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ENGLISH VERSION: FEATURES OF NF-KB-MEDIATED SIGNAL TRANSDUCTION AND DEVELOPMENT OF SYSTEMIC INFLAMMATION IN PATIENTS WITH DISEASES OF INTERNAL ORGANS ARE DETERMINED BY MICROBIAL FACTOR AND INDIVIDUAL REACTIVITY OF THE BODY (REVIEW OF OWN RESEARCH FINDINGS)*

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The paper identifies the etiological significance of periodontopathogenic microflora in the initiation of low-intensity systemic inflammation, which together with insulin resistance and lipid metabolism determines the development of atherosclerosis and coronary heart disease. On the basis of obtained data, the paper substantiates the concept of permanent activation of transcription factor NF-κB as the molecular foundation of systemic inflammation and other components that form the metabolic syndrome. The role of polymorphic variants of TLR 2,4,3,6 genes in shaping the individual reactivity of patients has been determined. The participation of genetic variation of receptor and structural proteins in determining the individual sensitivity, clinical course and complications of infectious diseases – hepatitis C, influenza, and EBV-viral infection has been justified. The up-to-date role of fundamental processes of innate and acquired immunity in the pathogenesis of atopic dermatitis, allergic rhinitis and bronchial asthma has been demonstrated. The efficiency of developed methods of therapy with additional inclusion of metformin and pioglitazone has been demonstrated, the application of pharmacogenetic approach to treatment has been substantiated. The obtained results will contribute to the formation of a systematic approach to the development and use of new technologies for prevention and effective pharmacogenetic treatment of diseases which are based on chronic inflammation.

Key words: systemic inflammation, transcription factor NF-κB, periodontopathogenic microflora, pharmacogenetic

I. The role of periodontal pathogenic microflora in the initiation of systemic inflammation, etiology and pathogenesis of atherosclerosis

Recent studies have attracted the attention of scientists to the specific source of systemic infection. It has been found that under certain conditions a change in biocenosis occurs and oral microflora changes its range toward the high pathogenicity, becoming not only the cause of inflammatory diseases of the dentition, but of inflam-

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matory diseases of other organs and systems as well, which is an extremely negative phenomenon [26].

Identifying the leading etiopathogenetic factors of the most common cardiovascular diseases such as coronary heart disease (CHD), myocardial infarction, angina pectoris, hypertension, peripheral vascular disease, stroke, has shown that among the entire range of factors, chronic infection and inflammation are the key ones [8, 9]. The presence of excessive quantities of periodontopathogenetic microflora in various inflammatory diseases of the mouth was the basis of assumption that in the diseases of dentition, the pathogenetic mechanisms of which involve the expressed immunological components, changes in organs or tissues of the cardiovascular system are observed.

Further research confirmed that not only periodontopathogenetic microflora is a key source which performs the triggering role in the development of local and systemic chronic inflammation, but also acts as an independent risk factor for CHD.

During examination of CHD patients with inflammatory diseases of the dentition, a number of risk factors were identified, including male sex (63.5%), hereditary nature of coronary heart disease (41.3%) and arterial hypertension – AH (76%), AH in anamnesis (57%), overweight and obesity (85.7%), diabetes mellitus type 2 (31.7%), inflammatory diseases of the dentition (3.2-84.1%), smoking (49.2 %), psycho-emotional stress (100%), systemic inflammation, impaired glucose tolerance (49.2%), dyslipidemia, microalbuminuria (23.8%). The presence of inflammatory pathology of the dentition (mono- or comorbidity) was observed in 95.3% of patients, median caries in 44.4%, chronic periodontitis in 36.5%, local periodontal disease in 84.1%, chronic generalized periodontitis in 3.2% of patients.

The results confirm that along with the already known risk factors (obesity, dyslipidemia, hypertension, carbohydrate metabolism) in patients with CHD the proportion of inflammatory diseases of the dentition is 95.2%. The established relationship between periodontal diseases and risk factors of CHD according to the correlation analysis influences the development of atherosclerotic process.

The results show that disorders of metabolic processes that occur in CHD (carbohydrate metabolism disturbance, dyslipidemia, systemic inflammation) and sensitivity of periodontium and its structures to the factors that form proatherogenic range of metabolic disorders are the basis for a close relationship with the condition of oral microflora and justify the risk of the pathology of systemic inflammatory component, including cardiovascular disease [37].

