

Mechanisms of Subcutaneous Allergen Immunotherapy

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KEYWORDS

- Allergy • Allergen immunotherapy • T regulatory cells
- Interleukin 10 • Transforming growth factor β
- Immune tolerance

Allergic inflammation takes place because of the development of an adaptive immune response induced by noninfectious environmental substances (allergens) in sensitized subjects, leading to several diseases including asthma, allergic rhinoconjunctivitis, anaphylaxis, urticaria, and atopic dermatitis.¹ Sensitization to an allergen depends on the capacity of the allergen to prime the helper T (T_H) subtype 2 cell response, during which interleukin (IL)-4 and IL-13 drive IgE antibody production by initiating IgE class switch in B cells. Binding of IgE to its high-affinity receptor (Fc ϵ RI) on mast cells and basophils results in secretion of biologically active compounds, mainly histamine, lipid-derived mediators, newly synthesized cytokines, chemokines, and growth factors associated with the immediate phase of allergic reaction.^{2–6} In addition, binding of IgE to Fc ϵ RI on dendritic cells and monocytes and to the low-affinity receptor of IgE (Fc ϵ RII) on B cells increases the uptake of allergen by antigen-presenting cells (APCs). These APCs present the allergen's T-cell epitope peptides and activate allergen-specific CD4⁺ T cells, which orchestrate the late-phase allergic immune response.⁷

Changes in the balance between allergen-specific T regulatory (Treg) cells and T_H2 and/or T_H1 cells are critical in the development and treatment of allergic diseases.^{8,9} In addition, recently identified T-cell subsets, such as T_H17 , T_H22 , and T_H9 , have been found to play a role in allergic diseases, and data regarding their relationship with

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allergic inflammation continue to accumulate.^{10–13} Antihistamines, leukotriene receptor antagonists, and glucocorticoids used for the management of allergic diseases provide a temporary relief of symptoms and signs because of the transient suppression of inflammation in allergic diseases.¹⁴ However, a long-term cure can be achieved by allergen-specific immunotherapy (SIT) with a disease-modifying effect, which might also lead to a decrease in the requirement of antiinflammatory and symptomatic medications.¹⁵ The basic principle of allergen-SIT depends on a desensitization strategy by the repeated administration of increased doses of the causative allergen to induce a state of tolerance through the constitution of allergen-specific Treg cells (**Fig. 1**).^{8,16–18}

TREG CELLS IN IMMUNE RESPONSE

In healthy individuals, immune response to allergens has included unresponsiveness of T cells or active peripheral tolerance induction by the subsets of Treg cells.^{19–21} Peripheral blood mononuclear cells (PBMCs) of healthy subjects secrete higher levels of IL-10 and transforming growth factor β (TGF- β) after allergen stimulation, leading to active suppression of specific T cell responses.²² In addition, in nonatopic individuals, active suppression against allergens is mediated by Tr1 cells or CD4⁺CD25⁺ Treg cells.^{23,24}

Forkhead box protein 3 (FOXP3) transcription factor is critical for the function of CD4⁺CD25⁺ Treg cells and the maintenance of peripheral immunologic tolerance.^{25–27} X-linked immune dysregulation, polyendocrinopathy, and enteropathy (IPEX) syndrome was described as because of mutations in FOXP3, resulting in nonfunctional CD4⁺CD25⁺ Treg cells.²⁶ The hallmark features of IPEX syndrome are enteropathy characterized by severe and refractory diarrhea; autoimmune endocrinopathies, which usually include early-onset insulin-dependent diabetes mellitus, thyroiditis, or both; hemolytic anemia; thrombocytopenia as autoimmune manifestations and chronic dermatitis; and elevated IgE levels as allergic manifestations.²⁸ Similar genotypes do not always accompany similar phenotypes in terms of disease presentation and severity, and FOXP3 expression does not correlate with disease severity.²⁹

