Mechanisms of desensitization with oral immunotherapy and epicutaneous immunotherapy

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ABSTRACT

Background: *Oral immunotherapy (OIT) and epicutaneous immunotherapy (EPIT) are emerging therapies for food allergy. With several recently published exploratory trials and randomized controlled clinical trials that support these procedures, there is a clear progress and interest toward making these treatment options available for allergist/immunologists and patients with food allergies entrusted to their care. However, there still remain many questions and concerns to be addressed before these procedures can be fully understood.*

Objective: *The purpose of the present report is to trace some of the important historical milestones in the development of OIT and EPIT that have contributed to their evolving clinical application to the treatment of food allergy, to describe some of the current understandings of the immunologic mechanisms by which these procedures elicit desensitization, and to provide some areas for future inquiry and research.*

Methods: *An extensive research was conducted in the medical literature data bases by applying terms such as food allergy, desensitization, tolerance, unresponsiveness, Treg cells, allergen immunotherapy (AIT), oral immunotherapy (OIT), and epicutaneous immunotherapy (EPIT).*

Results: *OIT and EPIT take their origins from AIT (also called desensitization), a procedure first reported for the treatment of hay fever over a 100 years ago in which slowly increasing doses of a specifically relevant allergen were administered until a maintenance dosage was achieved when the patient was free of symptoms. OIT and EPIT differ from AIT in certain aspects including the route of administration of the allergen as well as their relative shorter period of sustained unresponsiveness.*

Conclusion: *The origins and important historical landmarks that have been made in the field of food allergy immunotherapy are presented in the context of the immunologic mechanisms that contribute to the pathogenesis of these disorders. Although considerable progress has been made in recent years toward making these treatment options available for allergist/immunologists and patients with food allergies, there still remain many questions and concerns to be addressed before these procedures can be fully understood, which can be illuminated by future research.*

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Allergen immunotherapy (AIT) is a procedure first reported in 1911 by Gutermuth et al.[1] for the treatment of hay fever, in which slowly increasing doses of a specifically relevant allergen are administered by subcutaneous cutaneous immunotherapy (SCIT) to an individual with an allergy until a maintenance dosage is achieved when the patient is free of symptoms. The aim of AIT is to induce unresponsiveness (*i.e.*, reduced immune reactivity)[2] or even a definitive absence of reactivity (tolerance)[3] to the offending allergen. The AITs for food allergies currently under study include oral immunotherapy (OIT), sublingual immunotherapy (SLIT), epicutaneous immunotherapy (EPIT), and SCIT.[4] The present report will focus only on OIT and EPIT. The reader is referred to several recent articles that review SLIT and that provide the most current recommendations and guidelines for the use of SLIT AIT.[5–7]

OIT and EPIT are emerging new forms of AIT for food allergy based upon principles of SCIT, in which, in the case of OIT, increasing amounts of a food allergen are fed to an individual with an allergy, and, in the case of EPIT, an adhesive dermal patch that contains a small dose of food allergen is applied to the skin of a patient with an allergy with the common goal of each procedure of increasing the threshold that triggers an allergic reaction. Shown in

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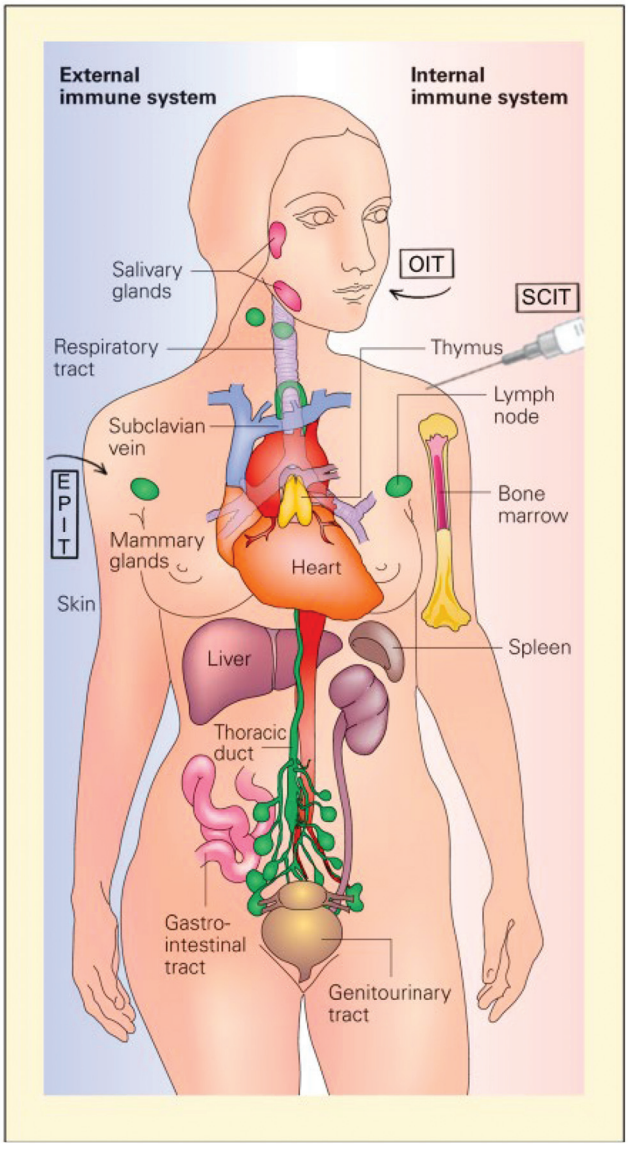

