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GENETIC VARIABILITY OF BIOMARKERS OF INNATE IMMUNITY AS A FACTOR DETERMINING THE CLINICAL DIVERSITY OF INFECTIOUS DISEASES

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ABSTRACT

Goal. Generalization of modern data on the role of genetic variability of innate immunity in the formation of clinical heterogeneity of infectious diseases using the example of respiratory syncytial infection, with an analysis of key molecular mechanisms and prospects for their clinical application.

Materials and methods. The analysis of publications published in the databases PubMed, Scopus, Web of Science, Google Scholar and eLibrary was carried out using the keywords: innate immunity, genetic polymorphism, PRR, cytokines, interferons, respiratory syncytial infection, clinical heterogeneity. The review mainly includes works from the last 5 years devoted to the molecular genetic aspects of the immune response and their clinical associations; studies with limited methodological significance are excluded.

Results and discussion. It has been shown that differences in the clinical course of infectious diseases, including RSV infection, are largely due to polymorphisms in the genes of innate immunity receptors, cytokines, and interferon signaling pathways. Genetic variants of TLR, RIG-I-like receptors, components of inflammasomes, and cytokine genes affect the strength and timeliness of the antiviral response, the severity of inflammation, and the risk of complications. It has been demonstrated that these same genetic factors can determine the variability of response to anti-infective therapy and the likelihood of adverse drug reactions. Special attention is paid to the clinical and epidemiological aspects of genetic heterogeneity identified during the COVID-19 pandemic.

Conclusion. The genetic variability of innate immunity is an important determinant of the clinical heterogeneity of infectious diseases. Taking into account genetic factors allows for a deeper understanding of the causes of differences in the course of infection and creates the prerequisites for the introduction of personalized approaches to prognosis, prevention and therapy in infectious diseases.

KEYWORDS: innate immunity; genetic polymorphism; clinical heterogeneity; infectious diseases; respiratory syncytial infection; cytokines; interferons.

INTRODUCTION

Infectious diseases remain one of the leading causes of morbidity and hospitalization in the world, while the clinical course of the same infection can vary significantly even in patients of similar age and without pronounced risk factors [1]. One of the most obvious examples of such clinical heterogeneity is respiratory syncytial infection, which is widespread among young children. According to the World Health Organization, more than 33 million cases of respiratory syncytial virus (RSV) infection are registered annually in the world, which leads to approximately 3.2 million hospitalizations and up to 60,000 deaths among children under 5 years of age [7]. In the Russian Federation, RSV also occupies one of the leading places in the structure of viral infections of the lower respiratory tract in children, accounting, according to various estimates, for up to 20-30% of hospitalizations with bronchiolitis and pneumonia during the season of increased incidence [8].

At the same time, the clinical picture of RSV infection varies from mild catarrhal manifestations to severe bronchiolitis, respiratory failure and the need for intensive therapy. Such a discrepancy in clinical outcomes cannot be explained solely by viral load or environmental factors [9-12]. More and more evidence indicates that the genetic variability of innate immunity plays a key role in the formation of individual susceptibility to infection and determines the severity of its course. Polymorphisms in the genes of pathogen recognition receptors, cytokines, chemokines, and transcription factors can change the nature and strength of the early antiviral response, thereby forming the clinical heterogeneity of the infectious process [2-5].

Despite the active development of molecular genetic research, the contribution of innate immunity to the variability of the course of infectious diseases is still poorly understood. Most studies focus on individual genes or populations, while a holistic understanding of the interaction of genetic factors of innate immunity and clinical manifestations of infection is still lacking [6]. This is especially true for RSV infection, for which no effective vaccine has existed for many years, and therapeutic options remain limited and mostly supportive. Thus, the analysis of the genetic determinants of the innate immune response seems to be an important direction for explaining the causes of clinical heterogeneity of infectious diseases and searching for new approaches to prevention and treatment [8-10].
The purpose of the review is to summarize current data on the influence of genetic variability of innate immunity on the clinical heterogeneity of infectious diseases using the example of respiratory syncytial infection and identify key molecular mechanisms and areas for further research.