The role of immune suppressive function of CD4⁺CD25⁺FOXP3⁺ Treg cells in allergic diseases has been described during the last decade.³⁰ In acute atopic dermatitis lesions, impaired skin infiltration of CD4⁺CD25⁺FOXP3⁺ Treg cells is observed.³¹ There are also higher frequencies of circulating CD4⁺CD25⁺FOXP3⁺ Treg cells, which correlate with atopic dermatitis severity and peripheral blood eosinophil counts.^{32,33} During bronchoalveolar lavage, CD4⁺FOXP3⁺ Treg cells are increased in patients with moderate to severe asthma compared with those with mild asthma and controls.³⁴ After systemic glucocorticoid treatment, there is an increase in the frequency of CD25⁺ memory CD4⁺ T cells and FOXP3 messenger RNA expression by CD4⁺ T cells.³⁵ During pollen season, there is a decrease in the allergen-specific suppressive capacity of CD4⁺CD25⁺ Treg cells in cell cultures obtained from patients with hay fever.³⁶ In murine models, transfer of CD4⁺CD25⁺FOXP3⁺ Treg cells suppresses the house dust mite–induced allergic airway inflammation in an IL-10–independent way.³⁷ The recruitment of FOXP3⁺ Treg cells in local draining lymph nodes of the lung is associated with spontaneous resolution of chronic asthma. In a mouse model of antigen-induced lung inflammation, CD4⁺CD25⁺ Treg cells promote migration of mast cell progenitors to the lungs.³⁸

Two subtypes of CD25^{high} T cells were defined because of the differential expression of the chemokine receptor CCR6. In contrast to regulatory activities, the activated CD25^{high} T cells that lack the expression of CCR6 enhance T_H2 responses.³⁹ There is an increase in CD4⁺CD25^{high} T cells in the peripheral blood of allergic children after

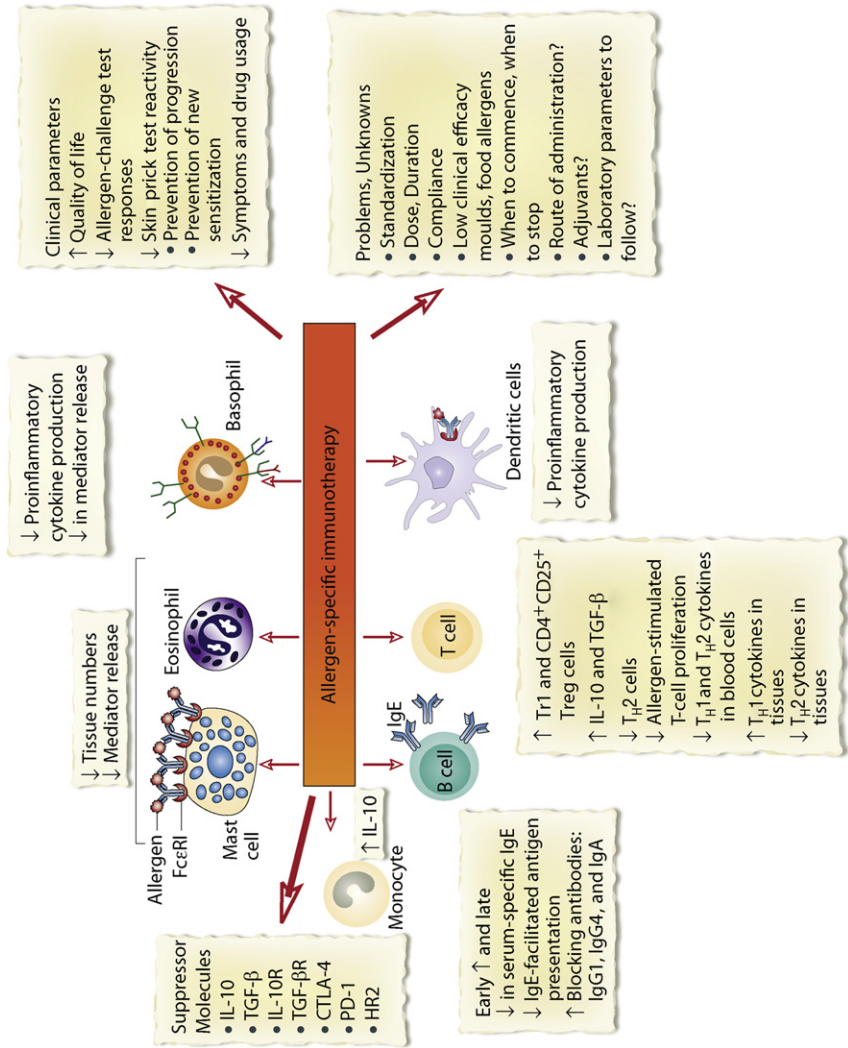
pollen exposure.⁴⁰ However, in patients with severe refractory asthma, the baseline CD4⁺CD25^{high} Treg cells in the peripheral blood are low compared with healthy subjects. During exacerbations, both in blood and in situ, there is further decrease in the number and function of CD4⁺CD25^{high} Treg cells with a decrease in IL-10 gene expression.⁴¹ The number of allergen-specific CD4⁺CD25^{high}FOXP3⁺ Treg cells does not show any difference between atopic and nonatopic subjects.⁴² CD4⁺CD25^{high}CD127^{low} Treg cells have been included in the recovery of allergic inflammation. It was shown that in allergic asthma, CD4⁺ invariant natural killer T cells selectively killed CD4⁺CD25^{high}CD127^{low} Treg cells in cocultures, and this cytotoxicity was positively correlated with asthma severity.⁴³ In allergic diseases, the function of Treg cells depends on the concentration and type of the eliciting agent, with different thresholds for individual allergens and patients with different genetic and immunologic backgrounds.⁴⁴ In addition, the stage of the disease, such as acute or chronic; remission or exacerbation; and affected tissue versus peripheral blood analysis show substantial differences. Furthermore, analysis methods and the type of antibody used have caused discrepancies in the previous findings.