Figure 1. *Schematic representation of the three forms of specific allergen immunotherapy: subcutaneous cutaneous immunotherapy (SCIT), in which allergen is administered by the subcutaneous injection; oral immunotherapy (OIT), in which the food allergen is fed; and epicutaneous immunotherapy (EPIT), in which a small dose of food allergen in an adhesive dermal patch is applied to the skin. (Reproduced with permission and modification from Ref. 8.)*

Fig. 1 is a schematic representation of the routes of allergen delivery in three forms of AIT: SCIT, in which an allergen is administered by subcutaneous injection; OIT, in which the food allergen is fed; and EPIT, in which a food allergen is applied to the skin.[8]

With several recently published multiple small exploratory trials and larger randomized controlled phase II trials[9–11] that support the new OIT and EPIT procedures, there is clear progress and interest toward making these new treatment options available for allergist/immunologists and for patients with food allergies entrusted to their care. Although OIT and EPIT take their origins from SCIT, several differences exist that present new challenges to be addressed before these procedures can be fully understood. The purpose of the present report is to trace some of the important historical milestones in the development of OIT and EPIT that have contributed to their evolving clinical application to the treatment of food allergy, to describe some of the current understanding of the immunologic mechanisms by which these procedures elicit desensitization and/or tolerance, and to provide some areas for future investigative inquiry.

IMPORTANT DIFFERENCES IN MEANING OF THE TERMS: DESENSITIZATION AND IMMUNOLOGIC TOLERANCE

As with all forms of AIT, the ultimate goal of OIT and EPIT is cure, which results in permanent unresponsiveness as defined by the absence of symptoms after ingestion of the food even after prolonged periods of avoidance,[12] and a variety of terms have been used to describe how the procedure works and how unresponsiveness is achieved. These include desensitization, immunologic tolerance, and sustained unresponsiveness. Perceptions of what is meant by these terms, however, are often confusing, and, even among experts working in this field, the terms are not only used interchangeably and without consensus but also can be frustrating both for allergist/immunologists and their patients. None of the terms fully convey how various forms of immunotherapy actually achieve their beneficial effects because their precise mechanisms of action remain poorly understood, supported mainly by a literature composed of descriptive clinical studies in the human and experimental mouse models.

HOW DOES DESENSITIZATION DIFFER FROM IMMUNOLOGIC TOLERANCE?

Desensitization, in the context of food allergy, generally refers to the improvement in food challenge outcomes after AIT and relies on continued exposure to the allergen. Tolerance, however, is a state of nonreactivity to the allergen even when regular exposure is discontinued and does not require continued exposure to the allergen. The ultimate goal of OIT and EPIT is to induce clinical tolerance, defined as no allergic response during oral food challenge (OFC) after withdrawal of the antigen therapy. Classic immunologic tolerance, however, is rarely if ever reached and only desensitization is achieved. Attempts at achieving true tolerance to foods after desensitization has been evaluated in only a few studies, with approaches varying from stopping the food

