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THE ROLE OF HOMOCYSTEINE AS A BIOMARKER OF CYTOKINE STORM IN IMMUNOONCOLOGY AND THERAPY OF COVID-19

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Abstract
Homocysteine is a sulfur-containing amino acid that can act as an important biomarker of inflammatory processes, including cytokine storm, observed in various pathological conditions such as cancer and COVID-19. In the conditions of the cytokine storm characteristic of severe forms of COVID-19 and progressive stages of cancer, elevated homocysteine levels can increase oxidative stress and inflammatory reactions, which, in turn, exacerbates tissue and organ damage. Studies show that homocysteine can play a significant role in the pathogenesis of these conditions, affecting the vascular and immune systems. Thus, monitoring of homocysteine levels is important for the diagnosis, prognosis and development of new therapeutic strategies in the field of immuno-oncology and treatment of COVID-19.

Keywords Homocysteine, cytokine storm, immuno-oncology, COVID-19, biomarkers, inflammation, oxidative stress, therapy.

INTRODUCTION

Modern medicine faces a number of complex challenges related to the diagnosis and treatment of diseases characterized by pronounced inflammatory reactions and immune system dysfunctions. One such pathological condition is the cytokine storm, observed in severe forms of COVID-19 and various oncological diseases. A cytokine storm represents an excessive activation of the immune system, leading to the release of large quantities of pro-inflammatory cytokines, which causes systemic inflammation, tissue and organ damage, and can potentially result in death.

In recent years, homocysteine, an amino acid involved in methionine metabolism, has garnered significant attention as a potential biomarker for inflammatory processes, including cytokine storms. Elevated homocysteine levels are associated with various pathological conditions, such as cardiovascular diseases, neurodegenerative disorders, and immune dysfunctions, making it a promising target for study in the context of new therapeutic approaches.

The relevance of this topic is driven by the need to identify and develop new biomarkers that could not only signal the onset of inflammatory processes but also serve as precise therapeutic targets for intervention. In the context of the COVID-19 pandemic and the rising incidence of

oncological diseases, it is crucial to have a deeper understanding of the pathogenic mechanisms of these conditions and their relationship with homocysteine.

The aim of this study is to investigate the role of homocysteine as a biomarker of cytokine storms, its impact on the pathogenesis of immuno-oncological diseases and COVID-19, and to assess the prospects for using homocysteine in the diagnosis and therapy of these conditions.

1. Mechanisms of Cytokine Storm Onset and Its Role in Disease Pathogenesis

A cytokine storm is an acute immunopathological condition characterized by the excessive release of pro-inflammatory cytokines, leading to systemic inflammation and multiple organ failure. Recent developments over the last 5-10 years have clearly linked this condition with two major contexts (among others): immuno-oncology and, more recently, COVID-19. Ongoing research focuses on identifying potential biomarkers that can reliably predict both the onset and progression of cytokine storms, using advanced molecular profiling techniques and large-scale clinical studies. The mechanisms of cytokine storm development are illustrated below in Figure 1.

