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Scientific Foundations of Allergen-Specific Immunotherapy for Allergic Disease

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Allergen-specific immunotherapy (AIT) was described as a therapeutic option for the treatment of allergies > 100 years ago. It is based on administration of allergen extracts and leads to the development of clinical allergen tolerance in selected patients. According to current knowledge, AIT results in the restoration of immune tolerance toward the allergen of interest. It is mainly accompanied by the induction of regulatory and suppressive subsets of T and B cells, the production of IgG4 isotype allergen-specific blocking antibodies, and decreased inflammatory responses to allergens by effector cells in inflamed tissues. Currently, AIT is mainly applied subcutaneously or sublingually and is suitable for both children and adults for pollen, pet dander, house dust mite, and venom allergies. It not only affects rhinoconjunctival symptoms but also has documented short- and long-term benefits in asthma treatment. Clinically, a fast onset of tolerance is achieved during desensitization, with a tolerable amount of side effects. The disease modification effect leads to decreased disease severity, less drug usage, prevention of future allergen sensitizations, and a long-term curative effect. Increasing safety while maintaining or even augmenting efficiency is the main goal of research for novel vaccine development and improvement of treatment schemes in AIT. This article reviews the principles of allergen-specific immune tolerance development and the effects of AIT in the clinical context.

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ABBREVIATIONS: AIT = allergen-specific immunotherapy; Br1 = IL-10-producing B regulatory; Breg = B regulatory cell; DC = dendritic cell; PLA = phospholipase A2; SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy; TGF-β = transforming growth factor-β; Th = T helper; TIM = transmembrane immunoglobulin and mucin; TLR = Toll-like receptor; Treg = T regulatory cell

Allergies are among the most common diseases worldwide, with rising disease prevalence and increasing rates of allergen sensitizations.[1] Symptoms of allergic disorders affect both upper and lower airways as well as eyes, skin, GI organs, and the whole body in the case of anaphylaxis. Seasonal and perennial allergens mainly comprise proteins that can be inhaled, ingested, or taken up by many other routes and induce

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an IgE-mediated local or systemic inflammatory process. Common therapies target such symptoms as inflammation with the use of antihistamines, topical and systemic corticosteroids, mast cell stabilizers, leukotriene antagonists, β-adrenergic agonists, and monoclonal anti-IgE antibodies. Currently, only allergen-specific immunotherapy (AIT) provides a disease modification effect leading to cure[2] in select patients and has proven to be effective for > 100 years. Despite that we are far from completely understanding the causes of allergic disease as well as the exact mode of action of AIT, the scientific community worldwide wants to understand the mechanisms of immune tolerance in the fields of allergies, autoimmunity, and organ transplantation. The mechanisms of action of AIT mechanisms have become increasingly clear in recent years.

Immune tolerance can be described as the adaptation of the immune system to external antigens or allergens. The ultimate goal for the therapy of immunologic diseases and conditions such as allergy, autoimmunity, and organ transplantation should be the induction of immune tolerance, a change in the immune response to specific antigens so that the discontinuation of the therapy results in continued long-lasting therapeutic benefits. It is, therefore, an active immune response to a particular epitope that leads to a clinical tolerance to allergens.

Mouse immune tolerance models have been well studied, and evidence has been obtained in adaptive transfer models on the role of T regulatory cells (Tregs) in allergen tolerance in mice.[3-6] Direct evidence at the level of mouse studies, for obvious reasons, are more difficult to obtain from human immunology studies.

Three levels of evidence prove this concept in humans. In the first level, the relationship of clinical nonreactivity (allergen tolerance) to allergens and immune tolerance could be observed in two types of direct tissue analysis in humans. One was the investigation of skin late-phase responses, and the second was the investigation of nasal mucosa biopsy specimens in allergic rhinitis. The data showed a decrease in T helper (Th) 2 cells and eosinophils in both cases by AIT and a parallel increase in Tregs and their cytokines in these tissues.[7,8] The same data were shown in T-cell epitope peptide immunotherapy.[9] In addition, allergen tolerance in beekeepers was associated with similar mechanisms and decreased skin late-phase responses.[10]

The second level of evidence came from direct analysis of human peripheral blood cells without any further culture. This level was obtained for mechanisms of allergen tolerance in healthy beekeepers, who are exposed to a high dose of venom allergens, and during AIT. Allergen tetramer-positive $CD4^+$ antigen-specific T cells were analyzed or cytokine-secreting cells were purified in these studies, and the data demonstrated that allergen-specific Treg levels increase in these clinical allergen tolerance models.[10,11] The third level of evidence was obtained from cell cultures. In both allergen extract and peptide immunotherapies, peripheral T-cell tolerance was shown with the development of decreased T-cell reactivity to whole allergens and their T-cell epitope peptides.[9,12]

Immune Mechanisms of Allergic Inflammation

The profound understanding of allergic inflammation is a prerequisite to finding a well-targeted therapy. In the early days, approximately 30 years ago, the allergic inflammation was believed to be solely caused by an imbalance between the effector Th subsets, with Th2 dominance over Th1. Multiple mechanisms that involve all immune system and resident tissue cell responses have become slowly understood over the past decades. In the sensitization phase, the allergens are presented to naive T cells by dendritic cells (DCs), and a Th2 switch and clonal allergen-specific T-cell expansion occurs.[13,14] Depending on the microenvironment and the nature of the allergen, either immune tolerance develops or IgE sensitization occurs. DCs express a variety of Toll-like receptors (TLRs), C-type lectin receptors, or scavenger receptors that are activated by the microenvironmental molecules around allergens and may contribute to allergic sensitization.[14] In the early phase, upon recognition of an antigen, DCs migrate to lymphoid tissues and activate T-cell maturation and differentiation by antigen presentation and cytokine release. In airway exposure, primary sensitization occurs mainly throughout the Waldeyer ring, whereas later B-cell expansion after reexposure takes place in lymph nodes that drain the upper and lower airways.[15] Today, evidence shows that IgE-producing plasma cells are also localized in the bone marrow. These cells have been suggested as the reason for long-term IgE memory to explain why reversal of IgE production within a short time is difficult.[16] Through insufficiently understood mechanisms in humans, naive T cells transform into Th2 cells in the presence of thymic stromal lymphopoietin, IL-4, IL-25, and IL-33. Th2 cells then drive naive B cells to undergo immunoglobulin class switching to IgE and expansion of allergen-specific IgE-producing B cells and plasma cells. Specific IgE antibodies engage their specific receptors (FcεRI) on mast cells and basophils, which concludes the sensitization phase (Fig 1). Upon reexposure to the same allergen, the