Investigation of coronary artery samples obtained at autopsy of patients who died of coronary artery disease and healthy people showed the presence of periodontopathogenetic microorganisms in atherosclerotic plaques of 83.9%. In determining the DNA of pathogens by polymerase chain reaction, in 51.6% of cases 2 or more microorganisms were manifested, among them most often – Porphyromonas gingivalis (64.5%), Treponema denticola (41.9%), Actinobacillus actinomycetemcomitans (32.3%), and less frequently – Bacteroides forsythus and Prevotella intermedia (12.9 and 6.5% respectively). It should be noted that only in 11.1% of coronary vessels samples, in plaques of which microorganisms were present, they were identified in intact tissues [34, 36].

The obtained data required to determine the maximum number of microbial flora and quantification of certain types of pathogenic and opportunistic microorganisms in atherosclerotic lesions of vessels, assessment of microcytosis, level of microflora imbalance which led to the development of the method for determining the microflora in atherosclerotic lesions of vessels with the release of microbial DNA followed by amplification and detection of the results [35].

Investigating the presence of different types of parodontopathogenic microorganisms in the blood vessels in CHD enabled us to come to the conclusion that their DNA detection rate reaches 100% in tissue samples of atherosclerotic plaques in coronary arteries. Analysis of own data and the data of other authors allowed us to identify the main mechanisms initiated by the impact of long-persistent oral microbiota in the development of atherosclerosis: the direct one – bacterial penetration with the bloodstream into the cells of vascular endothelium; and / or indirect one – bacterial stimulation of the production of mediators with atherogenic and proinflammatory systemic effects. Both ways cause the development of main manifestations of atherosclerosis, such as endothelial dysfunction, systemic inflammation, platelet aggregation and the formation of atheromatous plaques and require the modern approaches to prevention and treatment of diseases of the cardiovascular system, taking into account the mechanisms of influence of the bacterial infection in the development of atherosclerosis [26].

II. Genetic variability as a factor of influence on immune reactivity of the body to microbial factors

Recent studies show that individual reactivity and susceptibility to microbial infection and viral pathogens to a large extent depends on the genetic processes of implementation of hereditary information and epigenetic influences.

Taking into account the presence of parodontopathogenic microorganisms in atherosclerotic plaques and the surrounding tissues of patients who died of ischemic heart disease, there has been raised a question of possible connection of atherosclerosis and genetic factors, in particular the polymorphic variants of genes that mediate the processes of immune response, such as genes of Toll-like receptors (TLR). As is known, TLRs belong to the pattern-recognizing group of receptors. In particular, TLR2 recognizes peptidoglycan – the main structural component of the cell wall of gram-positive bacteria and microbial lipopeptides of gram-positive and gram-negative bacteria. TLR4 interacts with lipopolyssacharide (LPS) and lipoteichoic acid which is the main component of cell membranes of bacterial cells.

The study of coronary artery samples of patients who died of ischemic heart disease and those who died due to other causes, not related to coronary artery disease, was conducted. Asp299Gly polymorphic area of TLR4 gene was amplified using specific primers. Studies have shown that in patients who died of ischemic heart disease, the polymorphic allele of the gene TLR4 G 896 was significantly more common ($p = 0.04$), OR 2.92 (1.15-7.41).

Moreover, it was found that the presence of the polymorphic allele G of TLR4 gene in individual genotype determines the increased contamination of the plaque tissue by representatives of certain types of odontogenic pathogens: Lactobacillus spp., Enterobacterium spp., Sneathia spp. / Leptotrihia spp. / Fusobacterium spp.,

Mobiluncus spp. / Corynebacterium spp., Peptostreptococcus spp. The results showed the participation of these groups of microorganisms in the pathogenesis of atherosclerosis, and identified the etiologic role of polymorphic variant of TLR4 gene in increased microbial contamination of tissues of coronary arteries [36].