Repeated exposure of nonallergic beekeepers to bee venom antigens during the beekeeping season provides a suitable model to understand the mechanisms of T-cell tolerance induction in healthy immune response. On bee venom exposure, an immediate switch of allergen-specific T cells from T_H1 and T_H2 cells to IL-10-secreting Tr1 cells occurs. This leads to diminished T-cell-related cutaneous late-phase responses in parallel to decreased allergen-specific T-cell proliferation and T_H1 and T_H2 cytokine secretion. At the end of the beekeeping season, peripheral T-cell response returns to baseline level within 2 to 3 months.²³ Another role of CD4⁺CD25⁺ Treg cells in a healthy immune response to allergens has been demonstrated in cow's milk allergy. Children with cow's milk allergy who became tolerant had increased number of circulating CD4⁺CD25⁺ T cells and decreased in vitro proliferative responses to bovine β -lactoglobulin in PBMCs compared with children who still had clinically active allergy.⁴⁵

In patients with persistent allergic rhinitis, allergen-specific IL-10-secreting type 1 Treg cells are decreased in the peripheral blood, but the number and function of CD4⁺CD25⁺ Treg cells are not impaired.⁴⁶ When CD4⁺ inducible Treg cells are transferred to cockroach-sensitized and -challenged mice, the cells differentiated to IL-10-producing CD4⁺ type 1 cells in the lung and reversed airway hyperresponsiveness and airway inflammation via TGF- β , IL-10, interferon γ (IFN- γ), and cell surface receptor programmed death-1.⁴⁷

ROLE OF IL-10 AND TGF- β IN ALLERGEN TOLERANCE

IL-10 and TGF- β , the suppressive cytokines of T-cell proliferation and cytokine production, are necessary in peripheral tolerance to allergens, autoantigens, transplantation antigens, and tumor antigens.^{30,48–50} Transfer of ovalbumin (OVA) peptide-specific CD4⁺CD25⁺ T cells to OVA-sensitized mice resulted in an IL-10-dependent decrease in airway hyperreactivity, recruitment of eosinophils, and T_H2 cytokines to airways after allergen challenge. After transfer of CD4⁺CD25⁺ T cells, increased lung expression of IL-10 was detected and regulation was reversed by anti-IL-10R antibody.⁵¹ IL-10 directly affects APC functions by downregulating the expression of major histocompatibility complex class II and costimulatory molecules on the surface of macrophages and monocytes.³⁰ IL-10 inhibits the expression of a large number of proinflammatory cytokines and chemokines and many chemokine receptors.⁵² In addition to these indirect effects, IL-10 directly affects T-cell activation through suppression of CD28, CD2, and



inducible T-cell costimulator signaling via Src homology 2 domain-containing protein tyrosine phosphatase-1.⁵³ IL-10 suppresses the production of allergen-specific and total IgE and increases the level of IgG4, resulting in a decrease in allergic inflammation.⁴⁹ The cells that produce IL-10 also include dendritic cells⁵⁴ and B cells.⁵⁵ There is a 2-sided interaction between Treg cells and IL-10. The differentiation of Tr1 cells by tolerogenic dendritic cells necessitates the IL-10-dependent immunoglobulin-like transcript 4/human leukocyte antigen-G pathway.⁵⁶

