# POLYMORPHISM OF CYTOKINE GENES ASSOCIATED WITH INFECTIVE ENDOCARDITIS

***Sattarov O.Kh.***
***Assistant to the department of propaedeutics of internal diseases***
***Andijan State Medical Institute***
***Andijan, Uzbekistan***

Summary

Infectious endocarditis is a disease with the primary localization of the pathogen on the heart valves and parietal endocardium, occurring with possible generalization of the septic process and the development of immunopathological changes, which are very significant in the formation and course of the disease. Based on the fact that 30–50% of cases of infective endocarditis develop without the obvious involvement of classical risk factors ( invasive procedures or endovascular disorders), it can be assumed that molecular genetic factors are involved in the pathogenesis of the disease and its complications. There is reason to believe that the activation of inappropriate inflammation in response to microbial invasion may be due to polymorphism in genes that control cytokine activity . However, the information available today on the levels of various cytokines and the polymorphism of their genes in various clinical variants of infective endocarditis is very limited and often contradictory, which requires a more in-depth study of the pathogenetic connection of infective endocarditis with genetic defects of cytokines . In this regard, expanding the understanding of cytokine gene polymorphisms in the form of point mutations (SNPs) that can regulate the intensity of cytokine expression and their biological effects will make it possible to predict the risk of developing infective endocarditis, the severity of its course, the risk of possible complications, as well as individual selection of specific therapy for patients .

**Key words:** infective endocarditis, clinical variants, complications, cytokines , cytokine genes , genetic polymorphism, pathogenesis, diagnosis.

## Introduction

Infectious endocarditis (IE) is a disease of a bacterial nature with a predominant localization of the pathogen on the heart valves and endocardium and is accompanied by immunopathological manifestations with possible generalization of the septic process. The high-risk group for IE

includes patients with heart defects, degenerative changes in the valvular apparatus, immunodeficiencies, artificial valves, cardiac surgeries, and intravenous drug users, but increasingly (in 30–50% of cases) the disease occurs in the absence of obvious risk factors, which indicates possible involvement of genetic factors in pathogenesis [1, 2].
Currently, the causes of death in patients with IE are often thromboembolic complications (myocardial infarction, ischemic stroke, pulmonary embolism, etc.), the severity of which depends on the course of IE [3]. Moreover, if the acute variant of the course is more often characterized by a septic process with severe intoxication of the body and an unfavorable prognosis, then the subacute variant of IE is characterized by predominant damage to the valvular apparatus of the heart, transient septicemia and the development of severe immune complex pathology in the form of vasculitis , serositis , glomerulonephritis , myocarditis [1].

The basis for diagnosing IE is the Duke criteria (2015), including clinical features, echocardiography and blood culture results [4]. Meanwhile, the diagnosis of IE is difficult due to the pronounced polymorphism of the clinic, a wide range of pathogens and the increasing proportion of polymicrobial infection in the genesis of the disease, and the lack of specific diagnostic signs in the early stages of IE does not allow differentiating it from other infectious and tumor diseases, which are also characterized by anemia and leukocytosis , acceleration of ESR, increased levels of C-reactive protein (CRP), microhematuria and proteinuria in a general urinalysis , i.e., patients have laboratory signs characteristic of a number of other diseases [1, 5, 6].

The relevance of clarifying the issues of immunopathogenesis of IE is due to the continuous activation of humoral and cellular immunity in conditions of constant bacteremia, accompanied by significant changes in the spectrum of pro- and anti-inflammatory cytokines . At the same time, the study of the structure and expression features of genes encoding human protein molecules, as well as the introduction into routine laboratory practice of new diagnostic technologies for testing various gene polymorphisms are today considered promising directions in relation to predicting the risk of developing certain diseases in a particular individual [1]. In general, if the study of the pathogenetic role of cytokines can make it possible to predict the risk of development and severity of the disease and select specific personalized therapy, then the study of cytokine genes helps to detect a predisposition to IE [7].

Thus, from the point of view of the relevance of studying and introducing into practice additional immunogenetic criteria for laboratory assessment of prognosis and the risk of adverse outcomes

in patients with IE, it is of interest to analyze and systematize modern scientific information about the polymorphism of cytokine genes associated with this disease .