It was found that in the group of patients with atherosclerotically modified coronary vessels, there were 15 individuals with genotype AA (Asp299Asp) of TLR4gene, 3 – with genotype AG and 2 – with genotype GG. Genotypes AG and GG were combined into one group as the carriers of mutant allele G. The carriers of allele G (AG and GG) had a significantly higher content of microbial DNA of Lactobacillus spp. 4.20±0.62 as against 3.01±0.14 in carriers of allele A (AA) ($p<0.05$), Enterobacterium spp. – 4.68±0.87 as against 3.09 ± 0.17 ($p<0.05$), Sneatia spp. / Leptotrichia spp. / Fusobacterium spp. – 3.47±0.60 as against 1.78±0.16 ($p<0.05$), Mobiluncus spp. / Corynebacterium spp. – 3.06±0.46 as against 2.18 ± 0.10 ($p<0.05$), Peptostreptococcus spp. – 3.08±0.67 as against 2.00±0.11 ($p <0.05$) [35].

It was confirmed that investigated odontogenic pathogens play an important role in the pathogenesis of atherosclerotic lesions of the coronary vessels and the development of coronary artery disease. Important is the role of TLR4 gene polymorphism, when individuals with 299Gly allele have a chance of contracting CHD by 2.92 times more likely than those with the presence of 299Asp allele [34].

The data prompted us to pay attention to the relationship of microbial genetic factors with the change of genetic status of the immune system elements already in other pathological conditions.

Taking into account the possible involvement of TLR in the immunopathogenesis mechanisms of urogenital infections, we studied the population prevalence of SNP of TLR2 Arg753Gln genes with the replacement of G to A in position 2258 (rs5743708) and TLR4 Asp299Gly with the replacement of A for G in position 1187 (rs4986790), as well as Thr399Ile with the replacement of C to T in position 1487 (rs4986791) among the apparently healthy individuals of Poltava population and among patients with common urogenital diseases. We clarified the role of functional polymorphism in genes that encode TLR in the development of susceptibility to infection with the most common causative agents of urogenital infections [5].

Genotyping of the studied groups as to the polymorphisms of TLR2 Arg753Gln gene and TLR4 Asp299Gly gene, Thr399Ile was conducted using PCR and subsequent restriction analysis. Statistically significant association between A allele of TLR2 gene ($p = 0.0018$) and G allele of TLR4 gene ($p = 0.085$) with the presence of urogenital diseases was determined.

Analysis of the obtained data led us to the assumption of a reliable association between the presence of mutant alleles of TLR2 Arg753Gln and TLR4 Asp299Gly genes and increased risk of contracting common urogenital infections, in particular whose causative agents are Chlamydia trachomatis, Ureaplasma urealyticum, Mycoplasma genitalium, Gardnerella vaginalis, Neisseria gonorrhoeae, Trichomonas vaginalis.

The search for pathogenetic factors that would substantiate the mechanism of increased risk of infection directed the attention to the study of synthesis of proinflammatory cytokines (interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α)) and anti-inflammatory cytokines – IL-10 by mononuclear cells of peripheral blood (MCPB) in patients with various 896A/G polymorphic variants of TLR4 gene (rs4986790) under TLR ligands (LPS and zymosan) [6].

The results displayed the insufficient production of inflammatory cytokines IL-6 and TNF-α. It was concluded that the reduced ability to produce inflammatory cytokines (IL-6 and TNF-α) in response to LPS and zymosan in patients with existing 896G allele of TLR4 gene (rs4986790) can cause susceptibility to infection with gram-negative (in particular, urogenital) pathogens and cause immunodeficient condition that is of hereditary nature, involving at least the functional polymorphism of TLR4 (rs4986790).

An important step was the study of the mechanisms of immunoregulation in patients with atopic bronchial asthma (ABA) depending on the polymorphism 2258G/A of TLR-2 gene (rs5743708) [24]. The examination of representatives of patients with ABA from Poltava population showed that single-nucleotide polymorphism 2258G/A of TLR2 gene is revealed in them more often than in healthy individuals.

It was determined that there is a clear dependence of patients' immune status on TLR2 genotype. In patients with compensated course of ABA who carry homozygous allele G, a wide range of positive correlation relationships against the background of increased IL-4 level is formed. Heterozygous variant of TLR2 gene in patients with compensated ABA promotes the imbalance of immune system with activation of IL-10 production, a significant decrease in the number of correlation relationships of immune-dependent structures and direct linear relations between natural regulatory T cells and T-helper cells and lymphocytes.

