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MOLECULAR GENETIC MARKERS OF INFLAMMATION IN CARDIOVASCULAR PATHOLOGY

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ABSTRACT

The article summarizes modern ideas about the role of inflammation and immunomodulation in the pathogenesis of cardiovascular diseases, with an emphasis on the mechanisms of vascular wall and myocardial remodeling. Based on the analysis of domestic and foreign studies in recent years, the involvement of innate and adaptive immunity, key cytokines and inflammatory biomarkers in the development of atherosclerosis, coronary artery disease and heart failure has been considered. Special attention is paid to the diagnostic and prognostic significance of markers of systemic inflammation, as well as the possibilities of their integration into clinical practice. It has been shown that immunomodulatory therapeutic strategies go beyond the traditional lipid-lowering approach and open up prospects for targeted effects on the pathogenetic links of the disease. The presented data emphasize the scientific and clinical significance of an integrated approach to assessing the inflammatory status of a patient in the context of personalized cardiology.

KEYWORDS: cardiovascular diseases, inflammation, immunomodulation, biomarkers, myocardial remodeling, personalized therapy.

INTRODUCTION

Cardiovascular diseases (CVD) continue to be the leading cause of death in the world and in the Russian Federation, forming a significant medical, social and economic burden on health systems [1-4]. According to the World Health Organization, more than 17.9 million people die from CVD annually, while in Russia they account for over 45-47% of all deaths, despite the development of modern diagnostic and therapeutic methods [9-10]. In recent years, it has become increasingly clear that traditional risk factors, including dyslipidemia and hypertension, do not fully explain the progression and clinical instability of cardiovascular pathology. In this context, chronic inflammation and dysregulation of immune mechanisms are considered as key driving forces of vascular wall and myocardial remodeling [7]. Current evidence suggests that innate and adaptive immune responses are actively involved in the development of atherosclerosis, heart failure, coronary artery disease, and vascular complications [5].

Of particular interest is immunomodulation as a potential therapeutic area capable of influencing the pathogenesis of CVD beyond the classical lipid-lowering approach [9]. Experimental and clinical studies in recent years have emphasized the importance of cytokines, innate immune cells, PD-1/PD-L1 signaling pathways, TLR-dependent mechanisms, and inflammatory biomarkers in the formation of adverse cardiovascular outcomes [11]. However, despite the growing volume of data, many aspects of immune remodeling of the cardiovascular system remain poorly understood, especially in the context of clinical risk stratification and personalized therapy. In particular, there remains a shortage of comprehensive studies linking molecular inflammatory pathways with diagnostic markers and treatment response [12-15].

The urgency of this problem is reinforced by the fact that not all anti-inflammatory interventions have demonstrated clinical efficacy, which indicates the complexity of immune interactions in CVD. Modern diagnostic approaches increasingly include an assessment of the inflammatory status, including the use of highly sensitive C-reactive protein, the ratio of neutrophils to lymphocytes, and imaging techniques that reflect the activity of the inflammatory process. In this regard, the purpose of this review is to summarize current data on the role of inflammation and immunomodulation

in the development of cardiovascular diseases, as well as to analyze diagnostic and therapeutic approaches aimed at identifying and correcting immune-inflammatory mechanisms from the perspective of personalized medicine.

Inflammation as a key mechanism of the pathogenesis of cardiovascular diseases

Inflammation is currently considered as one of the key mechanisms of the pathogenesis of cardiovascular diseases, determining their initiation, progression, and clinical instability [21]. Accumulated evidence suggests that innate and adaptive immunity are actively involved in the development of atherosclerosis, coronary artery disease, and heart failure through complex cellular and molecular cascades of the inflammatory response [23]. Under the influence of traditional and new risk factors, chronic activation of the immune system is formed, accompanied by endothelial dysfunction, impaired vascular homeostasis and changes in the phenotype of immune cells. A significant contribution to the study of these processes was made by A.I. Kaminny et al., who showed that persistent inflammation is not only a marker, but also an active driver of cardiovascular pathology, as well as a potential therapeutic target.

In a broader context, Wang et al. It has been demonstrated that the immune system in conditions of cardiovascular diseases functions as a dynamic regulatory network capable of exerting both damaging and adaptive effects on the myocardium and vascular wall. Special attention is paid to the molecular mechanisms of immune regulation, including cytokine signaling pathways, activation of inflammasomes, and epigenetic reprogramming of innate immune cells. In this aspect of the research, Dakin et al. We have expanded our understanding of the role of enzymatic mechanisms associated with inflammation and their possible involvement in pathological vascular remodeling.

