responses and may prevent autoimmune disease.\cite{58} The recent phenotypic and functional characterization of suppressive Tregulatory (Treg) cells has led to a renaissance of interest in their therapeutic application in a number of immune-mediated diseases. Two broad subsets of CD3+CD4+ Treg cells have been described: constitutive or naturally occurring Treg cells and adaptive or inducible Treg cells. It has been recently proposed that Treg cells generated in the thymus appear sufficient for control of systemic and tissue-specific autoimmunity, extrathymic differentiation of inducible Treg cells affects commensal microbiota composition and serves a distinct, essential function in restraint of allergic-type inflammation at mucosal interfaces.\cite{59} In humans, there is strong evidence that these subsets are substantially overlapping. Other Treg cell populations, including CD8+ Treg cells, double negative (CD4–CD8–)Treg cells mediate tolerance in several experimental autoimmune diseases.\cite{60} The B regulatory (Breg) cell subset, particularly IL-10-secreting B cells have strong regulatory/suppressor properties.\cite{28, 61} In addition, natural killer (NK) cells, epithelial cells, macrophages and glial cells express suppressor cytokines such as IL-10 and TGF-beta.\cite{62} These cell types may efficiently contribute to generating and maintaining a regulatory/suppressor type of immune response.
Human inducible IL-10-secreting B regulatory 1 (Breg1) cells can produce high levels of IL-10 and potently suppress antigen-specific CD4+ T-cell proliferation. It has been demonstrated that IgG4 has been selectively confined to human Breg1 cells. In nonallergic beekeepers increased expression of IL-10 and IgG4 has been shown in B cells specific for the major bee venom allergen PLA. Also an increase in the frequency of IL-10+ PLA-specific B cells has been reported in bee venom allergic patients receiving AIT. These data point out two essential features of allergen tolerance: the suppressive B cells and IgG4-expressing B cells that are confined to IL-10+ Breg1 cells. B cells also require specific toll like receptor (TLR) stimulation, T-cell and plasmacytoid dendritic cell help for distinct activation of immunoglobulin production profiles. In response to TLR3, TLR7 and TLR9 triggering, human B cells proliferate and turn into antibody-secreting cells. This response cannot be influenced by stimulation with TLR2, TLR4, TLR5 and TLR8 ligands.

Although the ultimate goal of AIT is to modify the immune response towards allergens so that immune tolerance lasts after discontinuation of therapy, it is not clear whether this actually occurs with all therapies, because natural exposure to environmental allergens can vary. For example, many patients who receive grass pollen AIT continue to have environmental exposure to the allergen even after therapy is discontinued. This sustained exposure may likely contribute to maintaining tolerance.

**Histamine receptor 2 as a major player in peripheral tolerance**

As a small molecular weight monoamine that binds to 4 different G-protein-coupled receptors, histamine has recently been demonstrated to regulate several essential events in the immune response. Histamine receptor (HR) 2 is coupled to adenylate cyclase and studies in different species and several human cells demonstrated that inhibition of characteristic features of the cells by primarily cAMP formation dominates in HR2-dependent effects of histamine. Histamine released from mast cells and basophils by high allergen doses during SIT interferes with the peripheral tolerance induced during SIT in several pathways. Histamine enhances Th1-type responses by triggering the histamine receptor HR1 whereas both Th1 and Th2-type responses are negatively regulated by HR2. Human CD4+Th1 cells predominantly express HR1 and CD4+Th2 cells HR2, which results in their differential regulation by histamine. Histamine induces the production of IL-10 by DC. In addition, histamine induces IL-10 production by Th2 cells, and enhances the suppressive activity of TGF-b on T cells. All three of these effects are mediated via HR2, which is relatively highly expressed on Th2 cells and suppresses IL-4 and IL-13 production and T cell proliferation. Apparently, these recent findings suggest that HR2 may represent an essential receptor that participates in peripheral tolerance or active suppression of inflammatory/immune responses. Histamine also regulates antibody isotypes including IgE. High
amount of allergen-specific IgE is induced in HR1-deleted mice. In contrast, deletion of HR2 leads to a significantly less amounts of allergen-specific IgE production, probably due to direct effect on B cells and indirect effect via T cells.

