# Mechanisms of Aeroallergen Immunotherapy

## Subcutaneous Immunotherapy and Sublingual Immunotherapy

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**KEYWORDS**

• Allergy • Allergens • Immunotherapy • T regulatory cells • Tolerance

**KEY POINTS**

- SCIT and SLIT use similar immune mechanisms to induce tolerance development to allergens.
- Role of oral mucosa and tonsil immunity is noteworthy during SLIT, where allergens before reaching mast cells are mostly captured by tolerogenic dendritic cells.
- The very early desensitization effect and marked allergen-specific IgG4 responses are the outstanding features of SCIT.

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## INTRODUCTION

As the frequency of allergic disorders has increased in recent decades, concerns have been focused on how to develop preventive approaches and implement novel treatment strategies to control allergic disorders. Conventionally used pharmacotherapy regimens in various combinations with different routes of corticosteroids, antihistamines, and antileukotrienes and specific monoclonal antibodies can successfully control the symptoms in most cases during regular usage. However, on cessation of pharmacotherapy, relapse of symptoms and signs of allergic disorders emerge. Allergen immunotherapy (AIT) remains as the modality of choice and the most effective treatment of allergic disorders by targeting the underlying mechanisms and possibly altering the disease course by inducing a long-lasting tolerance to allergens.[1–3]

Allergen-specific subcutaneous immunotherapy (SCIT) has served as an active tool in the management of allergic rhinitis and allergic asthma and also for venom allergy. Sublingual immunotherapy (SLIT) has provided an alternative to SCIT in patients with allergic rhinitis and asthma in whom fear of adverse reactions and discomfort from injections limit the treatment chance. Both of these AIT routes provide a causal therapeutic approach in the management of allergic disorders, but more studies are needed to clarify certain clinical aspects.[4,5] Generation of allergen-specific peripheral tolerance is the principal event during AIT. T and B cells, mainly naturally occurring $Foxp3^{+}CD4^{+}CD25^{+}$ regulatory T cells (Treg) and inducible type 1 Treg cells, play key roles in tolerance development. Suppression of allergen-specific IgE production and induction of allergen-specific IgG4 antibody generation, in addition to other multiple suppressor roles on dendritic cells (DCs), T cell subsets, mast cells, basophils, and eosinophils, lead to improvement in tissue inflammation and attenuate early and late-phase inflammatory responses.[2,6,7] Hence, it is essential to describe the underlying mechanism of allergic disorders to generate more rationale and effective AIT regimens.

## ALLERGIC IMMUNE RESPONSE

Aeroallergens (mainly house dust mites, pollens, molds, animal dander), certain foods, and insect venoms constitute the most common allergens responsible for clinical symptoms of allergic disorders. Individual allergic immune response depends on various factors including the presence of atopy-genetic tendency to develop allergy. In addition to dose, type, and route of allergen exposure and presentation to the immune system, the status of the surrounding microenvironment with the dominant type of effector cells and their products, microbiota, and other small molecules with costimulatory and inhibitory activity may play a role.[6,8] Naive $CD4^{+}$ T cells can differentiate into T helper cell (Th) 1, Th2, Th9, Th17, or Th22 type effector and memory cells, depending on microenvironmental conditions.[6,9,10] Peripheral Th2 response is dominant and interleukin (IL)-4, IL-5, and IL-13 are the leading cytokines enrolled in Th2-type immune response of allergy.[11] It has been proposed that allergic immune response is an IgE antibody-mediated disorder caused by a dysregulation in T-cell immunity.[12] The concept of allergen-specific tolerance induction and the role of immune regulatory mechanisms over Th1 and Th2 imbalance have greatly increased understanding of the mechanisms of allergic disorders.[6]