Along with the deepening of fundamental knowledge, there is an increasing interest in inflammatory biomarkers that reflect the activity of immune processes and are associated with an unfavorable prognosis [15]. Despite significant progress, it remains obvious that the contribution of individual immune cells and inflammatory mediators to the structural restructuring of the vascular wall and myocardium requires more detailed consideration. In this regard, the analysis of cellular participants in the immune response and key inflammatory mediators that form the processes of remodeling of the cardiovascular system is of particular importance.

Immune cells and inflammatory mediators in vascular wall and myocardial remodeling

Cardiovascular diseases continue to occupy a leading place in the structure of global mortality, which underlines the importance of studying the mechanisms underlying the remodeling of the vascular wall and myocardium [18]. Current evidence suggests that immune cells, primarily macrophages and lymphocytes, as well as inflammatory mediators, including cytokines, chemokines, and components of inflammasomes, play a key role in these processes. A significant contribution to the understanding of systemic inflammation and its consequences was made by Traby et al., who showed that extracellular vesicles and circulating citrullinated histone H3 in patients with COVID-19 reflect the activation of innate immunity and are associated with endothelial dysfunction and thrombotic complications that are of direct importance for cardiovascular remodeling.

Houen and Trier expanded the understanding of the role of autoimmune mechanisms by demonstrating that antibodies to citrullinated proteins are not only markers of rheumatoid arthritis, but also indicators of chronic inflammation that can indirectly affect the vascular wall and myocardium. In the works of Rönnelid et al. It has been shown that autoantibodies form stable immune activation, which is accompanied by an imbalance of cytokines and supports a pathological inflammatory microenvironment, potentially contributing to the progression of cardiovascular diseases. These data emphasize that adaptive immunity, along with innate mechanisms, is actively involved in the remodeling of the cardiovascular system.

Of particular importance is the interaction of immune cells with the endothelium, where pro-inflammatory cytokines and chemokines enhance endothelial dysfunction, disrupting the regulation of vascular tone and permeability [19]. The activation of inflammasomes and the associated production of IL-1b and other mediators creates conditions for chronic inflammation that supports structural changes in the vascular wall and myocardium. The combination of these mechanisms, reflected in the studies presented in Table 1, indicates the multilevel role of the immune response in cardiovascular pathology.

Table 1: Immune cells and inflammatory mediators in vascular wall and myocardial remodeling [25-28]

Author, year	The object of research	Key immune mechanisms	Importance for the remodeling of the cardiovascular system
Traby et al., [27]	Patients with COVID 19	Extracellular vesicles, citH3, NETs, endothelial activation	Association of systemic inflammation with endothelial dysfunction and thrombosis
Houen & Trier, [28]	Autoimmune diseases	Antibodies to citrullinated proteins, chronic inflammation	Indirect effect of autoimmune inflammation on blood vessels
Rönnelid et al., [29]	Rheumatoid arthritis	Autoantibodies, cytokine imbalance	Persistent inflammation as a vascular risk factor
Adamo et al., [31]	Heart failure	IL 1b, IL 6, TNF α, macrophages	Immune-mediated myocardial remodeling

Alcaide et al., [32]	Cardiac tissue	Lymphocytes, chemokines, endothelial activation	Immune interactions in myocardial remodeling
Mann, [33]	Cardioimmunology	Innate and adaptive immunity	Integration of immune pathways into the pathogenesis of CVD
Wang et al., [34]	Atherosclerotic CVD	Immune modulation, inflammasomes	Therapeutic targeting of inflammation

Note. CVD - cardiovascular diseases; citH3 - citrullinated histone H3; NETs - neutrophil extracellular traps; IL - interleukin; TNF-α - tumor necrosis factor-α; VSMC - vascular smooth muscle cells.

The data presented in the table clearly demonstrate that immune cells and inflammatory mediators are not only involved in the remodeling of the vascular wall and myocardium, but also form measurable molecular signatures of systemic and local inflammation. This creates the prerequisites for the use of inflammatory markers in clinical practice, which justifies the transition to considering their diagnostic and prognostic significance.