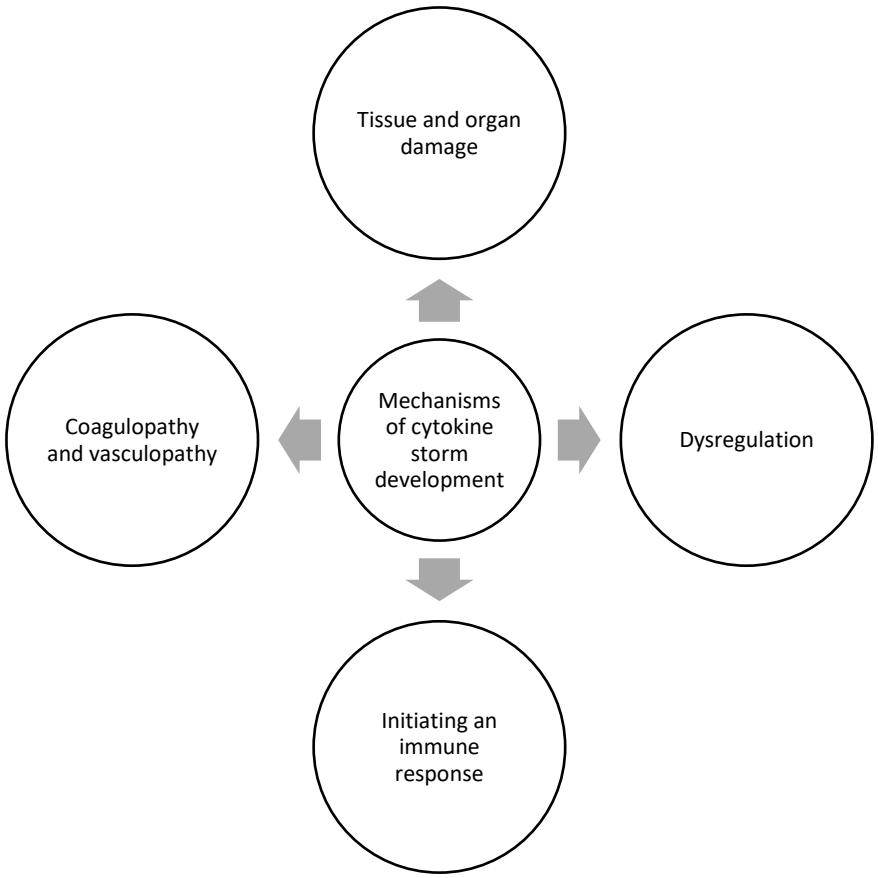

Fig.1. Mechanisms of cytokine storm development [1].

The renin-angiotensin-aldosterone system (RAAS) is a complex network of vasoactive peptides that play a crucial role in regulating blood pressure, circulating blood volume, and electrolyte balance, as well as participating in inflammatory processes. One of the central components of this system is angiotensin-converting enzyme 2 (ACE2), which is expressed in various organs, including the heart, kidneys, lungs, testes, and gastrointestinal tract. This enzyme catalyzes the conversion of angiotensin I (AT I) into angiotensin 1-9 (AT 1-9), which can subsequently be transformed into angiotensin 1-7 (AT 1-7) under the action of ACE or other peptidases. Moreover, ACE2 can directly convert angiotensin II (AT II) into AT 1-7. The peptide AT 1-7 possesses vasodilatory, antiproliferative, antithrombotic, and anti-inflammatory properties, allowing it to attenuate the activity of type 1 angiotensin receptors (AT1R). The interaction of AT 1-7 with the Mas receptor (MasR) leads to a reduction in the expression of inflammatory markers such as interleukin-6 (IL-6), tumor necrosis factor α (TNFα), and interleukin-8 (IL-8).

AT 1-7 exerts a positive effect through the activation of the MasR receptor, which is expressed in epithelial and smooth muscle cells of the bronchi. This allows AT 1-7 to participate in the regulation of both acute and chronic inflammatory processes in the lungs. Additionally, AT 1-7 influences the synthesis of interleukin-10 (IL-10), which stimulates the differentiation of type 2 helper T cells responsible for producing anti-inflammatory cytokines such as IL-4, IL-5, IL-9, and IL-13. Interleukin-10 may also play a role in preventing tissue damage.

Clinical data indicate that disruption of the RAAS plays a significant role in the pathogenesis of acute respiratory distress syndrome (ARDS) in COVID-19 [1]. Specifically, patients with COVID-19 exhibit elevated levels of AT II, which correlate with the severity of lung damage. Moreover, the use of ACE inhibitors and angiotensin receptor blockers for treating arterial hypertension is associated with a milder disease course and lower IL-6 levels in COVID-19 patients. A meta-analysis involving 24,676 COVID-19 patients confirmed that the use of RAAS inhibitors reduces the risk of death and/or severe conditions by 23% [1].

Clinical and epidemiological data suggest that patients with initially reduced ACE2 expression or impaired RAAS function (e.g., elderly men, as well as individuals with diabetes, hypertension, or obesity) experience more severe disease when ACE2 is depleted by the action of SARS-CoV-2 [1].

