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Sensitization to Food Allergens in the Context of Atopic Comorbidity

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ABSTRACT

The lecture considers a place of food allergy in the profile of allergic and, in particular, atopic diseases and its features, distinguishing this pathology from all other allergies. Three classes of food allergens are characterized, and sensitization to them involving cells and regulatory molecules, such as neurotransmitters, neuropeptides, cytokines, and others mediators, is described in detail.

At the current level of science, the mechanisms of oral tolerance and the causes of its breakdown are considered, resulting in clinical manifestations of food allergies, characterized by high polymorphism and complexity of diagnosis. Not only is a high rate of comorbidity of food allergies emphasized, but also its exceptional risks are pinpointed in terms of the development of anaphylactic shock, which is a difficult issue to explain in nutrition and digestion. The final part of the lecture is devoted to current and future therapeutic interventions in this pathology.

Keywords: food allergens, sensitization, comorbidity, anaphylaxis, oral tolerance

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Пищевая сенсибилизация в аспекте атопической коморбидности

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РЕЗЮМЕ

В лекции рассматриваются вопросы места пищевой аллергии в структуре аллергических и, в частности, атопических болезней, ее особенностей, отличающих данную форму патологии от всех других аллергий. Дается характеристика пищевых аллергенов трех классов и детальное описание процесса сенсибилизации к ним с участием клеток и регуляторных молекул: нейротрансмиттеров, нейропептидов, цитокинов и др.

На современном уровне рассмотрены механизмы оральной толерантности и причины ее срыва, что приводит к клинической манифестации пищевой аллергии, характеризующейся высокой полиморфностью и сложностью диагностики. Подчеркивается не только высокая коморбидность пищевой аллергии, но и ее исключительные риски в аспекте развития анафилактического шока, что является трудно объяснимым вопросом в феноменологии питания и пищеварения. В заключительной части лекции рассматриваются перспективы терапевтической интервенции при данной патологии.

Ключевые слова: пищевые аллергены, сенсибилизация, коморбидность, анафилаксия, оральная толерантность

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

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INTRODUCTION

Food intake is a complex daily physiological process, which is crucial for the existence and functioning of the human body. Therefore, any nutrition–related problems are unacceptable for good health and well-being and the work of all organs and systems, posing a threat to human life as well as an obstacle to the evolution of the species. Unfortunately, modern people often face food allergies [1], and almost half of humanity faces food intolerance – another form of pathology that is also associated with food problems, but is not related to the immune system [2].

In recent years, it has been shown that the extent to which the immune system is involved in the pathogenesis of food allergies varies in different patients. In this regard, several endotypes [3] were described: dominant immunoglobulin (Ig) E-mediated

(with high involvement of T helper 2 cells (Th2) in the pathogenesis), IgE-mediated (with low involvement of Th2 cells), and non-IgE-mediated – independent of the immune system. Special rare phenotypes are also identified, for example, alpha-gal syndrome (mammalian meat allergy).

According to various estimates, a steady increase in the incidence of food allergies and other atopies has been seen lately [4, 5]. At the same time, evolution has formed mechanisms of oral tolerance that resist the manifestations of food allergies [6]. In particular, dietary fibers should be currently added to the list of essential nutritional ingredients, which play the key role in the development of tolerogenic cells, that are crucial for maintaining oral tolerance. The sources of this component are both proper nutrition itself and the functioning of the beneficial gut microbiota [7, 8]. Although food allergies belong to the category of atopic diseases and syndromes, the development of oral tolerance mechanisms has provided this pathology with a number of features that other atopies lack: the absence of delineated subtypes of food allergies, an episodic course, a threat of severe anaphylaxis [6]. On the other hand, food allergies are characterized by pronounced atopic comorbidity [9].

The aim of the lecture was to analyze current views on food sensitization, the mechanisms of its development, and treatment approaches.