It was suggested that controllability of ABA course under conditions of heterozygous TLR-2 genetic apparatus and certain decrease in activity of innate immunity, is possible due to the direct interaction between regulatory T cells with other types of lymphocytes which creates a balance between effector and regulatory mechanisms of the immune response. The increased level of inducible IL-10 of T-reg cells in ABA allowed to confirm their important role in the diagnosis and promising outlook in the treatment of atopic states, especially in patients with functional genetic disorders.

Taking into account the multifactorial nature of ABA as pathology, gene polymorphism of Clara cells protein (A38G), with specific weight of 16 kDa (SS16) in adults of Poltava population, the features of clinical course of ABA and level of total IgE depending on changes in the genome [25] were investigated.

It was determined that polymorphic variant 38G of CC16 gene is significantly more common in patients with ABA than the group of population control ($p = 0.019$), and the level of total IgE is statistically and significantly higher in patients with heterozygous (AG) and homozygous (GG) variant of CC16 gene. The carriership of polymorphic allele 38G of CC16 gene influenced the ABA clinical manifestations: fungal sensitization, atopic dermatitis and tuberculosis in anamnesis were observed in patients; it necessitated more frequent administration of glucocorticoids.

An important step was the cumulative study of 2258G/A polymorphisms of TLR2 gene (rs5743708) and 896A/G of TLR4 gene (rs4986791), protein gene of Clara cells (A38G), with specific weight of 16 kDa (CC16) in adults of Poltava population and defining the features of

the immune status and clinical course of bronchial asthma depending on changes in the genome [23].

The results show that in patients with BA it is more likely to identify TLR2 gene (p = 0.04) against background of GA genotype (11.1%), in patients who are carriers of the mutant allele A of TLR2 gene in anamnesis pneumonia was observed more frequently (p = 0.046) and there were signs of candidiasis (p = 0.034) as compared with patients without polymorphism.

In the study of TLR 4 gene polymorphism it was found that AG genotype is statistically more likely (p = 0.04) to be found in the group with BA (15.6%) than in the control group. In patients with 896A/G polymorphisms of TLR4 gene the disease initiated in childhood (p = 0.03), food factors were detected in the sensitization spectrum (p = 0.02) and there were signs of other allergic pathologies (p = 0.045).

The results gave us the opportunity to affirm the importance of the study of 896A/G polymorphisms of TLR4 gene and 2258G/A of TLR2 gene, A38G gene of CC16 gene for the diagnosis, prevention and treatment of BA.

The latest data concerning the important role of TLR2 gene as a candidate gene in the development of asthma in children, possible connection of TLR2 gene polymorphism with allergic asthma contributed to determining the presence of relationship between TLR2 Arg753Gln polymorphism (NP_003255.2) and increased synthesis of specific E immunoglobulins in patients with allergic diseases [4].

It was confirmed that TLR2 Arg753Gln polymorphism is associated with increased levels of sIgE production in patients with allergic diseases. TLR2 polymorphism can also affect numerous functional consequences of TLR2 activation related to signalling pathways of NF-κB and MAPK, including sIgE production. The available results allowed to consider this as polymorphism as an additional predictive index used for genetic research of allergic diseases.

Similar results were also obtained by us in the study of association of Toll-like receptor 4 polymorphism (NP_612564.1) with increased production of specific IgE in patients with allergic diseases [15]. It was determined that Asp299Gly polymorphism of TLR4 gene is associated with increased production of sIgE in patients with allergic diseases.

Overall, the research results not only demonstrate the relationship of TLR2 (rs5743708) and TLR4 (rs4986790) polymorphisms with increased production of specific IgE in patients with allergic diseases, but also allows to use these single nucleotide replacements as additional prognostic features of individual susceptibility to these diseases [14].

The important property of TLR consists not only in the fact that it is a central link of the innate immune in antiviral immune response, but also in their ability to interact with the structures of viruses – proteins, glucoproteins, lipoproteins, RNA and DNA which significantly contributed to further study. Respiratory viruses – influenza, parainfluenza, adenoviruses, rhinoviruses and respiratory syncytial virus are the most common causes of acute respiratory viral infections (ARI) in children. Viral infection is one of non-specific factors that reinforce the effect of causal factors in atopic dermatitis, and is the most significant risk factor for atopic syndrome.