## ANTIGEN PRESENTATION, CELLULAR INTERACTIONS, AND ANTIBODY RESPONSES IN ALLERGIC IMMUNE RESPONSE

Skin and mucosal surfaces (airway mucosa and gastrointestinal mucosa) are a huge area of contact with external antigens or allergens.[13–15] Presentation of the antigen

or allergen is one of the pivotal steps, where a decision is made for development of immune response toward allergy. The highly specialized antigen-presenting cells, mainly DCs, reside as sentinels in an immature form at these entry surfaces. On activation, DCs migrate to local lymph nodes, where they lose their phagocytic properties with an improved antigen-presenting capacity and interact with T and B cells.[7,16] DCs can recognize the antigenic epitopes, process, and present them by coupling to major histocompatibility complex-II molecules to Th cells.

In allergic immune response, activated naive Th cells markedly differentiate into Th2-type cells in the presence of IL-4. They produce IL-4 and IL-13, which induces IgE class switch of B cells and development to allergen-specific IgE-producing plasma cells. IgE binds to its high affinity Fcϵ receptors on mast cells and basophils. On re-exposure with the relevant allergen, sensitized mast cells and basophils release their preformed mediators located within the intracellular granules and also synthesize new biogenic mediators, such as histamine, proteases, and newly generated lipid-derived mediators, such as leukotrienes and cytokines, causing the symptoms and signs of allergic acute-phase type-1 hypersensitivity reactions (**Fig. 1**).[17] IL-5 is another key cytokine in allergic inflammatory immune response, which exerts its function on eosinophils by recruiting, activating, and prolonging their survival and also has stimulatory effect on B-cell growth.[18]

Cytokines released from these effector cells increase vascular permeability, angiogenesis, and fibrosis, and prosecute infiltration by eosinophils, basophils, neutrophils, macrophages, and T cells, which augment the late-phase response that is thought to

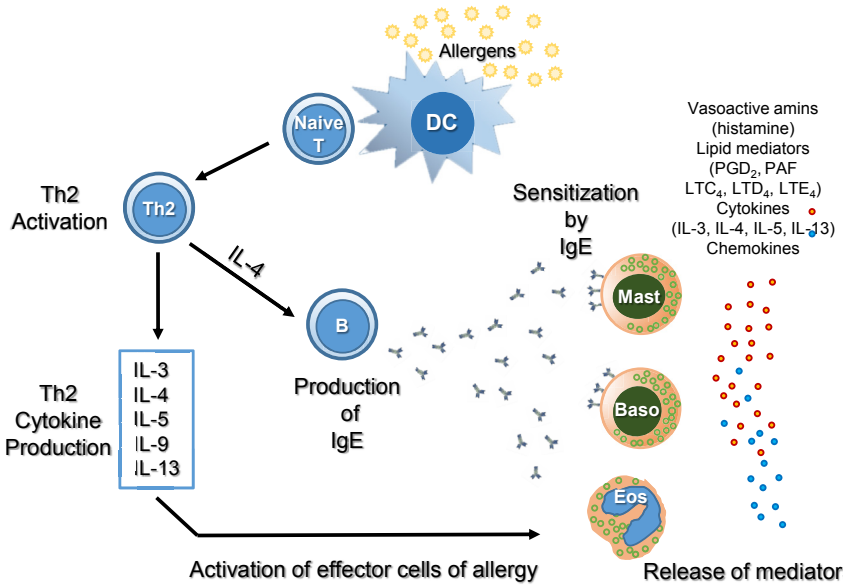


**Fig. 1.** Initiation of allergic response. Th2 cells are induced when allergen peptides are presented to naive $CD4^+$ T cells by DC, together with presence of IL-4. Th2 cells produce cytokines IL-3, IL-4, IL-5, IL-9, and IL-13, which are named as Th2-type cytokines. B cells class-switch to produce IgE, which binds to specific Fcϵ receptors on mast cells (Mast) and basophils (Baso) in sensitization phase. On encountering the same allergen for a second time, degranulation of mast cells and basophils leads to immediate hypersensitivity. Th2-type cytokines are important survival signals for mast cells, basophils, and eosinophils (Eos).