FOOD ALLERGIES AND SENSITIZATION TO THEM

Not all food proteins are allergens; therefore, to distinguish between allergen-containing and allergen-free foods, an allergenicity criterion is used (Table 1) [1, 10, 11]. Table 1 demonstrates, that allergenicity depends on many factors, including the structure and physicochemical properties of the allergen itself, as well as the influence of cofactors and the host immune system. Critical factors are the atopic constitution [6], disruption of gut barrier integrity [12, 13], and depleted tolerogenic gut microbiota [14–16].

Table 1

Allergenicity of Food Allergens [1]

Allergen-dependent factors	Biogenic cofactors	Factors of the immune system
Primary amino acid sequence in allergen epitopes	Presence of molecular patterns and adjuvants in food	Genetic predisposition to atopy
Molecular weight lower than 70 kDa		Disruption of oro-gastrointestinal epithelial barrier
Small isoelectric point (charge), low hydrophobicity, solubility in water		Route of exposure
Peculiarity of allergen molecule fold, and epitope proximity to one other		Depleted tolerogenic gut microbiota
Abundance in food		Insufficiency of sIgA
High stability and resistance to the extremes of food processing, as well as to digestive enzymes		

Among the large number of food allergens, eight stand out, which are called the “Big Eight.” The Big Eight shows the strongest allergenicity and causes up to 90% of all food allergy reactions. With age, the child outgrows allergies to cow’s milk, chicken’s egg, and wheat, acquiring oral tolerance [17, 18]. However, peanut-, fish-, shrimp-, and soy-specific memory cells tend to remain for life with a high degree of probability of anaphylactic shock. However, there is no definite answer to the question why some people develop shock when consuming a causal food allergen, while others do not [19–21]. Numerous studies have been conducted, including genetic, epigenetic, transcriptomic, and proteomic ones, which have failed to identify accurate biomarkers associated with a high risk of anaphylaxis in the target groups of patients.

There is another classification, which distinguishes three classes of food allergens [17, 22, 23]. Class 1 allergens are highly allergenic, and some of them (cow’s milk, chicken’s egg, and peanuts) are part of the Big Eight. They cause sensitization through the gastrointestinal tract and display severe clinical signs. Class 2 allergens (for example, apple, carrot, melon, and other vegetables and fruits) are cross-reactive dietary allergens with aeroallergens that trigger sensitization through the unified airway and cause an oral allergy syndrome that mimics seasonal pollen allergies. Class 3 allergens include small proteins weighing up to 10 kDa, dietary supplements, and

colorants (e.g. tartrazine), which cause sensitization through the unified airway or skin and frequently result in occupational allergies. Thus, class 2 and 3 allergens are comorbidity factors, while class 1 allergens may be life-threatening in some patients.

Food sensitization begins when a food allergen enters the body through one or more routes: 1) oral, 2) respiratory, and 3) cutaneous [17]. Another, rarer route is described – the urogenital one [6]. Following the penetration of the food allergen via any of these routes, a classic Th2-dependent IgE response develops, which involves antigen-presenting dendritic cells (DC), T helper 2 cells (Th2), and group 2 and group 3 innate lymphoid cells (ILC2 and ILC3). Subsequently, allergic inflammation develops, in which mast cells and eosinophils act as the main inflammatory cells (Fig,).

