NORMAL AND DISEASE-ASSOCIATED LEVELS OF SPECIFIC IGG AGAINST FOOD ANTIGENS

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Tolerance to food antigens is essential for body's sustainable development under constant antigenic load. Specific IgG against food antigens have been extensively studied in the literature over the recent years. The presence of those associated with various disorders and introduction of elimination diets for certain food products result in good treatment outcomes related not only to the gastrointestinal tract. Investigation of the impact of the long-term IgG-mediated hypersensitivity to food antigens associated with the increased blood-brain barrier permeability is also relevant when studying pathogenesis of the central nervous system disorders. However, identification of specific IgG in the generally healthy people having no history of allergy or inflammation currently provides no clear understanding of their nature and functional significance. Specific IgG are of great interest in terms of predicting the development of functional disorders, remission and treatment of disorders, changes in susceptibility to food antigens at certain age. The results of specific IgG studies are equivocal, which confirms the need to study their structure, epitopes capable of activating autoimmune processes considering the combined effects of medication, environmental conditions and social living conditions. The paper provides the analysis of the currently available research focused on studying specific IgG against food antigens. The data on identification of specific IgG in individuals with various disorders are provided, as well as the gender-related and age-related differences in antibody detection, the relationship between the antibody levels and the rate of food product consumption.

Keywords: food antigens, specific IgG, anergy, tolerance, atopy

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УРОВНИ СПЕЦИФИЧНЫХ IGG К ПИЩЕВЫМ АНТИГЕНАМ В НОРМЕ И ПРИ ПАТОЛОГИИ

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Толерантность к пищевым антигенам — необходимое условие для формирования устойчивого развития организма при постоянной антигенной нагрузке. В последние годы достаточно широко изучены специфичные IgG к пищевым антигенам. Их наличие при различных патологиях, а также введение элиминационных диет к определенным продуктам питания дают хорошие результаты в лечении заболеваний, и не только касающихся желудочно-кишечного тракта. Изучение влияния длительной IgG-опосредованной гиперчувствительности к пищевым антигенам, связанной с повышением проницаемости гематоэнцефалического барьера, актуально и при исследовании патогенеза заболеваний центральной нервной системы. Но выявление специфичных IgG у практически здоровых людей, не имеющих в анамнезе аллергии, воспалительных реакций, на данный момент не дает четкого понимания их природы и функциональной значимости. Специфичные IgG представляют большой интерес с позиции прогнозирования формирования нарушений функционирования организма, ремиссии и лечения заболеваний, изменения восприимчивости к пищевым антигенам в определенном возрасте. Результаты исследований специфичных IgG неоднозначны, что подтверждает необходимость изучения их структуры, эпитопов, способных активировать аутоиммунные процессы, учитывая сочетанное влияние лекарственных препаратов, экологической обстановки и социальных условий жизни. В статье проведен анализ современных исследований по изучению специфичных IgG к пищевым антигенам. Представлены данные о выявлении специфичных IgG при различных патологиях, гендерные и возрастные различия при выявлении данных антител, зависимости их концентрации от частоты употребления пищевых продуктов.

Ключевые слова: пищевые антигены, специфичные IgG, анергия, толерантность, атопия

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Food antigen ingestion associated with the development of the defense mechanisms aimed at ensuring tolerance to these antigens takes shape within a few months after birth. Interaction between food antigens and the immune system in the intestine results in generation of Tregs $CD4^+CD25^+$ specific for food antigens, which is crucial for induction of tolerance to these antigens. Furthermore, the Treg cells have an anti-inflammatory effect due to expression of IL10, TFGβ, as well as to inhibition of the basophil, eosinophil and mast cell activity. Anergy, being an essential mechanism underlying tolerance to food antigen ingestion, helps maintain gomeostasis in the intestine in cases of chronic high antigenic load. It should be borne in mind that the today's food production is often associated with exposure to chemical substances negatively affecting the immune system function by causing disruptions in the tolerance mechanism, breaking barriers and increasing

intestinal permeability to food antigens. The use of medications, such as aspirin and non-steroidal anti-inflammatory drugs, can interfere with the barrier function of the intestinal epithelium and increase its permeability, and the effect is enhanced in case of simultaneous food antigen ingestion [1–4]. Disruption of the intestinal barrier causes inflammation in the intestine and autoimmune disorders [5–11].

