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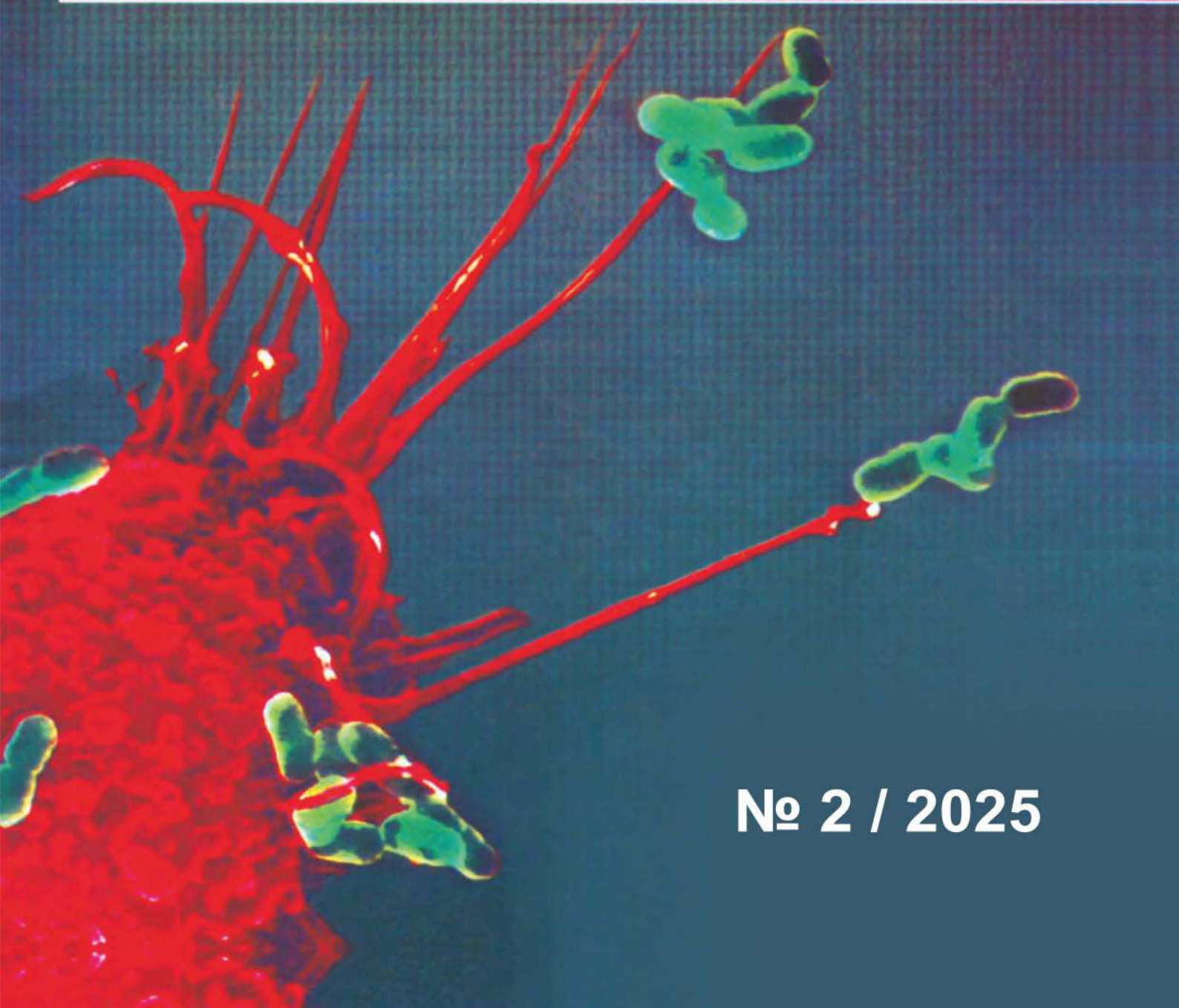

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MECHANISMS OF CELLULAR IMMUNE RESPONSE IN BRUCELLOSIS

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The review discusses the current state of the issue of interaction of Brucella with the macroorganism. Information is provided on the mechanisms of Brucella persistence in the host body due to their ability to persist for a long time in the cells of the immunophagocytic system. The role of macrophages in brucellosis infection has been demonstrated.

Brucella are facultative intracellular pathogens that cause disease in a large number of animals and humans [3,6,16]. Despite the fact that Brucella infects humans as a secondary host, 500 thousand new cases of human brucellosis infection are recorded annually in the world [16].