be responsible for the persistent, chronic signs and symptoms of allergy.[19] Moreover, IL-13 has essential roles on epithelial cell maturation and mucus production, airway smooth muscle contractility, and extracellular matrix protein production.[20] Th2 cell differentiation has been shown to be reprogrammed by transforming growth factor (TGF)-β with coexistence of IL-4, which leads to development of Th9 cells with capacity to produce IL-9 and IL-10.[21,22] IL-9 plays an essential role in the growth and survival of mast cells.[23,24]

Furthermore, IL-25, IL-31, and IL-33 are other cytokines mainly secreted by epithelial cells and DCs, which also contribute to Th2 responses.[25–27] However, Th22 cells have been shown to produce IL-22 together with low levels of IL-4, and their contribution to atopic diseases especially in atopic dermatitis has been revealed.[28] Additionally, Th17 cells express IL-17A, IL-17F, IL-6, IL-8, tumor necrosis factor-α, IL-22, and IL-26 and are shown to contribute to some autoimmune pathologies, whereas neutralization of IL-17- and Th17-related functions has been related to limitation of neutrophil infiltration in experimental models of asthma.[29]

Innate lymphoid cells (ILCs) are newly discovered subsets of the immune network, which may have possible contributions to inflammatory diseases. Type 2 ILCs have been found to have possible roles in asthma and upper respiratory inflammation and AIT to grass pollen has been shown to inhibit seasonal increases of peripheral population of type 2 ILCs.[6,30]

## IMMUNE TOLERANCE TO ALLERGENS IN HEALTHY IMMUNE RESPONSE

The immune system has the capacity to tolerate self-antigens and non-self-antigens, such as allergens caused by central and peripheral tolerance, as essential mechanisms of immune homeostasis. Excessive immune tolerance may lead to loss of defense against microorganisms and cancer. In contrast, exaggerated immune response to external antigens or allergens may lead to hypersensitivity reactions that may present as allergic rhinitis, asthma, atopic dermatitis, food allergy, and anaphylaxis. During developmental stages of T cells in the thymus and B cells in bone marrow, cells with tendency to autoreactivity are deleted via apoptosis before complete differentiation. Whereas B cells become unresponsive through receptor editing, some T cells can escape from thymic deletion and reach periphery.[31,32] Peripheral tolerance mechanisms regulate this condition through T-cell anergy, apoptosis, and action of Treg cells.[33] Because allergen-specific Th2 and Treg cell repertoire specific to same allergen are reported to be present in those with allergy and healthy individuals, their ratio is claimed to determine the outcome (**Fig. 2**).[19]

It has been shown that certain innate immune response signals including proinflammatory cytokines, such as IL-1β and IL-6, and danger signals, such as Toll-like receptor (TLR) 4 and TLR8 ligands, have the capacity to break allergen-specific T-cell tolerance in healthy subjects.[34] Several viral upper respiratory tract infections as triggers of innate inflammation are known to exacerbate asthma attacks. Human rhinovirus infection has been shown to induce proinflammatory cytokine profiles with elevated IL-1β, IL-2, IL-7, and IL-8 levels, whereas bocavirus infection cannot do so, or induce a Th1 or a Th2 cytokine profile. A simultaneous infection with both viruses has induced a non-Th2 but a modified cytokine response. Immunologic responses in acute wheezing are shown to depend on host (atopy-related inflammation) and virus-specific factors, and interaction of two different virus strains may modulate immune responses.[35] In addition, the development of a healthy immune response during high-dose allergen exposure in beekeepers and cat owners has been intensively