MATERIALS AND METHODS

The search and selection of literature were performed using the databases PubMed, Scopus, Web of Science, Google Scholar and eLibrary. The search was conducted by keywords: innate immunity, genetic polymorphism, PRR, cytokines, interferons, respiratory syncytial infection, clinical heterogeneity. A total of 150 publications were analyzed, of which 63 sources were selected for the final review that best meet the research objectives and quality criteria. Works with limited methodological significance, duplicate data, and low-quality research are excluded.

The molecular basis of innate human immunity

Innate human immunity is based on the ability of cells to quickly recognize an infectious threat and trigger an inflammatory response even before the formation of adaptive immunity [12]. Pattern recognition receptors (PRRS) play a key role in this process, which interact with the conserved structures of pathogens - pathogen-associated molecular patterns. As shown by the work of M.A. Kazumyan et al., it is the variability of the genes encoding the components of these receptor systems that largely determines individual differences in immune response and predisposition to immunopathological conditions.
The current understanding of PRR is much broader than the original concept, limited to bacterial structures such as lipopolysaccharides. Today, it is obvious that the innate immune system actively recognizes viral nucleic acids, both RNA and DNA, which accumulate in the cell during viral replication [18-20]. This mechanism is especially important in respiratory viral infections, where early activation of congenital cascades determines the severity of the clinical course, which is confirmed by data on RSV infection in children.
The most studied group of PRRS remains Toll-like receptors (TLRs) localized either on the cell surface or in endosomes. Their functional segregation is of fundamental importance: membrane TLRs react primarily to structural proteins and lipids of pathogens, whereas endosomal TLRs react to viral nucleic acids. According to Lapshtaeva A.V. et al., it is TLRs that play a leading role in the formation of the innate response to infections, including tuberculosis, and largely determine the outcome of the infectious process.
TLR activation triggers intracellular signaling cascades in which the key nodal elements are the adapter proteins MyD88 and TRIF. Through them, a signal is transmitted to the transcription factors NF-kB, MAPK, and regulatory factors of interferon, which leads to the synthesis of proinflammatory cytokines and type I interferons [22]. These mechanisms underlie a rapid antiviral response, but when overactivated, they can contribute to the development of inflammatory tissue damage.
In addition to TLR, cytosolic nucleic acid sensors - RIG-I-like receptors and DNA sensors that activate the MAVS and STING signaling pathways - play an essential role in virus recognition. These systems are especially important for epithelial cells of the respiratory tract, where viral replication occurs primarily in the cytoplasm. Studies by foreign and domestic authors show that disruption of these pathways can lead to a weakened interferon response and severe infection [23-25].
Special attention should be paid to inflammasomes, multi-protein complexes that activate caspase-1 and ensure the maturation of IL-1b and IL-18. These cytokines play a dual role: on the one hand, they enhance antiviral protection, on the other, when overactivated, they can contribute to tissue damage and the formation of complications. As B.G. Andriukov et al. emphasize, such molecular mechanisms reflect an evolutionarily formed balance between protection and the risk of immune damage.
Thus, innate immunity is a multilevel molecular recognition system in which PRRS, signaling cascades, and inflammasomes work in concert. The genetic variability of these components determines the individual characteristics of the inflammatory response and explains the clinical heterogeneity of infectious diseases, which is crucial for understanding the pathogenesis and developing personalized preventive and therapeutic approaches.

Genetic polymorphism of innate immunity receptors

The genetic polymorphism of innate immunity receptors is considered as one of the key factors determining individual differences in susceptibility to infectious diseases and the features of their clinical course [27]. Despite the universality of innate immune mechanisms, clinical observations show that when infected with the same pathogen, patients develop fundamentally different forms of the disease, from asymptomatic carriage to severe, life-threatening conditions. A significant part of this heterogeneity is explained by the variability of genes encoding pattern recognition receptors (PRRS), which ensure the initial detection of pathogens and the initiation of an inflammatory response [28-31].