**Genetic polymorphism of cytokines during the infectious process**

An important place in the induction of immune imbalance during the infectious process is given to disturbances in intercellular interaction mediated by the cytokine-receptor network [8]. At the same time, the synthesis and secretion of cytokines , which have a wide range of biological effects, are regulated by genetic mechanisms of their gene expression, the study of which is actively ongoing [9]. Normally, many cytokine genes are expressed with a high degree of individual variability, while in pathologies characteristic changes in expression can be observed both in the form of activation of specific genes and in the form of repression of initially active ones, along with which cascade gene expression can often be observed, when activation of one gene causes the expression of another or even groups of genes [10]. It is known that the expression of genes of biomolecules depends on their polymorphism: if with single nucleotide polymorphism ( SNPs ) as a result of point mutations there is a change in the DNA sequence (one nucleotide) in homologous regions of homologous chromosomes, then polymorphic genetic sites can be considered as markers of susceptibility or resistance to various diseases, in the pathogenesis of which cytokines play an important role [11]. Genetically determined dysregulation of cytokine formation causes not only chronicity , but also generalization of the inflammatory process, and can also determine the occurrence of early relapses of diseases. In particular, disturbances in the production of cytokines of the interleukin (IL) 1 family (IL-1β, IL-1RA, IL-1RI) determine the nature of inflammation and are one of the triggers of pathological processes [12], and markers of a prognostically unfavorable response to therapy can be alleles -308G TNF-α, -31T IL-1β, -592A IL-10.

A number of polymorphic variants are known in the promoter and intronic regions of proinflammatory genes cytokines TNF, IL-1β and their receptors associated with the level of their production necessary for the regulation of cell proliferation, differentiation and apoptosis , coagulation and lipid metabolism ( see table) [13–15].

| Table. Chromosome localization of cytikine genes and their receptors 14 | |
|---|---|
| Cytokine genes | |
| IL-1L | 2q13 |

| | |
|---|---|
| IL-1B | 2q13-21 |
| TNF- α | 6p23-q12 |
| IL-10 | 1q31-q32 |
| IL-6 | 7p16.4 |
| IL-4 | 5q23-32 |
| IFNg | 12q24.2 |
| IL-18 | 11q22.4_q22.5 |
| Cytokine receptor genes | |
| IFNgR1 | 6p23-25 |
| IFNgR2 | 21q22.2 |
| IL-6R | B 17 |
| IL-4RA | 16p12.1-11.3 |
| IL-10RA | 11q23 |

The promoter region of the TNF-α gene includes 8 polymorphic regions with single nucleotide substitutions: -1031T>C, -863C>A, -857C>T, -575G>A, -376G>A, -308G>A, -244G>A, -

238G>A, but the most significant are considered to be single-nucleotide substitutions of guanine to adenine at positions -308 and -238, which cause changes in the level of TNF-α production. Thus, the identification of the polymorphic allele TNF-α -308 *A in malaria is a high risk factor for the formation of the cerebral form of infection [16], and the presence of at least one copy of the allele -308 *A in the genome of a child with meningococcal infection increases the likelihood of an unfavorable outcome by 2 ,5 times [17, 18]. At the same time, cells of donors homozygous for the A / A genotype synthesize 3 times more TNF-α than cells of individuals with the G / G genotype, and when replacing guanine with adenine , on the contrary, there is a decrease in the production of this cytokine .

Functional polymorphism of genes encoding proteins of the proinflammatory IL-1 (IL-1β) family is caused by point nucleotide substitutions and tandem repeats of a gene segment [19], which causes defects in phagocytosis and initiation of inflammation, leading to chronicity of the infectious-inflammatory process [20 ] . Along with this, the identified connection between the genetic polymorphism of IL-1 and IL-4 in the process of developing sensitization to Streptococcus antigens pyogenes significantly increases the risk of complications in the presence of this pathogen [21]. Despite the lack of data on the expression of the IL-4 gene, there is convincing evidence that the polymorphism of the IL-4RA gene (1902A>G) leads to the replacement of the amino acid glutamine with arginine at position 551 (551G>A), which may affect IL-4 signal transduction [22], and the presence of polymorphic variants of the IL-4 and IL-17A genes can more often be detected in individuals with infection-related bronchial asthma (70.2 and 67.5%) [23] .

The most studied members of the IL-17 family are IL-17A and IL-17F, the effects of which involve oligonucleotide polymorphisms of the IL-17A (rs2275913) and IL-17F (rs763780) genes, the associations of which with serum IL-17 levels have been identified in women with miscarriage of infectious origin [24–26].