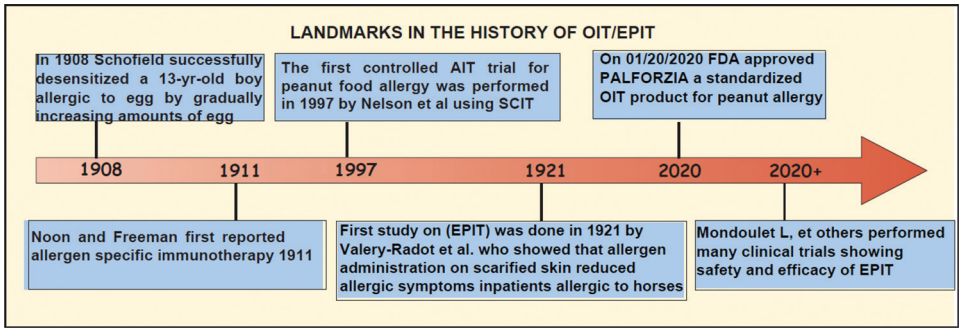

Figure 2. *Some important historical milestones in the development of oral immunotherapy (OIT) and epicutaneous immunotherapy (EPIT).*

for 2 weeks to a few months, followed by OFC.[13,14] Because of the ambiguity in differentiating desensitization from true tolerance, the term "sustained unresponsiveness" was introduced. In a landmark study by Burks *et al.*[15] the term was used to describe children who had been desensitized to egg by OIT to successfully undergo an oral food challenge and subsequently able to introduce the previously offending allergenic food into their diet ad libitum. The term was also used in a subsequent study by Vickery *et al.*,[16] in which sustained unresponsiveness developed in half of subjects with peanut allergy who were OIT peanut-desensitized 4 weeks after stopping OIT. Because of the uncertainty of whether the unresponsiveness was due to spontaneous recovery known to occur in food allergy as well as the unknown duration of unresponsiveness and the inability to define these results as tolerance, the conciliatory term sustained unresponsiveness seems to have been introduced. As will be described later in this report, the outcome of these different studies suggests that, although desensitization in the setting of food allergy can be achieved in most cases, most patients regain sensitization after interruption of food intake.

IMPORTANT HISTORICAL MILESTONES IN THE DEVELOPMENT OF OIT AND EPIT

Shown in Fig. 2 are some important historical milestones in the development of OIT and EPIT.

THE BEGINNINGS OF OIT

The first published report of food OIT appeared in the Lancet in 1908 by Schofield,[17] who successfully desensitized a 13-year-old boy who was highly allergic to egg by administering gradually increasing amounts of egg that were formulated in pills. The communication preceded by 3 years the communication of Gutermuth et al.[1] who first reported AIT in 1911. An important aspect of the procedure by Schofield[17] was a requirement for the continued presence of egg in the child's diet to maintain the unresponsiveness, an important finding that shall be described later in greater detail.

Despite this early success, there was a dearth of literature on food OIT for most of the 20th century, until the procedure was "rediscovered" in 1935[18] and again in the 1980s with the beginning of the food allergy epidemics.[19,20] The first controlled immunotherapy trial for peanut food allergy was performed by Nelson *et al.*[21] in 1997 by using the subcutaneous route. The protocol involved a rush schedule over a 5-day period to reach maintenance of 0.5 mL of 1:100 wt/vol aqueous peanut extract, followed by weekly injections for 1 year.[21] All subjects undergoing SCIT demonstrated increased thresholds of reaction on OFCs and decreased skin-prick test responses compared with controls, whose threshold and skin-prick test results were unchanged.[21] However, because rates of systemic reactions and required epinephrine usage were found to be unacceptably high during both buildup and maintenance phases SCIT, the procedure fell out of favor, stimulating investigation of alternative forms of AIT for food allergy such as OIT and EPIT. In Europe, Patriarca *et al.*[22] in Italy published some of the earliest clinically controlled studies on OIT in 2003. In a more recent review article by Barshow *et al.*[23] in 2021 that describes the mechanisms of OIT, a major limitation of OIT was highlighted. Although the majority of subjects receiving OIT treatment could be effectively desensitized, many experienced losses of desensitization after stopping daily dosing of the food allergen, with a higher risk of loss of desensitization over time.[23]

Thus, there are several conclusions relating to OIT that can be drawn from these earlier past experiences. Although subcutaneous AIT had been used for > 100 years for treating inhalant allergies associated with rhinitis, conjunctivitis, and asthma, initial attempts at subcutaneous AIT for food allergy were unsuccessful. In contrast to immunotherapy for aeroallergens, which induces long-term clinical benefit, sometimes even after cessation of treatment, OIT was associated with only short-term sustained unresponsiveness and there seemed to be a requirement for continued dosing with the food allergen for maintenance of long-term unresponsiveness.