The kallikrein-kinin system also plays an important role in the pathogenesis of COVID-19. This system includes kininogen precursors, from which bradykinin and its active metabolite des-Arg9-bradykinin are formed under the action of kallikrein. These peptides interact with bradykinin receptors of the first and second types, leading to vasodilation, lowered blood pressure, or the release of pro-inflammatory cytokines, depending on the receptor type. The kallikrein-kinin system is closely linked to the RAAS, as ACE2 is involved in the inactivation of bradykinin, and a decrease in its activity leads to an enhanced inflammatory response through the BKB1R receptor. The expression of kininogen and kallikrein genes in COVID-19 patients was significantly higher compared to the control group, accompanied by decreased ACE2 levels and increased bradykinin receptor expression.

The complement system, which includes proteins and their cleavage products, coordinates the inflammatory response to infection. Activation of the complement system can occur through the classical, lectin, and alternative pathways. The lectin pathway, involving mannose-binding serine

protease 2 (MASP-2), directly contributes to lung damage in coronavirus infection. The nucleocapsid protein of SARS-CoV-2 activates MASP-2, leading to a cascade of inflammatory reactions and lung tissue damage. Biomarkers that can identify a cytokine storm are shown in Figure 2. The next section will discuss homocysteine in more detail as a biomarker.

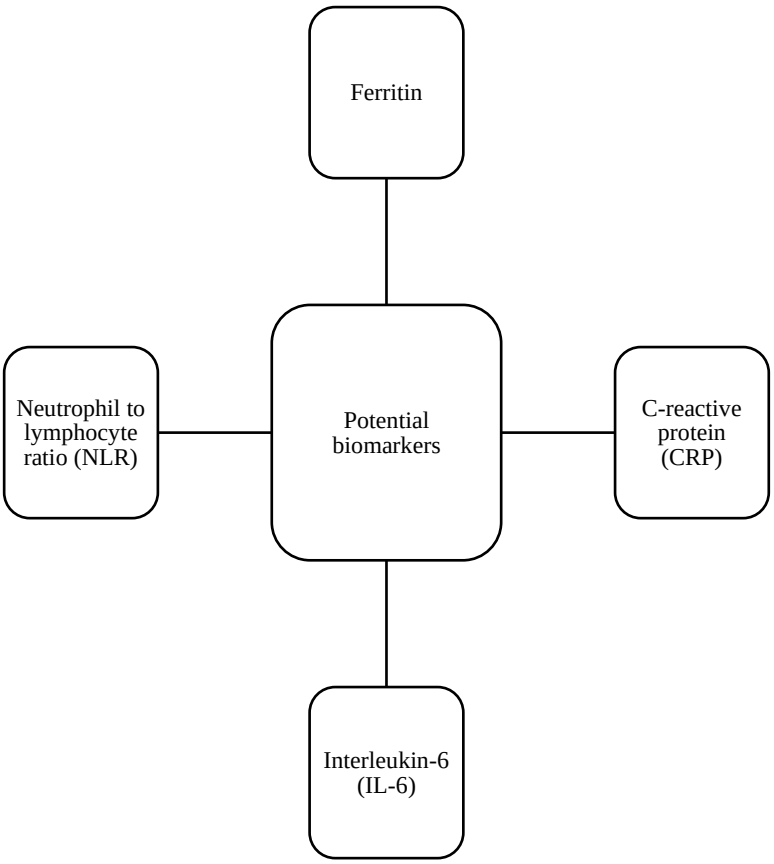

Fig.2. Potential biomarkers [2].

2. Homocysteine as a Biomarker: Biochemical Foundations and Clinical Significance

Homocysteine is an amino acid formed during the breakdown of methionine, which enters the human body through protein-rich foods such as meat, fish, eggs, and others (Fig. 3).

