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The Role of IL-17 in the Development of Food Hypersensitivity and Metabolic Disturbances

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Abstract

The indices of the specific hypersensitivity of the immune system to 111 food antigens, divided into clusters according to related antigens, were analyzed and the connection to the main clinical and immunological parameters of inflammation in patients with metabolic syndrome was estimated. It is found that IL-17 can be a marker of food hypersensitivity. Milk protein-casein is a trigger of inflammation in patients with metabolic syndrome.

Keywords: hypersensitivity, immunological tolerance, food antigens, metabolic syndrome

Relevance

IgG indices of mediated hypersensitivity to food antigens (food AG) are an easily accessible criterion of changes in food tolerance (FT) related to the quantitative characteristics of food, the quality of digestion, and the state of the immune system of the intestine. FT to the local food environment is a dynamic active process in human life that is implemented with a combination of factors: the genetics of digestive enzymes, the functional state of the microbiota, the expression of TLR2 and TLR4 on enterocytes, the production of sIgA, IgG, the ratio of pro-inflammatory and anti-inflammatory cytokines, dendritic cell activity, Treg- and Th17-lymphocytes [3, 7].

Signs of a manifest or temporary disturbance of FT (occurring for various reasons) are essentially protective reactions aimed at eliminating of the causative antigen, if it appears in the bloodstream. These known effector reactions are accompanied by the synthesis of specific IgG and/or IgE antibodies, the formation of circulating immune complexes, the reactions of

antibody-dependent cytotoxicity, the sensitizing of lymphocytes and releasing of mediators. Changes in immunoregulatory control of the processes of parietal and intracellular digestion depend on the attributes of antigens of food products, including the specific and quantitative characteristics of food AG. Effector reactions can be triggered by any of the listed ways aimed at maintaining control of homeostasis and FT but can also lead to the development of an AG-dependent chronic inflammatory process, including indicators of systemic metabolic disorders in the human body [2, 3, 7].

Changes in the dynamics of specific IgG to food AGs, divided into related clusters (associated with the properties of the structure of epitopes, a representative set of food AGs and typical digestive enzymes) can be calculated by the ImmunoHealth' methodology. This makes it possible to evaluate the criterion of "normal-abnormality" of hypersensitivity to food AG, and hence to estimate the potential activity of effector reactions. It is known that IL-17 is associated not only with the maintenance of immune homeostasis of FT in the intestinal mucosa, but also the development of autoimmune reactions [1].

Which makes IL-17 the object of close attention.

Objective

Evaluate the contribution of IL17 in the development of reactions of food hypersensitivity and metabolic disorders.

Methods

We examined the venous blood of the volunteers with different body mass index (BMI).

Volunteers with elevated BMI: 35 women and 35 men 20-55 years, BMI > 27. For volunteers with a BMI > 29.9, the waist circumference was > 94 cm in men, and > 80 cm in women. Volunteers with normal BMI: 15 women and 15 men 20-55 years, n = 15; men 18.5 < BMI < 25.

The main criterion for including in control group was the absence of diseases of the gastrointestinal tract in medical history. At the time of the study, they were not on clinical dispensary with chronic infectious and parasitic diseases.

The patients were divided into groups according to their BMI only.

The concentration of cholesterol in serum, triglycerides, HDL, LDL, glucose, C-reactive protein (CRP), ALT, AST and the total white blood cells (WBC) were determined.

The concentrations of IL-4, IL-6, IL-10, IL-17, INF-gamma, TSH, free T3, insulin was determined by ELISA. In addition, insulin resistance index and atherogenicity index (AI) were measured.

Specific IgG-mediated hypersensitivity to 111 food antigens was measured by a multicomponent ELISA using the methodology of ImmunoHealth [5]. The hypersensitivity marker was the concentration of specific immunoglobulins G (sIgG) to the food AG with a personified criterion of “norm-anomaly”. The study is a screening test of a statistically representative sample of food AG.

The biological environment of the model study in the situation “in vitro” was a serum sample of the patient. The test result represents a set of N values of concentration of sIgG (C_n), $1 \leq n \leq N$, where N is the total number of food AGs. From the point of view of applied problems of dietetics and allergology, the result of the ELISA test of IgG is the qualitative and quantitative evaluation of the probabilistic reaction of “hypersensitivity type III”. The “Type III hypersensitivity” reactions were identified by a personified “norm-anomaly” criterion, determined by a statistical analysis of the ELISA results.

The statistical processing of the data was carried out via programs Statistica v6.0, SPSS 19.0, using the Mann-Whitney criterion (U), the Spearman rank correlation coefficient, the Fisher criterion (two-sided) and the odds ratio (OR).

