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Immuno-Metabolic Aspects of Pathological Processes

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ABSTRACT

On an extensive panel of purulent-inflammatory, bronchopulmonary, and various other human diseases, the organismic and immuno-metabolic role of low-molecular-weight RNA, the state of oxidation of lipids, proteins, factors of the antioxidant system, and metabolic syndrome were studied. The relationship between clinical and laboratory parameters (haematological, biochemical, neurological, endocrine, and immune) has been analyzed. The effectiveness of modulators and antioxidants is discussed, and the pronounced laboratory-clinical activity of the drug combination is shown.

Key Words: Metabolic syndrome, Modulators, Antioxidants, Laboratory markers, Immuno-metabolic disorders, Targeted correction

INTRODUCTION

Immuno-metabolic disorders are a probable universal element of the pathogenesis of a wide range of diseases. It seems relevant to study these mechanisms and the possibilities of their targeted correction.¹

Functional Relationship of Immuno-Metabolic Mechanisms

Nucleic acid exchange

Its state is a marker of the severity of pathological processes and regulation of immune reactivity.² So, in the acute period of nonspecific bronchopulmonary diseases in patients, accumulation occurs in the blood, and in lymphocytes, the synthesis of nucleic acids (NA) is stimulated with a decrease in parameter values in the stage of remission and after effective therapy. An indirect confirmation of the stated pattern is the fact of an increase in urinary excretion of the components of NA guanine, uracil, cytidine, and thymine in children during the period of asthma attacks in the relatively calm period of bronchial asthma. In patients with the absence of normalization of nucleic acid metabolism, there was no clear recovery, and chronicity of the pathology was noted. A significant inverse correlation was found between the content of plasma RNA and “zero” lymphocytes with bronchial asthma,

chronic pneumonia, and a direct correlation with mature T and B cells.³ Perhaps RNA is one of the factors limiting the maturation of lymphocytes. A possible secondary messenger between NA and immune reactivity is the cyclic nucleotide system cAMP/cGMP.⁴

In patients with peptic ulcer disease and nonspecific inflammatory lung diseases, a direct correlation was established between the content of serum RNA with the level of T-cells and an inverse relationship with immature “zero” lymphocytes. Violation of RNA metabolism was closely related to the content of cAMP in the mucosa. In the case of gastric ulcer and to a lesser extent in the case of duodenal ulcer, the amount of cAMP in the mucosal area remote from the defect was overstated, and in the case of peptic ulcer of the anastomosis, it was reduced. In the area of direct injury, the amount of cAMP in the tissue was reduced.^{3,5} A direct correlation was established,^{6,7} between the content of the total pool of nucleic acids (DNA+RNA) in the blood serum in acute dysentery in proportion to its severity.

The role of low molecular weight ribonucleotides

In infection and immunity

The accumulation of RNA in the body in the initial period of the development of the infectious process stimulates

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the reproduction of microorganisms of various taxonomic groups, the selection of virulent clones, the production of exotoxins, which causes the potentiation of the infection.^{2,3,8} Later, the same factor causes an increase in antigenicity, immunogenicity, antibiotic sensitivity bacteria. To this should be added the activation of the mobility, absorption, and metabolic capacity of macrophages, the production of humoral defence factors, quantitative and functional characteristics of populations of lymphocytes, differentiation, cooperation of T- and B-lymphocytes, which provides an increase in the body's resistance.

Nucleic acids and, above all, RNA, replenish the fund of substances necessary for the normal functioning of the body. ATP is a source of energy, cytosine nucleotides are involved in the synthesis of lipids, uridine, and guanine nucleotides in the exchange of polysaccharides, and the latter is also involved in the synthesis of proteins. There is an indirect, mediated pathway of RNA action on cells through the system of cyclic nucleotides.

