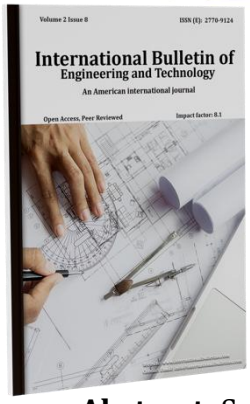

METABOLIC REPROGRAMMING OF LEUKOCYTES IN SEPSIS AND TREATMENT PROSPECTS

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Abstract: Sepsis is defined as a dysfunctional immune response that occurs in the body's response to infection and is one of the leading causes of hospital mortality worldwide. Recent studies have shown that metabolic reprogramming of leukocytes plays an important role in the pathophysiology of sepsis. The aim of this review article is to analyze the metabolic changes of leukocytes in sepsis, their impact on immune function, and potential opportunities for new treatment strategies based on scientific data published between 2015 and 2025. The article deeply studies the changes in the energy metabolism of leukocytes during sepsis, in particular the impact of glycolysis, oxidative phosphorylation, and fatty acid metabolism on the immune response. The imbalance between the M1 and M2 phenotypes of macrophages, as well as the metabolic adaptation of neutrophils and lymphocytes, is also reviewed. The key factors of metabolic reprogramming, including the activation of signaling pathways such as HIF-1α, mTOR, and AMPK, and their role in the inflammatory response have been revealed. Studies have shown that in the early stages of sepsis, there is often an increase in aerobic glycolysis, which leads to excessive production of inflammatory cytokines. Conversely, in the later stages, metabolic insufficiency develops, which is associated with immunosuppression. Understanding these metabolic changes provides an opportunity to develop new therapeutic approaches, for example, strategies aimed at restoring immune balance by modulating metabolic pathways. The article also provides information on various drugs that act as metabolic drivers and their clinical trials. In conclusion, a deep study of leukocyte metabolic reprogramming will allow us to better understand the pathogenesis of sepsis, as well as develop innovative approaches to its treatment, which will provide the prospect of improving outcomes in critically ill patients.

Keywords: sepsis, leukocytes, metabolic reprogramming, immunity, glycolysis, mitochondrial dysfunction, immunoparalysis, metabolic therapy, HIF-1α, mTOR

Research Objective

The main objective of this review article is to systematically analyze the molecular mechanisms of metabolic reprogramming of leukocytes in sepsis, its impact on the immune response, and the prospects for new treatment strategies aimed at targeting these processes, based on the scientific literature from 2015 to 2025. The study revealed the chronological dynamics of metabolic changes that develop in sepsis, differences in their expression in different leukocyte subpopulations (neutrophils, macrophages, lymphocytes), and the impact of these changes on immune function. The article also analyzed drugs aimed at restoring immune balance by modulating metabolic pathways and their clinical significance.

Research Methods

The principles of systematic literature review were followed in preparing this review article. For data collection, scientific database search engines such as PubMed, Scopus, Web of Science and Cochrane libraries were used. Keywords such as "sepsis", "leukocyte metabolism",

"metabolic reprogramming", "immunometabolism", "glycolysis", "mitochondrial dysfunction", "HIF-1α", "mTOR", "immunotherapy" were used in the search queries. The search was limited to articles published from January 2015 to April 2025. Based on the selection criteria, experimental and clinical studies conducted in humans and animal models, as well as high-quality review articles, were included. The obtained data were then grouped by topics: energy metabolism of leukocytes in sepsis, signaling pathways, metabolic changes in different leukocyte types and therapeutic approaches. During the analysis, special attention was paid to the consistency and reliability of the data, as well as the methodological quality of the published sources.

Introduction

Sepsis is a life-threatening clinical syndrome characterized by organ dysfunction in response to infection and is a leading cause of death in hospitals worldwide [1]. Global epidemiological data indicate that more than 30 million people are infected with sepsis each year and approximately 5 million die, making it a major global health problem [2]. The pathophysiology of sepsis is complex, encompassing a process that extends from initial hyperinflammation to a later stage of immunodeficiency (immunoparalysis). While traditional concepts have viewed sepsis primarily as an overactivation of the inflammatory and immune systems, recent studies have revealed the importance of immunometabolism, the interplay between immunity and metabolism [3].

