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Pathophysiological Justification for Allergen Immunotherapy in Food Allergy

Marta Chełmińska[1,2], Katarzyna Puźniakowska[2]

[1]Klinika Alergologii Katedry Pneumonologiii Alergologii, Gdański Uniwersytet Medyczny, Poland
[2]Klinika Alegologiii Pneumonologii, Uniwersyteckie Centrum Kliniczne, Gdańsk, Poland
Email: kpuzniakowska@wp.pl

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Abstract

Apart from avoiding exposure, allergen immunotherapy (AI) is the only causal method of treating allergic diseases. The results of numerous studies have been published concerning the safety and effectiveness of the AI in treating allergic rhinitis, asthma or allergy to the venom of *Hymenoptera* insects. It has also been proven that administration of increasing preparation doses of allergen extractions alleviates the symptoms in patients after the exposure to some sensitizing allergens. The effect of the AI remains visible many years after completion of the therapy. Studies have been done in an attempt to employ specific immunotherapy in patients with food allergy symptoms. They have been mostly concerned with populations of patients suffering from allergy to the protein found in cow's milk and hen eggs. It appears that a need arises to create a new therapeutic method for successful treatment of food allergies and specific allergen immunotherapy seems to be a promising step. Although still in its experimental phase, in many well documented cases the method allows for building patient's tolerance towards small doses of sensitizing allergen and seems conducive to protecting the patient from anaphylactic reactions after incidental allergen consumption.

Keywords

Food Allergy, Immunotherapy, Allergy, Pathophysiology

1. Introduction

Apart from avoiding exposure, allergen immunotherapy (AI) is the only causal method of treating allergic diseases. The first successful allergen immunotherapy (AI) described for food allergy was published in 1912 by Oscar Schloss [1]. The results of numerous studies have been published concerning the safety and effectiveness

of the AI in treating allergic rhinitis, asthma or allergy to the venom of *Hymenoptera* insects. It has also been proven that administration of increasing preparation doses of allergen extractions alleviates the symptoms in patients after the exposure to some sensitizing allergens. Apart from improving the patient's clinical condition, the aim of the AI is to obtain a proper immunological answer to prevent the development of possible allergies in the future. The effect of the AI remains visible many years after completion of the therapy [2]-[4].

2. Immunological Changes Due to Immunotherapy

The effectiveness of immunotherapy has been proven to depend on a change of lymphocyte profile Th2 into allergen-protective Th1. The change causes inhibition of the production of cytokines by Th2, such as interleukins (IL) -4, -5, and -13, and also an increase in the production of cytokines like interferon-γ (INF-γ) or IL-12. In the process of AI activation of regulatory T lymphocytes (Treg), synthesis increases of both the IL-10 and the transforming growth factor-β (TGF-β). Initially, an increase and then a decrease in immunoglobulin E (IgE) are observed along with some increase in IgG4 (the change of class IgG1 into IgG4) and/or IgA. Consequently, inhibition is seen of such effector cells as eosinophils, basofils and mast cells. Irrespective of the route of administering the allergen (subcutaneous or sublingual), the immunological answer is similar and strictly depends both on dose and length of the therapy [2] [5]-[7].

Analysis of the AI mechanism has been carried out along with some research on the role of the receptors for the fragment of Fc IgE of high affinity (Fcε receptor type I, FcεRI) and of histamine receptors (HR). The studies of Nowak *et al*. on the early inhibition of basophile activation during the AI by HR2 done on a group of patients undergoing immunotherapy has proven that it may have a significant importance in building a very early allergen tolerance and a distant desensitizing effect [8].

3. Pathomechanisms of Food Allergy

According to Gell and Coombs' classification, pathomechanism of food allergy (FA) involves all types of immunological responses [9].

Reactions Type 1 that are immediate and IgE dependent constitute about 50% of all FA cases. The occurrence of such reactions is connected with the activation of mast cells of the alimentary system (gastrointestinal associated lymphoid tissue, GALT), of the skin (skin associated lymphoid tissue, SALT), and of the bronchi (bronchial associated lymphoid tissue, BALT) [10]. As a result, from mast cells and basophiles mediators (e.g. histamine, serotonin) are released along with cytokines (TNF-a, IL-4, IL-5, IL-6, IL-8). Degranulation of mast cells and basofiles happening in the alimentary tract is analogical to that seen in the respiratory tract in that it binds specific IgE antibodies to the receptors located on them these receptors are of high affinity (FcεRI) and to the receptors of low affinity(FcεRII) on macrophages and neutrophils [11].

IgE-independent reactions, cytotoxic type II, type III—with the participation of immunological complexes, and type IV—cellular ones, are found in 6%, 10%, and 18% of cases, respectively. Due to hypersensitivity, symptoms in 28% of patients are caused by more than one type of reaction [12].

Cross reactions may also be responsible for the manifestation of symptoms and our insight into them allows for a more penetrating analysis of the development mechanism of symptoms seen in patients upon food products consumption. Differentiation of reaction types resulting from true allergy is necessary due to variations in treatment (symptomatic treatment or specific immunotherapy).

Cross-reactivity defined as an allergy to common epitopes binding specific IgE of various allergens is seen as one of the most important issues in modern allergy. Reactions are triggered when antibodies of class E produced primarily towards one allergen recognize a different source protein. This may possibly lead to a situation in which a patient experiences at the same time hypersensitivity to inhalant, food and contact allergens. Of basic pathogenetic importance is the similarity between structures of primary and tertiary allergen proteins and the aminoacid sequence whose compatibility of over 70% constitutes a real risk of cross-reactivity [13]-[15]. Commonly occurring *panallergens* (*profilins*, *chitinases* and *lipid transfer proteins*) have the leading role in triggering cross-reactions [15].