Results and Discussion

Volunteers with elevated BMI showed significantly increased concentrations of cholesterol, triglycerides, LDL, IL-6, IL-17, glucose, CRP, ALT, insulin, insulin resistance and atherogenicity indices. The concentration of HDL and IL-10 was statistically lower than that in volunteers with normal BMI (Table 1).

Studying the frequency of specific IgG-mediated hypersensitivity to 111 food AGs in two groups ($BMI > 27$ and $18.5 < BMI < 25$) showed that the most significant difference occurred for the products containing casein proteins-39 and 5%, soy- 41 and 19%, gluten-13 and 0%, respectively.

Moreover, the relationship between the established hypersensitivity to casein AG, the risk of atherogenesis ($AI > 3$) $OR = 2.3$ (2.8, 23.9), and the increased concentration of IL-17 was statistically significant ($p < 0.05$). A moderate statistically significant relationship was found between IL-17 and C-reactive protein ($p < 0.05$) in the group of patients with a $BMI > 27$. Our results show a significant association between IgG-mediated specific hypersensitivity to certain groups of food AGs and IL-17.

Hypersensitivity to casein had the highest frequency of occurrence in our study (Fig. 1 and 2).

One of the reasons for this phenomenon may be that casein, being a complex protein, is the most difficult protein to digest in the digestive tract, and in modern scientific studies there are indications of the role of casein antigens in

the development of diabetes in children, autoimmune thyroiditis and oncology [6].

If the proteases participating in digestion cannot completely break down the casein, its unsplit fragments can damage the intestine with the development of chronic inflammation of enterocytes and possibly influencing on obesity processes [2, 6, 7]. Chronic inflammation associated with increased intestinal permeability changes the activity of the immune system in the intestinal tract, leading to hyperactivation of Th-17 lymphocytes and the hyperproduction of pro-inflammatory cytokines: IL-6, IL-17.

The increase in IL-6 plays an important role in the development of insulin resistance and in development of metabolic syndrome [1, 3].

As a result, the number of different food AGs entering the bloodstream increases, as well as the synthesis of IgA, IgG and the formation of immune complexes, the rheology of blood changes [1, 4].

Conclusion

It was first established that IL-17 could be a marker of food hypersensitivity, which triggers the development of chronic inflammation and metabolic disorders in patients with elevated BMI.

The main role in this inflammation belongs to the milk protein-casein.

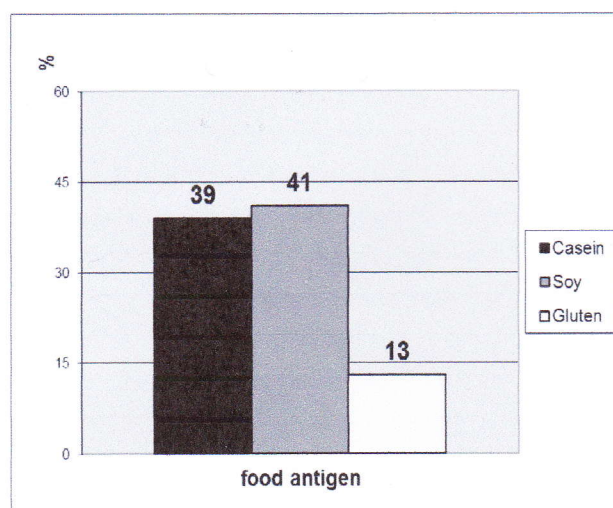


Fig. 1. Frequency of occurrence of specific hypersensitivity to different groups of food antigens in volunteers with an increased body mass index

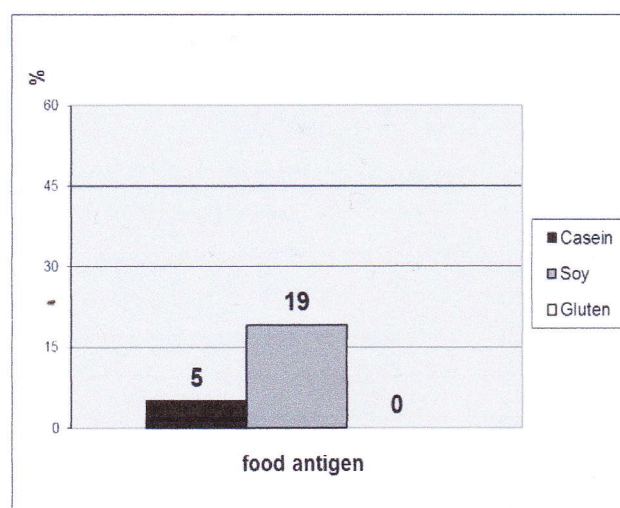


Fig. 2. Frequency of occurrence of specific hypersensitivity to different groups of food antigens in volunteers with a normal body mass index