The human immune defense mechanisms do not cope effectively with the causative agent of brucellosis; as a result, as a rule, a chronic relapsing disease develops, lasting indefinitely and leading to deep damage to the musculoskeletal system, many organs and tissues, and the central nervous system. Post-infectious immunity has weak tension and quickly decreases during the first year after infection, leaving deep allergic changes and a state of pathergy. As a result, the body remains susceptible to re-infection, and re-entry of the pathogen causes severe allergic processes with organic irreversible damage to parenchymal organs, connective tissue and the nervous system [12]. Brucella melitensis, B. abortus and B. suis are the most pathogenic Brucella species for humans. The US Centers for Disease Control and Prevention classifies Brucella of these species as agents of bioterrorism and they are included in the list of category B dangerous pathogens.

The death of host cells is the main outcome of host-pathogen interactions.

A critical component of the immune system that mediates host survival and thus maintains this chronic infectious state is IFN-γ. IFN-γ production results from the ability of Brucella components, including lipid A, to interact with Toll-like receptors (TLRs) with subsequent synthesis of IL-12 and TNF-α. At the same time, the production of regulatory IL-10 is also noted, which leads to decreased control over the infection. And although CD4 and CD8 T cells are clearly involved in the production of IFN-γ,

and CD8 T cells can be cytotoxic, the role of NK cells and cytotoxicity in protective immunity to brucellosis has not been experimentally substantiated (not studied) [14].

It has been shown that CD4+ T cells producing IFN-γ and dendritic cells producing inducible nitric oxide synthase are the main components of the protective immune response against the causative agent of brucellosis.

In humans, B. suis has been found to reduce apoptosis of monocytes and macrophages, thereby preventing the elimination of host cells. In mice that are not naturally colonized by this bacterium, brucellosis infection develops a type 1 (Th1) cellular immune response that clears the body of the bacteria. The development of this response is controlled by such major cytokines as TNF-α, IFN-γ and IL-12, which are produced at the beginning of infection. It has been noted that human macrophages infected with B. suis produce IL-1, IL-6, IL-10 and several chemokines, including IL-8, but do not secrete TNF-α. It has been shown that in Brucella mutants the outer membrane protein Omp 25 of Brucella is involved in the inhibition of TNF-α secretion. It is likely that the production of TNF-α induced by Omp25 contributes to the evasion of bacteria from the antimicrobial defense of the macroorganism. Firstly, by preventing autocrine activation of macrophages and, consequently, inhibition of innate immunity and, secondly, by disrupting the production of IL-12 and the development of Th1-type specific immunity.

Brucella exhibits strong tissue tropism for the lymphoreticular and reproductive systems with an intracellular life cycle. This property of the pathogen limits the manifestation of innate and adaptive immune responses, sequesters the body from the action of antibiotics, and causes clinical manifestations of the disease and pathology. Latent Brucella uses several routes to develop infection, including:

1) evasion of intracellular destruction by limiting the fusion of type 4 secretion system-dependent Brucella-containing vacuoles with lysosomal compartments;

2) inhibition of apoptosis of infected mononuclear cells;

3) prevention of dendritic cell maturation, antigen presentation, and activation of naive T cells [17].

Despite the pronounced polymorphism of the clinical manifestations of the disease, inflammation is the main symptom of brucellosis and affected tissues with the presence of inflammatory infiltrates. Since Brucella does not have exotoxins, exoproteases or cytolysins, the development of the disease is due to the inflammatory process, which is confirmed by the results of pathological studies. In recent years, the cellular and molecular basis of the immunopathological manifestations of pathogenesis have been deciphered. Brucella-infected osteoblasts, alone or together with infected macrophages, produce cytokines, chemokines, and similar phenomena occur in fibroblast-like synoviocytes. Overall, these events may contribute to the bone and cartilage destruction that is commonly seen in brucellosis arthritis and osteomyelitis. Proinflammatory cytokines may also be involved in the pathogenesis of neurobrucellosis. B. abortus and its lipoproteins cause inflammatory reactions in the central nervous system of mice, leading to astrogliosis, a characteristic feature of neurobrucellosis. Heat-killed bacteria and the lipidated form of the outer membrane protein of B. abortus induce apoptosis and astrocyte pro-

liferation, and TNF-α signal-dependent apoptosis. Brucella also infects and replicates in human endothelial cells, inducing the production of chemokines and IL-6, and increased expression of adhesion molecules. It is possible that a persistent inflammatory process derived from chronic infection of the endothelium is important for the development of endocarditis. Brucella induces a low-grade inflammatory response compared to other microorganisms, and its long-term intracellular persistence in infected tissues supports a long-term inflammatory response that mediates various pathways of tissue damage. Modeling the processes of inhibiting the invasion of host cells or limiting the intracellular survival of bacteria will allow us to find approaches to preventing the pathological consequences of brucellosis infection [15].

It has been shown that the active participation of macrophages, dendritic cells, CD4+ T cells producing IFN-γ, as well as cytotoxic CD8+ T cells is vital for overcoming infection.