With the development of the field of immunometabolism, it has become clear that metabolic pathways play an important role in regulating leukocyte activation and function. In a healthy organism, resting immune cells generate energy primarily through oxidative phosphorylation. However, when confronted with pathogens, such as infection or inflammation, leukocytes rapidly change their metabolic program, a phenomenon known as “metabolic reprogramming” [4]. This reprogramming provides immune cells with the energy and metabolites they need to perform tasks such as rapid proliferation, cytokine production, and phagocytosis. In the context of sepsis, the metabolic reprogramming of leukocytes is complex and often dysfunctional. In the early stages of sepsis, there is typically an increased glycolysis associated with hyperinflammation [5]. This process is often driven by transcription factors such as hypoxia-inducible factor 1-alpha (HIF-1α) and leads to the overproduction of inflammatory cytokines. However, in the later stages of sepsis, a metabolic derangement associated with immunosuppression develops, in which leukocytes become inefficient at energy production and mitochondrial dysfunction develops [6].

Different leukocyte subpopulations exhibit different metabolic changes in sepsis. For example, in neutrophils, increased glycolysis during the hyperinflammation phase increases their chemotactic and phagocytic activity, but this process soon leads to energy deficiency [7]. Macrophages maintain a balance between M1 (proinflammatory) and M2 (antiinflammatory) phenotypes, which is disrupted in sepsis. M1 macrophages rely on glycolysis, while M2 macrophages have a metabolism based on oxidative phosphorylation [8]. Lymphocytes, particularly T cells, are prone to apoptosis in sepsis, which is associated with a limitation in their metabolic flexibility [9].

Among the major signaling pathways that control metabolic reprogramming, HIF-1α, mTOR (mammalian Target of Rapamycin), and AMPK (AMP-activated protein kinase) are important [10]. HIF-1α is stabilized under conditions of hypoxia and inflammation and increases the expression of glycolytic genes. mTOR controls cell growth and proliferation, and

its activation is essential for meeting the metabolic demands of immune cells. AMPK, on the other hand, is activated under conditions of energy deprivation and promotes catabolic processes. In recent years, understanding the metabolic reprogramming of leukocytes has opened new perspectives in the treatment of sepsis. Therapies that target metabolic pathways, such as glycolysis inhibitors, mTOR modulators, or agents that restore mitochondrial function, have emerged as promising approaches to restore immune balance and improve sepsis outcomes [11]. However, further studies are needed to determine their efficacy and safety before these therapies can be introduced into clinical practice.

Ushbu sharhli maqola sepsisda leykotsitlarning metabolik qayta dasturlanishining molekulyar mexanizmlari, uning immunitet javobiga ta'siri va ushbu bilimlarning yangi davolash strategiyalarini ishlab chiqishdagi ahamiyatini chuqur tahli qiladi. Maqolada 2015-2025-yillar oralig'ida e'lon qilingan eng so'nggi ilmiy ma'lumotlar asosida ushbu murakkab jarayonlarni batafsil yoritishga harakat qilinadi.

Results

Changes in Leukocyte Energy Metabolism in Sepsis

Research over the past decade has clearly demonstrated that leukocyte energy metabolism undergoes significant changes in sepsis. These changes not only affect immune cell function but also contribute to the overall pathogenesis of sepsis.

Increased Glycolysis: Many studies have reported a significant increase in aerobic glycolysis in leukocytes during the early stages of sepsis [12]. This phenomenon, sometimes referred to as the “Warburg effect,” serves as a mechanism to rapidly provide energy and biosynthetic metabolites required for rapid activation of immune cells in response to infection. A study by Cheng and colleagues found increased expression of glycolytic enzymes (HEXOkinase-2, PFKFB3) and, consequently, increased lactate production in peripheral blood mononuclear cells of septic patients [13]. These changes correlate with the severity of the patients, suggesting that increased glycolysis plays an important role in the pathogenesis of sepsis.

Oxidative Phosphorylation and Mitochondrial Dysfunction: In the later stages of sepsis, oxidative phosphorylation and mitochondrial dysfunction develop in leukocytes [14]. Mitochondria have been shown to play an important role not only as a powerhouse for energy production but also in immune signaling. In sepsis, mitochondrial dynamics (fusion and fission) are disrupted, resulting in fragmentation of the mitochondrial network and reduced efficiency of oxidative phosphorylation [15]. This is particularly relevant to sepsis-associated immunosuppression. A study by Larsen and colleagues found decreased activity of mitochondrial respiratory chain complexes and overproduction of reactive oxygen species (ROS) in monocytes from septic patients [16].

Fatty Acid and Amino Acid Metabolism: Metabolic reprogramming of leukocytes affects not only carbohydrate but also fatty acid and amino acid metabolism. In sepsis, β-oxidation of fatty acids in leukocytes may be impaired, contributing to energy deficiency [17]. At the same time, increased glutaminolysis may be observed, which is important for M1 activation of macrophages and lymphocyte proliferation [18]. A study by Wang and colleagues found that the expression of enzymes involved in glutamine metabolism was increased in septic macrophages and that glutamine metabolites stimulated the production of inflammatory cytokines by macrophages [19].