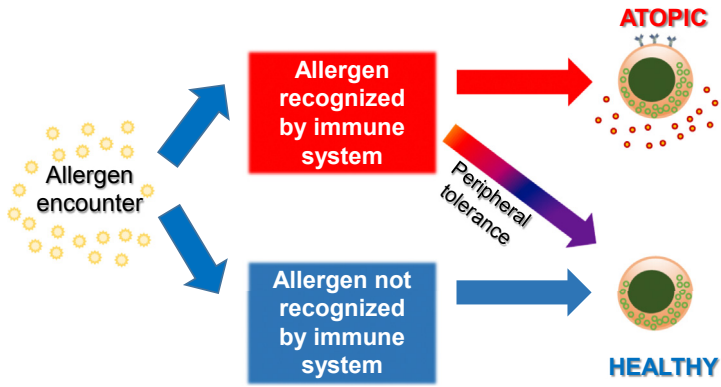


**Fig. 2.** Allergy versus tolerance. Allergic and nonallergic phenotypes are defined by genetic factors, which define the T-cell receptor specificity of an individual, and also by establishment and maintenance of specific tolerance to allergens. T cells with capacity to recognize allergens are present in healthy individuals and in individuals with allergy.

studied to understand mechanisms of allergen tolerance in humans. IL-10-secreting Treg cells and IgG4 production dominate the mechanisms in both models.[36–38]

## REGULATORY CELLS OF THE IMMUNE SYSTEM

In the course of normal immune responses, regulation is a sine qua non. This important role is maintained by several cells with suppressor capacity. Treg cells orchestrate cells and several cellular interactions. Naturally occurring thymus-derived Forkhead box P3 (Foxp3)$^+$ CD4$^+$CD25$^+$ Treg cells and inducible type 1 Treg (Tr1) cells are the major subsets of Treg cells that have regulatory roles on other effector cells of the immune system. Foxp3 is the lineage-specific transcription factor for Treg cells, which regulates Treg cell development.[39] Gut-associated lymphoid tissue serves as a primary area of peripheral conversion of CD4$^+$ cells to Treg cells, where numerous dietary antigens are tolerated as a requisite for healthy immune response.[40] Although FoxP3 is the transcription factor for Treg cells, GATA3 drives Th2 cell differentiation. Both of these transcription factors have been upregulated simultaneously in CD4$^+$ T cells of sensitized subjects, which may suggest that Treg cells and effector T cells have the capacity to be converted to each other.[41]

It has been reported that CD4$^+$CD25$^+$ Treg cells from nonsensitized healthy donors have the capacity to suppress allergen-specific proliferative responses compared with cells obtained from sensitized individuals.[42] In addition to naturally occurring thymus-derived Treg cells in the presence of TGF-β, CD4$^+$CD25$^-$FOXP3$^-$ cells can be induced into Treg cells in the periphery.[43] Tr1 cells regulate immune homeostasis by coordinating peripheral T-cell tolerance. Treg cells have distinct cytokine profiles other than Th1 and Th2 cells, are characterized by IL-10 and TGF-β secretion capacity, and express suppressor molecules, such as cytotoxic T-lymphocyte-associated protein 4 and programmed cell death protein 1. IL-10 is the leading cytokine, which in Treg cell–B cell interaction suppresses specific IgE production. In addition, IL-10 induces specific IgG4 production. IgG4 and probably IgG1 compete with IgE on the surface of mast cells and basophils for allergen binding.[44] Novel techniques are expected to enlighten mechanisms at the single cell level. It has been recently demonstrated that clonal distribution of the peanut Ag-specific T cells changes with peanut oral

immunotherapy, supporting the T-cell "replacement" hypothesis as a mechanism of food oral immunotherapy.[45]