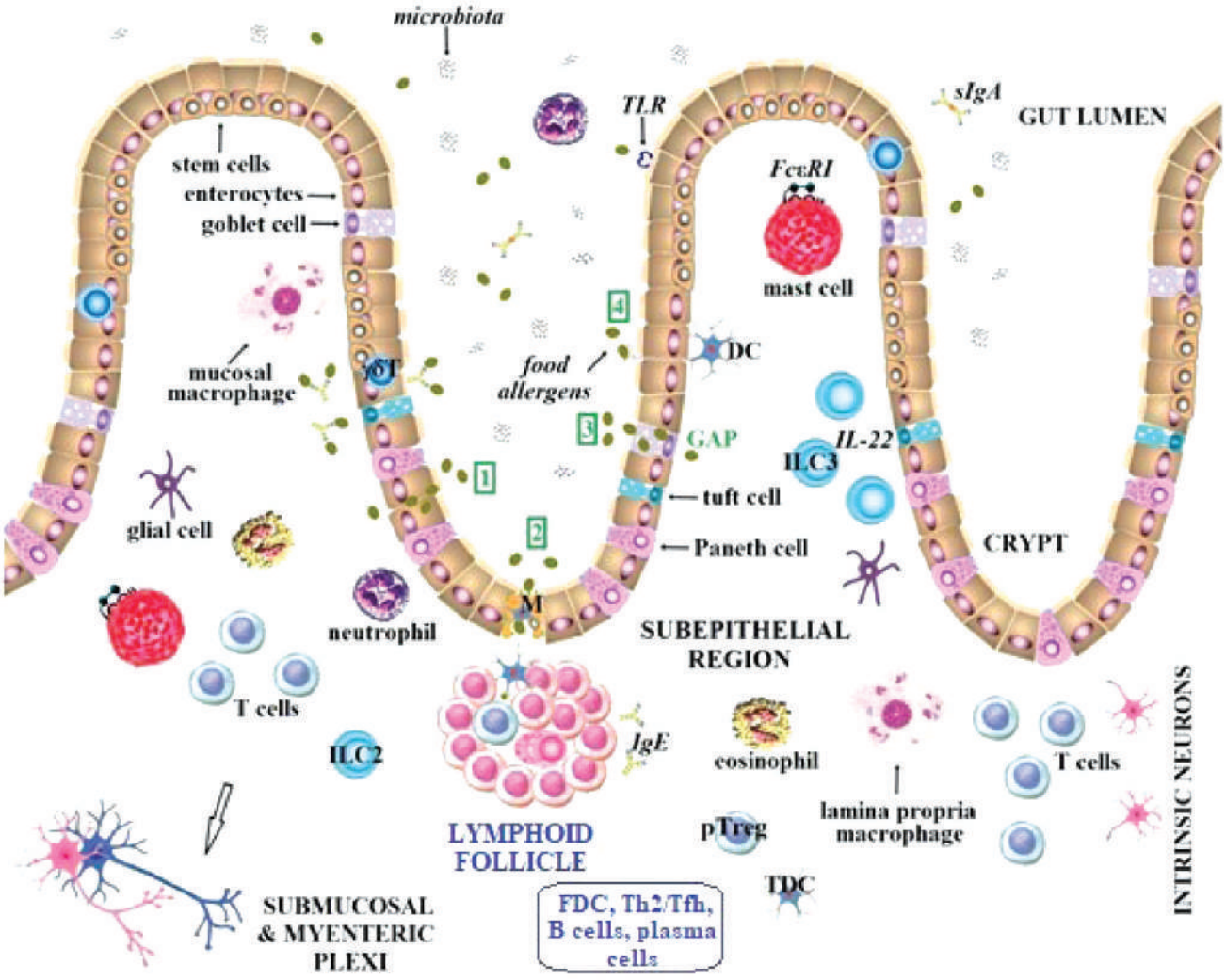

Fig. Food allergen sensitization

The gut epithelium landscape is currently revised due to a new transcriptomic technology, the single-cell RNA-sequencing. Absorptive enterocytes in the small intestine and colonocytes in the large intestine are prevalent cell lineages. In total, the gut epithelium consists of epitheliocytes and stem cells, and many interepithelial cells perform the main function to protect the subepithelial region and internal environment against invaders and allergens. However, under certain conditions, food allergens can penetrate the epithelial barrier using one or some of four routes: (1) due to impaired epithelium integrity or leak; (2) via specialized M cells; (3) by GAP; and (4) due to uptake by long dendrites of DC.