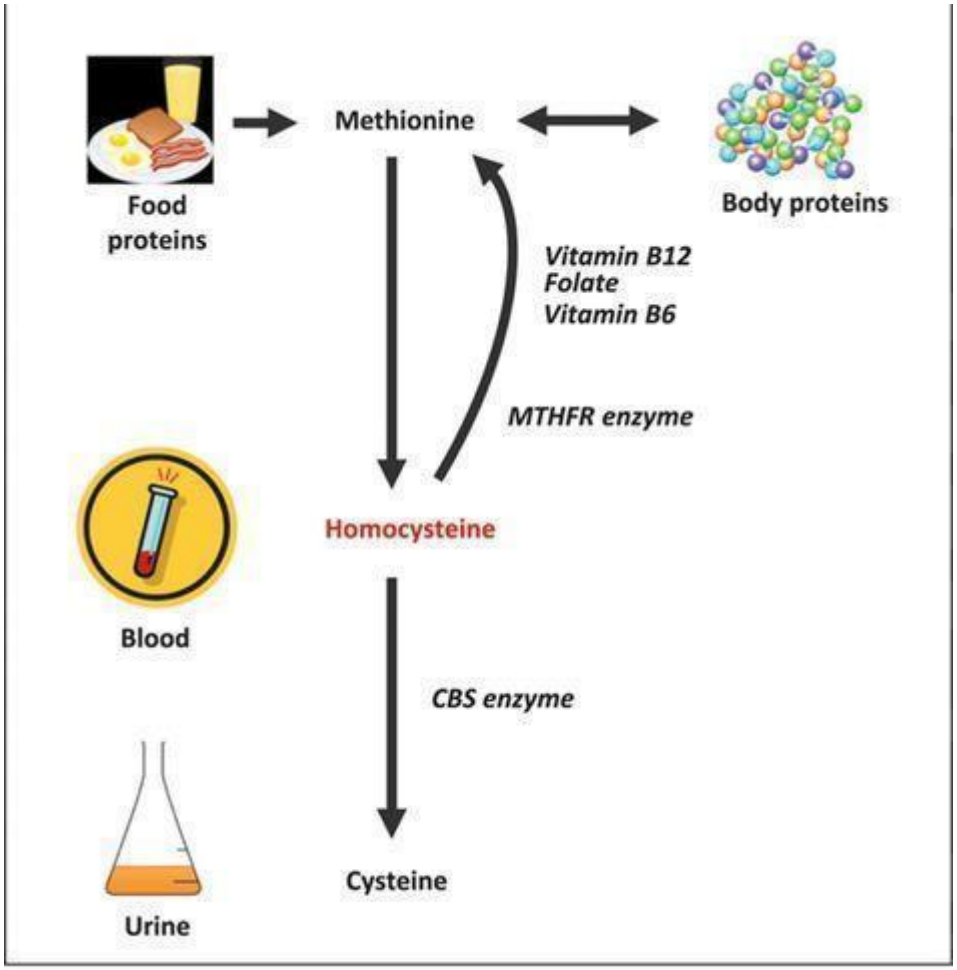

Fig.3. Homocysteine.

It is important to emphasize that these are some of the most prominent potential biomarkers currently under close scrutiny, with the group of interleukins leading the list.

In modern medicine, significant attention is given to studying factors that can affect endothelial damage. Endothelial dysfunction is fundamental to the pathogenesis of various diseases across the cardiorenal continuum, including cardiovascular, neurological, and obstetric-gynecological pathologies. These conditions are associated with the development of serious complications, which in turn lead to increased mortality and disability. Among the many markers indicating endothelial dysfunction, homocysteine has received considerable attention.

Homocysteine is an amino acid structurally similar to cysteine but differing by one methylene group. This chemical component was first described in 1932 and is formed in the human body from methionine, which is obtained from animal proteins. Excess homocysteine can be converted back into methionine, and this process depends on the availability of vitamins such as folic acid, pyridoxine, and cyanocobalamin. A deficiency in these substances can lead to elevated homocysteine levels in the blood, a condition known as hyperhomocysteinemia.

The relationship between high homocysteine levels and arterial diseases was noted as early as the 1960s [3]. Cases were found where a deficiency in the enzyme cystathionine synthase, which is involved in homocysteine metabolism, led to severe disorders such as homocystinuria, intellectual disability, and bone deformities. These conditions were typically accompanied by early development of cardiovascular diseases and thromboembolism, often resulting in death before the age of 30. In 1975, based on these observations, it was proposed that homocysteine be considered one of the key risk factors for atherosclerosis. Subsequent research has supported this hypothesis, highlighting the need for further study of this issue.