Therefore, at the next stage the association of 896A/G polymorphism of TLR4 gene with features of clinical course in atopic dermatitis in children with a tendency to frequent SARS was studied [21].

Analysis of the obtained data showed that in the group of children with atopic dermatitis with susceptibility to frequent SARS the mutated 896G allele of TLR4 gene is detected significantly more frequently (9.3%) as compared with the control group ($\chi 2 = 4.33$; OR = 5.06 ; CI = 1.28-20.08, p = 0.038). The presence of mutant 896G alleles of TLR4 gene was associated with severe course of the disease (p=0.0485); concomitant adenoid vegetations combined with allergic rhinitis and / or BA (p=0.0248) and allergic rhinitis (p = 0.0053); polyvalent allergy to 4 types of allergens (p=0.0485). It is concluded that the presence of 896A/G polymorphism of TLR4 gene is essential in determining the severity of atopic dermatitis and development of complications.

Detecting the presence of 1196C/T polymorphisms of TLR4 gene (rs4986791) and 2258G/A of TLR2 gene (rs5743708) in children with atopic dermatitis and possible association of these polymorphisms with increased susceptibility to infection did not produce credible results [22].

The research determined that 2258G/A polymorphism of TLR2 gene (rs5743708) is important in determining the course of allergic rhinitis (AR), confirming the pathogenetic link between innate and adaptive immunity in AR [30.32].

In particular, the significant difference between the groups of patients with AR with the presence of mutant 2258G/A allele of TLR2 gene and homozygous carriers of the “wild” alleles in terms of $CD4^+$ (U (n = 42; n = 3) = 12.00; p = 0.020) was revealed. In patients with AR, mutant 2258G/A allele of TLR2 gene, the level lymphocytes was significantly higher than in homozygous carriers of the “wild” allele (U (n = 42; n = 3) = 11.50; p = 0.019) with AR.

A broader study embraced the determining of the role of genes polymorphisms, not only 2258G/A of TLR2 gene (rs5743708), and 896A/G of TLR4 gene (rs4986790) and galectin-10 gene (rs420297 C/T)) in the pathogenesis of AR, in order to improve knowledge of immunological mechanisms of this disease [29, 33].

The study of allergic anamnesis revealed that in 76% of cases AR in patients is largely of hereditary nature on the mother’s side (36%), it mostly begins in childhood and adolescence (88%) and in 44% is accompanied by other allergic diseases. 89% of patients with AR had positive skin tests for domestic, epidermal, pollen, food and fungal allergens, 82% had polyvalent sensitization to two or more groups of allergens.

In the study of the immune status of patients with AR it was found that in 15% of patients eosinophilia, increased average levels of total immunoglobulin E, the relative increase in the number of CD4+CD25+Foxp3+ Treg cells with reduction of IL-10 and increased IL-4 were observed.

In the group of patients with AR, prevalence of TLR2 gene polymorphism (rs5743708) was established: GG genotype was 93.3%, genotype GA – 6.6%, genotype AA was not observed.

The spread of TLR4 gene polymorphism (Asp299Gly): AA genotype was 92.3%, genotype AG – 7.7%, GG genotype was not observed. The significant difference between the frequencies of genotypes in the control group and patients with AR (p = 0.03) was detected. In patients with AR, G allele carriers for 896A/G polymorphism of TLR4 gene, the atopic pathology was

detected: concomitant BA (p = 0.0003), concomitant AD (0.0031) and BA in combination with AD (p = 0.0005).

The spread of rs420297 polymorphism of galectin-10 gene among persons living in Poltava region is CC-76%; CT-22%; TT-2%. The significant difference between the frequencies of genotypes in the control group and patients with AR (p = 0.04) and the frequency of T allele of CLC-10 in the group of patients was observed: by 30% as compared with the control group, 13% ($\chi 2 = 6.42$; p = 0.011), rs420297 polymorphism of CLC-10 gene was significantly more common in the group of patients with RA. The development and course of allergic rhinitis is associated with rs420297 polymorphism of CLC-10 gene (a year-round form of AR occurs significantly more often in patients with AR mutant allele CLC-10 (p = 0.0001)).