GAP – goblet cell-associated allergen passage, DC – dendritic cell, Th2 – type 2 helper T cell, Tfh – T follicular helper cell, FDC – follicular dendritic cell, ILC2 and ILC3 – group 2 and group 3 innate lymphoid cells, TDC – tolerogenic dendritic cell, pTreg – peripheral regulatory T cell, TLR – Toll-like receptors

According to the Fig., there are four possibilities for allergens to penetrate the intestinal epithelium [12]. Following the penetration, food allergens get to the submucosal layer filled with various cells of the immune system. Activated epithelium produces special alarmin cytokines [24]: interleukin (IL)-25, IL-33, and thymic stromal lymphopoietin (TSLP), stimulating ILC2, DC, and Th2 cells. Activated ILC2 secrete IL-5, IL-9, and IL-13 acting on mast cells and eosinophils. Food allergens are phagocytosed by DC, processed, and presented to Th2, which upregulate a B cell-driven Th2 response with IgE production and memory B and T cell formation. This process occurs in lymphoid follicles – Peyer's patches [25]. Th2 produce IL-4, IL-5, IL-9, IL-13, and IL-33 and stimulate allergic inflammation. IL-33 is considered as a major maturation factor for mast cells [19]. T follicular helper (Tfh) cells secrete IL-21, IL-4, and IL-13 that are important for plasma cell maturation, switching to IgE synthesis, and affinity growth [6]. Tolerogenic neurotransmitters and neuropeptides of the enteric nervous system, TDCs, and peripheral regulatory T cells (pTreg) do not allow food allergens to break allergen tolerance, however, if this occurs, especially with repeated ingestion of food allergens, food allergy manifests clinically. Its symptoms are usually very polymorphic, which makes accurate diagnosis difficult.

ORAL TOLERANCE

Oral tolerance is an essential result of evolution which mitigates threats to modern civilization associated with current changes in the nature of nutrition [1]. Table 2 shows the main mechanisms for maintaining allergen (oral) tolerance.

Table 2

Cellular and Molecular Mechanisms of Oral Tolerance

Mechanisms	References
Tolerogenic dendritic cells, including $CD103^+$	[26, 27]
Peripheral allergen-specific $FoxP3^+$ pTreg cells	[28, 29]
Subsets originated from pTreg: Tr1, Th3, and Tr1-like cells	[6, 30–32]
Regulatory B (Breg) cells and blocking antibodies	[33]
Type M2a (alternatively activated) macrophages localized close to the gut epithelium, in Peyer's patches, and lamina propria	[6, 26, 34]
Protolerogenic cytokines: IL-10, transforming growth factor (TGF) β, IL-35, and IL-27	[6, 35, 36]
Coinhibitory molecules	[37]
Protolerogenic neurotransmitters and neuropeptides	[6, 38, 39]
Tolerogenic gut microbiota	[14–16, 40, 41]

End of table 2

Note. FoxP3 is a master transcription factor of pTreg.

Oral tolerance depends on daily consumption of dietary proteins, the dynamic gut microbiota, changing influence of neurotransmitters and neuropeptides, and continuous traffic of proinflammatory cells and molecules. An important positive role is attributed to a specialized subpopulation of $CD103^+$ TDC, acting in the intestines and mesenteric lymph nodes with the involvement of heterodimeric integrin αEβ7 [27, 42].

In general, risk factors, especially for children, can be genetic predisposition to atopy, epigenetic modifications, and environmental effects [4, 43]. Among them, caesarean birth of an infant, exposure to domestic and farm animals, smoking of parents, air pollution, and insufficient care are of great importance [43]. Disrupted integrity of the epithelial barrier in the oral mucosa may predispose to food allergies, at least in profilin-mediated allergic reactions to peanuts, kiwi, celery, melon, etc. Histological signs of progressive remodeling (increased acanthosis, angiogenesis, and high-density collagen fibers) were found in the oral mucosa of patients. These histological features are comparable to those described in gingivitis and periodontal disease [44].

On the whole, oral tolerance and its loss are the result of a complex interaction between allergens in food, the microbiota that inhabits the gut, and the profile of immune and non-immune cells in gut-associated lymphoid tissue (GALT) and specialized neuromolecules found in the enteric nervous system.