Other immune cells have been shown to suppress allergen-specific responses. Inducible IL-10-secreting B regulatory cells have recently been demonstrated, which contribute to allergen tolerance through suppression of effector T cells and induction of IgG4 antibodies.[2,46,47] Although not studied as aeroallergen immunotherapy so far, it was demonstrated that early peanut oral immunotherapy induced an oligoclonal and somatically hypermutated allergen-specific B-cell receptor repertoire.[48] Natural killer cells are important key players of immunity to viral infections and tumors, and they also contribute to immune regulation by their cytokine secretions. A subset of natural killer cells with capacity to produce IL-10 and suppress allergen-specific T-cell responses has also been described.[49,50] Strategies to modulate natural killer cell functions may contribute to treatment of allergy.[51]

## MECHANISMS OF ALLERGEN-SPECIFIC IMMUNOTHERAPY

Allergen-specific immunotherapy is an efficient disease-modifying treatment option in the management of allergic disorders with apparent immune regulatory functions. The major aim of a successful AIT is to induce a long-lasting clinically tolerant state to allergens by using peripheral immune tolerance mechanisms. Disease modification in AIT leads to decreased severity of disease together with decreased need for medications, and prevention of further IgE sensitizations to other allergens, all of which may end up with a long-term curative effect.[6,52]

Mechanisms of action of AIT are claimed to be the induction of Treg cells, modulation of T- and B-cell responses, skewing of specific-antibody isotype to IgG4 predominance from IgE, early desensitization of mast cells and basophils, and decreases in numbers and activity of eosinophils and mast cells in the tissues.[53–57] After AIT, allergen-specific Treg cells are generated, which produce IL-10 and TGF-β cytokines that suppress proliferative and cytokine responses against major allergens and their recognition sites.[58,59] Suppressive role of IL-10 on T cells is marked by CD2, CD28, and inducible costimulator costimulatory signal blockage via use of Src-homology-2 domain-containing protein tyrosine phosphatase 1 that dephosphorylates CD2 and inducible costimulator in the rapid signal transduction cascade.[60] Local induction of Treg cells in the nasal mucosa in response to AIT has been observed in patients with allergic rhinitis.[61] Recent studies suggested a role for Treg cells with novel surface molecules, which can be used as a biomarker.[62] Deletion of allergen-specific Th2 cells as a consequence of repeated high-dose allergen stimulation may possibly be an independent mechanism to restore allergen-specific tolerance during immunotherapy.[63] Induction of allergen-specific IgG4 antibodies and reduction of mast cell and eosinophil numbers with increased thresholds for mediator release are also marked after successful AIT.[64,65] Peripheral tolerance induction as a consequence of AIT influences antibody isotypes. Serum levels of IgE decrease gradually whereas allergen-specific IgG4, namely blocking antibodies, increase during AIT, which is the result of class-switching of B cells from IgE to IgG4. This switching effect is the result of IL-10, which promotes a noninflammatory phenotype. IgG4 competes with Fcϵ receptor-bound IgE for binding allergens, which limits activation and degranulation of mast cells and basophils (**Fig. 3**). IgG4 has important roles in limiting the activation of $CD4^+$ T cells, by inhibition of CD23-mediated IgE-facilitated antigen presentation.[44,57,66,67] Presence of IgG4-isotype antibodies has importance in defining the therapy-responsive phenotype in sensitized individuals, whether this individual will show clinical reactivity. IgG4 has been demonstrated to inhibit peanut-induced