Metabolic Changes in Different Leukocyte Subpopulations

Neutrophils: Neutrophils are the first line of defense in sepsis, and their metabolic flexibility is crucial for their function. In the early stages of sepsis, increased glycolysis in neutrophils increases their chemotactic, phagocytic, and neutrophil network (NET) formation capacity [20]. However, these metabolic changes are not sustainable and soon lead to energy depletion, which leads to neutrophil apoptosis and subsequent immune suppression [21]. In a study by Deng and colleagues, it was found that the administration of 2-deoxy-D-glucose (2-DG), an inhibitor of the glycolytic pathway, to septic neutrophils significantly reduced the migratory and phagocytic capacity of neutrophils [22].

Macrophages/Monocytes: Macrophages are one of the most studied immune cells in metabolic adaptation. In sepsis, the balance between the M1 (proinflammatory) and M2 (anti-inflammatory) phenotypes of macrophages is disrupted [23]. M1 macrophages have a glycolytic metabolism driven by the HIF-1α and mTOR pathways, which increases their production of proinflammatory cytokines such as IL-1β, IL-6, and TNF-α [24]. In contrast, M2 macrophages rely on oxidative phosphorylation and fatty acid β-oxidation. In sepsis, excessive activation of M1 macrophages leads to organ damage, while the subsequent increase in M2 macrophages contributes to immune dysfunction [25]. A study by Liu and colleagues found that the mTOR inhibitor rapamycin promoted the switch from the M1 to the M2 phenotype in septic macrophages, thereby improving sepsis outcomes [26].

Lymphocytes: Lymphocytes, especially T cells, undergo significant metabolic changes in sepsis. When T cells are activated early in sepsis, they increase glycolysis and glutaminolysis [27]. However, in later stages of sepsis, T cells develop metabolic insufficiency, which limits their ability to proliferate and produce cytokines [28]. This metabolic insufficiency is associated with mitochondrial dysfunction as well as increased expression of inhibitory receptors such as PD-1 [29]. A study by Chang and colleagues found that septic T cells have reduced expression of PGC-1α, a protein that stimulates mitochondrial biogenesis, and that this is associated with functional insufficiency of T cells [30].

Signaling Pathways Controlling Metabolic Reprogramming

HIF-1α Pathway: Hypoxia-inducible factor 1-alpha (HIF-1α) plays a central role in the metabolic reprogramming of leukocytes in sepsis [31]. HIF-1α is stabilized not only by hypoxia but also by inflammatory cytokines and bacterial toxins. Activated HIF-1α increases the expression of many glycolysis-related genes (GLUT1, HK2, LDHA), thereby promoting the transition of leukocytes to glycolytic metabolism [32]. In addition, HIF-1α promotes M1 differentiation of macrophages and NET formation of neutrophils [33]. However, excessive activation of HIF-1α can lead to hyperinflammation and organ damage.

mTOR Pathway: The mTOR complex (mTORC1 and mTORC2) is essential for the regulation of immune cell growth, proliferation, and differentiation [34]. Activation of mTOR stimulates anabolic processes such as glycolysis, protein synthesis, and lipogenesis. In sepsis, mTOR pathway activity is altered in a time- and context-dependent manner [35]. While early activation of mTOR is required for rapid activation of immune cells, later inhibition of mTOR promotes autophagy, helping cells survive stress [36]. AMPK Pathway: AMPK functions as an energy sensor and is activated under conditions of energy deprivation [37]. Activated AMPK promotes catabolic processes (autophagy, glycolysis) and inhibits anabolic processes (protein synthesis, lipogenesis). Altered AMPK activity in sepsis affects the metabolic flexibility of immune cells [38]. Some studies suggest that AMPK activation may reduce inflammation and improve mitochondrial function [39].

Sirtuins: Sirtuins, particularly SIRT1 and SIRT3, act as metabolic regulators and influence leukocyte function in sepsis [40]. SIRT1 regulates glucose metabolism and inflammatory pathways, while SIRT3 regulates mitochondrial function. Decreased Sirtuin activity in sepsis contributes to mitochondrial dysfunction and hyperinflammation [41].

Therapeutic Approaches Targeting Metabolic Pathways

In recent years, understanding the metabolic reprogramming of leukocytes has opened up new avenues for the treatment of sepsis.

Glycolysis Modulators: Since excessive glycolysis is a major problem during the hyperinflammation phase of sepsis, agents that inhibit glycolysis are being considered as a potential therapeutic strategy [42]. 2-Deoxy-D-glucose (2-DG), a hexokinase inhibitor, has been shown to improve the hyperinflammatory phase of sepsis in animal models [43]. However, the timing and dose of glycolysis inhibition are important, as it may negatively affect the ability of immune cells to clear pathogens.

mTOR Inhibitors: Rapamycin and its analogs inhibit the mTOR pathway and affect the metabolic adaptation of immune cells [44]. In animal models, the use of rapamycin may be beneficial during the hyperinflammatory phase of sepsis, but may be detrimental during the immunocompromised phase [45]. This highlights the timing and context-dependent nature of metabolic therapies.