FOOD ALLERGY AND ATOPIC COMORBIDITY

It has been proven that all atopic diseases and syndromes have a common basis – the atopic constitution [6], which can be characterized as a polygenic condition associated with an evolutionary dead-end – hyperproduction of IgE on proteins found in the genome of ancient mites (ectoparasites) on the skin of humans who lived about one million years

ago. This understanding resulted from genetic studies of mites of the *Dermatophagoides* genus, which are the main source of modern allergens, and their closest relatives who live a parasitic lifestyle on mammals and birds (*Psoroptidia* mites) [45, 46].

Food allergies often coexist with other atopic diseases: allergic rhinitis, allergic asthma, and atopic dermatitis. Children sensitized to food allergens are two to four times more likely to have asthma, particularly poorly controlled asthma [47, 48]. Consumption of snails by patients allergic to *Dermatophagoides* mites can exacerbate the course of severe asthma, while aeroallergens, such as wheat, fish, and seafood, can lead to so-called food-induced asthma [49, 50]. Children who are cosensitized to food and aeroallergens suffer from more severe clinical signs of allergic rhinitis [51]. In addition, exposure to airborne food particles during air travel can cause asthma attacks in predisposed patients [52].

Research has found that children with atopic dermatitis are six times more likely to develop food allergies than their healthy peers. In addition, the risk of developing IgE-mediated food allergies is about 40% in children with moderate-to-severe atopic dermatitis. It is known that allergy-free diets cannot cure atopic dermatitis, but may have adverse effects, such as nutritional deficiencies, slow body growth in childhood, and reduced quality of life [53]. In most cases, immune tolerance to causative allergens is restored due to allergen-specific immunotherapy, which results in prolonged remission of the disease. However, in some patients, tolerance is not established, and the disease may progress in the form of eczema, lichenification, and reactivation of secondary bacterial, fungal, and viral infections.

Given high comorbidity and a threat of fatal anaphylactic shock in food allergies, developing drugs for allergen-specific immunotherapy remains urgent. The first such drug for the treatment of peanut allergy was developed, passed all stages of clinical trials, and was approved [54]. This is Palforzia®. Alternative technologies are being developed for the establishment of immune tolerance in exclusively breastfed children from an early age by early introduction of a potentially dangerous product [12, 55], which is based on the fundamental theory of immune tolerance [56]. For example, after about 24 months of oral immunotherapy with hen's egg, 75% of children were able to tolerate a cumulative 5 g of an egg [5]. However, a fully effective result has not been attained [57, 58].

Currently studies on biologics in food allergies and other atopies are being carried out. In particular, phase II clinical trials showed the efficacy of lebrikizumab, a high-affinity IL-13 inhibitor based on monoclonal antibodies, in moderate-to-severe atopic dermatitis in adults [59]. However, we have to admit that new approaches to intervention in food allergies have not emerged in the last 57 years.

CONCLUSION

The steady increase in the prevalence of allergic atopic diseases and syndromes is now becoming as pressing as such problems as global warming, the threat of famine, wars, and new pandemics, because food allergies are a challenge to human civilization and our species [6].

On the one hand, the gastrointestinal tract was created by evolution as a zone of tolerance, but on the other hand, it is here that the most severe and fatal forms of allergies can originate – food anaphylactic shock [60]. Other food allergy-related problems should be mentioned [6]: significant difficulties in accurate diagnosis, high-risk diagnostic procedures, broad differential diagnosis due to the polymorphism of symptoms, and harder to achieve therapeutic efficacy compared to other atopies.

The enteric nervous system in the gastrointestinal tract produces many neutrotransmitters and neuropeptides [61, 62] and contains the largest microbial community in the body [17]. It makes it one of the control centers in the human body that interacts with the brain via the gut – brain axis [63]. It should be recognized that this system has not yet been sufficiently studied, and its value in terms of function and phenomenology is not fully understood.

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