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Mechanisms of allergen-specific immunotherapy: Multiple suppressor factors at work in immune tolerance to allergens

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Allergen-specific immunotherapy (AIT) has been used for more than 100 years as a desensitizing therapy for IgE-mediated allergic diseases and represents a potentially curative way of treatment. The mechanisms of action of AIT include the induction of very early desensitization of mast cells and basophils; generation of regulatory T and regulatory B (Breg) cell responses; regulation of IgE and IgG_4; decreases in numbers and activity of eosinophils and mast cells in mucosal allergic tissues; and decreases in the activity of basophils in circulation. Skewing of allergen-specific effector T and effector B cells to a regulatory phenotype appears as a key event in the course of AIT and normal immune response to allergens. Recently, inducible IL-10–secreting Breg cells were also demonstrated to contribute to allergen tolerance through suppression of effector T cells and selective induction of IgG_4 isotype antibodies. Allergen-specific regulatory T and Breg cells orchestrate a general immunoregulatory activity, which can be summarized as suppression of cytokines from inflammatory dendritic cells; suppression of effector T_H1, T_H2, and T_H17 cells; suppression of allergen-specific IgE and induction of IgG_4; and suppression of migration of mast cells, basophils, eosinophils, and effector T cells to tissues. A detailed knowledge of the mechanisms of AIT is not only important in designing the prevention and treatment of allergic diseases but might also find applications in the treatment of autoimmune diseases, organ transplantation, chronic infection, and cancer. (J Allergy Clin Immunol 2014;133:621-31.)

Key words: *Regulatory T cells, immunotherapy, IgE, T cells, IL-10, TGF-β, allergen immunotherapy, T helper cells, immune tolerance, IgE, IgG, T cells, B cells, mast cells, basophils, eosinophils*

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, 2 types of AIT are in clinical practice, subcutaneous immunotherapy and sublingual immunotherapy (SLIT), and several novel AIT approaches are being evaluated in clinical trials.[1,2] There is moderate-level evidence for the efficacy of specific immunotherapy against atopic dermatitis[3] and SLIT for the treatment of allergic rhinitis and asthma provided by recent meta-analyses.[4] Dysregulated immune function plays an essential role in many IgE-mediated diseases, including asthma, atopic dermatitis, allergic rhinitis, food allergy, and venom allergy, as well as autoimmune diseases, organ transplantation, tumors, chronic infections, and successful pregnancy.[5,6] Multiple mechanisms of immune regulation take place depending on the type, place, intensity, and chronicity of the immune response, as well as antigens/allergens, adjuvants, cytokines, or small molecules in the micromilieu. In addition, the type of 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 coexposure with stimulators of innate immune response, such as infections or commensal bacteria. Allergens enter the body through 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.[5-8] Immune tolerance to allergens is characterized by establishment of long-term clinical tolerance.[9,10] The mechanisms by which allergen tolerance is established in human subjects have been studied through various modes of AIT, as have the processes by which a healthy immune response develops during high dose of allergen exposure in beekeepers and cat owners.[1,2,11-13] Although many mechanisms are not fully elucidated, they include changes in the characteristics of allergen-specific memory T- and B-cell responses and the production of specific antibody isotypes to skew the immune response toward no inflammation, as well as decreased activation, tissue migration, and mediator release of mast cells, basophils, and eosinophils. After the discovery of T_H1 and T_H2 cell subsets in 1986, during the last 27 years, it is well understood that there is

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Terms in boldface and italics are defined in the glossary on page 622.

Abbreviations used

AIT: Allergen-specific immunotherapy
B_R1: IL-10–secreting regulatory B
Breg: Regulatory B
CTLA-4: Cytotoxic T lymphocyte antigen 4
DC: Dendritic cell
FOXP3: Forkhead box protein 3
HR: Histamine receptor
ICOS: Inducible costimulator
LPR: Late-phase response
PD-1: Programmed death 1
pDC: Plasmacytoid dendritic cell
PLA: Phospholipase A_2
SHP-1: Src homology domain 2–containing protein tyrosine phosphatase 1
SLIT: Sublingual immunotherapy
TLR: Toll-like receptor
T_R1: IL-10–secreting regulatory T
Treg: Regulatory T
VIT: Venom immunotherapy

reciprocal regulation between individual T_H cell subsets, such as T_H1, T_H2, ***T_H9***, ***T_H17***, and T_H22[14-16]; however, regulatory T (Treg) cells play a major role in the suppression of effector T-cell responses in different diseases.[6,10]

Allergic diseases are complex disorders with several disease variants caused by 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 provide any insight into the pathomechanisms that underpin the diseases. An important unmet need in patients with AIT is the identification and validation of biomarkers that are predictive of clinical response. It is now thought that some clinical trials might have been unsuccessful in the past because they were performed without attempting to classify patients with AIT into subgroups that are defined by a distinct pathophysiology, namely ***endotypes***.[17,18] 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 and maybe also even for the selection of the type of vaccine or route of application.