A review of the literature revealed a strong correlation between elevated homocysteine levels in the human body and an increased risk of heart and coronary diseases. Additionally, data indicate that patients with cytokine storms caused by COVID-19 also have elevated levels of this biomarker.

The normal range of homocysteine levels in the blood varies, with different sources providing different values that reflect age and physiological changes. For example, the normal level in adolescents and adults ranges from 5-15 μmol/L, while in pregnant women, this indicator may be lower due to physiological changes during pregnancy. Some researchers believe that the lower limit of normal should be considered even lower than is currently accepted.

The term "hyperhomocysteinemia" is often used when homocysteine concentrations exceed 15 μmol/L. A moderate increase in homocysteine levels can be observed in chronic kidney failure and folate deficiency. This condition may also be due to hereditary factors, such as a mutation in the methylenetetrahydrofolate reductase gene, which reduces the activity of the enzyme involved in folic acid metabolism, leading to elevated homocysteine levels.

The role of homocysteine in the development of endothelial dysfunction is well-studied. High levels of this amino acid contribute to hemostatic disorders, increasing the risk of thrombosis and the progression of atherosclerosis. Homocysteine also affects nitric oxide synthesis, reducing its bioavailability, which may explain the decreased effectiveness of vasodilators in patients with elevated homocysteine levels. Experimental studies confirm that hyperhomocysteinemia accelerates the development of atherosclerotic changes, but appropriate vitamin therapy, particularly involving B vitamins, has been shown to slow this process.

Furthermore, homocysteine is associated with the development of extragenital diseases, such as diabetes and its complications, as well as an increased risk of cerebrovascular disorders. Experimental models and clinical studies have confirmed the link between elevated homocysteine levels and cognitive impairment, stroke, and diseases like Alzheimer's and Parkinson's.

Homocysteine has a significant impact on pregnancy, causing endothelial dysfunction and increasing the risk of complications such as preeclampsia and fetoplacental insufficiency. Elevated homocysteine levels can lead to thrombosis and impaired placental blood flow, which in turn may cause fetal hypoxia and low birth weight.

Studies indicate that polymorphic variants of the methylenetetrahydrofolate reductase gene can be an independent risk factor for pregnancy loss. This is supported by research in various populations, including Asian and European. Finally, folate deficiency is associated with the development of

neural tube defects in the fetus, making folic acid supplementation before and during pregnancy essential.

For adequate correction of the folate cycle, it is important to use a comprehensive therapy that includes B vitamins and nicotinic acid. The correct dosage of folates and other vitamins remains a subject of debate, requiring further research. Overall, high homocysteine levels in the blood are a serious predictor of various pathologies, necessitating a comprehensive approach to their prevention and treatment [4].

Thus, homocysteine remains an important subject of research, capable of shedding light on the mechanisms of many diseases and aiding in the development of effective methods for their prevention and treatment.

3. The Role of Homocysteine in Immuno-Oncology and COVID-19 Therapy: Prospects and Challenges

Under normal conditions, homocysteine is rapidly neutralized through interactions with vitamins B6, B12, and folic acid, which facilitate its conversion into harmless substances. However, when these vitamins are deficient, homocysteine levels in the blood begin to rise, leading to negative consequences for the body. Studies show that a 5 μmol/L increase in homocysteine levels is associated with a 30-70% increase in the risk of cardiovascular diseases and mortality. Hyperhomocysteinemia is also linked to an increased risk of cerebrovascular disorders and peripheral vascular pathology. This condition can be accompanied by secondary autoimmune reactions, making it a potential cause of antiphospholipid syndrome [5].

In immuno-oncology, homocysteine is considered a biomarker due to its ability to induce oxidative stress, leading to the formation of free radicals. These radicals, in turn, can damage DNA, contributing to mutations that underlie carcinogenesis. Additionally, homocysteine plays a role in maintaining chronic inflammation, a known factor in tumor progression. Chronic inflammation creates a microenvironment that is conducive to tumor growth and metastasis [6].

