Mechanisms of allergen immunotherapy for inhaled allergens and predictive biomarkers

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Allergen immunotherapy is effective in patients with IgE-dependent allergic rhinitis and asthma. When immunotherapy is given continuously for 3 years, there is persistent clinical benefit for several years after its discontinuation. This disease-modifying effect is both antigen-specific and antigen-driven. Clinical improvement is accompanied by decreases in numbers of effector cells in target organs, including mast cells, basophils, eosinophils, and type 2 innate lymphoid cells. Immunotherapy results in the production of blocking IgG/IgG$_4$ antibodies that can inhibit IgE-dependent activation mediated through both high-affinity IgE receptors (FcεRI) on mast cells and basophils and low-affinity IgE receptors (FcεRII) on B cells. Suppression of T$_H$2 immunity can occur as a consequence of either deletion or anergy of antigen-specific T cells; induction of antigen-specific regulatory T cells; or immune deviation in favor of T$_H$1 responses. It is not clear whether the altered long-term memory resides within the T-cell or the B-cell compartment. Recent data highlight the role of IL-10–producing regulatory B cells and "protective" antibodies that likely contribute to long-term tolerance. Understanding mechanisms underlying induction and persistence of tolerance should identify predictive biomarkers of clinical response and discover novel and more effective strategies for immunotherapy. (J Allergy Clin Immunol 2017;140:1485-98.)

Key words: *Immunotherapy, mechanisms, allergic rhinitis, allergic asthma, long-term tolerance, T cells, B cells, type 2 innate lymphoid cells, IgE-FAB, biomarkers*

Abbreviations used

Breg:	Regulatory B
C1Q:	Component 1Q
CRTH2:	Chemoattractant receptor–homologous molecule expressed on T$_H$2 lymphocytes
DAO:	Diamine oxidase
DC:	Dendritic cell
DCreg:	Regulatory dendritic cell
ELIFAB:	Enzyme-linked immunosorbent–facilitated antigen-binding assay
FOXP3:	Forkhead box P3
ILC:	Innate lymphoid cell
ILC2:	Group 2 innate lymphoid cell
iTreg:	Inducible regulatory T
LT:	Leukotriene
nTreg:	Natural regulatory T
RIPK4:	Receptor-interacting serine/threonine-protein kinase 4
sIgE:	Allergen-specific IgE
sIgG:	Allergen-specific IgG
T$_{FH}$:	Follicular helper T
T$_{FR}$:	Follicular regulatory T
Treg:	Regulatory T
VLA4:	Very late antigen 4, integrin α4β1

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Allergen immunotherapy is effective in selected patients with allergic rhinitis, including those with mild/moderate asthma.[1,2] There is heterogeneity in the populations studied, the different allergen products and protocols used, and the clinical outcomes used to document efficacy and safety.[3] Nonetheless, recent guidelines[4] confirm that immunotherapy is particularly effective in patients with seasonal rhinitis, and recent data strongly support its use in perennial allergy caused by house dust mites.[5]

Subcutaneous immunotherapy involves weekly updosing injections, followed by monthly maintenance injections for at least 3 years.[1,6,7] In view of occasional systemic allergic side effects, subcutaneous immunotherapy requires administration in a specialist allergy clinic with access to resuscitative measures. Sublingual immunotherapy involves daily drops or tablets placed under the tongue. Sublingual immunotherapy is effective and safer than subcutaneous immunotherapy, such that it is self-administered by the patient at home.[1,8] Sublingual and subcutaneous immunotherapy are effective generally within 2 to 4 months of initiating treatment and can be given presesonally/coseasonally for short-term benefit. Indirect

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Terms in boldface and italics are defined in the glossary on page 1486.

comparisons have suggested that immunotherapy might be more effective than antiallergic drugs. In contrast to antiallergic drugs and currently available mAb therapies, when allergen immunotherapy is given continuously for 3 years, both routes have been shown to be disease-modifying, manifest as long-term remission of symptoms for at least 2 to 3 years after discontinuation.[9,10]

In this review we explore historical and recent data on the mechanisms of immunotherapy for inhalant allergens. Our expectation is that a greater understanding of the underlying mechanisms of tolerance will identify potential biomarkers that could predict and/or monitor the response to treatment. Such knowledge could inform new potential treatment strategies.