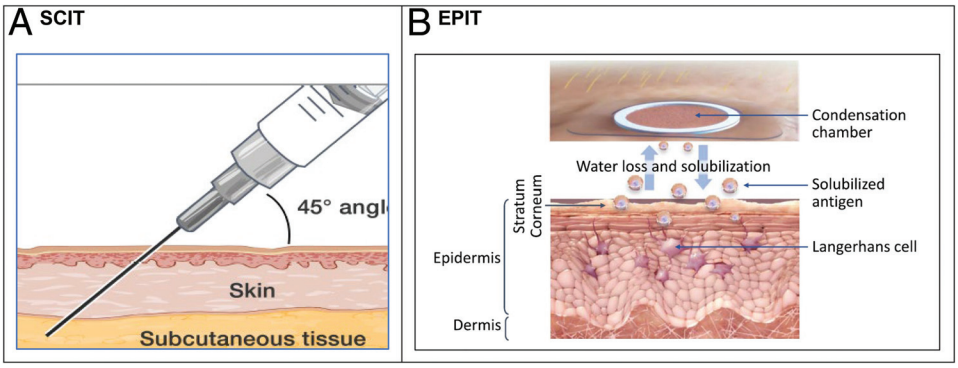

Figure 3. *Schematic representation of method of delivery of allergen in allergy immunotherapy by SCIT and EPIT. (*A*) In SCIT, allergen is delivered by SC injection into the fatty layer of SC tissue just below the epidermal and dermal layers of the skin. (*B*) In EPIT, allergen is delivered* via *an adhesive patch in which the allergen is contained within a condensation chamber. After the patch is affixed to the skin, because of the humidity created in the condensation chamber, the allergen diffuses into the epidermis where it encounters dendritic cells (Langerhans cells) and undergoes antigen processing and interaction with T cells and the initiation of the immune cascade responsible for tolerance induction by Treg cells. (Reproduced with permission from Ref. 33.) SCIT = Subcutaneous cutaneous immunotherapy; EPIT = epicutaneous immunotherapy; SC = subcutaneous; Treg = T regulatory.*

THE BEGINNINGS OF EPIT

The first case study of successful allergy EPIT was reported in 1921 by Vallery-Radot,[24] who found that allergen administration onto scarified skin reduced systemic allergic symptoms in patients allergic to horses (Fig. 2). Later, in 2010, Dupont *et al.*[25] evaluated EPIT in children with cow's milk allergy in a pilot study designed to test clinical efficacy and safety of EPIT by using a patented epicutaneous delivery system (Viaskin; DBV-Technologies, Paris, France).[37] The study showed a tendency toward an increased cumulative tolerance dose after a 3-month treatment period but missed statistical significance. Treatment was well tolerated, with no systemic anaphylactic reactions, but a significant increase of local eczematous skin reactions was observed, which raised safety concerns. In 2020, the U.S. Food and Drug Administration approved Palforzia; developed by Aimmune Therapeutics, Inc., 8000 Marina Boulevard, Brisbane, CA (Peanut [*Arachis hypogaea*] Allergen Powder-dnfp) for oral administration to mitigate allergic reactions to peanut, including anaphylaxis (Fig. 2). After a series of seminal studies by Mondoulet *et al.*[26,27] to substantiate these early findings, many clinical studies have been performed by several investigators that show safety and efficacy of EPIT with the Viaskin epicutaneous delivery system in patients with peanut allergy,[28–31] and the procedure is currently being reviewed for approval by the U.S. Food and Drug Administration.

THE EPIT TECHNOLOGY

EPIT uses the skin's immune properties to induce desensitization.[27,32,36] The technology involves embedding the allergen contained within a condensation chamber imbedded in an electrostatic patch that promotes diffusion of allergen in the thickness of the stratum corneum and toward the immune cells of the epidermis without any skin preparation or adjuvant.[26] Shown in Fig. 3 is a comparison of the two methods of delivery of allergen in allergy immunotherapy by subcutaneous injection (i.e., SCIT) and by direct epicutaneous application to skin via an adhesive patch (i.e., EPIT). In EPIT, the patch is affixed to the skin, and, because of the humidity created in the condensation chamber, the allergen diffuses into the epidermis (Fig. 2).[33,34] Application of allergen to intact skin by using EPIT requires a single noninvasive procedure and allows for long-lasting contact of the allergen with the host in contrast to SCIT or OIT, which requires multiple dosing and the need for injection as in SCIT or ingestion as in OIT.[5]

COMPARATIVE FEATURES OF SCIT, OIT, AND EPIT

A common characteristic of all forms of AIT is the requirement for continued presence of food allergen at maintenance to sustain a continued period of unresponsiveness. The AITs for food allergies currently under study include OIT, SLIT, EPIT, and SCIT with modified allergen, as well as lysosomal-associated membrane protein DNA based vaccines.[4] An overview of the AIT modalities for SCIT, OIT, and EPIT is provided below and compared in Table 1.