According to the data provided by the US Food and Drug Administration, the main foods causing food allergy in 90% of cases include milk, eggs, peanuts, hazelnuts, shellfish, wheat, soybeans, fish and other food products containing these allergens as direct or hidden ingredients [12]. Corn, sesame, meat, celery, lupine, honey, fruit and vegetables also have high allergenic potential [13]. However, the allergic reaction is caused not by the food product itself, but by certain allegens it contains. For example, these are casein and whey proteins for milk [14], ovomucoid, ovotransferrin, conalbumin, lysozymes, ovalbumin, etc. for eggs [15], tropomyosin, arginine kinase, myosin light chain for shellfish [16], parvalbumins, gelatin, enolase, aldolase, tropomyosin, etc. for fish [17]. Processed foods may contain certain hidden allergens, which also induce immune response in the body.

There are several mechanisms underlying crossing the intestinal mucosal barrier by food antigens. These can permeate through the small intestinal epithelium due to passages formed by secretory epithelial cells (SAPs), which allows food antigens to enter the underlying mucous membranes of the small intestine. SAP formation is induced by the IL13 cytokine through the STAT6-independent and CD38-cADPR (cyclic adenosine diphosphate ribose)-sensitive pathway, it requires IL-4Rα expression by the small intestinal epithelium [18]. Another variant is represented by capture and transport of food antigens by goblet cells (GAP) associated with developing tolerance to these antigens by means of maintaining the level of the $CD4^{+}Foxp3^{+}$ regulatory T cells and stimulation of the IL10 anti-inflammatory cytokine secretion by macrophages in the lamina propria [19]. Thus, tolerance to the ingested foreign antigen is formed. Food antigen ingestion also becomes possible when the intestinal epithelium tight junctions are disrupted, which is observed in individuals with inflammatory disorders of the gastrointestinal tract. Furthermore, food allergens and some food emulsifiers can have the same effect, increasing epithelial permeability, transport, and allergic sensitization, causing pro-Th2 cytokine activation, and facilitating permeability to other food allergens [20, 21]. Transcytosis mediated by microfold cells (M cells) is the best-studied mechanism underlying food antigen entry. The M cell function is to transport luminal substances in order to induce IgA and T cell responses in the Peyer's patches and lymphoid follicles. Infections, aging, inflammation can reduce M cell density, thereby increasing the body's susceptibility to infections [22]. Moreover, food antigens can be captured directly by the lamina propria antigen-presenting cells (LP-APC) via elongation of transepithelial dendrites (TEDs) into the intestinal lumen. TEDs are capable of squeezing through epithelial cells to capture bacteria without epithelial barrier disruption [23, 24].

The data on the gender-related differences in the range of identified specific IgG against food antigens are ambiguous, however, the majority of researchers note that elevated levels of such IgG are observed in women. According to the findings, women have higher levels of specific IgG against all foods than men, except for IgG against chicken and corn [25]. Women had much more specific IgG against wheat (74% vs. 25.5% in males), corn (77.3% vs. 22.7%) and kola nut (71.9% vs. 28.1%) [26]. A significant increase in the levels of anti-egg and anti-shrimp IgG was also reported in women [27]. Food intolerance is much more prevalent among women than among men [28, 29], which is probably due to the fact that female sex hormones (estrogens) have a pro-inflammatory effect and increase susceptibility to atopy, while testosterone is a potent inhibitor of histamine that is known to suppress the mast cell degranulation [30, 31]. The findings of studies focused on the age-related features of identification of specific IgG against food antigens are also equivocal. There is evidence that individuals under the age of 40 have higher levels of specific food IgG against gliadin, egg white proteins and barley compared to elderly patients [26]. According to the findings, the levels of anti-shrimp and anti-crab IgG increase with age; the levels of IgG against tomatoes, chicken, pork, and codfish decrease starting from childhood and then slightly increase by the age of 45; the concentrations of IgG against eggs, milk, soybeans, wheat, corn, and rice decrease with age [27].