TGF- β superfamily has many immunoregulatory functions that are important for angiogenesis, cancer,⁵⁷ and wound healing.⁵⁸ TGF- β induces FOXP3 expression, leading to the conversion of naive CD4⁺CD25⁻ T cells into CD4⁺CD25⁺ T cells.⁵⁹ TGF- β signaling is, also, required for in vivo expansion and immunosuppressive capacity of CD4⁺CD25⁺ T cells.⁶⁰ TGF- β not only contributes to the differentiation of suppressive Treg cells but also is involved in the differentiation of inflammatory T_H17 cells through SMAD2 receptor.⁶¹ TGF- β induces the expression of some other molecules involving runt-related transcription factors 1 and 3, which are associated with the development and suppressive functions of FOXP3⁺ inducible Treg cells.⁶² The role of TGF- β in the pathogenesis of asthma, particularly in airway remodeling and fibrosis, has been emphasized.⁶³ TGF- β 1 induces epithelial-mesenchymal transition in primary airway epithelial cells. However, the number of cells undergoing epithelial-mesenchymal transition is higher in airway epithelial cultures from patients with asthma.⁶⁴ Administration of anti-TGF- β antibody or neutralizing TGF- β through SMAD3 significantly reduces peribronchial fibrosis, airway smooth muscle proliferation, and mucus production, but the intensity of accompanying airway inflammation does not change.^{65,66} The extracellular TGF- β released from airway epithelial cells stimulates autocrine synthesis of collagen-I,⁶⁷ whereas TGF- β decreases the production of enzymes such as collagenase.⁶⁸ Furthermore, in cytotoxic T lymphocytes and natural killer cells, TGF- β is an antagonist of IFN- γ production and cytolytic activity. In addition, TGF- β has a negative regulator effect on B-cell proliferation and differentiation⁶⁹ and on most immunoglobulins, except mucosal IgA, which is increased.⁷⁰ Coexpression of TGF- β 1 and IL-10 permitted Treg cells to completely suppress airway hyperreactivity in a mouse model of asthma.⁷¹

ALLERGEN-SIT AND TREG CELLS

Allergen-SIT results in the generation of allergen-specific Treg cells and suppressive cytokines.^{72–74} There is no well-defined distinction between the subsets of Treg cells in humans in whom CD4⁺CD25⁺ Treg cells and IL-10- and TGF- β -secreting Tr1 cells represent overlapping populations in the circulation.⁷⁵

Changes in the frequencies of antigen-specific T cells with a loss of IL-4-producing T cells and acquisition of IL-10-producing CD4⁺CD25⁺ T cells are associated with allergen-SIT.^{76,77} There is increase in local FOXP3⁺CD25⁺ T cells in the nasal mucosa,

Fig. 1. Clinical and immunologic effects of allergen-SIT. Allergen-SIT induces the development of Treg cells and suppressive cytokines IL-10 and transforming growth factor β ; decreases tissue numbers and mediator release of mast cells and eosinophils; increases IgG4 and decreases IgE; and decreases proinflammatory cytokine production of dendritic cells. Clinically, allergen-SIT decreases symptoms and medication use and prevents the development of new allergic sensitizations. There are still some problems and still unknowns about allergen-SIT; standardization of allergens, optimal dose and duration of allergen-SIT, most efficient and convenient route of administration, laboratory parameters (predictors) to decide to start, optimum time to stop and follow the efficacy. CTLA-4, cytotoxic T-lymphocyte antigen 4; HR2, heptad repeat 2; PD-1, programmed death-1.

