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Allergen-specific immunotherapy for food allergy: latest advances in vaccines

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Abbreviations: IgE, immunoglobulin E; ILC2, innate lymphoid cell; WHO, world health organization; GALT, gut-associated lymphoid tissue; OIT, oral immunotherapy; sublingual immunotherapy; FAST, food allergy specific immunotherapy; EPIT, epicutaneous immunotherapy; TGF, transforming growth factor; IFN, interferons; FDA, food and drug administration

Food allergies and the "old re-emerging" treatments

Allergic diseases pose a global and growing health concern which has increased worldwide in the last years. Allergy results from a complex interaction between environmental factors and genes. In light of the increase in prevalence and costs of food allergy, both in developed and developing countries, effective methods of prevention and treatment would be clinically desirable since food is an integral part of life, but in some cases it can also be deadly for many people.

Although great progress has been made to elucidate the molecular and cellular basis of allergic disorders, it is not completely understood why some individuals develop allergic sensitization to some foods, while the majority of individuals are immunologically tolerant. In addition, it is yet not fully understood which is the molecular basis involved in the immunopathogenesis of the mechanisms elicited against the food harmless antigens. Once diagnosis of food allergy is achieved and the offending allergen or allergenic food is identified, the first clinical or even familial indication is avoidance of the suspected food. Currently, there is no definitive treatment for food allergy: the avoidance of food allergens and treatment of food allergen-induced systemic reactions with adrenaline remain the standard of care. This implies that the patients and their family should be well educated about precautionary measures to avoid exposure to the responsible allergen, and foods should be adequately labeled in terms of allergen content. At present, efforts are being made to develop a disease-modifying therapy. Despite the advances achieved in this field in the last decades, there is still no approved immunotherapy for food allergies. Since the first report of immunotherapy in 1911,[1] many efforts have been made by the scientific community to optimize efficacy and minimize toxicity. Immunotherapy is at present a treatment procedure to induce, enhance or suppress an immune response in different immunological disorders (cancer, autoimmunity, allergy, allorecognition, etc). Although allergen specific immunotherapy has been used for the treatment of IgE-mediated allergy for more than a hundred years, the first randomized clinical trial of oral immunotherapy for food allergy was conducted in 2005.[2] Of note, this therapeutic procedure, although showing great promise, has not been accepted as a routine treatment for food allergy. The induction of adverse reactions during treatment, as well as the uncertainty about long-lasting effect after treatment completion, remain as the main drawback of these therapeutic strategies.

It is widely accepted that the aim of food allergy immunotherapy is to step-wise induce immune desensitization followed by a permanent restoration of oral tolerance. The term *desensitization* accounts for a temporary hypo-responsiveness to the allergen during the regular ingestion of the food, as dosing is discontinued, the protective effect is lost. *Tolerance* is defined as a prolonged ability to ingest large amounts of food proteins with no detrimental reaction, being immunotherapy completed. In spite of the clinical trials with patients and studies using food allergy mouse models, our understanding of the immune mechanisms underlying food allergy and of how the therapeutic conversion to sustained unresponsiveness take place has not been fully achieved.

Mucosal vaccines based on the hygiene hypothesis premises

Mucosal vaccines exploit the potential of these tissues to induce or enhance the regulatory circuits that affect the local and systemic inflammation that undergoes when the immune system is exposed to antigenic components. These complex mechanisms control the inflammatory process that is elicited against pathogenic microorganisms and avoid immune activation against commensals of the microbiota, food and environmental harmless antigens (hypersensitivity), and self antigens (autoimmunity). Although these vaccines have been mainly focused for optimal protection against pathogens that infect the host through mucosal surfaces, they constitute a challenging therapeutic procedure for immunopathologies in which restoration of tolerance is critical to control aberrant immune activation. Reprogramming T cells through an oral immunotherapy has been successfully achieved in autoimmunity, cancer and alloimmune diseases, being food allergy on the scope for an efficient tolerance induction that suppress the local and systemic memory specific Th2 cells, IgE-producing B cells and innate cells such as basophils, mast cells, eosinophils and type 2 innate lymphoid cell.