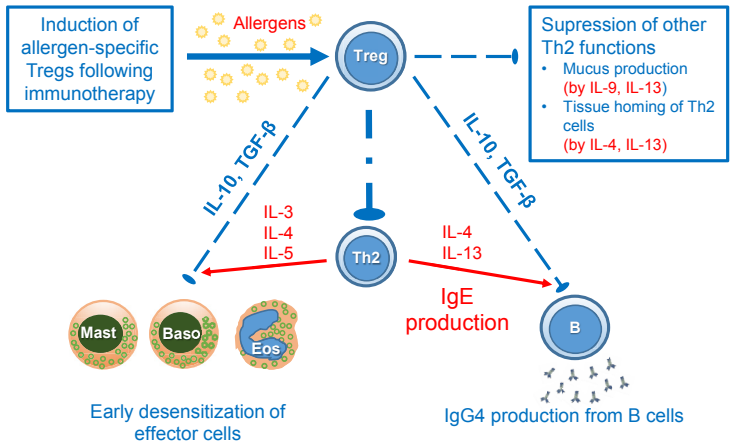


**Fig. 3.** Development of allergen tolerance. Allergen-specific immunotherapy and natural encounter with high-dose allergens induce Treg cells. As a consequence, peripheral tolerance is induced, which in turn regulates the effector cells of allergy in various ways. Treg cells suppress Th2 cells and their cytokine production (IL-3, IL-4, IL-5, IL-9, and IL-13), which are indispensable for the differentiation, survival, and activity of mast cells, basophils, eosinophils, and mucus-producing cells and for tissue homing of Th2 cells. IL-10 and TGF-β suppress IgE production, while inducing IgG4, a noninflammatory immunoglobulin isotype.

basophil and mast cell activation in peanut-tolerant children sensitized to peanut major allergens.[44] These findings in human cell cultures and tissues have been recently supported in a study in mouse model of AIT. It has been demonstrated that peripherally induced Ag-specific Foxp3$^+$ Treg cells and thymic Foxp3$^+$ Treg cells play essential roles in mouse model of AIT. Thymic Treg cells by promoting IL-10 production in Foxp3$^-$ T cells also crucially contribute to the effectiveness of allergen-specific immunotherapy.[68]

## INNATE IMMUNE RESPONSES IN SUBLINGUAL IMMUNOTHERAPY AND SUBCUTANEOUS IMMUNOTHERAPY

SCIT and SLIT are the two globally accepted routes of AIT with worldwide clinical usage.[5,69] SLIT is also used for food allergy with promising results,[70] but in a recent head-to-head study oral immunotherapy was more efficient compared with SLIT.[71] Many other immunotherapies have been suggested or are under development with efficient results[72,73]; however, their mechanisms of action were demonstrated in single studies so confirmation is needed in further studies. Although routes and doses of allergen administration in SLIT and SCIT regimens differ, mechanisms of action of both routes show similarities on an immunologic basis in many aspects.[74] The oral mucosal area is an important entry site for commensal microbes and numerous daily dietary antigens, where peripheral tolerance is induced in a quick manner to maintain immune homeostasis. The sublingual area stands as a quick tolerance induction area by inducing Th1/Treg cells in the absence of danger signals.[75] The oral cavity hosts several subsets of tolerogenic DCs, which induce Treg cell responses. Subsets of DCs include CD11b$^+$CD11c$^-$ and CD11b$^+$CD11c$^+$ myeloid DCs at the mucosal/submucosal interface, plasmacytoid DCs found in submucosal tissues, and a minor subset of CD207$^+$ Langerhans cells located in the mucosa itself. Both myeloid and plasmacytoid oral DCs have been shown to capture and process the antigen

efficiently and can elicit interferon-$\gamma$ and/or IL-10 production in naive $CD4^+$ T cells.[76] Plasmacytoid DCs have capacity to secrete interferon-$\alpha$ in response to TLR7 and TLR9 stimulation, and may have roles in tolerance induction following AIT.[77] IgE receptor bearing antigen-specific DCs take up allergens that activate IgE and IgG receptors simultaneously. Both of these stimulatory and inhibitory signals in costimulation of pattern recognition molecules TLR4 and CD14 induce tolerogenic mechanisms. Activated DCs migrate to local lymphoid tissue where they induce Th1 and Treg cells.[78] Lower numbers of mast cells and eosinophils in the upper layers of the oral cavity arise as proposed mechanisms about the safety concern of sublingual allergen administration.[79] During SLIT allergens are mostly captured by tolerogenic DCs, before reaching mast cells, which gains advantage over SCIT with virtually no risk of severe systemic reactions.[78,80]