The variability in the concentration of anti-inflammatory IL-10 is 50–70% due to genetic factors [27]. Among the polymorphisms of the promoter region of the IL-10 gene that affect the levels of IL-10 mRNA transcription, the most studied are the IL-10 SNPs A-1082G (rs1800896) and A-592C (rs1800872), associated with the level of production of this cytokine , as well as the nature of the course and outcome of various diseases [28, 29].

The important regulatory role of IFN-γ and the polymorphism of its genes in the infectious-inflammatory process is indicated by a deficiency of IFN-γ production in children with recurrent infection, accompanied by a violation of the migratory function of neutrophils and the activity of natural killer cells [30]. There is also an assumption that IFN-γ polymorphism, which contributes

to the formation of weakened anti-infective immunity, can prevent inflammation-related diseases ( cardiovascular , osteoarthritis , osteoporosis and diabetes) [31].

Thus, there is increasing evidence to support the concept of the influence of genetic polymorphism on susceptibility to infectious diseases and on their outcomes. In particular, a connection has been established between TNF-α and IL-6 SNPs and the development and outcomes of sepsis [32]; between susceptibility to severe sepsis and the rs1800629 variant of the TNF gene [33]; between genetic variants in TNF receptor-associated factor 6 (TRAF6) and increased susceptibility to sepsis-induced acute lung injury [34]; between genetic variants of the $\beta_2$-adrenergic receptor and increased susceptibility to bacterial meningitis [35]; between Toll-like receptor (TLR) gene variants and infectious and autoimmune diseases [36]; and also between IL-17A gene variability and sensitivity to Gram-positive infection and severe sepsis [37]. However, a significant portion of the genetic component of an infectious disease may be due to the cumulative effect of many rare mutations with limited penetrance [38], while the likelihood that any one gene will be associated with an infectious disease is very low [39].

Of particular interest is the assessment of genetic predictors of endothelial dysfunction, among which well-studied candidate genes are the genes for endothelin 1, angiotensin-converting enzyme, and angiotensin II receptor type 1 , which predispose to the development of cardiovascular diseases and have an adverse effect on their course [40]. In this regard, it is important to note the discovery of an association between the expression of proinflammatory IL-6, TNF-α and the activity of angiotensin II, which confirms the position of the involvement of proinflammatory cytokines in the development of atherosclerosis and the formation of endothelial dysfunction [41]. Meanwhile, information on the influence of polymorphisms in the genes of the “first wave” inflammatory mediators - IL-17A (G197A, rs2275913), IL-1β (T511C, rs16944), TNF-α (G308A, rs1800629) and IL -4 (C589T, rs2243250) on the risk of developing cardiovascular diseases in world populations [42, 43].

**The role of single nucleotide polymorphism of cytokine genes in the development of IE**

Up to 30–50% of IE cases develop without any obvious involvement of classical risk factors ( invasive procedures or endovascular disorders), which indicates the possible involvement of molecular genetic factors in the pathogenesis of the disease, as well as its complications [44]. As with other diseases of an infectious nature, the initiation and progression of IE are a consequence of the complex connection of a huge number of genes with various environmental factors, and differences in susceptibility to IE may be associated with genetic variability not only of the host organism, but also of the microorganism, since gene variability , encoding the virulence of S.

aureus , its resistance to antibiotics, as well as the adaptive capabilities of the host organism , can contribute to the occurrence of IE during bacteremia [45].

Very few molecular genetic studies of IE conducted in the last decade are mainly devoted to the study of associations of IE with polymorphisms of genes of the innate immune system, among which expressed cardiomyocytes and TLR endothelial cells [46], the genes of which determine susceptibility to bacterial agents and may be candidate genes for IE. In particular, the diagnostic significance of the TLR-6 gene polymorphism (rs3775073) was revealed, in which a synonymous mutation in the first exon of TLR6 leads to an average 2-fold reduction in the risk of developing IE, while a non-synonymous polymorphism in the same exon of TLR-6 (C745T, rs5743810 ) is associated with an increased risk of developing IE [47].

The known key role of the expression of pro- and anti-inflammatory cytokine genes in the development and course of many pathological processes in the human body suggests that single nucleotide polymorphisms in the genes of diagnostically significant cytokines can also influence the development and course of IE. Thus, polymorphism of the rs1817537 gene of the trigger receptor of myeloid cells (TREM-1), which controls the secretion of a number of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) and chemokines (IL-8, MCP-1), is associated with a reduced risk of developing IE [47], while an increased risk of developing IE in heterozygous carriers of the minor T allele is evidenced markers of endothelial dysfunction, in particular E-selectin rs5370 (EDN1) [48].