Profilins constitute a family of proteins of specific weight from 15 to 18 kDa. Found in grass, tree and weed pollens and many fruits and vegetables, they regulate the actin binding in eukaryotic cells and are responsible for passing the signal along the phosphatidylinositol path [16]. Allergy to profilin is diagnosed in 20% - 43% of patients with pollen and food allergy [17] [18].

Chitinases are recognized as two groups of proteins: chitinases of class I and class II. Hevein, a protein of specific weight of 30 - 45 kDa, represents class I. It constitutes the main allergen found in fruit that is connected with the so called latex-fruit syndrome (*Hev b* 11 and *Hev b* 6.02). Class II chitinases show a 60%-homology to class I. The two classes are found in avocados, bananas and chestnuts (*Castanea sativa*) [16]. Endochitynase 4A is the main allergen in grapes that is responsible for severe anaphylactic reactions. It has been also found to keep its properties in wine. Also grapes have LTP which is responsible for the cross-reaction with peaches [19].

Lipid transfer proteins (*LTP*) are proteins of specific weight from 10 to 13 kDa that are widely spread in nature and are highly stable and resistant to being digested with pepsin. They take part in transport of lipids within the cellular membrane and contribute to plant protective mechanism against various environmental pathogens. They are also present in fruit, vegetables and legume as well as grass, tree and weed pollens [20]-[23]. Hypersensitivity to this group of allergens is the cause of severe anaphylactic reactions [16]. The symptoms are usually stronger than those seen in oral allergy syndrome (OAS), and may be of systemic character [21] [24]. These proteins are resistant to temperature and allergic reactions they trigger may develop after consuming thermally processed food. Cross-reactions between LTP of various allergens are known as LTP syndrome.

Cross-reactive carbohydrate determinants (*CCDs*) are common for plant, fruit and vegetable pollens [25]-[27]. They are N- and O-glycans constituting glycoproteins of plants and organisms of invertebrates. The clinical symptoms associated with CCDs are infrequent, yet in some patient groups they manifest dramatically [28]. Such symptoms are noticed in people allergic to wasp, bee venom and latex [16] [29]-[31], and particularly in individuals consuming too much alcohol [32]-[34]. Yet another important allergen belonging to the group specified above is bromelain found in pineapples (Ana c 2) [20].

Other plant- origin allergens that cause cross-reactions have not been found to create this dependence on latex allergen. Such allergens include *polycalcines*-allergen proteins of pollens which have the ability to bind calcium [16] [35], and homological proteins with Bet v 1 (*pathogenesis-related protein PR*-10). Studies have also been done on *cyclophylins, taumatin proteins and storage proteins* [16] [36].

Similarly, among the allergens of non-plant origin, there are allergens that have the ability to trigger cross-reactions whose the reactivity, however, towards latex allergy has not been proven. *Tropomyosin*, one of these allergens, originates from muscle fibres of shrimps, crabs and oysters and is a marker of cross-reactions between house dust mites, shellfish and cockroaches [37]. *Parvalbumin*, another allergen of the kind, is found in various fish species and causes cross-reactions between different fish species and amphibians [38]-[41]. The allergen that triggers a reaction to fish is the allergen of fish parasite (*Anisakis simplex*) [14] [42]. Another protein of animal origin is *serum albumin*. Present in blood, milk, eggs and meat (chicken, beef), it is responsible for cross-reactions between the albumin of various animal species (pork-cat, beef-dog syndrome [43]-[45]. Drouet [46] presented a case of a severe anaphylactic reaction that ended in death of a patient previously diagnosed with pork-cat syndrome, who ate boar meat. What builds a link between plant and animal worlds is *lipocaine* isolated both from plant allergens (apples, cherries, strawberries, pepper) and animal allergens (dog, cat, mouse, cow, horse, cockroach). Lipocaine has been found to trigger limited cross-reactions between species [14].

4. Conclusions

Studies have been done in an attempt to employ specific immunotherapy in patients with food allergy symptoms. They have been mostly concerned with populations of patients suffering from allergy to the protein found in cow's milk [47] [48] and hen eggs [49]-[51]. All the authors have stressed the high efficacy and safety of the therapy measured by determining specific IgE, IgG4 and IgG1. Changes in humoral and cellular immunity associated to AI determine occurrence of desensitisation and long-term tolerance [52]. Some investigations have been published in which patients allergic to peanuts, hazelnuts and fruit [53]-[56] have undergone immunotherapy. Some studies have employ recombinant allergens and Fernandez-Rivas, for example, presented the results of a six-month therapy with peach allergen (e.g. Pru p 3) which belongs to LTP [57]. The results of phase 2 study of recombinant hypoallergenic vaccine (Cyp c1) for fish allergy are under evaluation [58]. A case of successful sublingual immunotherapy in patient with severe anaphylactic reactions due to kiwi fruit allergy was described [59] [60]. Possibility of long term tolerance was established by change in IgE and IgG status [60].

Genetically modified food was first used a few years ago for AI [61] [62] and this method requires further thorough and specific studies.

It appears that a need arises to create a new therapeutic method for successful treatment of food allergies and

specific allergen immunotherapy seems to be a promising step. Although still in its experimental phase, in many well documented cases the method allows for building patient's tolerance towards small doses of sensitizing allergen and seems conducive to protecting the patient from anaphylactic reactions after incidental allergen consumption. Creating recombinant allergens and standardized concentrations of allergens in vaccines allows credible comparison of the results of immunotherapy [57]-[59]. Achieving repeatable long-term tolerance by AI protocols is a next step in determining the future management of food allergy [2] [5] [52] [63].

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