Detailed mapping of the oral cavity has gained interest. Recently, in comparison of sublingual and vestibular regions, higher numbers of DCs have been observed in the vestibular region, which may result with faster induction of IgE-blocking factors. Taken together, these differences between the regions led to discovery of a novel route: oral vestibule immunotherapy. However, study investigating the differences of conventional SLIT and oral vestibule immunotherapy has revealed similar results of IgE-blocking factor and no significant differences between adverse effects of the two different routes. Further studies are needed before application of the vestibular route in clinical settings.[81]

As an alternative mechanism for allergen-presentation and induction of local Treg cells tonsils are strategically located in the gateway of the alimentary and respiratory tracts representing the first contact point of food and aeroallergens with the immune system. Lingual tonsil is anatomically big and remains intact lifelong. Only palatine tonsils and sometimes adenoids are removed by tonsillectomy. High numbers of allergen-specific $CD4^+Foxp3^+$ Treg cells are identified in human tonsils.[82] A positive correlation between the percentages of $Foxp3^+$ Treg cells and pDCs is observed in tonsils from individuals with no atopy. Tonsiller plasmocytoid DC can induce Treg cells.

ILCs play an essential role in many inflammatory diseases including allergic diseases and asthma.[83–85] Recent data suggest roles for them for persistence and chronicity of these diseases.[86,87] Lung type 2 ILCs play a critical role in priming the adaptive type 2 immune response to inhaled allergens, including serum IgE levels, recruitment of eosinophils, and Th2 cytokine production. They respond to IL-33 from epithelial cells and initiate inflammation.[88] The effect of grass pollen SCIT on type 2 ILCs in patients with seasonal allergic rhinitis has been recently demonstrated, and their seasonal increase was to be inhibited by subcutaneous grass pollen immunotherapy.[30]

## INFLUENCE OF SUBLINGUAL IMMUNOTHERAPY AND SUBCUTANEOUS IMMUNOTHERAPY ON T-CELL RESPONSES

In SCIT, allergen-specific T-cell proliferation has been reduced because of peripheral tolerance mechanisms. Treg cells are induced in SCIT and their immunoregulatory activity has been claimed to be the main mechanism for clinical efficacy of SCIT. Production of IL-10 and TGF-$\beta$ from and expression of cytotoxic T-lymphocyte-associated protein-4 by Treg cells have importance in immune regulation in SCIT.[89] Increase in Treg cell numbers in IL-10 and TGF-$\beta$ mRNA expression in response to SLIT has been revealed,[90] whereas levels of IL-17 in SLIT have been negatively correlated with the success of SLIT.[91] Immune deviation of Th2 responses to a more protective

Th1 profile as a consequence of SCIT has also been suggested.[89] In response to SCIT, IL-12 mRNA expression in skin macrophages has been found to be increased, together with the presence of Th1 cells and diminished numbers of Th2 cells, which has been correlated with inhibited allergen-induced late cutaneous responses.[92,93] The main difference in SLIT is the use of oral mucosa, which is a site for induction of immune tolerance, namely a protolerogenic site.[94] In summary, SCIT and SLIT induce similar effects, but with some degrees of difference, which requires further studies for conclusive data.