which correlates with the clinical efficacy after pollen immunotherapy.⁷⁸ When PBMCs were stimulated with Der p 2 after 1 year of immunotherapy with house dust mite, IL-10-secreting CD4⁺CD25⁺ Treg cells increased more than the control group together with downregulation of nuclear factor κ B expression.⁷⁹ In OVA-sensitized mice with asthma, the depletion of CD4⁺CD25⁺ T cells hampers tolerance induction.⁸⁰ Immunotherapy might lead to differential induction of Treg cells. At the end of the SIT induction phase, increased number of IL-10-secreting Tr1 cells has been shown followed by a reduced ratio of allergen-specific T_H2/IFN- γ ⁺ T_H1 cells by 1 year.⁸¹ The differential T-cell activation and regulatory patterns induced by SIT depend on the severity of the underlying allergic sensitization. The increment in natural and acquired Treg cells develops earlier and reaches higher levels in less severe subjects.⁸² CD8⁺CD25⁺FOXP3⁺ Treg cells expressing IL-10 also increased in response to house dust mite SIT in patients with asthma (Fig. 2).⁸³ Grass pollen immunotherapy increased the expression of mucosal and peripheral T-cell IL-10⁸⁴ and TGF- β .⁸⁵ Similarly, peptide-based immunotherapies were also able to induce peripheral T-cell tolerance by decreasing the systemic T_H1 and T_H2 cell response to allergens via induction of Treg cells.^{86–88} Venom peptide (phospholipase A₂) immunotherapy increased the production of IL-10 and transcription of the suppressor of cytokine signaling (Socs) 3 gene in mild honey bee allergy.⁸⁹

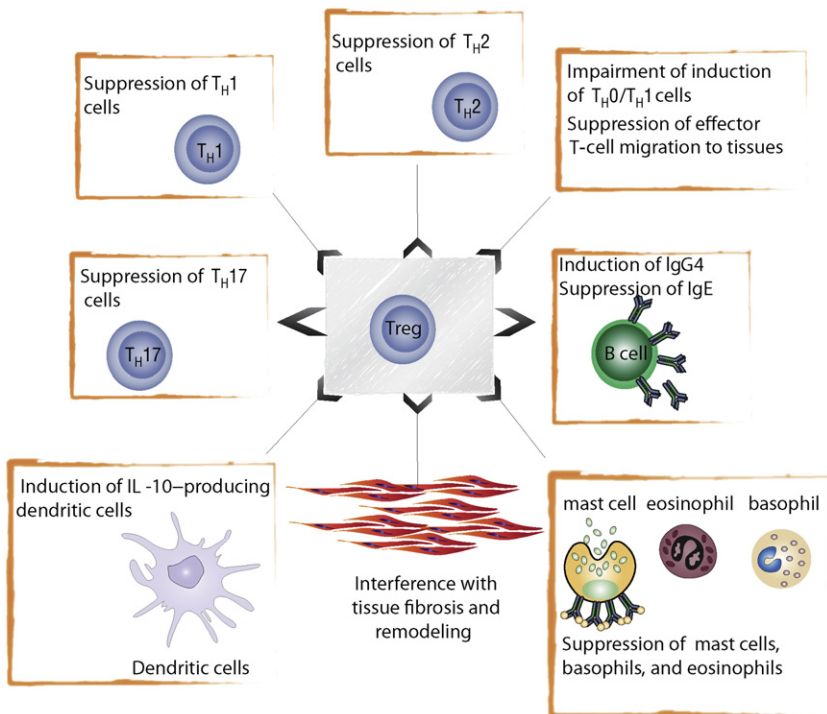


Fig. 2. Roles of Treg cells (FOXP3⁺CD4⁺CD25⁺ and Tr1 cells) in allergen-SIT. Suppression of T_H1, T_H2, and T_H17 cells; induction of IL-10-producing dendritic cells; suppression of mast cells, basophils, and eosinophils; interference with tissue fibrosis and remodeling; suppression of allergen-specific IgE; and induction of IgG4 and/or IgA.