A number of good references of AIT modalities are available for further reading. For SCIT and SLIT, the article by Penagos and Durham[5] provides data that support long-term efficacy of the sublingual and subcutaneous routes in AIT. They also provide limited "duration data" on SLIT with pollens and dust mites. A clinical trial of both grass pollen SLIT and SCIT

Table 1 **Comparison of the of allergen-specific immunotherapies for food allergy currently under study and characteristics of the different allergic disorders in which they are used**

Feature	SCIT	OIT	EPIT
Allergic disorder to be prevented	Respiratory allergy (rhinitis, sinusitis, asthma)	Food allergy	Food allergy
Allergens	Inhalant allergens	Peanut, cow's milk, egg, wheat, multifood	Peanut, cow's milk
Etiology	Primarily IgE; also, non-IgE	Primarily IgE; also, non-IgE?	Primarily IgE; also, non-IgE?
Currently available FDA-approved vaccine products	Yes (wide variety of inhalant allergenic vaccines)	Yes (only peanut); Palforzia	None (investigational only)
Route of vaccine administration	Subcutaneous	Oral	Epicutaneous (patch)
Mechanism	Immune tolerance (?)	Immune tolerance (?)	Immune tolerance (?)
Specific immunologic component of tolerance	Treg cells	Treg cells	Treg cells
Tissue inductive site	Skin and draining lymph nodes	GI tract and draining lymph nodes	Skin and draining lymph nodes
Tissue protective effector site	Primarily respiratory tract and other sites	Primarily GI tract and other sites	Primarily GI tract and other sites
Duration	Limited data are available	Limited data are available	Limited data are available
Requirement for continued application of allergen at maintenance	Usually essential	Yes	Yes

SCIT = Subcutaneous immunotherapy; OIT = oral immunotherapy; EPIT = epicutaneous immunotherapy; IgE = immunoglobulin E; FDA = U.S. Food and Drug Administration; Treg = T regulatory; GI = gastrointestinal.

showed that 2 years of immunotherapy were efficacious but insufficient to induce long-term tolerance.

For OIT, Wasserman[35] points out the limited amounts of data that address the optimal dose, dosing frequency, and duration of OIT maintenance. He suggests that, although using higher maintenance doses, more frequent dosing, and a long dosing duration increase the likelihood of attaining sustained unresponsiveness, this regimen also increases the burden of care on the patient on OIT and his or her family. He recommends when used, the OIT maintenance regimen should be individualized.

THE MECHANISMS OF AIT

The mechanisms of AIT involve the integrated involvement of several components of both the innate and the adaptive immune systems, shown in Fig. 4. The initial immunologic response(s) to encounter with allergen are performed by cells of the innate immune system, which carry out the basic functions of phagocytosis and inflammation. Housed within the innate immune system are macrophages, neutrophils, mast cells and basophils, natural killer cells, innate lymphoid cells, and dendritic cells (DC) as well the biologic amplification systems of complement and the coagulation system.[8] Within the adaptive immune system are found components of the helper T (Th) $CD4^+$ population together with their subpopulations Th1, Th2, Th17, and T regulatory (Treg) cells and the cytotoxic $CD8^+$ T cells. Components of the innate immune system are initially activated as part of the host's inflammatory response and together with subsequent involvement of Th2-driven immunoglobulin E (IgE) mediated responses of the adaptive immune system are responsible for many of the clinical and laboratory findings seen in food allergy. (*e.g.*, hives, pruritus, eczema, angioedema, and wheezing). The immunologic responses shown in Fig. 4 are based upon established principles of immunologic processes concerned with the recognition and elimination of foreign substances, and in which the immunologic responses that are subsequently stimulated are dependent upon the efficiency of elimination of the foreign agent, and in which the outcome may be either beneficial if the degree of elimination is efficient or detrimental if ineffectual.[8,38] Successful immune elimination of antigen by the innate and adaptive immune systems is associated