The delivery of antigens through the gastrointestinal tract remains a major challenge due to unfavorable physiological conditions (pH and enzymes) and significant gastrointestinal biological barriers, which restrict the uptake of antigens. To improve mucosal vaccine efficiency and delivery, several mucosal adjuvants and bioadhesive delivery systems are being investigated and numerous advantages, including protection from degradation, increasing concentration of antigen in the vicinity of mucosal tissue for better absorption, extending their residence time, and/or targeting them to sites of antigen uptake, have been proposed. The use of pharmacological, immunological or microbe-derived adjuvants in human mucosal vaccines to enhance the recipient's immune response to a supplied immunogen, while keeping the injected foreign material at minimum, constitutes a challenge.[3,4] Mucosal vaccines that deviate the allergen-specific Th2 cells, which are central for atopy, into allergen-specific regulatory T cells (Treg), which mediate desensitization and tolerance, may offer a potential treatment for food allergy.

Since Treg are pivotal controllers of innate and adaptive immune responses that govern inflammation in allergic diseases, and impaired Treg numbers, homing properties and/or functioning have been associated with allergies.[5,6] Treg subsets have become frequently investigated as targets for more specific immunotherapy. Particularly, antigen-specific targeting of Treg would enable local and tailor made interventions, while obviating the negative side effect of general immunosuppression. In this respect, the restoration of tolerance in allergic patients may constitute a therapeutic strategy to revert allergic symptoms and the underlying Th2-mediated immunologic mechanisms that may potentially induce life-threatening reactions, such as anaphylaxis, upon exposure to the allergen.

The Hygiene Hypothesis premises give rise to the fundamental basis for modulatory or tolerogenic immunotherapies. Although it may still be debatable, this hypothesis states that the germfree life style of the developed or westernized countries has promoted control of the main chronic infectious diseases, such as measles, TBC, hepatitis, etc, while it has induced a marked rise in the incidence of immunopathologies such as Type 1 diabetes, Crohn´s disease, asthma, food allergy, multiple sclerosis, etc. This observation, firstly stated by Stracham et al.,[7] and then modified by Bach et al.,[8] has led us to understand or interpret the rise in the incidence of asthma, hay fever, atopic dermatitis, food allergy, etc witnessed during the last decades. This epidemiologic shift could be attributed to gene-environment interactions, and to changes in the exposure to pathogenic and commensal microorganism, mainly in early life, which have had an impact on the dynamic and reversible epigenetic modification of human genome. Changes in gene activity or gene regulation facilitate the adaptation of a cell to the environment but it may also increase the risk of chronic inflammatory diseases (cancer, autoimmunity, allergy, metabolic syndrome, etc). Understanding this complex gene-environment interaction will allow us to develop novel generation of treatments that could modify aberrant immune activation and chronic diseases. Based on theses premises the use of Th1 pro-inflammatory[9,10] or immunosuppressant components[11,12] may compensate the deprived immune stimulation and promotion of counter-regulatory circuits that control the Th2-mediated immunity that governs allergic diseases. However, it is currently suspected that not only can microorganism exposure influence the development of the complex immunoregulatory circuits at mucosal sites, but diet and microbiota-derived metabolites are also implicated.

As mentioned before, several reports have demonstrated that tolerance is impaired in allergic patients and that upon active immunotherapy Tregs are expanded,[13,14] and FoxP3 is epigenetically controlled.[15,16] Subsequently, expanded Tregs can control other cells such as innate (ILC2, dendritic cells, basophils and mast cells) and adaptive cells (T and B cells), and the allergic reaction. Hopefully our better understanding of epigenetics will increase our possibilities to develop pro-active treatments to prevent, ameliorate or revert allergy.