Metabolic immunomodulation

Antioxidant protection

It is carried out by a system of high-molecular enzymes (superoxide dismutase (SOD), catalase, glutathione peroxidase, glutathione reductase), and low-molecular bio-antioxidants proteins containing metals with variable valence (transferin, ferritin, ceruloplasmin-CP). The second non-enzymatic group of AOD is made up of carotenoids (β -carotene, retinol), α -tocopherols, polyunsaturated phospholipids, ascorbic acid, glutathione, some amino acids, urea, uric acid, and selenium compounds. High-molecular antioxidants are associated with various cellular structures, while low-molecular antioxidants are relatively freely distributed between cells, intercellular fluids, and blood. A decrease in the antioxidant potential is accompanied by the need to replenish the pool of low molecular weight metabolites by their exogenous introduction into the body.⁹

Free radical oxidation processes lipids and proteins

They are central to cell metabolism. The products of this process are a source of energy, plastic material for the creation and renewal of cellular structures, are directly involved in the metabolism of carbohydrates, lipids, proteins, nucleic acids, the biosynthesis of prostaglandins, and catecholamines, and regulate the permeability of biological membranes.¹⁰ FRO reactions are an indicator of resistance stationary mode of biochemical transformations in the body, regulating its adaptive capabilities. The main laboratory parameters of FRO are malondialdehyde (MDA), diene conjugates (DC), ketodienes (KD), bityrosine cross-links (BC), Schiff bases (SB).

Therapeutic metabolic modulation

Immunodeficiency states are realized through targeted stimulation of the AOS (antioxidant system). The most widely used antioxidant drugs are **energizers** riboflavin and nicotinamide, free fatty acids, pantothenate and carnitine, **glycolysis activators** thiamine, riboxin, **beta-oxidation stimulants** biotin, thiamine, lipoate, **antioxidants** β -carotene, retinol, α -tocopherol, ascorbic acid, ubiquinone, polyunsaturated phospholipids, **hepato-protectors** essential, carsil, lipostabil, phosphoglyph, **medicinal enzymes** trypsin and other proteolytic drugs.⁹

Immuno-metabolic associations

The correlation dependence of metabolic parameters on the indices of the T-link of immunity was revealed, and positive correlations undoubtedly prevailed over negative ones. The level of total T-lymphocytes had a positive relationship with thymol "test", blood amylase, cholesterol, prothrombin, the antioxidant activity of blood plasma (AOA), the activity of superoxide dismutase, and negative with ALAT (alanine-aminotransferase). All three types of regulatory cells had a negative significant association with ALAT. The absorption capacity of leukocytes, assessed by the phagocytic index (PI) and phagocytic number (PN), was under the "negative control" of prothrombin, ALAT, thymol "test", free and bound bilirubin, and under the "positive control" of cholesterol. Prothrombin was negatively associated with the metabolic activity of neutrophils, and total bilirubin, ASAT (aspartate aminotransferase), and total protein were positively "dependent" on them.¹¹

The coordinated dynamics of key tests of the formula of immune system disorders with metabolic parameters in patients with proinflammatory diseases is of theoretical importance.¹² In pyoderma, the formula $CIC_3^+NKc_3^+IL6_3^+$ (deciphering the designations of the formulas in the text and the table) with the total antioxidant blood activity (AOA), total thiols, SB, CP, with pyelonephritis of the formula $B_3^+MVM_3^+NBTsp_2^-$ with vitamin E (VE), SOD, respectively, with chronic adnexitis $T_3^+IgM_3^+IL6_3^+$ with SB, CP, KD, and in chronic cystitis of the formula $Tc_3^+IgA_2^-IL6_3^+$ with DC, BE, BC. These regularities changed after the correction.

Pathogenesis of metabolic syndrome (MS)

The pathogenesis of MS is based on insulin resistance, which entails hyperinsulinism. There is evidence that it is visceral obesity, an increase in the activity of many counterinsular hormones (insulin antagonists) that provoke and maintain insulin resistance. As indicated by Talantov et al. and Shevchuk (cited from¹³), patients with MS have decreased levels of TSH (thyroid-stimulating hormone), thyroid hormones T_3 and T_4 , STH (somatotrophic hormone) with a simultaneous increase in ACTH (adrenocorticotrophic hormone) levels,

cortisol, aldosterone. Analysis of the state of the immune system in patients MS without concomitant chronic infections and thyroid pathology disorders of the immune system were revealed in a decrease in the number of T-lymphocytes and dysimmuno-globulinemia, with this pathology there is an inversion of the immune status with a deficiency of T-suppressors, T-helpers, NK-cells. Autoimmune thyroiditis was detected in 54%, chronic infectious diseases in 58.3%, their combination in 29.2%.¹³

