THE IMMUNE STATUS AND LABORATOR DIAGNOSIS OF SEPSIS

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Sepsis is a life-threatening syndrome of organ dysfunction caused by dysregulation of the body's response to infection. The mortality rate from sepsis is quite high, so there is a search for additional methods of treatment that could affect certain components of pathophysiological shifts, particularly in the immune system.

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Patients with sepsis have at least 2 variants of immune abnormalities: decompensation of the state occurs against the background of immunosuppression or due to reactivation of excessive inflammation caused by infection [10, 15].
Hyperinflammation and immunosuppression can occur sequentially or simultaneously. If the immune system quickly eliminates pathogens at an early stage of the systemic inflammatory response, the immune balance can be quickly restored. If pathogens are not eliminated in a timely manner, this will lead to an imbalance in immune regulation and the development of persistent inflammation and immunosuppression syndrome may occur, which is common in a variety of conditions [1,3,5,7].

The unacceptably high mortality rates from severe infections and sepsis justify the realization that additional immunotherapy is needed to modulate the body's unregulated response. However, immune function can vary considerably from patient to patient [6,7,8].

Treatment approaches should take into account the endo-type classification of sepsis. Classification of patients into subgroups (based on biomarkers, stage of disease, severity) may be effective and crucial for determining more specific treatment, which should ultimately lead to improved clinical outcomes [15].

The goal of immunoregulatory therapy is to restore immune cell function to eliminate the infection that caused sepsis and prevent secondary infections. In patients with sepsis, several strategies can be used to modify immune status, including targeting cytokines, immune checkpoint inhibitors, cellular and humoral immunity.

Targeting immune checkpoints. Another very promising area is to target immune checkpoints on the surface of various cells. The most studied are programmed cell death protein-1 (PD-1) and the natural PD-1 receptor (PD-L1) [13,14].

Studies have shown that PD-1 and PD-L1 are closely associated with the progression of human cancer and are promising agents for its therapy. Moreover, the interaction between PD-1 and PD-L1 is one of the important mechanisms by which human tumor cells cause immune evasion [12].

Several drugs targeting checkpoint inhibitors, including PD-1 and PD-L1, have been developed and approved for the treatment of various cancers [4,14], but no such therapies have been approved for the treatment of sepsis. By targeting immune suppression, especially with immune checkpoint inhibitors, preclinical studies have demonstrated reversal of immunocyte dysfunction and establishment of host resistance to infection [7,8,9,10,11].

For example, PD-1 inhibition with nivolumab is a promising method for the treatment of patients with immunosuppression caused by sepsis. It reactivates T-lymphocyte function and restores immunity to fight infection [1,2,3,4,5,6,14].

Of the other immune checkpoint molecules, the most interesting are: Cytotoxic T-lymphocytes antigen-4 (CTLA-4), T-cell membrane protein-3 (TIM-3), Lymphocyte-activation gene-3 (LAG-3) and B- and T-lymphocyte attenuator

receptor (BTLA). Cytotoxic CTLA-4 is an immune control molecule that is mainly expressed on activated T cells and regulatory T cells (Treg), inhibits T cell activation and regulates immune homeostasis. Given the important involvement of CTLA-4 in T cell biology, immunotherapy approaches targeting CTLA-4 have been developed to treat autoimmune diseases as well as cancer [15,16,24,25].

Clinical symptoms associated with sepsis are unreliable and laboratory indicators are not always specific, making early diagnosis of sepsis difficult. Diagnosis based on the use of a single laboratory marker does not provide sufficient accuracy. The lack of specific laboratory tests for diagnosis and the high rate of negative microbiologic tests even in patients with sepsis exacerbate the situation [20,21,22,23].

Failure to detect sepsis in its early stages delays effective treatment, resulting in high patient mortality. To overcome these limitations, medical researchers are constantly searching for better laboratory tests to be able to distinguish sepsis from other non-infectious causes of systemic inflammatory response syndrome [17,18,19].

To identify the infection, today classical methods of microbiological diagnostics, which are considered the “gold standard”, are more often used. However, the answer about the presence/absence of the infectious agent takes 24-72 hours (there are cases of getting an answer in 5-7 days), this is primarily due to the capabilities of the laboratory, its technical equipment [7,8,9,14,15].

Advances in molecular biology in recent decades have made it possible to detect and identify pathogen DNA/RNA by real-time polymerase chain reaction (PCR-RV) in any biological material obtained from patients. Moreover, it is possible to determine the resistance of the isolated pathogen to ABP. These interventions reduce the number of adverse outcomes in patients with sepsis [1,2,3,12,13].

Thus, at present, due to the heterogeneity of the nature of the septic process and insufficient specificity of clinical manifestations, there is no universal laboratory method for early diagnosis of sepsis. The use of a combination of microbiological, molecular-biological and immunochemical methods can provide not only accurate laboratory diagnosis, but also clarify the pathogenesis of the disease. The development of new, integrated approaches and improvement of methods of laboratory diagnosis of sepsis guarantee the possibility of early diagnosis,

monitoring and prediction of reduction of adverse outcomes in conditions of generalization of infection [6,7,8,9,10,11].

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