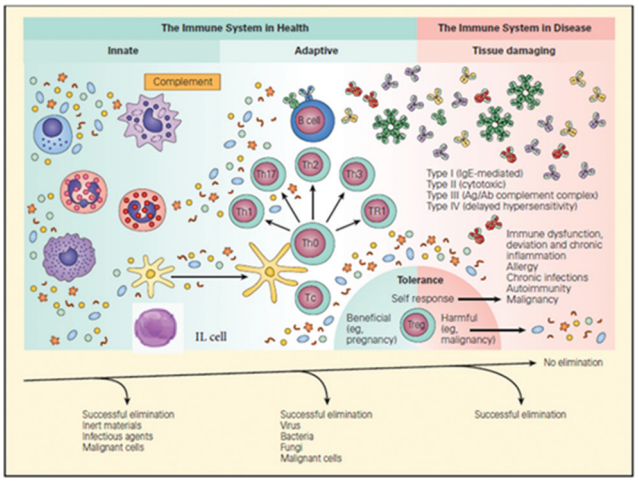

Figure 4. *Schematic representation of the total immune capability of the host based on efficiency of elimination of foreign substances, showing the three phases of the immune response: the innate immune response, the adaptive immune response, and the tissue-injuring phase. (Reproduced with permission from Ref. 8.)*

with the immune system in health and conversely with persistence and failure to eliminate antigen, constitutes the immune system in disease.

Superimposed in Figure 4 and bridging both the beneficial and detrimental outcomes of the immune response are the immune-silencing Treg cells, which are critically involved in tolerance.[8] Defective function or deficient numbers of Treg cells, which normally function to suppress or regulate immune responses, have been shown to substantially contribute to the loss of peripheral tolerance associated with the inflammatory clinical sequelae of both the allergic diseases and the autoimmune disorders.[39,40] A major therapeutic strategy for the treatment of the autoimmune and allergic diseases involves a search for modalities that can increase the diminished quantities or functions of Treg cells in these disorders. Fortuitously, for the field of allergy/immunology, AIT is the singular modality in all of medicine that provides a clinically acceptable treatment regimen for allergic disease by the induction of Treg cells. The mechanism by which Treg cells conduct their immune silencing properties is mediated primarily by a decrease of the interleukin-4 (IL-4) secreting Th2 cell population in which transforming growth factor β plays a pivotal role in maintaining tolerance. Recently, a separate set of regulatory immunosuppressive B cells has been described[41] that is numerically deficient and/or dysfunctional in allergic diseases that can modulate immune responses by the secretion of IL-10, IL-35, and transforming growth factor beta (TGF-β) but their mechanistic role in AIT is unclear. Nonetheless, the goals of AIT are to thwart allergic inflammation by efficiently and safely targeting these immunosuppressive components to induce a state of unresponsiveness to subsequent challenge by the offending allergen in which the Treg cells are considered to play a major role.

For ease of discussion, the components of the immune systems can be organized into four groups, shown in Fig. 5. Before activation of the innate and adaptive immune systems, the skin and mucosal surfaces of both the respiratory and gastrointestinal systems provide a constitutive barrier function (group 1) to prevent penetration of epithelial surfaces by allergens, microbes, and other foreign and potentially noxious substances. When this system is breached, components of the innate immune system (group 2) are first called into play. The DCs as key antigen-presenting cells provide an important bridge to the adaptive immune system by instructing T lymphocytes and B lymphocytes