There is a frequent combination of diabetes mellitus with thyroid pathology, which may also indicate the interest of the immune system in the latter.¹⁴

Ischemic and hemorrhagic strokes, burdened with metabolic syndrome

The layering of this pathology on various diseases causes a probable, but insufficiently studied, change in the homeostasis of the body. It was found that patients with similar processes develop a qualitatively similar, quantitatively more pronounced reaction in hemorrhagic stroke in the form of an imbalance of the primary and secondary products of free radical oxidation of lipids and proteins, preferential activation of enzymatic and non-enzymatic mechanisms of the antioxidant system against the background of accumulation of pro-inflammatory cytokines.¹⁵

Ischemic heart disease, aggravated

Metabolic syndrome

This complication causes pathological stimulation of carbohydrate and lipid components of the antioxidant system, cytokine, endocrine, and other indicators - glucose, insulin, glycosylated haemoglobin, HOMA-IR, IL-1 β , IL8, thyroglobulin, γ -interferon (γ -IFN).¹¹

The functional unity of the central nervous system, Endocrine and immune regulatory systems

The ability of various parts of the brain to regulate the severity of immune reactions, innervation of the central and peripheral organs of the immune system, and conditioned reflex and intellectual modification of its functions was established. As well as the production of various regulatory peptide hormones by the organs of the immunocompetent sphere, and the CNS of mediators of the immune system, the "endocrine-like" effect of cytokines with the reproduction of endocrine function and the presence of common receptors in nerve and immunocompetent cells, stimulating and suppressive immunotropic potencies of hormones. It is essential that the restoration of disorders of one system - the immune, is accompanied by changes at the level of the organism, causing modifications in the endocrine status, metabolic parameters, the nervous system.^{16, 17, 18, 19}

RELATIONSHIP OF IMMUNO-METABOLIC DISORDERS WITH CLINICAL COURSE OF DISEASES

Severe asphyxia in newborns

In these sick children, a significant negative relationship was found between the levels of CD3, CD4, CD8, CD95 lymphocytes and the degree of anti-infectious resistance. At the same time, the concentration of IgA in the umbilical cord blood correlated with the formation of atopic dermatitis (AD) in the child, anaemias, CD56 lymphocytes with intestinal dysbiosis, urinary tract infection, vulvovaginitis.²⁰ The correlation analysis revealed a negative dependence of the NB Tac of neutrophils in the umbilical cord blood and oligohydramnios, CD4 levels on days 4-5, and polyhydramnios, vaginal candidiasis in the mother during pregnancy, endometritis, and the content of CD95 lymphocytes and gestosis. A positive relationship was found in the value of PN with a long anhydrous gap in the mother and the number of CD56 lymphocytes on days 4-5 with perinatal damage to the central nervous system of the child.

The role of metabolic processes in the Genesis of diseases

Evidence of their participation in pathology is the accumulation of low molecular weight nucleic acids in thyrotoxicosis, primary rheumatic heart disease, infiltrative tuberculosis, dysentery, poisoning, radiation damage, and a decrease in rheumatoid arthritis, obstructive jaundice, infectious hepatitis, diabetes mellitus, peptic ulcer of the gastrointestinal tract and alcohol intoxication.²¹ At the same time, clinical models of eight variants of cerebrovascular diseases have shown the involvement of lipid peroxidation and antioxidant system factors in key immune mechanisms of metabolic reactions as the severity of the pathological process increases.^{5, 12}

CORRECTION OF IMMUNO-METABOLIC DISORDERS

Metabolic effects of immuno-modulators

Poly- and lipopolysaccharides

Thus, the metabolic action of this group of drugs is expressed in the intensification of protein synthesis, activation of the "adenylate cyclase - cAMP" system, various enzyme systems, and the inclusion of ³H-thymidine into the spleen cells.²²

Prodigiosan

Under its influence,²³ the activity of glycolytic dehydrogenases was significantly stimulated (cytoplasmic α -GPDG [α -glycerophosphate dehydrogenase] and LDG [lactate dehydrogenase]), the activity of the key enzyme hexose monophosphate shunt (G-6-PDG). The general effect of prodigiosin on

the body was expressed in the mobilization of the hormonal system “pituitary-adrenal cortex”, activation of lymphoid cells, macrophages, plasmocytes, synthesizing immunoglobulins.