Immunotherapies for food allergy

Allergen immunotherapy (also called allergy vaccine therapy) involves the administration of gradually increasing quantities of specific allergens to patients with IgE-mediated conditions with no subsequent clinical reaction upon further natural exposure to the allergen. Due to the fact that proteins and glycoproteins previously used in allergen immunotherapy were extracted from natural sources such as pollens, molds, pelt, insect venoms and foods, they were originally called allergen extracts. In 1998, the World Health Organization (WHO) proposed the term "allergen vaccine" to replace "allergen extract," since allergen immunotherapy is an immune modifier as are vaccines, and are currently performed with purified or recombinant components. Given that many components in the natural source endow adjuvant properties to the allergen extract, the use of purified components in vaccine should be accompanied by additional adjuvants to achieve a directed and more effective induction of immune response.

Although it has been demonstrated in several approaches for food allergy immunotherapy that desensitization is achievable using purified allergens, and that patients can tolerate higher doses of allergen while continuing with treatment, the use of additional components with adjuvant capacity is being explored to enhance its immunomodulatory effect. The use of native, modified ore fragments of allergens containing either B or T epitopes with adjuvants (Th1- or tolerogenic-adjuvants), drugs (corticoids, rapamycin, cytokines, etc) or natural products, such as the nonspecific Chinese herbals, combined with mucosal delivery routes may have a positive impact on the outcome of immunotherapy for food allergy. Nevertheless, minimizing adverse reactions, and sustaining a prolonged immunoregulatory effect that promotes clinical tolerance after treatment is completed and controlled allergen exposure is discontinued; still remain as the major unmet needs for these disease-modifying treatments. In mechanistic terms the establishment of sustained immune tolerance implies the induction of memory Tregs that control memory Th2 and B cells in the absence of regular allergen exposure. This active process is evolutionary induced in the gut-associated lymphoid tissue (GALT), where CX3CR+ macrophages and CD103+ tolerogenic dendritic cells are critical to coordinately sample food antigens from the lumenal intestine, or antigens translocated into the lymphoid follicules, and induce Tregs from naïve T cells in the mesentheric draining lymph nodes.[17] As previously mentioned, Tregs are impaired in patients with food allergy, and following oral immunotherapy in peanut allergic patients, oral tolerance is achieved with hypomethylation of the Treg-specific demethylated region in FOXP3 locus, with the subsequent chromatin accessibility and transcription of this critical factor that endows T cell with regulatory functions.[18] These Tregs behave as conventional effector T cells, and exert critical regulatory mechanisms through which they control the different stages of an immune response. Therefore, it has been shown that an effective tolerogenic immunotherapy is associated with the expansion of mucosal IL-10- and/or TGF-β-secreting FOXP3+ Treg and the development of unresponsiveness to allergen exposure, both in patients and experimental animal models.[18,19] However, additional cells or cell subsets may be involved in the resolution of food allergy (regulatory ILC, regulatory B cells, regulatory dendritic cells, etc).

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Immunotherapy protocols that have showed promise to desensitize individuals to food allergens represents tremendous progress in treating food allergy, however much effort is required to develop immunotherapies with a long-lasting tolerance induction. Desensitizing immunotherapy is generally delivered orally, sublingually or through the skin.

Oral immunotherapy

Some studies have shown hopeful results for oral immunotherapy (OIT) with milk, peanut and egg allergens. However, the risk of severe reactions during allergen administration is of concern.[20,21] (OIT) consists of a daily consumption of milligrams to grams of the selected allergen, which is incrementally raised over weeks to months with the goal of inducing desensitization and then tolerance.[22–24] In the first randomized double-blind placebo-controlled OIT trial performed by Skripak et al.,[24] children with IgE-mediated cow's milk allergy were randomized given milk or placebo. The main point of this study was that patients tolerated 128times higher amounts of milk compared with patients before treatment or with placebo-treated patients,[24] although patients experienced transient adverse reactions after OIT treatment. Keet et al.,[25] showed tolerance in 40 % of subjects receiving milk OIT who passed an oral food challenge when treatment was ceased for 6weeks,[26] while, in other study, three to five years after OIT with milk was completed, 25% of patients consumed normal amounts of milk without any symptoms, and 20% of treated patients experienced anaphylactic reactions during the follow-up period.[25] Similar results were observed in OIT with egg and peanut allergens in non anaphylactic children.[27] These findings suggest that optimization is needed and further studies are mandatory for a complete understanding of therapy to achieve a long-term tolerance.