Table 1. Laboratory indicators of volunteers with elevated and normal body mass index, Me (P25-P75)

Index	Reference Values	Women with normal BMI (n=15)	Women with high BMI (n=35)	Men with normal BMI (n=15)	Men with high BMI (n=35)
		Me (P25-P75)	Me (P25-P75)	Me (P25-P75)	Me (P25-P75)
Cholesterol, mmol/l	<5,2	4,3(4,0-4,9)	5,5(5,1-5,9)*	4,8(4,7-5,2)	5,6(4,9-6,2)*
Triglycerides, mmol/l	<1,71	0,6(0,4-1,1)	1,3(0,9-1,6)**	0,9(0,6-1,1)	1,8(1,4-2,7)**
HDL, mmol/l	W: 1,0-2,1 M: 0,9-1,8	1,7(1,5-2,0)	1,4(1,2-1,7)*	1,4(1,3-1,6)	1,2(1,0-1,3)*
LDL, mmol/l	<3,5	2,9(2,1-3,1)	3,6(3,1-4,2)**	3,0(2,8-3,5)	3,5(3,1-4,4)*
Atherogenicity index	<3,0	1,4(1,1-2,1)	3,0(2,1-3,6)**	2,4(2,1-2,8)	3,8(3,2-4,7)**
ALT, U/l	W: <31 M: <40	14(10-16)	23(16-34)**	19(14-27)	32(21-47)**
Glucose, mmol/l	3,5-6,1	4,2(4,0-4,8)	5,5(4,7-5,8)*	4,8(4,5-5,4)	5,2(4,9-5,4)*
Insulin, McU/ml	2,7-10,4	5,5(4,1-9,1)	6,9(5,4-16,7)*	5,1(3,9-6,7)	9,7(6,3-16,9)**
Insulin resistance index	<2,7	1,1(0,6-1,6)	1,8(1,3-3,8)*	1,1(0,8-1,3)	2,5(1,4-3,9)**
WBC, G/l	4-8	5,5(5,2-7,2)	6,5(5,7-8,9)*	5,3(5,1-5,7)	6,0(5,3-9,2)*
C reactive protein mg/l	0-5	1,1(0,5-1,7)	2,8(1,7-3,1)*	0,9(0,3-1,4)	2,4(1,1-2,9)*

IL-4, pg/ml	0-10	0,7(0,0-1,3)	0,9(0,4-1,5)	0,8(0,7-1,2)	0,4(0,0-1,2)
IL-6, pg/ml	0-10	0,8(0,3-1,5)	2,2(0,9-3,5)**	0,9(0,2-2,1)	2,1(1,4-3,2)*
IL-10, pg/ml	0-20	2,7(0,9-5,2)	1,2(0,6-2,7) *	4,0(1,0-5,4)	2,1(0,9-4,8)*
IL-17, pg/ml	0-20	0(0-0,1)	0,2(0,1-2,2)*	0(0-0,1)	0,3(0-0,5)*
Inf- γ , pg/ml	0-10	0(0-0,1)	0(0-0,2)	0(0-0,1)	0(0-0,1)

Note: * – $p < 0,05$; ** – $p < 0,01$ – In comparison with the control group

REFERENCES

1. Galushko, E.A. The modern view on the pathogenesis of spondyloarthritis – molecular. Galushko, A.V. Gordeev // Scientific and Practical Rheumatology – 2015. – №. 3. – pp. 299-307.
2. Golovach T.N. Allergenicity of milk proteins and ways to reduce it / T.N. Golovach, V.P. Kurchenko // Proceedings of BSU– 2010. – t.5, № 1. – pp. 9-44.
3. Kiseleva, E.P. Acceptive immunity is the basis of symbiotic relationships / E.P. Kiseleva // Infection and immunity. – 2015. – t.5, № 2. – pp. 113-130.
4. Kologrivova I.V. Molecular aspects of the T-helper type 17 functions / IV. Kologrivova, E.N. Kologrivova, E.T. Suslova // Bulletin of Siberian Medicine. – 2011. – №. 4. – pp. 93-96.
5. Rosenstein, M.Yu. Modern laboratory methods for diagnosing of food intolerance / M.Yu. Rosenstein, A.Z. Rosenstein, S.E. Kondakov, N.A. Cherevko // Bulletin of Siberian Medicine –2016. – t.15, № 1. – pp. 69-79.
6. Andrew, C. Archaeology: The milk revolution / C. Andrew // Nature. – 2013. – Vol. 500, N July 31. – pp. 20-22
7. Burks, A.W. Oral tolerance, food allergy, and immunotherapy: Implications for future treatment / A.W. Burks, S. Laubach, S.M. Jones // Journal of Allergy and Clinical Immunology. – 2008. – Vol. 121, N 6. – pp. 1344-1350.