Regarding the role of homocysteine in COVID-19, it influences inflammatory processes and vascular conditions. Since homocysteine promotes thrombosis, this is particularly relevant in the context of COVID-19. Thrombotic complications, such as venous thromboembolism, significantly worsen the prognosis for COVID-19 patients, and elevated homocysteine levels may contribute to their development. Furthermore, homocysteine can exacerbate inflammation and promote the development of the so-called cytokine storm, a key factor in severe cases of COVID-19. This is due to its ability to modulate the immune response, enhancing the production of pro-inflammatory cytokines.

Research indicates that one of the key manifestations of COVID-19 is endothelial dysfunction, accompanied by coagulopathy, which is associated with more severe lung damage and a higher risk of fatal outcomes. Systemic inflammation plays a significant role in the development of these pathological conditions. Observations suggest that folate and one-carbon metabolism, which are critical for purine synthesis and the antioxidant glutathione, are hijacked by the coronavirus for replication in infected cells. Metabolic disturbances, such as decreased folate and vitamin B12 levels in the blood serum and increased homocysteine levels, are commonly observed in COVID-19 patients [6].

Clinical studies [7] have identified a correlation between the severity of COVID-19 and increased homocysteine levels in the blood serum. Carriers of the minor allele of the MTHFR C677T single

nucleotide polymorphism, involved in folate metabolism, are at higher risk for hyperhomocysteinemia and vascular diseases, as well as increased morbidity and mortality from COVID-19. The negative impact of hyperhomocysteinemia on the progression of vascular damage in various diseases, along with the activation of angiotensin II type 1 receptors induced by homocysteine, suggests that homocysteine levels and genetic markers of folate metabolism could be considered potential predictors of adverse outcomes in COVID-19 [7].

CONCLUSION

Thus, homocysteine not only serves as a biomarker but also plays an active role in the pathological processes linked to cytokine storms, particularly through its contribution to oxidative stress and endothelial dysfunction. Elevated homocysteine levels are associated with heightened inflammatory responses and oxidative stress, making it a key element for a more precise understanding of the pathogenesis of these conditions and the development of targeted therapeutic approaches. Incorporating homocysteine into the monitoring and treatment of these diseases could contribute to improved clinical outcomes and personalized treatment strategies.

REFERENCES

1. Petrov V. I. et al. Mechanisms of cytokine storm development in COVID-19 and new potential targets of pharmacotherapy //Pharmacy and Pharmacology. - 2020. – Vol. 8. – No. 6. – pp. 380-391.
2. From Pathogenic Infections to Inflammation and Disease - the Tumultuous Road of the 'Cytokine Storm'. [Electronic resource] Access mode: https/www.frontiersin.org/research-topics/15743/from-pathogenic-infections-to-inflammation-and-disease---the-tumultuous-road-of-the-cytokine- storm (accessed 08/21/2024).
3. Abduganieva E. A. The role of homocysteine as a pathogenetic factor in the development of thrombophilic conditions //Siberian Medical Review. – 2023. – №. 2 (140). – Pp. 8-16.
4. McCaddon A., Miller J. W. Homocysteine—a retrospective and prospective appraisal //Frontiers in Nutrition. – 2023. – Vol. 10.
5. Baykulov A. K., Yusufov R. F., Ruziev K. A. Dependence of endothelial dysfunction with homocysteine content in the blood in experimental hypercholesterolemia //education science and innovative ideas in the world. – 2023. – vol. 17. – No. 1. – pp. 101-107.
6. Carpenè G. et al. Homocysteine in coronavirus disease (COVID-19): a systematic literature review //Diagnosis. – 2022. – Vol. 9. – No. 3. – pp. 306-310.
7. Zeimakh I. Ya. et al. The effect of correction of homocysteinemia on the clinical outcomes of lung damage associated with COVID-19 coronavirus infection //Bulletin of physiology and pathology of respiration. – 2023. – №. 87. – pp. 8-17.