The function of CD4 lymphocytes is of limiting importance and consists of a direct effect on infected macrophages, as well as stimulation of clonal proliferation of cytolytic CD8 cells. In these processes, Vγ9Vδ-T-cell receptors play a role. An increase in the number of γ/δ-CD4 and CD8 lymphocytes is characteristic of brucellosis [7,13]. Studies by a number of authors have shown that the main role in brucellosis is given to the effects of γ-IF, which stimulates the production of reactive oxygen species and NO by macrophages, the induction of apoptosis, enhances the differentiation of lymphoid cells and the synthesis of cytokines, ensures the prevalence of IgG subclass 2a, and increases the expression of major histocompatibility complex molecules (MHC – major histocompatibility complex). It was found that the severity of the effects of γ-IF depends on the polymorphism of its gene. It turned out 19 that people homozygous for the +874A allele are more prone to developing brucellosis and tuberculosis. Typically, with brucellosis, the level of γ-IF in the blood is increased [7]. The studies carried out revealed disturbances in various parts of the immune system in patients with brucellosis, namely: T- and B-cell parts, mononuclear-phagocytic part, as well as cytokine status. The study of T- and B-cell immunity in patients with brucellosis revealed a significant decrease in the absolute number of CD3, CD4 and CD8 lymphocytes in the peripheral blood compared to the control group. A more significant decrease in these cells was detected in patients with acute brucellosis. A comparative in vitro study of spontaneous and stimulated production of cytokines in a culture of mononuclear cells isolated from the peripheral blood of patients with acute and chronic brucellosis showed characteristic dynamics of changes in immunological parameters during the chronicization of brucellosis infection. The work of a number of authors has shown that in patients with acute brucellosis there is an increase in the number of DM 16 lymphocytes in the blood, an increase in the activity of neutrophils according to the NBT test and the activity of macrophages due to an increase in their production of IL1β and TNFα. During the process of chronic brucellosis, a decrease in the absolute number of neutrophils in the peripheral blood and a decrease in the activity of macrophages is observed due to the low level of production of IL1β and TNFα. In acute brucellosis, there is an increase in

the activity of plasma cells, as indicated by an increase in the level of differentiation of B-lymphocytes into plasma cells in these patients, as evidenced by immunoglobulins of all classes in the blood serum. However, the final processes are indicated by a low level of IL6 production and an increase in the content of CD21 lymphocytes in the blood. In patients with chronic brucellosis, the activity of plasma cells decreases, as indicated by a low level of IgM production. The differentiation of B lymphocytes into plasma cells is impaired at all stages, as evidenced by the low level of production of IL6 and IL4. The activity of the cellular component of immunity in acute brucellosis is reduced, as evidenced by a decrease in the number of CD3 and CD4 lymphocytes and low production of IL2. In patients with chronic brucellosis, the impairment of cellular immunity progresses, which is confirmed by a decrease in the number of not only CD3 and CD4, but also CD8 lymphocytes, as well as a low level of production of IL2 and IL4. A decrease in the absolute number of neutrophils, monocytes, CD4, CD8, CD21 lymphocytes and Ig M in the peripheral blood, as well as a decrease in spontaneous and stimulated production of IL1R, IL4, IL6 and TNFα in a mixed culture of mononuclear cells in vitro can be regarded as an unfavorable prognosis for chronicity brucellosis. Thus, the discovery of biologically active substances - cytokines, regulating the proliferation and level of functional activity of cells both in normal conditions and in pathology, allows us to evaluate from a new perspective the mechanism of formation of inflammatory reactions, allergic and immune conditions and to develop new methods for predicting the nature of an infectious disease.

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РЕЗЮМЕ
МЕХАНИЗМЫ КЛЕТОЧНОГО ИММУННОГО ОТВЕТА ПРИ БРУЦЕЛЛЕЗЕ

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Ключевые слова: бруцеллез, иммунитет, макрофаги.

В обзоре обсуждается современное состояние вопроса взаимодействия бруцелл с макроорганизмом. Приведены сведения о механизмах персистенции бруцелл в организме хозяина за счет их способности длительно сохраняться в клетках иммунофагоцитарной системы. Показана роль макрофагов в бруцеллезной инфекции.

REZUME
BRUCELLOZDA HUJAYRA IMMUN JAVOBINING MEXANIZMLARI

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Kalit so‘zlar: brutselloz, immunitet, makrofaglar.

Xulosa: Sharhda brusellaning makroorganizm bilan o‘zaro ta’siri masalasining hozirgi holati muhokama qilinadi. Immunofagotsitar tizim hujayralarida brucellalarning uzoq vaqt saqlanish qobiliyati tufayli organizmida to‘planish mexanizmlari haqida ma’lumot berilgan. Brutsellyoz infektsiyasida makrofaglarning roli ko‘rsatilgan.