Currently, the fact of the influence of single SNPs on the infectious process has been convincingly proven in relation to sepsis and other bloodstream infections, however, information on the connection of SNPs with the induction and nature of the course of IE is very limited [49]. In this regard, the data of M. Weinstock are of interest et al . [50] about three variant SNPs cytokines that may determine susceptibility to IE: IL-1β c.315C>T; IL-6 c.471+870G>A and IL-6 c . -237C>G). Despite the fact that the data obtained by the authors on the high frequency of the T allele of the “IL-1β c.315C>T” variant in patients with IE were not confirmed by other researchers [51], the convincingly proven increase in the frequency of polymorphisms of the IL-6 gene ( variant “c.471+870G>A”), which determine the sensitivity of individuals to IE [50].

For genes such pro-inflammatory cytokines , such as TNF and IL-1β, necessary for the regulation of cell differentiation, proliferation, and apoptosis , there are many SNPs in the promoter and intronic regions of genes associated with the level of their production [13]. At the same time, a decrease in the risk of developing IE is associated not only with the A/G genotype of the rs1130864 polymorphism of the CRP gene and the G allele of the rs1801197 polymorphism of the calcitonin receptor gene (CALCR), but also with the G/A genotype of the

rs1143634 polymorphism of the IL-1β gene, the genotype of the G/T polymorphism rs3212227 of the IL-12B gene, while the identification of heterozygous genotypes of polymorphisms (rs1143634 and rs3212227) was accompanied by an increase in the content of IL-1β and IL-12 in the blood plasma, which indicates their pathogenetic role in IE [51, 52]. In addition, it is known that TNF, by binding to specific membrane receptors, can cause activation of transcription factors that regulate genes of other proinflammatory cytokines (IL-1, IL-6), prostaglandins, platelet activating factor, transforming growth factor β (TGF-β), some hormones (adrenaline) [53], and carriage of minor frequency alleles A in the -238 promoter region of the TNF gene , and the presence of any of the three GGA/GAA/AGA haplotypes was more frequent in patients with IE [54].

However, there are studies that failed to confirm the results of the association of the IL-6 and TNF genes with IE, which may be due to a small sample and intragroup differences (gender, age, ethnic origin, etiology and clinical picture of the disease) [55] . That is why the determination of the pathogenetic connection of IE and the formation of its complications with genetic factors remains an open question that needs more in-depth study to determine the true influence of polymorphism of genes for an extended spectrum of cytokines in the pathogenesis of IE.

**Conclusion**

The era of personalized genomic medicine at this stage of its development is characterized by broad opportunities. The latest advances in molecular genetics make it possible to isolate and study immunogenetic markers in patients with various diseases. The uniqueness of modern molecular medicine lies in its focus on resolving the disease in a particular patient, taking into account the characteristics of his genome, as well as prevention, when information about genes is obtained before the disease, which can prevent the development of a pathological condition. Since the functioning of the cytokine network is based on the mechanisms underlying the regulation of cytokine gene expression , the study of genetic factors such as allelic variants of polymorphic loci and cytokine gene expression , as well as the content of cytokines themselves in the blood, will allow us to assess their key role in the pathogenesis of different course options IE, as well as determine their prognostic significance regarding the development of its thromboembolic complications. Identification of genetic variants associated with an infectious disease makes it possible to identify patients at an early stage at a higher risk of adverse outcome from specific diseases - pneumonia, IE, sepsis, acute respiratory distress syndrome , etc., which contributes to the development of new, possibly individually selected methods treatment of these patients.

Meanwhile, the frequent inconsistency in world literature data regarding the pathogenetic role of genetic polymorphism may be due to the general lack of all genetic and epidemiological works on IE, in particular, an insufficient sample size due to the relatively low frequency of IE, low reproducibility of results due to bias in the selection of candidate genes , as well as the influence of many other genes and environmental factors on phenotype, epigenetics , as well as a lack of understanding of patterns of variation in the human genome.

Nevertheless , there is hope that the capabilities of modern molecular genetic research and new technologies, more accessible from an economic point of view, will make it possible to minimize the influence of these factors on research results and successfully solve the problem of diagnosing IE and predicting its possible complications based on polymorphism of genes of pathogenetically significant cytokines .

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