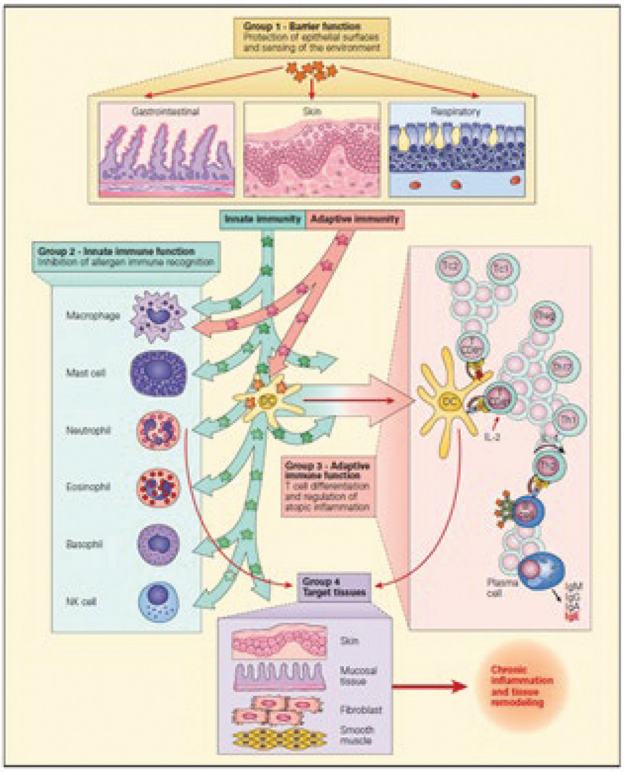

Figure 5. *Schematic representation of the integrated participation of the constitutive, innate, and adaptive immune responses in allergic inflammation arranged into four groups. Group 1 responses are provided by the protective barrier functions of epithelial surfaces of skin and mucous membranes. Group 2 responses include components of the innate immune system. Group 3 consists of the interactive components of the T and B cells of the adaptive immune system. Group 4 responses represent the cumulative effects of the innate and adaptive immune responses, leading to target cell injury. This phase may be of short duration if allergen can be effectively eliminated or more protracted with the failure of allergen clearance, which results in chronic inflammation and tissue remodeling. (Reproduced with permission from Ref. 8.)*

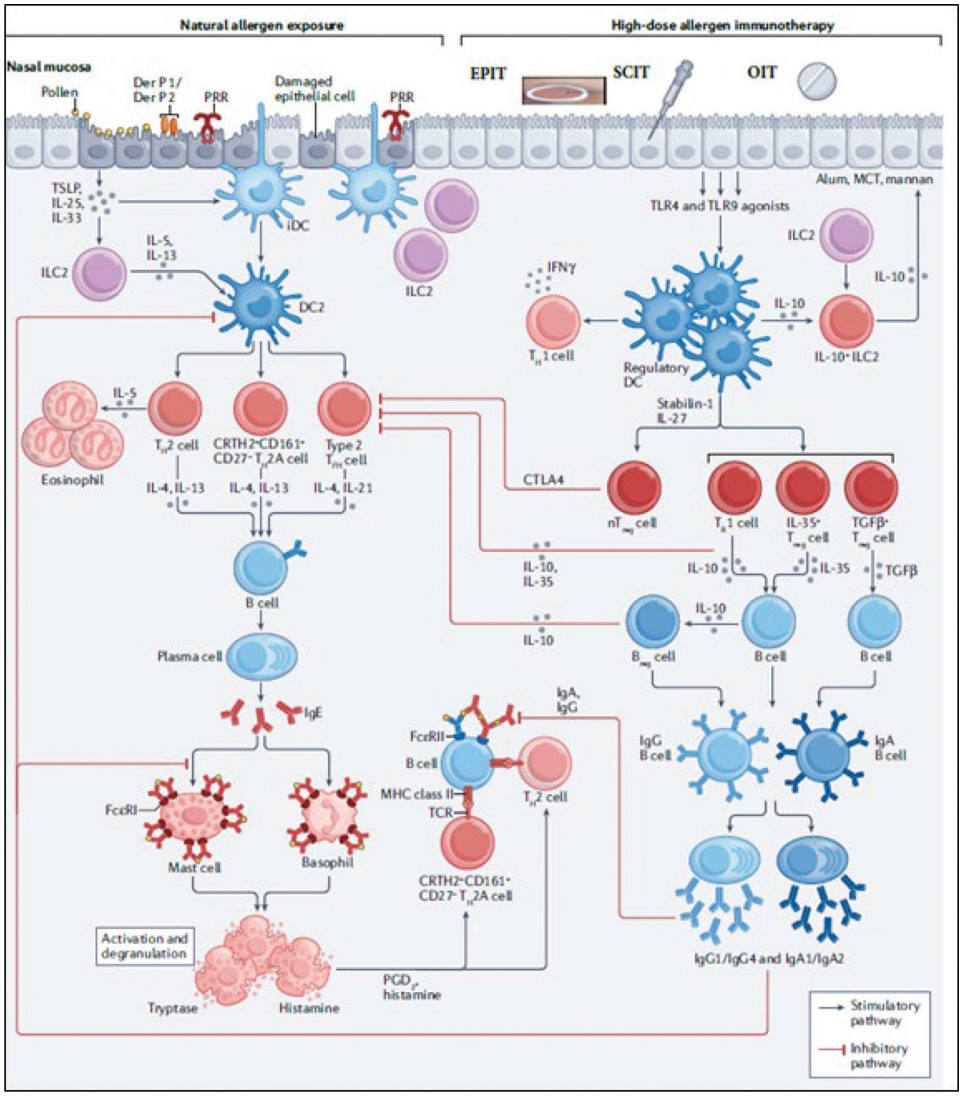

Figure 6. *Mechanisms of allergic inflammation and immunotherapy. (Reproduced with permission and modification from Ref. 42.)*