The most studied group of PRRS are Toll-like receptors (TLRs), which recognize a wide range of viral, bacterial, and fungal molecular structures. Polymorphisms in the TLR2 and TLR4 genes are associated with changes in the binding affinity of pathogen-associated molecular patterns and, as a result, with variations in the intensity of activation of NF-kB signaling pathways and the production of proinflammatory cytokines. In clinical practice, this is manifested by differences in the severity of intoxication syndrome, the incidence of pneumonia, and the risk of infection generalization. Carriers of certain TLR2 and TLR4 allelic variants are more likely to have a prolonged or complicated course of the infectious process, which is especially significant in viral respiratory diseases [32].

Along with TLR, NOD-like receptors and related components of the inflammasome play an important role in the formation of the innate immune response. Genetic variations in the genes regulating the assembly and activation of inflammasomes can change the level of production of interleukins IL-1b and IL-18, which are involved in the formation of systemic inflammation. Clinically, this may be reflected in differences between moderate and severe infection, as well as a tendency to hyperinflammatory reactions. For a number of viral infections, polymorphisms of the inflammasome genes have been shown to be associated with an increased risk of developing pneumonia and respiratory failure [33-36].

A special place is occupied by RIG-I-like receptors responsible for the recognition of viral RNA in the cytoplasm of infected cells. Polymorphisms in the genes of these receptors can reduce the effectiveness of the early antiviral response, which leads to insufficient production of type I interferons and delayed control of viral replication. Clinically, this is reflected in a longer course of the disease, increased viral load, and a greater likelihood of complications, especially in children and those with concomitant risk factors [38].

The genetic polymorphism of innate immunity receptors forms an individual "immunological profile" of the patient, which determines not only the probability of infection, but also the nature of the clinical response to the pathogen. Taking these features into account allows for a deeper understanding of the causes of clinical heterogeneity of infectious diseases and is considered as a promising direction for the development of personalized prognostic and therapeutic approaches [40]. Generalized data on the most significant PRR polymorphisms and their clinical associations are presented in Table 1.

Table 1: Genetic polymorphism of innate immunity receptors and clinical significance

The gene/ receptor	Polymorphism (SNP)	Functional and clinical significance
TLR2	rs5743708	Decreased sensitivity of the receptor to viral and bacterial ligands; association with increased risk of severe infections and pneumonia
TLR4	rs4986790 / rs4986791	Decreased activation of pro-inflammatory signaling cascades and changes in cytokine production; association with severe viral infections
CARD8	rs2043211	Regulation of the activity of inflammasomes and caspase 1; possible protective effect in case of excessive inflammation
IL18	rs2043211	Changes in IL-18 expression and strength of the inflammatory response; effect on the risk of severe viral infections
CD40	rs1883832	Modulation of the interaction of innate and adaptive immunity; influence on the humoral immune response

The presented data demonstrate the role of genetic polymorphism of innate immunity receptors in the formation of differences in the immune response and the clinical course of infectious diseases. Next, we consider the genetic variations of cytokine and interferon signaling pathways that have a significant impact on the effectiveness of antiviral protection.

Genetic variations of cytokine and interferon signaling pathways

Genetic differences in the genes of cytokines and interferon signaling cascades largely determine the individual strength of the inflammatory response in viral infections, including COVID-19 [41]. In the works of Rodrigues et al. It has been shown that the activation of inflammasomes and associated IL-1 and TNF-α pathways is closely related to the severity of SARS-CoV-2 infection, which highlights the role of congenital hyperinflammation in adverse outcomes. Research by Mukherjee et al. These data are supplemented by demonstrating that disorders of innate signaling, including TLR-dependent pathways, indirectly enhance the production of key cytokines such as IL-6 and TNF-α, forming a more pronounced inflammatory background. At the same time, the variability of IFN-I/III interferon pathways can affect the early antiviral response, determining the balance between effective infection control and the development of excessive inflammation [44]. The contribution of the adaptive link to this regulation is reflected in the work of Speletas et al., where it was shown that CD40 polymorphism is able to change the intensity of immune responses, which indicates a close relationship between cytokine and interferon signals and intercellular interactions. Collectively, the data of these authors confirm that polymorphisms of the IFN-I/III, IL-1, IL-6, and TNF-α genes form individual differences in the inflammatory response and may explain the clinical heterogeneity of the course of viral diseases.