Moreover, the significant association between the presence of polymorphic alleles of CLC-10 gene and $CD4^+$ levels (p=0.014), $CD4^+CD25^+$ (p=0.012) was revealed; in the group of homozygous carriers of polymorphic allele T and allele C of CLC-10 gene the significant association between the presence of polymorphic allele of CLC-10 gene and $CD4^+CD25^+Foxp3^+$ levels (p=0.037), CD4 + (p = 0.014) was established. It was determined that individuals who have polymorphic allele of CLC-10 gene have significantly higher levels of IgE (p = 0.013) and IL-4 (p = 0.004) and lower level of IL10 (p = 0.038) [31].

One of the most common bacterial infections is caused by Helicobacter pylori (H.pylori), promoting the development of gastric diseases, immune and inflammatory responses. However, the severity of inflammation may depend on the interaction of certain factors such as the virulence of pathogen, reactivity, external factors. Among etiopathogenetical factors, genetic influences play a certain role.

The features of H. pylori infection in children with ASP299GLY polymorphism of TLR4 gene were investigated [1].

In children with Asp/Gly SNP Asp299Gly genotype of TLR4 gene the decrease in expression of TLR4 in bioptic material of gastric mucosa, and the decrease in water-soluble sCD14 level while maintaining severe inflammatory changes in the mucosa were observed. It was determined that in children with chronic gastroduodenal inflammatory diseases Asp/Gly SNP Asp299Gly genotype of TLR4 gene is observed significantly more often than in healthy children. It is concluded that the presence of Asp/Gly SNP Asp299Gly genotype of TLR4 gene in children causes susceptibility to infection with H. pylori.

Scientific achievements of corporate authors suggest that the clinical course of HIV infection in patients with Asp299Gly polymorphism of TLR4 gene may have certain features that require further research in this area [13].

It was determined that in HIV-infected patients Asp299Gly polymorphism of TLR4 gene is observed significantly more frequently than in healthy subjects (12.0% and 2.1% respectively, p <0.005).

Comparisons of clinical and immunological characteristics of HIV patients according to the presence of the Asp299Gly polymorphism of TLR4 gene suggest that in HIV-infected patients with existing polymorphism there are features of clinical course and immune status that should be considered during examination and treatment. In particular, the HIV heterozygous genotype (AG) of TLR4 gene is associated with increased risk of mixed pathologies of viral, bacterial and parasitic etiology. The development of opportunistic infections in the presence of Asp299Gly polymorphism of TLR4 gene is implemented at a higher level of CD4 lymphocytes, which raises the question as to the appropriateness to reconsider the prescription of antiretroviral therapy and chemoprophylaxis of opportunistic infections.

Equally important medical problem is the search for etiopathogenic markers of such a widespread and unpredictable in terms of clinical course viral disease as influenza. The current stage of science defines the study of genetic factors associated with the development of influenza and its complications as the main focus of research.

The prevalence and prognostic significance of Arg753Gln polymorphisms of TLR2 gene, Leu412Phe of TLR3gene, Asp299Gly of TLR4 gene in influenza were investigated [3].

Studies have shown that the frequency of heterozygous Asp/Gly genotype of TLR4 in patients with influenza is 12.69%; influenza-associated pneumonia – 14.28%, which exceeds the population control by 3.8-4.3 times (3.33% p <0.005). It was determined that the homozygous Phe/Phe genotype of TLR3 in patients with influenza-associated pneumonia is in 18.37%, which is more than in patients without influenza complications (4.76%, p = 0.02) and healthy individuals (5.0 %, p = 0.03).

The combination of mutant genotypes of TLR2, TLR3 and TLR4 was defined only in cases of influenza and influenza-associated pneumonia with the rate of 11.11-14.28% (p <0.005).

It was concluded that the presence of polymorphomodified genotypes of TLR3 and TLR4, their combinations with TLR2 allows predicting the development of influenza and influenza-associated pneumonia. The risk of influenza in terms of odds ratio is 4.2 times higher than in people with Asp/Gly genotype of TLR4 gene, by 15 – in combination of mutant genotypes of TLR2, TLR3 and TLR4, and the risk of influenza-associated pneumonia is by 4.5 times higher in patients with homozygous mutant genotype Phe/Phe of TLR3.