Synthetic modulators

Synthetic double-stranded RNA poly I: C, poly-A: U, poly G: C

They increased the incorporation of ³H-thymidine into lymphoid and other cells, stimulated the formation of adenylate cyclase, cAMP, and had colossal immunomodulatory activity.²⁴

Thymusderivatives, myelo peptides

Potentiated the synthesis of protein and nucleic acids in various cells.^{25, 26} The former proved to be additionally powerful regulators of lipid metabolism, reduced blood glucose levels, and normalized liver function indices. In patients with superficial vasculitis, thymomimetics determined from the level of traditional treatment the normalization of tryptophan in the blood, and in the urine of cystic acid, taurine, glutamic acid, proline, glycine, alanine, a-aminobutyric acid, cystine, lysine, 1-methylhistidine, arginine, 2-methylhistidine, the number of amino acids. Among other changes in the biochemical parameters of blood, taktivin caused a decrease to the norm of the initially increased level of glucose, alkaline phosphatase, ASAT, ALAT, cholesterol, triglycerides, LDG, calcium, and an increase to the norm of creatinine, total bilirubin, albumin, iron, creatinine phosphokinase, a total of 13 parameters. In the urine, there was an increase in the reduced content of creatinine and a decrease in sodium.

Sodiumnucleinate

Its effect on cell metabolism turned out to be very broad.² In the spleen lymphocytes, the synthesis of RNA, DNA, the protein was stimulated, ATP and ADP accumulated, monoamine oxidase, α -GPDG were activated, the biosynthesis of mitochondrial, nuclear, cytoplasmic RNA increased in the liver, the activity of tryptophanpyrrolase increased. In the granulocytes of healthy individuals, oxygen consumption increased, and the rate of glycolysis decreased.

The differentiated effect of monoribo-nucleotides on lymphocyte receptors has been established. AMP had the highest activity, minimal GMP, the combination of complementary GMP+CMP was also highly active, with minimal changes on T-helper and T-suppressor.²⁷

In patients with acute dysentery CMP and UMP stimulate the formation of antibody-forming cells by 9-19 times, and AMP decreases them by 10 times. AMP inhibited antigen-specific responses and increased delayed-type hypersensitivity.²⁷

Immuno modulatory effects of metabolic

A wide panel of combined studies was performed on various clinical models of proinflammatory diseases (PID). They consisted of exacerbation of deep pyoderma (EDP) and chronic pyelonephritis (ECPN), ECPN + urolithiasis disease (ULD), purulent soft tissue infection (PSTI)+AD, +true eczema (TE), acute salping-oophoritis (ASO), and exacerbation of chronic salping-oophoritis (ECSO), ECSO+bacterial vaginosis (BV), urogenital chlamydia, nonspecific inflammatory diseases of the lungs, which included mixed, exogenous and endogenous bronchial asthma (mBA, exBA, enBA), chronic obstructive lung disease (COLD), mBA+COLD, mBA+AD. The effect of the “traditional” treatment of diseases and its combination with the antioxidant hypoxene, immunotropic drugs with antihypoxic, antitoxic, metabolic, haemo-stimulating, immunological properties, cygapan metabolic (food supplement containing 63 micro-and macroelements, amino acids, vitamins) was studied, tycveolum (realizing hepatoprotective, regenerative, immunostimulating, anti-inflammatory effects), limontar (a preparation of citric and succinic acids, which are stimulators of nucleic acid metabolism and redox processes) and metabolites of nucleic acid origin with sodium nucleinate, derinate (official drug, high molecular weight DNA), isoprenaline on immune, haematological, biochemical, bacteriological and clinical parameters.^{28,29,30}