A relatively new form of non-specific immunotherapy for food allergy is the anti-IgE therapy (with humanized anti-IgE monoclonal antibody-Omalizumab), which has been successfully used in asthma. Sampson et al. started a phase II clinical trial with Omalizumab in 150 patients with peanut allergy; however, the study was terminated early due to the severe reactions that occurred during the peanut challenge.[28] Recently, a combination therapy was studied using the anti-IgE antibody in patients undergoing OIT. Subjects with history of milk anaphylaxis received Omalizumab prior to rapid high-dose initial escalation phase (one day) of orally administered milk, followed by a slower dose escalation (few days and weeks) when Omalizumab was discontinued. Although an enhanced frequency of natural or milk-specific Treg was not evidenced, cell proliferation of milk-specific T cells was consistently abrogated and a plausible explanation was that anergy was induced in memory T cells through a somehow IL-10- and TGF-β-independent mechanism. An increase in IFN-γ/IL-4 and IFN- γ /IL-13 ratios were uniformly evidenced, thus suggesting that immunomodulation was involved. This novel treatment was probed to be effective at inducing immunological desensitization, and patients tolerated more than 200ml of daily intake milk. This study may reflect original findings in experimental animal models which stated that oral tolerance with high doses of antigen administration produced exhaustion of T cells, while low dose administration enhanced Foxp3+ Treg.[29]

Despite the number of promising OIT studies and the increasing interest of the medical community in the development of a routine OIT, a percentage of patients still suffer from adverse side effects. The use of monoclonal antibodies specific for IgE combined with OIT has been explored to increase safety, allowing the immune system to be desensitized to food allergens more quickly and safely than OIT alone. Nevertheless, this protocol should be further optimized to achieve a sustained desensitization during dose maintenance or tolerance induction upon natural diet is resumed.

Although OIT is not FDA approved, studies have consistently found that clinical desensitization is possible with current protocols, while some variables should still be optimized or modified (optimal delivery carriers, novel adjuvants, pure native, recombinant or modified allergenic proteins, etc) to achieve sustained tolerance with minimal adverse reactions and maximum adherence.

Sublingual immunotherapy

Sublingual immunotherapy (SLIT) involves frequent placement of less than micrograms of allergen in solution or in dissolving tablets under the tongue, where it is held for several minutes before spitting out or swallowing. Then, a daily allergen doses with gradually increasing amount of allergen over a period of days or weeks is administered.[30] Cochrane analyses have confirmed the efficacy and safety of sublingual therapy for allergic rhinitis with long-term benefits (1-2years).[31] The first reported double-blind, placebo-controlled clinical trial using the sublingual route for food allergy was done by Enrique et al.,[2] Although most of the SLIT studies have focused on inhalant allergies, emerging clinical trials with SLIT have shown promising results at inducing desensitization in food allergy.[32,33] However, SLIT is not currently recommended for treatment of food allergy.[34] Only few studies have been done in peanut, nuts, kiwi, peach and cow´s milk allergy,[35–39] and they showed lower frequencies of adverse reactions compared with OIT, which is likely due to lower doses of allergen administration and the capacity of the mouth mucosa to induce intestinal tolerance. However, the efficacy of SLIT is still debated and characterization of regulatory cells and mechanisms at the buccal mucosa are emerging.[40] Considering that the induction of Treg is the key mechanism underlying desensitization and tolerance, it has been reported that the current protocols of SLIT have a lower efficiency as compared to OIT.[30,41] Nevertheless, SLIT protocols used for egg, cow´s milk or peanut allergy[42] showed a significant increase in the threshold dose of the food allergen to induce allergic symptoms, a decrease in serum specific IgE along with a rise in serum IgG4 levels , and induction of Tregs.[43] There are only two randomized studies comparing oral and sublingual immunotherapies. Keet et al., found in a clinical trial with 30 milk allergic patients comparing SLIT alone versus SLIT followed by OIT, that similar number of total adverse food reactions were elicited between groups, however, the frequency of systemic reaction was higher in OIT groups. Of note, the oral challenge performed after 60weeks of maintenance doses, rendered a higher allergen threshold in SLIT followed by OIT treated patients compared with SLIT-treated patients.[26,44] Narisety et al.,[44] performed a similar randomized study with peanut allergic patients to compare the safety and efficacy of OIT and SLIT. They found a partial desensitization with at least a 10-fold increases in peanut challenge threshold compared with baseline. They similarly found that efficacy of OIT was greater than SLIT, although safety is still greater in patients receiving SLIT compared with OIT.[44]