Mitochondrial Function-Repairing Agents: As mitochondrial dysfunction plays a key role in the immunoparalytic phase of sepsis, agents that restore mitochondrial function are a promising approach [46]. Resveratrol, NAD+ precursors (nicotinamide riboside), and mitochondrial antioxidants (MitoQ) have been shown to improve mitochondrial function and restore immunity in animal models [47].

Metabolic Checkpoint Inhibitors: Immune checkpoint molecules such as PD-1 have been shown to regulate not only immunity but also metabolism [48]. PD-1 inhibitors have been shown to restore T-cell function by restoring glycolytic metabolism [49]. However, these approaches have not yet undergone extensive clinical trials in sepsis.

Discussion

The data presented in this review article demonstrate that metabolic reprogramming of leukocytes is a central aspect of sepsis pathogenesis. Metabolic changes not only affect the function of immune cells but also determine their future potential. Although increased glycolysis during the hyperinflammatory phase of sepsis is essential for rapid activation of immune cells, this process quickly leads to energy depletion and the accumulation of toxic metabolites, which contribute to subsequent immune dysfunction.

The signaling pathways that control metabolic reprogramming (HIF-1α, mTOR, AMPK) are emerging as potential therapeutic targets. However, the complexity of these pathways and their time- and context-dependent activity pose significant challenges in the design of therapeutic interventions. For example, inhibition of glycolysis may be beneficial in the early stages of sepsis, but may further impair immunity later in life. Similarly, mTOR inhibitors may be beneficial in the hyperinflammation stage but may be detrimental in the immunocompromised stage.

The differences in metabolic alterations in different leukocyte subpopulations suggest that a “one-size-fits-all” therapeutic approach may not be effective. Instead, more specific approaches are needed that address the metabolic needs of individual leukocyte types. For example, modulating the glycolytic metabolism of neutrophils may improve their migratory

and phagocytic capacity, while restoring mitochondrial function in T cells may improve their proliferation and differentiation.

The clinical translation of metabolic therapies is still in its infancy. Many promising drugs have only been tested in animal models and further studies are needed to determine their efficacy and safety in humans. In addition, the integration of metabolic therapies with existing treatment protocols (antibiotics, water therapy) must be addressed.

Future research should focus on a clearer understanding of the dynamics of metabolic changes and their relationship to the functional state of immune cells. New technologies such as single-cell metabolomics and transcriptomics will provide a deeper understanding in this area. Also, the identification of metabolic biomarkers will provide an opportunity to improve the prognosis of sepsis and develop personalized therapeutic approaches.

Conclusion

In conclusion, metabolic reprogramming of leukocytes is an important aspect of the pathogenesis of sepsis and is closely related to the initiation, development and lethality of the immune response. This review article analyzes the changes in leukocyte energy metabolism in sepsis, the metabolic adaptations in different leukocyte subpopulations, the signaling pathways that control these processes, and potential therapeutic approaches, based on studies conducted between 2015 and 2025.

Data suggest that, although increased glycolysis during the hyperinflammatory phase of sepsis is essential for rapid activation of immune cells, this process soon leads to energy depletion and accumulation of toxic metabolites. In the later stages of sepsis, mitochondrial dysfunction and metabolic dysfunction contribute to immune dysfunction. Signaling pathways such as HIF-1α, mTOR, and AMPK play important roles in controlling these metabolic changes.

Different leukocyte subpopulations (neutrophils, macrophages, lymphocytes) employ different metabolic strategies in sepsis, which affects their functional status. These differences should be taken into account when developing personalized therapeutic approaches.

Therapies targeting metabolic pathways, including glycolysis modulators, mTOR inhibitors, mitochondrial function restorers, and metabolic checkpoint inhibitors, offer new perspectives in the treatment of sepsis. However, the clinical translation of these approaches is still in its infancy and further studies are needed to determine their efficacy and safety.

Future studies should focus on a clearer understanding of the dynamics of metabolic changes and their relationship to the functional state of immune cells, as well as the identification of metabolic biomarkers. This will provide an opportunity to improve the prognosis of sepsis and develop personalized therapeutic approaches.

Overall, a deeper understanding of leukocyte metabolic reprogramming will allow for a better understanding of the pathogenesis of sepsis, as well as the development of innovative approaches to its treatment, which will provide the prospect of improving outcomes in critically ill patients.

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