of the adaptive immune system (group 3) through a myriad of secreted and cell-bound cytokines. The Th2-mediated pathway responses predominate in allergic inflammation and favor production of allergen-specific IgE antibodies. The cumulative end consequence of these total interactions results in the priming, recruitment, and activation of inflammatory cells and release of inflammatory mediators and cytokines, which leads to target cell injury (group 4). Thus, the epithelium serves more than a barrier function. It is becoming increasingly recognized that the epithelium has functional capability as an environmental responder, both at the initiating point of antigen entry (group 1) and at the target cell level (group 4) directing subsequent immune responses by releasing alarmins and proinflammatory cytokines. The resultant target cell injury could be of short duration and of limited intensity with acute inflammation if the allergen can be effectively eliminated or more protracted with failure of allergen clearance and persistence of the allergen (Fig. 4). In the latter case, chronic inflammation and tissue remodeling may result, which represent the most deleterious consequences of the allergic response.

Shown in Fig. 6 is a schematic summary of the immunologic pathways that are stimulated during AIT.[42] During SCIT, OIT, and EPIT, the production of IL-10 and IL-12 by high-dose allergen exposure by regulatory DCs inhibits Th2 cell responses and promotes induction of Treg cell and regulatory B cell responses and immune deviation in favor of a Th1 cell response. This is accompanied by preferential B-cell isotype switching toward IgG and IgA, which results in IgE-blocking activity, which inhibits both IgE-mediated activation of mast cells and basophils, and IgE-facilitated antigen presentation and Th2 cell responses.

MODALITIES THAT MAY ENHANCE EFFICIENCY OF AIT

In recent years, major efforts have explored ancillary modalities that can enhance the efficiency of AIT.

Table 2 **Ancillary modalities to enhance efficiency of AIT**

Induction of Tregs
Administer SCFAs
Probiotics (*Lactobacillus, Bifidobacterium*)
Nucleic acid vaccines and CpG oligodeoxynucleotides for AIT
Use of biologics
Coadministration of omalizumab
Other biologics
Microbial therapy with protolerogenic bacteria
Fecal microbiota transplantation?

AIT = Allergen immunotherapy; Treg = T regulatory; SCFA = small chain fatty acid.

These have included the use of probiotics, biologic agents, and modified allergens to optimize and improve upon existing paradigms (Table 2). These have included procedures to enhance the production of Treg cells, *e.g.,* small chain fatty acids,[43,44] nucleic acid vaccines and CpG oligodeoxynucleotides,[45–47] use of biologics,[48,49] and microbial therapy with protolerogenic bacteria[50,51] to optimize and improve upon existing paradigms. It is hoped that through this multitargeted approach, the field will gain more successful treatment and preventive for the management of food allergy.[52]

CONCLUSION

In summary, the origins and important historical landmarks that have contributed to the field of food allergy immunotherapy have been presented in the context of the progress that has been made in recent years toward making these treatment options available for allergist/immunologists and patients with food allergies entrusted to their care. And yet, there remain many unanswered questions that require a better understanding of all the variables that may affect the efficacy and safety of immunotherapy. These include the following: route of administration, dosing, duration for persisting benefit, evidence of disease modification, greater knowledge of the immunologic response(s) involved, efficacy of treatment with multiallergen mixtures, and safety and convenience.[2] The current immunologic mechanisms that contribute to the pathogenesis of the allergic disorders are presented together with the most up-to-date understanding of the immunologic mechanisms by which OIT and EPIT elicit desensitization. However, there still remain many questions and concerns to be addressed before these procedures can be fully understood. Current procedures achieve desensitization in which only partial success is accomplished by demonstration of an increased threshold that triggers an allergic reaction. Foremost among the challenges is the need for continued research to discover safer and more effective ways toward achieving complete and sustained unresponsiveness to the offending foods so that they can be ingested in unlimited amounts and without the fear of adverse and sometimes fatal reactions.

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