Serum levels of specific IgG associated with various disorders are rather extensively studied, which can be useful for the diagnosis of adverse food reactions. However, the role of these antibodies in the disease pathogenesis is still poorly understood and the clinical benefits of testing for the antibodies are highly questionable. It has been shown that depression in adolescents is associated with higher detection rate of IgG antibodies to food antigens against the background of elevated histamine, S100b protein, and homocysteine levels. Furthermore, the authors believe that the chronic food antigen-specific IgG-mediated hypersensitivity reaction or chronic food intolerance, not chronic low-grade inflammation, underlies the adolescent depression pathogenesis [32]. The IgG antibodies against rice, tomatoes, egg yolk/white, wheat, and corn are most often identified in individuals with Crohn's disease. In this case introduction of the elimination diet contributes to induction of the long-term remission [33]. The feature of response to food antigens is that some of antigens have the structure homologous to that of the body's tissues; when the intestinal barrier is disrupted, ingestion of such antigens causes the immune response, triggering the autoimmune processes [34, 35]. The following food products show the highest degree of homology to proteins of human tissues: milk, wheat, food proteins rich in glycine, glucans, pectins, shrimp tropomyosin, and pork [36–40]. Similarity of the peptide sequences of the antibody against wheat gliadin (EQVPLVQQ) and antibody against the cerebellar nervous tissue (EDVPLLED) has been found in children with autism, thus, antibodies against both Purkinje cells and gliadin peptides can be produced in such patients, which can be the cause of certain neurological symptoms of autism [41]. Type 1 diabetes mellitus is an organ-specific autoimmune disease, which is linked to the effects of the cow's milk proteins by some researchers [42]. It is also assumed that the produced antibodies against the cow's milk albumin can cross-react with the surface protein specific for β-cells (p69) and, therefore, cause their dysfunction. Furthermore, similarity of the cow's milk proteins to proteins of human tissues is considered to be the cause of such disorders, as uveitis, multiple sclerosis, systemic lupus erythematosus, Crohn's disease [43, 44]. High similarity of human aquaporins and aquaporins found in plant-based foods (soybeans, corn, spinach, tomatoes), as well as inhibitors of serine proteinases (serpins) of legumes (beans, lentils, peas, peanuts, lupine, alfalfa, and clover) has been revealed. Aquaporins are membrane proteins found, inter alia, on the blood-brain barrier astrocytes and involved in maintaining homeostasis and water metabolism, electrical activity, neurotransmission modulation, and excitability. Aquaporins of plant-based foods are very stable and, therefore, are ingested in the unmodified form. These can

trigger autoimmune responses to aquaporins of human tissues, which results in sensory impairment and neuroautoimune inflammatory disorders [45]. Glycines of food proteins of meat, chicken, eggs, fruit, vegetables, grains, cereals, rice, soybeans, etc. show molecular similarity to collagen, keratin, actin, and human ribonucleoprotein, thus, their penetration through the intestinal barrier can trigger auroimmune responses. Hypersensitivity reaction to food antigens of cereals and dairy products has been revealed in children with autism spectrum disorder [46]. Hypersensitivity reaction to casein is reported in individuals with metabolic disorders and insulin resistance [47]. Furthermore, the researchers assume that the IgG-mediated hypersensitivity to the casein and soybean antigens increases the risk of anemia and hypothyroidism [48]. Food antigens can play a role in etiology and symptoms of Hashimoto's thyroiditis, which is associated with the significantly higher levels of IgG antibodies specific for plums; a negative correlation between the combined levels of IgG against coffee, tea and the number of symptoms has also been revealed [49]. Food allergy is associated with the decrease in the intestinal IgA levels, increased allergen absorption and microflora alteration [50]. Specific food IgG against kola nut, yeast, wheat, kidney beans, peas, corn, and egg white proteins are most often found in patients having symptoms of allergy and no laboratory confirmed allergy [14]. The data on the effects of the rate of food product consumption on the levels of specific IgG are equivocal. There are papers showing that food consumption is not correlated to the IgG levels [49]. The authors of other papers point to the direct relationship between food product consumption and the levels of specific IgG [25, 51].

CONCLUSION

Specific IgG against food antigens are revealed in individuals with the gastrointestinal tract diseases, metabolic disorders, neurodegenerative diseases, autoimmune disorders, etc. However, the mechanisms underlying intestinal permeability alteration and abnormal tolerance to food products are poorly understood. Despite the studies focused on introduction of elimination diets and its beneficial effects, the role of specific IgG in the disease pathogenesis is still unclear, and the clinical benefits of testing for such IgG are questionable. Identification of IgG against food antigens has some gender-related and age-related features. Thus, exploring the mechanisms underlying the association of abnormal tolerance to food antigens can provide the basis for the development of the therapy methods during treatment and the methods to predict the risk of disorders.

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