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The future of biologics: Applications for food allergy

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Allergic diseases affect millions worldwide, with growing evidence of an increase in allergy occurrence over the past few decades. Current treatments for allergy include corticosteroids to reduce inflammation and allergen immunotherapy; however, some subjects experience treatment-resistant inflammation or adverse reactions to these treatments, and there are currently no approved therapeutics for the treatment of food allergy. There is a dire need for new therapeutic approaches for patients with poorly controlled atopic diseases and a need to improve the safety and effectiveness of allergen immunotherapy. Improved understanding of allergy through animal models and clinical trials has unveiled potential targets for new therapies, leading to the development of several biologics to treat allergic diseases. This review focuses on the mechanisms that contribute to allergy, with an emphasis on future targets for biologics for the treatment of food allergy. These biologics include immunotherapy with novel anti-IgE antibodies and analogs, small-molecule inhibitors of cell signaling, anti–type 2 cytokine mAbs, and T_H1-promoting adjuvants. (J Allergy Clin Immunol 2015;135:312-23.)

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Hundreds of millions of persons worldwide are affected by atopic diseases, including atopic dermatitis, allergic rhinitis, food allergy, and allergic asthma, and the frequency has continued to increase over the past several decades.[1,2] A clear progression from early-life atopic dermatitis to later allergic rhinitis, food allergy, and asthma has been commonly observed and is now termed the atopic march.[2] Atopy links these diseases, manifesting as excessive production of IgE antibodies and hypersensitivity to environmental and food triggers.

Abbreviations used

AIT:	Allergen immunotherapy
DARPin:	Designed ankyrin repeat protein
DC:	Dendritic cell
EC:	Epithelial cell
EoE:	Eosinophilic esophagitis
Foxp3:	Forkhead box protein 3
IEC:	Intestinal epithelial cell
ILC:	Innate lymphoid cell
NKT:	Natural killer T
PAF:	Platelet-activating factor
TLR:	Toll-like receptor
Treg:	Regulatory T
TSLP:	Thymic stromal lymphopoietin

Current standard therapies for atopic diseases involve treatment with corticosteroids to reduce inflammation, antihistamines and leukotriene inhibitors, allergen immunotherapy (AIT), and allergen avoidance.[3-6] Although these therapies control symptoms for the majority of patients, some patients experience treatment-resistant inflammation or adverse reactions. Thus there is a pressing need for new therapeutic approaches to treat patients with poorly controlled atopic diseases.

Current research is focused on identifying new targets for the development of biologics, or biopharmaceuticals derived from natural sources such as human subjects, animals, or microorganisms, to treat atopic diseases.[7] Most current biologic treatments are mAbs directed against IgE and cytokines, such as IL-4 and IL-5 produced by T_H2 cells, eosinophils, mast cells, innate lymphoid cells (ILCs), and basophils, which promote allergic inflammation.[8] Omalizumab, an IgE-targeted mAb, is the only approved biologic for treatment of allergic disease but presently only for use in patients with asthma or chronic urticaria.[9,10] Responses to cytokine-directed therapies have been variable, likely because of the heterogeneity of allergy and asthma phenotypes, but therapies targeting specific patient populations, such as anti–IL-4 receptor α antibodies in patients with persistent T_H2-driven asthma, have proved more successful.[11] Thus there is interest in molecular phenotyping and development of biologics that might improve options for personalized medicine approaches to allergy.

The status of biological agents for the treatment of asthma and atopic dermatitis is reviewed elsewhere in this issue of the *Journal of Allergy and Clinical Immunology.* Here we will review the general mechanisms that contribute to atopy with an emphasis on food allergy and discuss future targets for biologics to treat food allergy, a disease lacking any approved therapeutic options.

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Terms in boldface and italics are defined in the glossary on page 313.

FOOD ALLERGY OVERVIEW

Food allergy is as an immune-mediated response to food proteins leading to symptoms affecting the skin, gastrointestinal tract, or respiratory tract. Up to 8% of children and 5% of adults self-reported an allergy to at least 1 food.[12] The incidence of food allergy has steadily increased by more than 18% between 1997 and 2007, suggesting that environmental influences might promote food allergy.[13] The term food allergy encompasses both IgE and non–IgE-mediated diseases, including eosinophilic esophagitis (EoE) and food protein–induced enterocolitis syndrome. This review will focus on IgE-mediated food allergies. Other recent reviews have covered non–IgE-mediated disorders.[14,15]

Despite the increasing prevalence of food allergy, there are currently no approved treatments beyond allergen avoidance and treatment of reactions to accidental ingestion. The reported rates of reaction to accidental ingestion vary widely, with some reports indicating 5% per year for peanut allergy and 42% per year for milk allergy.[16,17] Although the incidence of food allergy-related mortality is low, avoidance and fear of accidental ingestion significantly impair quality of life for children with food allergy and their caregivers.[18]

Oral and sublingual AIT for the treatment of food allergy is an area of active investigation.[19-21] AIT involves the gradual increase of exposure to food allergens to induce desensitization and promote permanent immunologic tolerance to the food allergen.[22] Although the efficacy of AIT for food allergy is still being actively investigated, the considerable rate of adverse reactions, the lengthy time required for therapy, and evidence of rapidly waning protection on cessation of active therapy for many patients are already emerging as significant limitations.[23,24] Thus there is a need for new alternatives or adjunctive therapies that improve the safety and effectiveness of AIT.