The influence of genetic factors of innate immunity on the clinical course of infectious diseases

The genetic features of innate immunity largely determine how severe infectious diseases are and how quickly the clinical picture develops [50]. In a review by Mukherjee et al. polymorphisms in the TLR2 and TLR4 genes have been shown to

be able to change the strength of the initial inflammatory signal, thereby affecting the risk of complications and adverse outcomes in bacterial and viral infections. The work of Rodrigues et al. She supplemented these data by demonstrating that the activation of inflammasomes and variations in genes associated with this process are closely related to the severity of COVID-19 and the severity of systemic inflammation. Satış and colleagues have shown that the level of IL-18 and the genetic factors affecting its production can serve as a prognostic marker of severe infection and an unfavorable outcome. A study by Vergara et al. It was emphasized that the interindividual differences in IL-18 concentrations in chronic viral infections are largely due to hereditary variants, and not only to the activity of the pathogen itself [51]. Zhang et al. We have expanded the understanding of the role of cytokine genes, showing that IL-10, IL-18, and IL12B polymorphisms affect the nature of the inflammatory response and the tendency to pathological consequences, which confirms the universality of these mechanisms for various diseases [52]. Collectively, these data indicate that the genetic variants of innate immunity determine not only the probability of infection, but also the rate of progression, severity and outcome of the disease, which is summarized in Table 2.

Table 2: The role of polymorphisms of innate immunity genes in the clinical course of infections

Gene / path	Polymorphism	Infectious disease	Clinical impact (extended)
TLR2 / TLR4	rs5743708, rs4986790/91	COVID 19, bacterial infections	A decrease in the sensitivity of receptors to viral and bacterial ligands leads to a later activation of the innate immune response and a weakened production of pro-inflammatory cytokines and interferons. As a result, the infection process is more severe, the risk of developing pneumonia increases, and the patient's likelihood of hospitalization increases.
NLRP3 / CARD8	rs2043211	COVID 19	The genetic variants involved in the regulation of inflammasomes alter the degree of caspase-1 activation and the level of IL-1b and IL-18 production. This can lead to both an increased hyperinflammatory response and a partial protective effect due to the containment of excessive inflammation.
IL18	rs1834481	COVID 19, HIV, HCV	The polymorphism is associated with fluctuations in serum levels of IL-18, which directly affects the intensity of the systemic inflammatory response. This affects the risk of severe infection, the development of pneumonia, and the likelihood of adverse clinical outcomes in viral diseases.
IFIT1 / IFIT2	rs304478, rs4934470	Tick-borne encephalitis	Disruptions in the genes of interferon-induced proteins weaken the early control of viral replication and reduce the effectiveness of the antiviral response. As a result, the viral load increases, the progression of the disease accelerates, and the risk of developing severe, including neurological, forms of infection increases.
DDX58 (RIG-I)	rs3739674	Tick-borne encephalitis, enterovirus infections	Disruption of viral RNA recognition and subsequent activation of interferon signaling pathways weakens the early antiviral response. This contributes to a more severe clinical course of the infection and increases the likelihood of complications.

The presented data show that the influence of genetic factors of innate immunity is not limited to the features of the course of infection, but also affects the mechanisms of therapeutic response. The next section discusses the genetic prerequisites for the variability in the effectiveness of anti-infective therapy in patients.

Genetic causation of response variability to anti-infective therapy

The genetic conditioning of the response to anti-infective therapy is manifested in the fact that in different patients the same drug can give different efficacy, rate of action and risk of complications, which is associated with hereditary features of the immune response and drug metabolism [54]. For biological drugs, in particular anti-TNF, it has been shown that certain genetic variants enhance the immunogenicity of therapy and promote the production of antibodies to the drug, which is why the effect of treatment weakens or is completely lost over time. The most stable data were obtained for variants of the FCGR3A and TNFRSF1B genes, as well as for the HLA-DQA1*05 allele, which is repeatedly associated with an increased risk of developing antibodies to anti-TNF and secondary loss of clinical response [55]. At the same time, studies show that the influence of these genetic factors is not absolute and may be weakened by the use of therapeutic drug monitoring, which allows maintaining optimal concentrations of the drug in the blood.