III. The nuclear transcription factor κB from the standpoint of syntropy of infectious and non-infectious pathologies

Studies of recent decades have shown that nuclear transcription factor κB is in the centre of many pathological conditions. Its signalling pathway of receives signals from many stimuli of both infectious and non-infectious nature, it plays the role of the leading proinflammatory way.

A number of published papers and the results of our own research allowed to formulate the concept of long-term and low intensity activation of NF-κB as a possible molecular basis for syntropy of internal diseases which is based on evolutionary aspect and action conditions of advanced modern factors [7, 12].

According to the concept of syntropy and syntropic pathology, the most common diseases and pathological conditions such as insulin resistance, chronic systemic inflammation, type 2 diabetes, hepatocellular failure, atherosclerosis, osteoporosis, bronchial asthma, chronic obstructive pulmonary disease, Alzheimer's and Parkinson's have common pathogenetic mechanisms, or separate elements of these mechanisms [9].

In favour of the concept are the positive results of targeted therapy with agents that affect the activity of NF-κB and the expression of its target genes (IL-1β, IL-6, TNF-

α), influence the process of insulin resistance (biguanide, activators of PPAR- γ).

In particular, the data were obtained indicating the decrease in NF-κB activity, concentrations of proinflammatory cytokines and CRP using biguanides (metformin) and PPAR-γ activators (pioglitazone) [2, 16, 18, 19].

It should be noted that the results were obtained confirming that genetic polymorphism of proteins that are associated with a cascade of NF-κB-mediated reactions – PPAR-γ2, angiotensin receptor II type 1, TLR 2 and 4 – may influence the development of internal diseases [8], thus forming the foundation for further research and bind in certain pathogenic cascade the following elements: pathogen – perceiving (receptor) cell apparatus – interaction with signalling NFκB cascades – implementation of the inflammatory response.

IV. Preconditioning of anti-inflammatory pathway of NF-κB as a mechanism to influence syntropy

Our data suggest that polymorphisms of genes that provide immune response of the body underlie the genetic susceptibility to immune-mediated diseases and determine the high susceptibility to infectious and allergic diseases. According to the concept of long-term and low-intensity activation of NF-κB as a possible molecular basis for syntropy of internal diseases, we conducted the research related to the mechanisms of preconditioning of proinflammatory NF-κB pathway.

The strategic target for therapy of a number of diseases in which the NF-κB signalling cascade is involved is the systemic inflammatory response with hyperlipidemia and insulin resistance related to it. Thiazolidinediones – receptor agonists that activate proliferation of peroxisome-γ (PPAR-γ) – are successfully used in modern therapy for regulation of these processes.

Adding pioglitazone to the standard therapy for patients with coronary heart disease and metabolic syndrome resulted in lower concentrations of triglycerides, b-lipoproteins, total cholesterol and total lipids in serum, not only in comparison with the original parameters in these patients before treatment, but with the parameters of the comparison group after standard therapy [2].

The obtained data confirm that the prescription of pioglitazone effectively influences the processes associated with insulin resistance, helps to significantly reduce the concentration of immunoreactive insulin and reliably – the blood glucose, indicating a decrease in the severity of insulin resistance.

The use of pioglitazone in the treatment of patients with coronary heart disease and metabolic syndrome lowers systemic inflammation and lipid metabolism and significantly reduces insulin resistance. The inclusion of pioglitazone into the therapy in patients with complex coronary artery disease (exertional angina) against the background of metabolic syndrome does not increase cardiovascular risk and improves the clinical course of the disease, increases the effectiveness of standard treatment of coronary artery disease. The study allows us to recommend the inclusion of pioglitazone therapy in the comprehensive therapy of CHD and metabolic syndrome.

Another drug that has anti-inflammatory and insulinosensitizing activity is metformin. The assessment of its effect on NF-κB-signalling pathway in patients with coronary artery disease against the background of metabolic syndrome was conducted. The inclusion of monthly course of metformin into the comprehensive therapy in CHD reduced production of proinflammatory cytokines IL-1β, IL-6, IL-8 and TNF-α, as well as reduced the level of C-peptide concentration in serum [18].

It was concluded that the inclusion of metformin in comprehensive therapy of CHD with metabolic syndrome prevents activation of NF-κB under the action of endogenous inflammatory cytokines.

