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IMMUNOGENETIC AND CYTOKINE MARKERS FOR ASSESSING IMMUNOINFLAMMATORY RESPONSES IN BRUCELLOSIS

Urunova Dilbar Mahmudovna
Doctor of Medical Sciences (DSc)
Head of Department
Laboratory of Epidemiology of Infectious Diseases
Republican Scientific and Practical Medical Center for Epidemiology, Microbiology, Infectious and Parasitic Diseases
Tashkent, Uzbekistan
https://orcid.org./0000-0001-6022-8961
E-mail: d.urunova@yandex.com
+998909253802

Abdullayeva Dilfuza Kadamovna
Doctoral Student
Tashkent Research Institute of Vaccines and Sera
Tashkent, Uzbekistan
https://orcid.org./0009-0006-1002-6409
dilfuza_abdullayeva_infec@mail.ru
+998995282355

Abstract. Brucellosis, a widespread zoonotic infection caused by *Brucella* species, continues to pose a substantial public health challenge, particularly in endemic areas. This paper examines the fundamental mechanisms involved in brucellosis pathogenesis, including pathogen recognition processes, immune evasion strategies utilized by *Brucella*, and the integrated roles of innate and adaptive immune responses in disease development. Particular attention is given to the ability of *Brucella* to alter host immune regulation, thereby promoting persistent and chronic infection. From an epidemiological perspective, the study addresses the major routes of transmission, associated risk factors, and the wider impact of brucellosis on global health. In addition, recent progress in diagnostic methodologies, especially molecular diagnostic tools and the identification of novel biomarkers, is reviewed to improve disease detection and monitoring. The paper also evaluates current therapeutic approaches, including standard antimicrobial regimens and emerging immunotherapeutic strategies, highlighting their challenges and future directions. By providing a clearer understanding of the molecular and immunological basis of brucellosis pathogenesis, this study emphasizes the value of multidisciplinary strategies in advancing diagnosis, treatment, prevention, and clinical management of this persistent infectious disease.

Keyword: Brucellosis, host immune response, persistent (chronic) infection, diagnostic approaches, inflammatory processes.

BRUTSELLYOZDA IMMUN YALLIG‘LANISH JAVOBNI BAHOLASHDA IMMUNOGENETIK VA SITOKIN MARKERLARINING AHAMIYATI

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Urunova D.M., Abdullayeva D.K.
Respublika epidemiologiya, mikrobiologiya, yuqumli va
parazitar kasalliklar ilmiy amaliy tibbiyot markazi, Toshkent sh., O‘zbekiston

Annotatsiya. Brutsella turlari keltirib chiqaradigan keng tarqalgan zoonoz infeksiya bo‘lgan brutsellyoz, ayniqsa endemik hududlarda, jamoat salomatligi uchun jiddiy muammo bo‘lib qolmoqda. Ushbu maqolada brutsellyoz patogenezida ishtirok etuvchi asosiy mexanizmlar, jumladan, qo‘zg‘atuvchini aniqlash jarayonlari, brutsellalar tomonidan qo‘llaniladigan immun qochish strategiyalari hamda kasallik rivojlanishida tug‘ma va moslashuvchan immunitet javoblarining yaxlit roli ko‘rib chiqiladi. Brutsellalarning xo‘jayin immun boshqaruvini o‘zgartirish qobiliyatiga alohida e’tibor qaratiladi, bu esa doimiy va surunkali infeksiyani rag‘batlantiradi. Epidemiologik nuqtai nazardan, tadqiqot brutsellyozning asosiy yuqish yo‘llari, ular bilan bog‘liq xavf omillari va global sog‘liqni saqlashga kengroq ta’sirini ko‘rib chiqadi. Bundan tashqari, kasalliklarni aniqlash va nazorat qilishni takomillashtirish uchun diagnostika usullari, ayniqsa molekulyar diagnostika vositalari va yangi biomarkerlarni aniqlash sohasidagi so‘nggi yutuqlar ko‘rib chiqiladi. Shuningdek, maqolada hozirgi terapevtik yondashuvlar, jumladan, standart antimikrob sxemalar va rivojlanayotgan immunoterapevtik strategiyalar baholanib, ularning muammolari va kelajakdagi yo‘nalishlari yoritib berilgan. Brutsellyoz patogenezining molekulyar va immunologik asoslarini aniqroq tushunish orqali, ushbu tadqiqot ushbu doimiy yuqumli kasallikni tashxislash, davolash, oldini olish va klinik boshqarishni rivojlantirishda ko‘p tarmoqli strategiyalarning ahamiyatini ta’kidlaydi.

Kalit so‘zlar: Brutsellyoz,organizm immun javobi, persistent (surunkali) infeksiya, diagnostik yondashuvlar, yallig‘lanish jarayonlari.