Recently, there has been increased interest in the use of biologics for the treatment of allergic diseases, particularly asthma. Relatively few studies have investigated applications of biologics for the treatment of food allergy. Below we will outline the pathophysiology of allergy in the context of food allergy and current or proposed targets for the development of future biologics.

MECHANISMS OF ALLERGY

Allergy is characterized by pronounced type 2 inflammatory responses and circulating and cell-bound allergen-specific IgE. The pathophysiology of allergy is thought to involve 3 main mechanisms: breakdown of tolerance, allergen sensitization, and allergen reactivity leading to anaphylaxis.

Tolerance

Tolerance is the mechanism by which potentially antigenic substances do not elicit an immune response.[25] Tolerance is mediated by several immune cells, including ***antigen-presenting cells***, such as dendritic cells (DCs) and macrophages, and regulatory T (Treg) cells, which are important suppressors of cellular and humoral immune responses (Fig 1). DCs at mucosal surfaces sample luminal contents through the epithelium, receive antigens delivered by goblet cells, or internalize or acquire antigen at secondary lymphoid tissues.[26-28] After antigen recognition, DCs migrate to lymph nodes for antigen presentation to T cells, which is thought to be crucial for the development of tolerance. For example, $CX_3CR1^-CD103^+$ DCs in the gut home to the mesenteric lymph nodes, where they induce the generation of $CD4^+$ forkhead box protein 3 (Foxp3)–positive Treg cells and IL-10–producing type 1 regulatory (T_R1) cells through production of retinoic acid and TGF-β.[29-31] Notably, a

GLOSSARY

ANERGY: A state of immune unresponsiveness induced when a T-cell receptor is stimulated without a second signal from an antigen-presenting cell.

ANTIGEN-PRESENTING CELLS (APCs): Cells that present foreign antigens through MHCs on their surfaces to T cells through T-cell receptors.

T_H3 CELLS: T cells that protect mucosal surfaces in the gut from nonpathogenic non–self-antigens by secreting the anti-inflammatory cytokines TGF-β and IL-10. T_H3 cells inhibit T_H1 and T_H2 cells.

B-CELL CLASS-SWITCHING: A mechanism that changes the antibody production of B cells to a different isotype.

CpG OLIGODEOXYNUCLEOTIDES: Short single-stranded synthetic DNA molecule motifs that act as immunostimulants when unmethylated. CpG motifs are considered pathogen-associated molecular patterns recognized by the pattern recognition receptor Toll-like receptor 9, which is constitutively expressed only in B cells and plasmacytoid dendritic cells.

C-TYPE LECTIN RECEPTORS (CLRs): A large family of receptors that bind to carbohydrates in a calcium-dependent manner. These receptors are expressed on most cell types, including macrophages and dendritic cells, and are involved in fungal recognition and modulation of the innate immune response.

FCεRI: The high-affinity receptor for the Fc region of IgE, an antibody isotype involved in allergic diseases and parasitic immunity.

FCεRII (CD23): The low-affinity receptor for IgE involved in the regulation of IgE levels. Unlike many of the antibody receptors, CD23 is a C-type lectin found on mature B cells, activated macrophages, eosinophils, follicular dendritic cells, and platelets.

IL-4 RECEPTOR α: A receptor that can bind IL-4 and IL-13 to regulate IgE antibody production in B cells and promote differentiation of T_H2 cells.

IL-25: A cytokine known to be involved in gut immunity that induces the type 2 cytokines IL-4, IL-5, and IL-13.

IL-33: From the IL-1 family of cytokines, IL-33 potently drives production of type 2 cytokines. It is also a ligand for IL33R (IL1RL1), an IL-1 family receptor that is selectively expressed on T_H2 cells and mast cells.

PLATELET-ACTIVATING FACTOR (PAF): A potent mediator of inflammatory responses that is a regulator of anaphylaxis. Studies have indicated that blocking the effects of PAF prevents fatal anaphylaxis.

PBMC: Blood cells consisting of lymphocytes (T, B, and NK cells), monocytes, and dendritic cells characterized by a round nucleus.

SPLEEN TYROSINE KINASE: An enzyme expressed in a variety of tissues that can transmit signals from the B-cell and T-cell receptors, as well as a variety of other cell-surface receptors.

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

TOLL-LIKE RECEPTORS (TLRs): A class of receptors expressed on macrophages and dendritic cells that recognize conserved microbial particles that can activate an immune response.

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