In addition to efficacy, genetic markers are also associated with the risk of adverse reactions, including an increased incidence of side effects in carriers of certain gene variants involved in the regulation of apoptosis and inflammation [56]. Similar patterns can be observed for antimicrobial drugs, where polymorphisms in the genes of mitochondrial DNA, transporters and metabolic enzymes can increase the risk of toxicity or, conversely, reduce the concentration of the drug

to an ineffective level. Taken together, these data show that genetic predictors are able to determine both the success of anti-infective treatment and the likelihood of complications and adverse reactions, emphasizing the promise of a personalized approach to therapy based on the patient's genetic profile [57-59].

Clinical and epidemiological aspects of genetic heterogeneity of infectious diseases

During the COVID-19 pandemic, it became apparent that the clinical course of SARS-CoV-2 infection varies significantly between people, from asymptomatic forms to severe respiratory failure, which highlights the clinical and epidemiological aspects of the genetic heterogeneity of infectious diseases [48-50]. Accumulated data have shown that part of this variability is due to the genetic characteristics of the host, which are distributed differently between populations and can both increase susceptibility and have a protective effect [60]. Large-scale population studies, including GWAS, have made it possible to identify genetic loci associated with the severe course of COVID-19, however, such approaches mainly reflect general patterns and are less likely to capture rare but clinically significant variants. At the same time, cases of severe disease in young and previously healthy patients indicate the role of rare mutations and congenital immune disorders, which is of direct importance for practical infectious diseases and a personalized approach to patient management [61]. Ethnogenetic differences formed by the historical pressure of pathogens may explain the different frequency of risk factors and severity of infection in different populations, which is important to take into account when interpreting epidemiological data. Thus, the combination of clinical observations, population genetics, and molecular research forms a more holistic understanding of the causes of the heterogeneity of infectious diseases and opens up opportunities for targeted prevention and therapy.

Prospects for the introduction of genetic markers of innate immunity into clinical practice

The introduction of genetic markers of innate immunity into clinical practice opens up new opportunities for personalized assessment of the risk of infectious diseases and prediction of their course. Current research shows that individual genetic variants can determine both susceptibility to infection and the likelihood of severe forms and complications, including severe inflammation or adverse drug reactions [27-29]. The analysis of such markers allows us to identify in advance groups of patients with an increased risk of ineffective therapy or the development of side effects, which is especially important when using anti-infective and immunoactive drugs.

The combination of genetic data with clinical and immunological characteristics makes it possible to more accurately stratify patients according to the degree of risk and choose the optimal treatment tactics [36]. This is of practical importance in the management of viral infections, including COVID-19, where the variability of the immune response directly affects the duration of immunity and the outcome of the disease. Genetic markers of innate immunity can also be used to predict the effectiveness of vaccination and the formation of a post-infectious immune response [32].

A promising direction is the integration of such data into clinical decision-making algorithms, which helps to individualize therapy and reduce the frequency of adverse outcomes. Together, this brings infectious diseases closer to the model of precision medicine, focused not only on the pathogen, but also on the genetic characteristics of the immune response of a particular patient.

CONCLUSION

The review shows that the genetic variability of innate immunity is an important factor determining the clinical diversity of infectious diseases, including differences in severity, rate of progression, and outcomes of infection. Using the example of respiratory syncytial infection, it was possible to demonstrate that the same pathogens can cause fundamentally different clinical scenarios depending on the individual genetic characteristics of the immune response. The data reviewed confirm that polymorphisms of PRR genes, cytokines, and interferon pathways affect not only the risk of complications, but also the effectiveness of anti-infective therapy. The work shows that taking into account genetic factors allows for a deeper understanding of the causes of clinical heterogeneity that go beyond viral load and external factors. The generalizations obtained emphasize the practical value of the study and point to the promising use of genetic markers of innate immunity for the development of personalized approaches in infectious diseases.

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Contribution of the authors
The authors have made an equal and significant contribution to the collection of empirical data, their processing and the writing of the article.

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