The long-term protection from honeybee stings by terfenadine premedication during rush immunotherapy with honeybee venom in a double-blind, placebocontrolled trial was analysed. After an average of 3 years, 41 patients were re-exposed to honeybee stings. Surprisingly, none of 20 patients who had been given HR1-antihistamine premedication, but 6 of 21 given placebo, had a systemic allergic reaction to the re-exposure by either a field sting or a sting challenge. This highly significant difference suggests that antihistamine premedication during the initial dose-increase phase may have enhanced the long-term efficacy of immunotherapy. Expression of HR1 on T lymphocytes is strongly reduced during ultrarush immunotherapy, which may lead to a dominant expression and function of tolerance-inducing HR2. Administration of antihistamines decreases the HR1/H2R expression ratio, which may enhance the suppressive effect of histamine on T cells. Further studies are required to substantiate these promising findings supporting the use of antihistamine pre-treatment in all venom SIT patients.

Immune tolerance induced in sublingual immunotherapy

SLIT has a well-established safety profile, with more than several hundred millions of doses administered to humans and considered an alternative to subcutaneous AIT. Immunological mechanisms SLIT are less well established than those for SCIT. Meta analyses concluded IgG4 levels increase, but IgE levels remain stable in adults. In addition, allergen-specific IgA is induced. There is conflicting data concerning lymphoproliferative responses. The effects of SLIT on T cell reactivity and cytokine secretion vary between studies. T-cell proliferation was reduced in allergic patients successfully treated with house dust mite SLIT. In a different study of SLIT, IL-10 mRNA increased, and TGF-beta mRNA positively correlated with IL-10 and negatively correlated with IL-5. After 6 months of SLIT, ECP and serum IL-13 are decreased. Nasal tryptase secretion after nasal allergen challenge test decreases. During 2 years of SLIT in children with grass pollen allergens, no significant effects on in vitro T cell immune responses or immunoglobulins were observed, although the SLIT reduced the need for rescue medication.
Table 2. Differences and similarities in mechanisms of SCIT and SLIT

<table>
<thead>
<tr>
<th>Mechanisms</th>
<th>SLIT</th>
<th>SCIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very early desensitization</td>
<td>Not known</td>
<td>+</td>
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<tr>
<td>T cell tolerance</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>T regulatory cell generation</td>
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<td>+</td>
</tr>
<tr>
<td>Role of TGF-β</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Decreased tissue mast cell functions</td>
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<td>+</td>
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<td>Decreased tissue eosinophils and mediators</td>
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<tr>
<td>Decreased IgE</td>
<td>+/-</td>
<td>++</td>
</tr>
<tr>
<td>Increased IgG4</td>
<td>+/-</td>
<td>++++</td>
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</table>

Conclusion

Immune tolerance to allergens is essential to develop a healthy immune response to allergens in highly exposed individuals. Allergen-specific tolerance involves a deviation in T cell response to Tr1 cells, B cell response to IL-10-secreting Br1 cells, increased IgG4 isotype specific antibody response, decreased activation of effector cells, such as basophils, mast cells and eosinophils. Multiple mechanisms and receptors play a role in this such as IL-10, TGF-beta, CTLA-4, PD-1 and HR2. Despite the benefits of AIT for most treated individuals, not everyone improves, life threatening side effects can occur, treatment effect may not be permanent and the duration of the treatment is long. Therefore, the development of advanced vaccines, novel adjuvants as well as reliable biomarkers to select patients with a good clinical response are strongly expected. There is a strong rationale to develop novel biomarkers related to genetical, epigenetical state of the patient, allergen/antigen tolerance capacity as well as tissue responses in AIT. Biomarkers should be easily measured in body fluids that are readily accessible (e.g. blood, saliva, nasal secretions, skin scrapings); they should be cost effective; and they should fulfill the unmet needs for, prediction and better patient care. Different biomarkers for AIT and different stages of allergic diseases and endotypes are expected to be developed in the near future.

AIT-based curative approaches may also find application for the prevention of allergic disease. The major challenges for the prevention include the requirement for very early intervention, safety problems for a pediatric usage, and missing early biomarkers of who will develop allergy. The future should be exciting, because advances in immunology and bioengineering are being applied to the development of multiple immune modifier biologicals. In particular, the combination of immune response modifiers with AIT might provide a way for efficient immunomodulation of allergic diseases.
References