MECHANISMS OF AIT

Cellular and molecular events that take place during the course of AIT can be classified into 4 groups (Fig 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 start to take place within hours when natural allergens are used. The second group of events are generation of allergen-specific Treg and regulatory B (Breg) cells and suppression of allergen-specific effector T-cell subsets. The third group of events include regulation of antibody isotypes demonstrating an early increase in specific IgE levels, which later decrease, and an early and continuous increase in specific ***IgG_4***

GLOSSARY

CYTOTOXIC T LYMPHOCYTE ANTIGEN 4 (CTLA-4): Also known as CD152, CTLA-4 is expressed on activated T cells, is a member of the immunoglobulin superfamily, and contains an immunoreceptor tyrosine-based inhibition motif. CTLA-4 binds to B7 and limits T-cell activation. CTLA-4–deficient mice have lymphoproliferative disease.

ENDOTYPES: A definition of a disease subtype that is defined by the underlying pathobiology, as opposed to a phenotype, which is defined by the clinical characteristics. An example of an asthmatic endotype would be aspirin-exacerbated respiratory disease.

GM-CSF: GM-CSF stimulates stem cells to produce granulocytes and monocytes.

IgG_4: IgG_4 has been associated with the development of immune tolerance to antigens, including foods, and the ratio of specific IgE to IgG_4 might be useful in the context of desensitization. IgG_4 does not bind complement and blocks IgE binding to allergens.

IL-5: IL-5 promotes the survival, activation, and chemotaxis of eosinophils. Its receptor shares a common β chain with the IL-3 receptor.

IL-6: IL-6 is released by dendritic cells, primes for T_H2 effector cells, and inhibits the suppressive functions of $CD4^+CD25^+$ Treg cells.

IL-19, IL-20, IL-22, IL-24, IL-26: All are members of the IL-10 family. IL-19 is produced by B cells and monocytes in response to GM-CSF and increases the production of IL-4 and IL-13. IL-20 is involved in cutaneous inflammation, such as that seen in patients with psoriasis, and produced by keratinocytes and monocytes. IL-22 is produced by activated T cells, as well as mast cells, and largely targets hepatocytes to induce acute-phase reactants. IL-24 is produced by monocytes, macrophages, and T_H2 cells. It controls cell survival and proliferation through signal transducer and activator of transcription (STAT) 1 and STAT3. IL-24 plays important roles in wound healing, psoriasis, and cancer. IL-26 is expressed in certain herpesvirus-transformed T cells but not in primary stimulated T cells. IL-26 signals through IL-20 receptor 1 and IL-10 receptor 2.

PROGRAMMED DEATH 1 (PD-1): A member of the CD28 family, PD-1 binds to its ligands, PD-L1 and PD-L2, to limit immune response development. PD-1 blockade with an mAb has recently been used in patients with B-cell lymphoma.

RUNT-RELATED TRANSCRIPTION FACTOR (RUNX): A family of transcription factors that cause epigenetic changes for gene silencing or activation. For example, Runx3 inhibits IL-4 production in conjunction with T-box transcription factor (T-bet) in T_H2 cells and increases IFN-γ production in T_H1 cells.

T_H9: A T-cell subset that is defined by the production of IL-9 and promoted in the presence of IL-4 and TGF-β1. IL-9 has a number of functions, including increased mucus production, in asthmatic patients.

T_H17: T_H17 cells are defined by IL-17A, IL-17F, IL-6, IL-21, IL-22, and TNF-α production and are involved in autoimmune diseases, such as inflammatory bowel disease. IL-23 increases IL-17 production and activates the transcription factor signal transducer and activator of transcription 3 to maintain a T_H17 phenotype of $CD4^+$ T cells. IL-17 in turn induces IL-1β and IL-6.

TOLL-LIKE RECEPTOR (TLR): Essential members of the innate immune system, TLRs are pattern recognition receptors that bind both endogenous and exogenous ligands. TLR4 binds LPS from gram-negative bacteria, heat shock protein 6, and respiratory syncytial virus protein F. TLR7 and TLR8 bind single-stranded RNA and are important for antiviral defense, whereas TLR3 binds double-stranded RNA. TLR9 binds CpG.

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