ALLERGEN-SIT AND SPECIFIC ANTIBODY RESPONSE

In some of the nonatopic healthy individuals, there is no detectable antibody response or is low. However, in high dose of allergen exposure, relatively high amounts of specific IgG4 and specific IgG1 and IgA have been observed in response to allergen with no or low specific IgE response.⁹⁰ Although low amounts of antigen exposure might lead to immunologic ignorance resulting in no antibody response in mice,⁹¹ very low dose (eg, a single bee sting) is sufficient to induce IgE and/or IgG production against phospholipase A₂ in humans.⁹²

Activation of the complement cascade is an important feature of IgG subclass of immunoglobulins except IgG4. IgG4 fails to fix complement and binds only Fc γ RII and Fc γ RIII weakly, but it does not induce immune complex formation.⁹³ It is a dynamic molecule with a continuous exchange of heavy and light chains, referred as Fab-arm exchange. This exchange enables the expression of 2 different antigen-binding sites on a single IgG4 molecule. The increase in systemic IgG4 levels indicates that antiinflammatory, tolerance-inducing mechanisms have been activated and are associated with a decrease in allergic symptoms.^{94,95} Nonallergic beekeepers have approximately 1000 times high ratio of specific IgG4 to specific IgE compared with allergic individuals.⁹⁶ There is a positive correlation between bee venom-specific IgG4 and the number of annual stings and years spent in beekeeping. Nearly half of the beekeepers who were stung less than 25 times a year had a history of systemic allergic reactions to bee venom, compared with no allergy in those with more than 200 stings per year.⁹² However, there are controversial data in other forms of sensitizations. In a longitudinal study, after high exposure to cats, 2 groups of individuals were observed: 1 group developing high IgG responses to cat allergen without sensitization and wheeze and the other group with sensitization, IgG, and respiratory symptoms.⁹⁷ The degree of exposure to the allergen might affect the sensitization. In an adult population, the prevalence of sensitization to cat was significantly decreased in the lowest and highest cat-exposed groups.⁹⁸

During allergen-SIT, IL-10 production occurs early with low doses of allergen at 2 to 4 weeks, but the increase in serum allergen-specific IgG4, IgA, and IgE occurs later at 6 to 12 weeks, which takes place at higher allergen doses leading to inhibition of early skin responses.⁹⁹ IgG4 suppresses IgE-mediated degranulation of mast cells and basophils, antigen presentation by direct allergen competition, and inhibitory Fc γ RIIb IgG receptors and mediates inhibition of basophil activation by Fc γ RIIIa and IgG Fc γ RIIb receptors. It also reduces the number of allergen-specific memory B cells that have undergone class switching to IgE.^{100–104} There is a transient increase in serum-specific IgE, followed by gradual decrease over months or years of treatment.^{105,106} The seasonal increase in IgE decreases after the buildup phase of allergoid immunotherapy.¹⁰⁷ The increase in antigen-specific IgG4 is more than the increase in IgE; therefore, the ratio of specific IgE to IgG4 significantly decreases from 6 months to 3 years.¹⁰⁶ In predicting the clinical response, higher pretreatment ratio of allergen-specific IgE to total IgE is associated with an effective clinical response at the end of the SIT period.¹⁰⁸ Allergen-SIT also induces a serum-blocking activity, presumed to be because of allergen-specific IgG that blocks the formation of allergen-IgE complexes and binding to CD23⁺ B cells, which results in the inhibition of IgE-facilitated allergen presentation to T cells.⁸⁴

Other antibody classes might also contribute to clinical efficacy of SIT. The increase in TGF- β observed during house dust mite SIT is associated with a significant increase in specific IgA to Der p 1.²² The IgA response to allergen-SIT is selective for IgA2. It

correlates with increased nasal mucosal TGF- β expression and enhanced monocyte IL-10 expression.⁸⁵

Both allergen-specific IL-10-secreting Tr1 cells and CD4⁺CD25⁺ Treg cells from healthy individuals induce IgG4 and suppress IgE production in the PBMCs and purified B-cell cultures of humans. This effect is particularly because of IL-10 production by these cells.¹⁰⁹ In contrast, IgA production is independent of T-cell help, and the role of Tr1 or Treg cells is limited, whereas it was highly induced by direct B-cell activation via toll-like receptor (TLR)7 and TLR9.

These data suggest that Treg cells may contribute to the suppression of allergic diseases by suppression of IgE and induction of IgG4, whereas IgA production is enhanced by B-cell activation via TLR7 and TLR9.