Diagnostic and prognostic significance of inflammatory biomarkers

In recent years, the diagnostic and prognostic significance of inflammatory biomarkers has been considered as an important addition to traditional models of cardiovascular risk, reflecting the immune-inflammatory component of disease pathogenesis [27]. A classic example of this approach remains the highly sensitive C-reactive protein (hs-CRP), which, as shown in large cohort studies, makes it possible to refine the risk of a first cardiovascular event, especially in individuals with an intermediate probability of an adverse outcome. The contribution of hs-CRP is not so much to replace traditional risk factors, but rather to identify a residual inflammatory risk that is not reflected by indicators of lipid metabolism. Within the framework of the concept of cardioimmunology, summarized in detail by D.L. Mann, inflammatory markers are considered as functional indicators of activation of innate and adaptive immunity in the cardiovascular system.

In this context, special attention is paid to interleukins, primarily IL-1b and IL-6, which occupy a central place in the inflammatory cascade and are closely associated with the progression of atherosclerosis and myocardial remodeling [30]. Summarizing the data from experimental and clinical studies, Wang et al. It has been shown that the circulating levels of these cytokines have both prognostic and potential therapeutic significance. At the level of the vascular wall, the inflammatory profile reflects the cellular diversity of leukocytes, which was demonstrated in detail in a meta-analysis by Zernecke et al., who revealed a link between the immune cell composition and the activity of the atherosclerotic process. Along with individual markers, new immune-inflammatory parameters are becoming increasingly important, including chemokines, endothelial activation molecules, and components of inflammasomes reflecting more complex levels of immune regulation. Their diagnostic value increases especially when assessing the instability of atherosclerotic plaques and the risk of acute coronary syndromes, which is emphasized in the review by Fahed and Jang. In clinical practice, this has led to the formation of multibiomarker panels combining markers of inflammation, lipid metabolism, and cellular activation for more accurate risk stratification. This integrative approach makes it possible to better take into account the heterogeneity of inflammatory phenotypes of cardiovascular diseases and individual differences in patients [31]. Taken together, these data emphasize that the assessment of inflammatory biomarkers logically links immune mechanisms with clinical outcomes, preparing the way for a discussion of the role of immune cells and inflammatory mediators in vascular wall and myocardial remodeling.

Immunomodulatory therapeutic strategies for cardiovascular diseases

Immunomodulatory therapeutic strategies for cardiovascular diseases are formed at the junction of classical pharmacotherapy and modern concepts of the role of inflammation in damage and repair of cardiac tissue [17]. A significant contribution to the understanding of cellular repair mechanisms after myocardial infarction was made by Kologrivova et al., showing that immune cells not only initiate an inflammatory response, but also actively participate in its resolution and structural remodeling of the myocardium. Against this background, traditional drugs, primarily statins, are considered not only as means of correcting lipid metabolism, but also as potential immunomodulators. Their pleiotropic effects are associated with suppression of pro-inflammatory signaling pathways, reduction of endothelial dysfunction, and modulation of immune cell activity, although the clinical significance of these effects remains a matter of debate.

In parallel, the direction of targeted action on key inflammatory cascades is developing, which is substantiated in detail in the works of P. Libby devoted to the inhibition of the inflammasome and cytokines of the interleukin-1 and interleukin-6 families. These approaches have made it possible to move from non-specific suppression of inflammation to more selective interventions focused on pathogenetically significant targets. The clinical confirmation of this strategy was the RESCUE study, in which Ridker et al. They demonstrated a decrease in inflammatory activity and atherosclerotic risk with IL-6 inhibition.

A special place among immunomodulatory agents is occupied by colchicine, which has the ability to suppress the activation of the inflammasome and the migration of leukocytes, which makes it an effective addition to standard therapy. The results of clinical studies have shown that anti-inflammatory intervention can reduce the frequency of recurrent ischemic events even against the background of optimal lipid-lowering and antithrombotic therapy [33-35]. An important aspect remains the comparison of the speed and severity of the clinical effect of various strategies, which is clearly presented in Table 2, which shows the time to achieve therapeutic benefit for different classes of drugs.

Table 2: Modern immunomodulatory approaches in the treatment of cardiovascular diseases [33-36]