OVERVIEW OF MECHANISMS OF ALLERGIC RHINITIS AND ASTHMA

IgE and mast cells

The cardinal features of allergic rhinitis include increased allergen-specific IgE concentrations to clinically relevant allergens, IgE-dependent activation of mast cells, and local eosinophilia in target organs. In addition to systemic and regional lymphatic sources of IgE, specific IgE can be synthesized and produced locally by B cells within the respiratory mucosa,[11] thereby accounting for the occasional phenomenon of "local allergic rhinitis" with symptoms on allergen exposure in the absence of detectable serum specific IgE or positive immediate skin test results to relevant allergens.[12]

IgE-dependent activation is detectable during the immediate (0- to 60-minute) response after nasal allergen provocation. Allergen cross-linking of adjacent surface IgE molecules on mast cells and basophils triggers within seconds or minutes the release of preformed mediators, such as histamine[13] and tryptase,[14] contained within intracytoplasmic granules. Newly formed mediators derived from arachidonic acid within the membrane lipid include sulphidopeptide leukotrienes (LTs; LTC_4, LTD_4, and the terminal metabolite LTE_4),[12] platelet-activating factor, and prostaglandin D_2. The biological properties of these mediators are consistent with the local vasodilatation, edema formation, local neurogenic stimulation, and mucus secretion that characterize typical nasal allergen–induced immediate type I hypersensitivity. In the lower airways bronchial smooth muscle contraction, as well as edema and mucus hypersecretion, contribute to acute bronchoconstriction. A proportion of subjects have a late response at 2 to 10 hours after challenge. The late response is characterized by tissue eosinophilia, nasal congestion, and mucosal hyperreactivity to both allergic and nonallergic triggers that can last for days or even weeks after a single nasal allergen challenge. In contrast

GLOSSARY

Bet v 1: A potent allergen from trees within the order Fagales, which is the main cause of type I allergies observed in early spring and characterized by hay fever, dermatitis, and asthma.

METHYLATED CpG SITES: CpG sites are regions of DNA in which a cytosine nucleotide occurs next to a guanine nucleotide separated by only 1 phosphate. Methylation of the cytosine within a gene can turn the gene off.

c-kit (CD117): A cytokine receptor most notably expressed on the surfaces of hematopoietic stem cells and other cell types, including mast cells. CD117 is a receptor tyrosine kinase type III protein that binds to stem cell factor and forms a dimer that activates its intrinsic tyrosine kinase, resulting in phosphorylation and activation of signal transduction molecules that produce cell signaling.

CYTOTOXIC T LYMPHOCYTE–ASSOCIATED PROTEIN 4 (CTLA-4): A receptor that functions as an inhibitory signal and downregulates immune responses when bound to CD80 and CD86. CTLA-4 is constitutively expressed in regulatory T cells but only upregulated in conventional T cells after activation.

IFN-γ: A type II interferon, IFN-γ is a cytokine required for innate and adaptive immunity against viral, bacterial, and protozoal infections. IFN-γ has been shown to be an important activator of macrophages and inducer of class II MHC molecule expression. IFN-γ is produced predominantly by natural killer (NK) and NKT cells as part of the innate immune response and by CD4 T_H1 and CD8 cytotoxic T lymphocyte effector T cells once antigen-specific immunity develops.

ImmunoCAP (A REGISTERED TRADEMARK OF PHARMACIA DIAGNOSTICS AB): An *in vitro* quantitative assay that measures allergen-specific IgE levels in human serum. ImmunoCAP assays can be performed on hundreds of allergens by using cellulose polymer, which provides high binding capacity of clinically relevant allergen proteins, including those present at very low levels.

IL-3: A growth-promoting cytokine capable of supporting the proliferation and activation of a broad range of hematopoietic cell types, including basophils.

IL-6: A cytokine also known as IFN-β2 and implicated in a wide variety of inflammation-associated disease states, IL-6 has been associated with B-cell maturation and has been shown to act as an endogenous pyrogen capable of inducing fever in patients with autoimmune diseases or infections.

IL-12: A cytokine produced by dendritic cells, macrophages, neutrophils, and human B-lymphoblastoid cells (NC-37) in response to antigenic stimulation and has been shown to be required for differentiation of naive T cells into T_H1 cells.

IL-21: A cytokine expressed in human $CD4^+$ T cells and found to be upregulated in T_H2 and T_H17 subsets and follicular T cells, which induces cell division/proliferation of various cells of the immune system, including natural killer cells and cytotoxic T cells.

IL-25: A proinflammatory cytokine that shares sequence similarity with IL-17 and has been shown to favor the T_H2-type immune response. IL-25 can induce nuclear factor κB activation and stimulate IL-8 production.

IL-33: A member of the IL-1 family of cytokines expressed on T_H2 cells, mast cells, and group 2 innate lymphocytes that potently drives production of T_H2-associated cytokines.

IL-35: An IL-12 family cytokine produced by regulatory, but not effector, T and B cells that plays a role in immune suppression.

PROGRAMMED CELL DEATH 1 (PD-1): A cell-surface receptor that plays an important role in downregulating the immune system and suppressing inflammatory T-cell activation. PD-1 is an immune checkpoint that serves a dual role of promoting apoptosis in antigen-specific T cells while simultaneously reducing apoptosis in regulatory T cells.

THYMIC STROMAL LYMPHOPOIETIN (TSLP): A cytokine that stimulates T-cell maturation through activation of antigen-presenting cells, such as dendritic cells and macrophages.

TGF-β: A cytokine secreted by many cell types, including macrophages, that controls proliferation, cellular differentiation, and inflammatory processes in a variety of cells. It also plays a role in T-cell regulation and differentiation.

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