ALLERGEN-SIT AND MAST CELLS, EOSINOPHILS, AND BASOPHILS AS EFFECTOR CELLS

Allergen-SIT efficiently modulates the thresholds for mast cell and basophil activation and decreases IgE-mediated histamine release. Long-term venom immunotherapy resulted in a continuous decrease in serum mast cell tryptase concentration over time, which might involve a decrease in the function or number of mast cells.¹¹⁰ Treg cells directly inhibit the Fc γ RI-dependent mast cell degranulation through cell-cell contact involving OX40-OX40L interactions between Treg cells and mast cells, respectively. Activated mast cells show increased cyclic adenosine monophosphate concentrations and reduced Ca⁺⁺ influx in the presence of Treg cells. The *in vivo* depletion or inactivation of Treg cells causes enhancement of the anaphylactic response.¹¹¹ Loss of interaction between mast cells and Treg cells may contribute to more severe allergic reactions.

Allergen-SIT has been associated with a decrease in the influx of activated eosinophils and activated CD4⁺ T cells into target tissues after allergen stimulation. Decreased number and activation of circulating basophils have also been observed after allergen-SIT.^{112–114} Inhibition of seasonal increases in both nasal mast cells and eosinophils, which correlates with symptomatic improvement because of the reduced local expression of IL-5 and IL-9.^{115,116} IL-10 downregulates eosinophil function and activity and suppresses IL-5 production by human resting T_H0 and T_H2 cells.¹¹⁷ During SIT, reduced plasma levels of eosinophil cationic protein and chemotactic factors for eosinophils and neutrophils correlated with decreased bronchial hyperreactivity.¹¹⁸ Allergen-SIT also prevented seasonal rises in the number of cells expressing eotaxin and regulated on activation, normal T-expressed, and presumably secreted (RANTES).¹¹⁹

Effects of allergen-SIT on dendritic cells have also been identified. In allergic patients, human blood dendritic cells have impaired IFN- α production by CpG stimulation through TLR9. During maintenance phase, allergen-SIT leads to increase in concentrations of IFN- α in response to CpG in PBMC, suggesting the contribution of allergen-SIT in dendritic cell TLR9-mediated innate immune function.¹²⁰ The T-cell immunoglobulin and mucin domain (TIM)4 molecule, expressed by dendritic cells, is the natural ligand of TIM1. Dendritic cell-derived TIM4 can bind TIM1 on CD4⁺ T cells and drive them to develop into T_H2 cells. Allergen-SIT suppresses TIM4 expression in dendritic cells of patients with allergic rhinitis, resulting in suppression of T_H2 responses. In addition, interaction of antigen-specific IgG and Fc γ RII downregulates TIM4 production by dendritic cells.¹²⁰

Long-term allergen-SIT is associated with the reduction of not only the immediate response to allergen provocation but also the late-phase reaction in the nasal and

bronchial mucosa or in the skin. The mechanism of late-phase reaction involves the recruitment, activation and persistence of eosinophils, and activated T cells at the sites of allergen exposure. Successful allergen-SIT is concerned with decreased responses to nonspecific stimulation so that bronchial, nasal, and conjunctival hyper-reactivities to nonspecific stimuli, which seems to reflect the underlying mucosal inflammation, decrease after allergen-SIT and correlate with clinical improvement.¹²¹

SUMMARY

Different types of Treg cells, the naturally occurring, thymic-selected CD4⁺CD25⁺FOXP3⁺ Treg cells¹²² and the inducible type 1 Treg cells,^{23,123} control diverse steps of inflammation in various diseases^{124,125} and allergen-specific immune response via suppression of APCs¹²⁶; inhibition of the development of T_H2, T_H1, and T_H17 responses^{123,127,128}; suppression of allergen-specific IgE and induction IgG₄ and IgA¹⁰⁹; suppression of mast cells, basophils, and eosinophils¹¹¹; interference with tissue fibrosis and remodelling¹²⁹; and impairment of induction of T_H0/T_H1 cells (see Fig. 2).¹³⁰

Peripheral tolerance to allergens induced by allergen-SIT involves control of allergen-specific immune response in multiple steps, which are being investigated for the achievement of safer approaches and more efficient ways of allergen-SIT. In addition, targeting of T cells through allergen-specific therapy leads to modification of the balance between T_H1, T_H2, and Treg cells. Better understanding of all these mechanisms will provide a basis for the development of novel therapeutic and also prophylactic modalities in the future.

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