In summary, SLIT for milk and peanut has been clearly associated with a substantially reduced risk and severity of adverse reactions, although efficacy and long-term effectiveness are the main drawbacks.

Subcutaneous and epicutaneous immunotherapy

The major form of allergen-specific immunotherapy is the subcutaneous immunotherapy (SCIT), which involves the subcutaneous injection of the allergen. Although, it is widely used for treatment of allergy, it is not accepted as a routine therapy, especially

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for children with food allergy. Recruitment of patients and then (less that 5% of all allergic patients) adherence to SCIT (less than 25% of patients drop out within the first year of treatment) are difficult to achieve.[45] SCIT has proved efficacy in respiratory allergy with comparable results to SLIT. Nevertheless, clinical trials of SCIT in peanut allergic patients showed that anaphylactic side-effects induced during the administration of the native allergen are highly frequent.[46,47] The first attempt to improve this protocol was done by The European multicenter consortium that conducts the prospective Food Allergy Specific Immunotherapy (FAST) project to evaluate the use of alum-adsorbed hypoallergens to control fish and peach allergy. Recombinant mutated allergens, with decreased IgE-binding capacity and intact T cell-reactivity capacity, were included in the SCIT. Patients will be enrolled for a phase I/IIA initial clinical trial, while animal models will be used to evaluate the allergenicity of the recombinant hypoallergenic proteins developed and efficacy of the immunotherapy.[48]

New routes of skin administration were explored and the epicutaneous administration has been more recently investigated in food allergy. Epicutaneous immunotherapy (EPIT) with micrograms of allergen-embedded patch daily administration has been carried out. One of the first clinical trials for EPIT evaluated 18 children with cow´s milk allergy during three months. Although EPIT showed no serious systemic adverse effects, only local pruritus and discomfort was reported with no compromise of patient adherence to the treatment.[49] Phase I,[50] phase IIa[51,52] and phase III [53] clinical trials conducted with peanut allergic patients showed that only mild to moderate local reactions were elicited with induction of desensitization, and an increase in cumulative reactive allergen-dose from baseline. Sampson et al demonstrated using an adjuvant-free mouse model of food allergy that the epicutaneous administration of an allergen induced a particular gut-homing of FOXP3+ TGF-β-producing Treg that suppressed experimental anaphylaxis.

Although EPIT seems to be the less efficacious immunotherapy to achieve desensitization, this route of delivery seems to have fewer and less intense side effects than OIT, with no systemic reaction, and patients prefer wearing a skin patch to orally consuming the same food allergen each day.

Conclusion

Our understanding of the immunobiology of food allergy still remains to be completed. Great efforts are being made to develop novel strategies in animal models exploring combination of mucosal routes,[54] bioadhesive carrier systems,[34,55] novel immunomodulatory and/or tolerogenic adjuvants,[9,10,55,56] immunological drugs to expand Tregs[12] and nanoparticles[56] to prevent or revert food allergy. These finding will undoubtedly provide new parameters to analyze the induction of novel regulatory cell subsets, and cellular and molecular biomarkers for regulatory cell activation, with a direct impact in the design of safer and more effective treatments. Defining markers for tolerance induction are critical for clinical trials. Although the traditional standard of care has been allergen avoidance, there is recent progress in using allergen exposure to induce desensitization in patients. It is to be hoped that in the near future sustained unresponsiveness following the natural exposure of food, without requiring continued exposure to the food allergen, will be achieved with novel and promising disease-modifying immunotherapies.

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Conflicts of interest

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