Taking into account the obtained results, the data of scientific literature were considered as to the molecular mechanisms of metformin and pioglitazone and role of nuclear transcription factors: NF-κB and PPAR-γ.

The results of own research show a significant reduction of inflammatory cytokines when metformin and pioglitazone are included into in the comprehensive therapy of coronary artery disease in patients with metabolic syndrome. In older women it took place both in the presence of abdominal obesity, and without it, indicating the crucial role of systemic inflammation and insulin resistance in the pathogenesis of metabolic syndrome.

It seems probable that the overall action mechanism of these drugs, despite their belonging to groups with different action mechanisms, is their influence on the suppression of chronic systemic inflammation of low intensity, which is the basis of all chronic human pathologies. The data confirm that it is appropriate to introduce determining the markers of inflammation and insulin resistance into the panel of necessary studies in order to establish the risk tendency of modern man to the development of the most common diseases, such as cardiovascular disease, type 2 diabetes, chronic obstructive pulmonary diseases, neoplastic diseases and others.

It is an already admitted idea that insulin resistance is the pathogenetic basis for metabolic syndrome. It is assumed (Egger G., 2011) that hypertrophied metabolically active adipose tissue produces inflammatory cytokines and angiotensinogen which renders blockade of intracellular signalling pathways of insulin with the development of insulin resistance, activation of the renin-angiotensin system with the development of hypertension, endothelial dysfunction, hyperlipidemia and inflammatory damage to the artery wall with the development of atherosclerosis.

The conclusion was made about the need to shift the focus to the studies of the molecular mechanisms of the immune system activation, suggesting as to insulin resistance the etiologic role of chronic systemic inflammation. Recognition of chronic systemic inflammation as the etiological factor for insulin resistance, whether this be chronic systemic inflammation either acquired or genetically determined, can, in our opinion, ultimately provide metabolic syndrome with the status of a nosology instead of a syndrome (the assembly of just pathogenetically related symptoms that do not have common etiology) and, even more, not “the community of individual, not related risk factors for cardiovascular disease”. In its turn, the study of external, genetic and molecular factors of chronic systemic inflammation and insulin resistance will open new pathways for prevention and treatment of human chronic diseases [17].

In subsequent studies it was shown that the combination of metformin and ramipril (1000 mg and 5 mg per day respectively) in the treatment of metabolic syndrome within 6 months leads to improved clinical course of coronary artery disease, reducing the number and duration of painful heart attacks, reduced functional class of angina, decrease of chronic heart failure, normalization of blood pressure and reduction of abdominal obesity.

This effect can be seen as prevention of type 2 diabetes and its cardiovascular complications. The combina-

tion of metformin and ramipril in treatment of metabolic syndrome is an effective and safe treatment option [27, 28].

In order to confirm the obtained data, the effectiveness of the medium-term inclusion of metformin into the comprehensive therapy of patients with type 2 diabetes combined with coronary artery disease was studied in order to justify the rational timing and dose of the medication. In 52 patients suffering from type 2 diabetes and coronary artery disease the influence of metformin inclusion (1 g daily) into the comprehensive therapy for 3 month was studied as compared to the primary level and the results obtained after 1 month of treatment.

The results showed that after 3 months, the tendency to clinical parameters improvement is maintained, reducing the functional class of angina, the severity of heart failure, blood pressure, and retaining the achieved reduction in body mass index are observed. There is further improvement in lipid metabolism, decrease of total cholesterol, triglyceride and atherogenic index. The levels of glycosylated hemoglobin, C-peptide, insulin resistance index and systemic inflammation achieved within a month, are preserved as well. The results indicate that administration of metformin in patients suffering from type 2 diabetes and coronary heart disease within 3 months is an effective and safe treatment for these patients [20].

Thus, the signal transduction of nuclear transcription factor κB is a critical point, in which the main inflammatory, metabolic and regulatory pathways involved in the development of chronic inflammation are intercrossed. It is subject to correction of the preconditioning state of regulatory systems, especially in the presence of polymorphic variants of genes encoding key enzymes, receptors and regulatory proteins [10, 11].

The obtained results will contribute to the formation of a systematic approach to the development and use of new technologies for prevention and effective pharmacogenetic treatment of diseases based on chronic inflammation.

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