In patients by the rank method (used to compare the effectiveness of immuno corrections, when immune markers in patients receiving drugs, the greatest changes are measured by rank 1, then by rank 2, etc., and the minimum sum of ranks reflects the maximum effect of the action), the normalizing the effect of antioxidants and metabolites on grouped (divided into groups) laboratory parameters, built the final rating algorithm of complex treatment (determined by the degree of immune disorders of the indicators, which are arranged in the order of decreasing significant deficiency from the specified values), identified the key targets of the drug action on the immune system (see the table for the ITF decoding) with an indication of the order of the parameters in the formulas, vectors and the degree of their dynamics from the initial level.³⁰

Hypoxene (Hp)

Patients Hp causes an ambiguous positive effect on the studied parameters of patients suffering from various PID. Thus, the predominant normalization of immune parameters was achieved in patients with ACPN, PIST+TE, haematological parameters with EDP, ECPN, ECPN+ULD, PIST+AD, bacteriological parameters with PIST+AD, clinical patients with ECPN, PIST+AD. In total, an increase in the final effectiveness of complex treatment due to hypoxene was shown in five cases out of seven (EDP, ECPN, ECPN+ ULD, PIST+AD, PIST+TE). With mBA, the antioxidant increased the final efficacy of the complex treatment.

When determining the spectrum of targets of hypoxene in the immune system in patients with six types of bronchopulmonary diseases, leukocytes, lymphocytes, Th, NK, Ig of three classes, PI, IL4 concentration with a stimulating vector turned out to be key.

In patients with nonspecific inflammatory lung diseases, a high immuno-clinical effect of sodium nucleinate has been shown.³ The maximum normalizing effect of the modulator in patients with mBA, ecBA, mBA+AD, enBA, COLD, mBA+ COLD was found in biochemical, immune and clinical action, which included markers of T cells, their regulatory subpopulations, B-lymphocytes, IgA and M, CEC, absorption and metabolic activity of neutrophils, cytokines. In principle, positive clinical and laboratory results were obtained in patients with ECPN, PIST, and DP using the nucleic acid modulators ridostin, derinat, and isoprinosine.

Thus, various metabolites and antioxidants against the background of traditional treatment of pyoinflammatory and non-specific bronchopulmonary diseases in most cases significantly increase the final clinical and laboratory effectiveness of complex effects on patients and fundamentally change the sets of signal markers in the formulas of targets for immunocorrection of drugs.

Comparative effectiveness of immunomodulatory and immuno-metabolic therapy of diseases

On clinical models of PID (pyoderma, pyelonephritis, adnexitis), we studied the effect of the GI modulator and its combination with the antioxidant hypoxemia (GI + Hp) on the grouped clinical, laboratory, and signalling immuno-

metabolic parameters.³¹ The data obtained are summarized in Table 1.

The data in the table indicate that in patients with deep pyoderma, immunotherapy with Galavit relative to traditional treatment led to the normalization of three groups of markers - haematological, metabolic, and clinical, with four CPNs - G, I, M, C, with CA of one haematological one. The combination of GI with Hp led to a modification and an increase in the clinical and laboratory effect.

Specifically, in DP, galavit provided a decrease in the level of pro-inflammatory TNF, total lymphocytes and lymphocytes with apoptosis receptor expression, hyperimmunoglobulinemia M, in CPN - IL4, phagocytic index, and T-regulators turned out to be signalling targets, and in CA, thymus-dependent NK, CIC, IgM turned out to be supporting markers. When using a combination of GI+Hp in patients with DP, CPN, CA, typical ITFown were accordingly modified (NKc₃⁺PI₂⁺IL8₃⁺, which affected cytotoxic natural killers, phagocytic index and interleukin-8), in CPN, respectively, Th₃⁺IL8₃⁺B₃⁺ that affected T-helpers, IL8 and B-lymphocytes, with CA, respectively, IgM₂⁺Tc₃⁺NKc₃⁺, which affected immune globulins M, T-cytotoxic lymphocytes and cytotoxic NK cells).³² Thus, in patients with DP, the composition of ITFown during galavit was expressed in AOA₂⁺MDA₁⁺Ct₁⁻ and, in the case of a combination of GI+Hp, in turn, MDA₂⁻SOD₂⁺VE₁⁺.