## INFLUENCE OF SUBLINGUAL IMMUNOTHERAPY AND SUBCUTANEOUS IMMUNOTHERAPY ON ANTIBODY RESPONSES

Both SCIT and SLIT have influences on antibody responses. AIT decreases allergen-specific IgE production and promotes allergen-specific IgG4 production, which competes with IgE by blocking the binding of allergens to FcεRI on the surface of mast cells and basophils.[95] IL-10 reduces allergen-specific IgE production through IL-4-induced IgE switching by decreasing epsilon transcript expression and enhances allergen-specific IgG4 production by potentiating IL-4-induced IgG4 switching by inducing IL-4-induced gamma4 transcript expression, and also by enhancing growth of cells already committed to produce IgG4.[58,96,97] It has been recently reported that although after grass tablet SLIT allergen-specific IgE and IgG4 responses have been initially upregulated with increased IL-4-producing cell numbers, this phase has then been followed by a shift from Th2 profile toward Th1, with downregulation of allergen-specific IgE production and increased allergen-specific IgG4 production.[98] The long-term tolerance after SLIT has been accompanied by selective persistence of blocking antibodies. After 2 years of successful SLIT, immunotherapy-induced grass pollen–specific IgG1 and IgG4 levels have been normalized to pretreatment levels, and cellular assays that have detected binding of IgE-grass pollen allergen complexes to B cells have shown that inhibitory bioactivity of allergen-specific IgG antibodies has remained unchanged.[53] SLIT also elicits mucosal IgA responses, which may significantly contribute to induction of allergen tolerance.[99] SCIT has similar, but more pronounced effect on antibody responses. Grass pollen SCIT has reduced seasonal increases in serum allergen-specific IgE, whereas 60- to 80-fold increases in allergen-specific IgG and 100-fold increases in allergen-specific IgG4 have been observed.[100] Similarly, inhibitory activity by blocked IgE-facilitated binding of allergen-IgE complexes to B cells has been observed after SCIT.[64] Measuring IgG4 levels has been proposed to be a good indicator of clinical efficacy of AIT during follow-up.

## INFLUENCE OF SUBLINGUAL IMMUNOTHERAPY AND SUBCUTANEOUS IMMUNOTHERAPY ON EFFECTOR CELLS

The effector cellular players of allergic inflammation are eosinophils, basophils, and their tissue counterpart mast cells. These cells regulate inflammatory events and anaphylaxis during allergic inflammation. Triggering of mast cells and basophils is responsible for the release of cellular mediators, which increases vascular permeability, edema formation, angiogenesis, and fibrosis development in the long term. Histamine is one of the major mediators released from effector cells. Effects of histamine are mediated by histamine receptors, the four types of which are defined as H1 to H4. Although H1R is known for its proinflammatory and cell-activating properties, H2R is claimed to be involved in establishment of immune tolerance[101,102] by downregulating T-cell and DC responses.[6] Immunosilencing of FcεRI-activated basophils by

means of selective suppression mediated by H2 receptors has induced desensitization effect after venom immunotherapy. It has been proposed that early desensitization of FcεRI-bearing mast cells and basophils has been marked in allergen-specific immunotherapy.[103] In addition, basophil expression of diamine oxidase is suggested as a novel biomarker of AIT response.[104] It has been proposed that histamine and leukotrienes are shown to be released without inducing systemic anaphylaxis, probably because their release is under systemic anaphylaxis thresholds during AIT. The granule content of mediators may be depleted and it may become harder to activate mast cells and basophils to emerge anaphylactoid symptoms, which is known to be a short-term effect of AIT.[105–107] However, the number of cutaneous mast cells after immunotherapy has reduced in correlation with the clinical response in terms of seasonal symptoms after grass pollen SCIT.[108] Also, successful grass pollen immunotherapy was associated with inhibition of seasonal increases in basophils and eosinophils in the nasal epithelium.[109]

## SUMMARY

AIT has been used for more than 100 years as a desensitizing and immune tolerance–inducing therapy for allergic diseases and represents the only allergen-specific way of treatment. It is a milestone disease-modifying treatment with the possibility of cure of allergic diseases. Its mechanisms of action include changes in memory-type allergen-specific T- and B-cell responses and increased thresholds for mast cells and basophil activation. Besides SCIT and SLIT, novel routes of AIT, such as intralymphatic, epicutaneous, and intranasal immunotherapy, are under investigation.[110] Expanded knowledge in AIT is also expected to contribute to treatment of other immune tolerance–related diseases, such as autoimmune diseases, chronic infection, organ transplantation, and cancer.[2]

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