Therapeutic strategy	The immune target	The key mechanism of action	Clinical significance	Current prospects
Statins (pleiotropic effects)	Innate immunity, endothelium	Suppression of isoprenoid pathways, decreased Rho/ROCK activity, decreased cytokine response	Reduction of residual inflammatory risk and stabilization of atherosclerotic plaques	Reassessment of the role of non-lipid lowering effect in combination therapy
Inhibition of IL 1/IL 6	Cytokine cascade	Blockade of key pro-inflammatory cytokines of systemic inflammation	Reducing the frequency of recurrent ischemic events in high-risk patients	Development of more selective and safe biological agents
Colchicine	Inflammasomes, neutrophils	Inhibition of NLRP3 activation and leukocyte migration	Reducing the risk of stroke and unstable angina after a myocardial infarction	Optimization of doses and duration of therapy to reduce side effects
PCSK9 inhibitors	Lipid-associated inflammation	Reduction of apoB lipoproteins without direct effect on inflammatory markers	Regression of atherosclerotic plaques in intensive care	Combination with anti-inflammatory drugs
Cellular and gene approaches	Immune cells and signaling pathways	Modulation of macrophage and T cell phenotype	Potential myocardial recovery and reduction of fibrosis	The transition from preclinical models to clinical research
Multibiomarker-oriented therapy	Systemic inflammation	Individualization of treatment based on the patient's inflammatory profile	Improving the accuracy of secondary CVD prevention	Development of personalized cardiology
Therapeutic strategy	The immune target	The key mechanism of action	Clinical significance	Current prospects

As shown in Table 2, modern immunomodulatory strategies combine the pleiotropic anti-inflammatory effects of traditional cardiovascular therapy with targeted interventions that selectively affect key mechanisms of immune inflammation. Their integration into clinical practice reflects the transition from universal treatment regimens to more personalized management of inflammatory risk in cardiovascular diseases.

Prospects for a personalized approach, taking into account the inflammatory status of the patient

The prospects of a personalized approach in cardiology are increasingly associated with taking into account the inflammatory status of the patient as an independent modifiable risk factor [39]. Current data show that chronic low-grade inflammation forms a so-called residual risk, which persists even against the background of optimal standard therapy [41-44]. In this context, the use of inflammatory biomarkers is of particular importance for more accurate risk stratification and individualization of treatment strategies.

As Kurt et al. emphasize, markers such as hsCRP and IL-6 reflect different levels of the inflammatory cascade and carry complementary information about the pathophysiology of heart failure. hsCRP characterizes an integral systemic inflammatory load and is highly reproducible, which makes it a convenient tool for clinical practice. At the same time, IL-6, according to genetic and experimental studies, occupies a central position in inflammatory signaling and is closely related to the mechanisms of myocardial remodeling.

Works by Ridker et al. We have made a key contribution to understanding the causal role of IL-6-mediated inflammation by demonstrating that its targeted inhibition leads to a reduction in atherosclerotic risk in patients with severe residual inflammation. These results confirmed the concept of moving from universal treatment to the selection of patients potentially sensitive to anti-inflammatory therapy. Thus, inflammatory biomarkers are beginning to be considered not only as prognostic markers, but also as tools for choosing therapeutic tactics [50-52].

A personalized approach also involves taking into account the clinical context and concomitant conditions affecting the patient's immune-inflammatory profile. In this regard, the clinical recommendations summarized by Horberg et al. emphasize the need for a comprehensive assessment of chronic inflammation in patients with concomitant infectious and systemic diseases. Although these recommendations mainly apply to other clinical populations, they emphasize the universality of the principle of individual assessment of inflammatory status.

An important area of further research remains the development of combined risk models that combine clinical parameters, classical biomarkers, and immune-inflammatory parameters. Such models can improve the accuracy of prediction and allow early detection of patients with an unfavorable inflammatory phenotype. In addition, the use of dynamic monitoring of inflammatory markers to assess the effectiveness of therapy and adapt treatment over time is considered promising.

In general, the integration of inflammatory status into clinical algorithms opens up opportunities for more targeted intervention and the rational use of anti-inflammatory strategies. The implementation of this approach will require large prospective studies aimed at validating biomarker thresholds and their impact on clinical outcomes. Nevertheless, today the concept of personalized cardiology, taking into account inflammation, forms a new direction in the prevention and treatment of cardiovascular diseases.

CONCLUSION

The analysis confirms that inflammation and immune dysregulation are integral components of the pathogenesis of cardiovascular diseases and largely determine their clinical course and prognosis. Immune cells and inflammatory mediators are involved in the processes of vascular and myocardial remodeling, forming both damaging and adaptive responses. The use of inflammatory biomarkers makes it possible to refine risk stratification and identify patients with persistent residual inflammatory risk. Modern immunomodulatory approaches demonstrate the potential to increase the effectiveness of therapy, subject to rational patient selection. Taken together, the data obtained emphasize the value of integrating immune-inflammatory mechanisms into diagnostic and therapeutic algorithms and substantiate the further development of personalized strategies for managing patients with cardiovascular pathology.

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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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