DISCUSSION

The article describes the problem of immuno-metabolic aspects of pathological processes, which is practically new

Table 1: The efficiency of immunotherapy for proinflammatory diseases in 1-3 weeks from the start of treatment

Preparationons	Normally grouped indicators						Typical formulas	
	G	I	M	C	B	% "Normal" indicators	ITFown	MT Fown
Deep pyoderma (DP)								
Galavit	4	33*	23*	17*	6	50*	TNF ₃ ⁻ Ma ₃ ⁻ IgM ₂ ⁺	AOA ₂ ⁺ MDA ₁ ⁺ Ct ₁ ⁻
Galavit +Hypoxene	31*	48*	38*	26*	9	83*	NKc ₃ ⁺ PI ₂ ⁺ IL8 ₃ ⁺	MDA ₂ ⁻ SOD ₂ ⁺ VE ₁ ⁺
Chronic pyelonephritis (CPN)								
Galavit	47*	30*	21*	44*	4	50*	IL4 ₂ ⁺ PI ₃ ⁺ Tr ₃ ⁺	MDA ₁ ⁻ SB ₂ ⁻ OAA ₂ ⁺
Galavit +Hypoxene	33*	38*	46*	20*	10	50*	Th ₃ ⁺ IL8 ₃ ⁺ B ₂ ⁺	SOD ₂ ⁺ OAA ₂ ⁺ SB ₂ ⁻
Chronic adnexitis (CA)								
Galavit	17*	0	15	7	6	17*	NKt ₃ ⁺ CIC ₃ ⁻ IgM ₃ ⁻	SB ₁ ⁻ DC ₁ ⁺ Ct ₁ ⁺
Galavit + Hypoxene	25*	42*	23*	12	10	67*	IgM ₂ ⁺ Tc ₃ ⁺ NKc ₃ ⁺	SOD ₂ ⁻ SB ₂ ⁻ MDA ₂ ⁻

Legend: G, I, M, C, B - haematological, immune, metabolic, clinical, bacteriological indicators, * reliability of differences, with P< 0.05, ITFown, MTFown - immunoprotection and metabolic target formulas regarding basic treatment; own - own effect of some modulators, Ma - CD95+ lymphocytes, Ct - common thiols, the rest see the text

for clinical immunology, and its formulation and consideration mainly belongs to the authors of this article. In fact, for the first time, the relationship between immune-metabolic mechanisms in the implementation of immune responses is discussed. The greatest importance is attached to the state of nucleic acid metabolism as a marker of the severity of immunopathology and a regulator of immune reactivity. His condition turned out to be key in the development of immuno-associated diseases, infectious pathology and substantiated new approaches for nucleic acid replacement immunotherapy. The most important role of the antioxidant defence system, free-radical oxidation of lipids and proteins was shown, which made it possible for the first time to propose therapeutic metabolic modulation. New information is presented on the currently intensively studied metabolic syndrome, its effect on patient homeostasis. A large body of information with the discussion of new aspects covers various pathologies, including diabetes, cardiovascular diseases, psoriasis, the relationship of immuno-metabolic disorders with the clinical course of various infectious and non-infectious diseases, correction of developing disorders by various immunotropics and, which is especially important, novelty drugs is postulated low molecular weight RNA. In this area, serious research has been done and excellent clinical results have been obtained. As a result, the discussion of new aspects of immuno-metabolic associations led to the creation of a new direction in clinical immunology - immunomodulatory metabolism therapy and new approaches to correcting immune and metabolic disorders in the body with a wide range of pathology.

CONCLUSION

On a wide range of pyoinflammatory, Broncho-pulmonary and other diseases, the general body and immuno-metabolic function of low molecular weight nucleic acids, lipid oxidation products, proteins, factors of the antioxidant system, metabolic syndrome, association of clinical parameters with haematological and biochemical parameters, nervous, endocrine and immune processes, the realization of complex effects by modulators and antioxidants and high clinical and laboratory activity of the combination of metabolic with correctors were analyzed.

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Software- V.S.D.;

Validation - V.M.Z., V.A.Z.;

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Supervision- V.N., P.K.N.

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