ИММУНОГЕНЕТИЧЕСКИЕ И ЦИТОКИНОВЫЕ МАРКЕРЫ ДЛЯ ОЦЕНКИ ИММУНОВОСПАЛИТЕЛЬНЫХ ОТВЕТОВ ПРИ БРУЦЕЛЛЕЗЕ

Урунова Д.М., Абдуллаева Д.К.
Республиканский научно-практический медицинский центр эпидемиологии, микробиологии, инфекционных и паразитарных заболеваний, г. Ташкент, Республика Узбекистан

Аннотация. Бруцеллез, широко распространенная зоонозная инфекция, вызываемая видами бруцелл, по-прежнему представляет собой серьезную проблему для общественного здравоохранения, особенно в эндемичных районах. В данной работе рассматриваются фундаментальные механизмы, участвующие в патогенезе бруцеллеза, включая процессы распознавания возбудителей, стратегии иммунного уклонения, используемые бруцеллами, а также комплексную роль врожденных и адаптивных иммунных ответов в развитии заболевания. Особое внимание уделяется способности бруцелл изменять иммунную регуляцию хозяина, способствуя тем самым персистирующей и хронической инфекции. С эпидемиологической точки зрения в исследовании рассматриваются основные пути передачи, связанные с ними факторы риска и более широкое влияние бруцеллеза на глобальное здоровье. Кроме того, рассматривается недавний прогресс в диагностических методологиях, особенно в молекулярной диагностике и выявлении новых биомаркеров для улучшения выявления и мониторинга заболеваний. В статье также оцениваются текущие

терапевтические подходы, включая стандартные антимикробные схемы и развивающиеся иммунотерапевтические стратегии, подчеркиваются их проблемы и будущие направления. Предоставляя более четкое представление о молекулярной и иммунологической основе патогенеза бруцеллеза, данное исследование подчеркивает ценность междисциплинарных стратегий в развитии диагностики, лечения, профилактики и клинического ведения этого персистирующего инфекционного заболевания.

Ключевое слово: Бруцеллез, иммунный ответ хозяина, персистирующая (хроническая) инфекция, диагностические подходы, воспалительные процессы.

Introduction.

Brucellosis is a widespread zoonotic infection caused by bacteria of the *Brucella* genus and represents an important concern for both public health and animal husbandry. Although effective control measures have reduced its incidence in high-income countries, the disease remains endemic in many regions, including the Middle East, Sub-Saharan Africa, South and Central Asia, and parts of Latin America. The World Health Organization classifies brucellosis as a neglected tropical disease due to its frequent underdiagnosis and its considerable socioeconomic impact, along with its tendency to cause long-term illness in affected individuals [1]. Human infection typically occurs through direct exposure to infected animals or by consuming contaminated animal-derived food products. Clinically, brucellosis is characterized by intermittent (“undulant”) fever, joint pain, fatigue, and in some cases neuropsychiatric symptoms. The ability of *Brucella* species to survive intracellularly, alter host immune responses, and evade immune clearance makes the disease difficult to diagnose, treat, and prevent through vaccination [2,3]. The complex immunopathogenesis of brucellosis requires thorough investigation to support the development of more effective therapeutic strategies and control measures.

MECHANISMS OF PATHOGEN DETECTION AND IMMUNE SYSTEM EVASION

Brucella species are Gram-negative intracellular pathogens capable of persisting within host cells and causing chronic infection through multiple immune evasion strategies [4]. They alter their lipopolysaccharide (LPS) structure to weaken recognition by TLR4, thereby reducing activation of pro-inflammatory signaling pathways. After entering macrophages, *Brucella* avoids fusion with lysosomes and survives by replicating within specialized intracellular vacuoles [5]. In addition, it suppresses host oxidative killing mechanisms by inhibiting NADPH oxidase activity and inducible nitric oxide synthase (iNOS), leading to decreased production of reactive oxygen species (ROS) and nitric oxide (NO).

The pathogen also influences host cell death pathways by modulating Bcl-2 expression and activating MAPK signaling cascades. Furthermore, it disrupts autophagy by interfering with LC3 lipidation and Beclin-1 complex formation, thereby preventing effective intracellular bacterial clearance [6]. Through these mechanisms, *Brucella* establishes long-term intracellular survival, resulting in persistent infection and chronic low-grade inflammation. This ongoing inflammatory state is often associated with granuloma formation, immune dysfunction, and clinical manifestations such as recurrent joint pain and fatigue. On the adaptive immune level, *Brucella* employs the effector protein TcpB to inhibit TLR signaling and suppress NF-κB activation, ultimately impairing antigen presentation and T-cell responses [7]. These immune evasion strategies facilitate persistent infection while also highlighting potential targets for immunotherapy, including nanoparticle-based vaccines and immune checkpoint modulation currently under investigation [8,9]. Evidence suggests that dysregulation of immune checkpoints such as PD-1/PD-L1 and CTLA-4 contributes to T-cell exhaustion in chronic brucellosis. In experimental mouse models, blockade of these pathways has partially restored T-cell function and reduced bacterial load, indicating possible benefit as adjunctive therapy in difficult-to-treat cases [10,11].

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THE CONTRIBUTION OF THE INNATE IMMUNE SYSTEM TO BRUCELLOSIS PATHOGENESIS

Brucella enhances its intracellular survival by actively modulating the innate immune system to evade host defenses. It inhibits the pro-inflammatory M1 macrophage response while promoting polarization toward the anti-inflammatory M2 phenotype, which has reduced microbicidal activity and facilitates immune escape. The effector protein TcpB interferes with TLR2/4 signaling pathways, further shifting macrophages toward an M2-like state and weakening their ability to eliminate the pathogen [12].

During the early stages of infection, IFN-γ produced by innate lymphoid cells (ILCs) and natural killer (NK) cells contributes to enhanced macrophage antimicrobial functions [13]. However, an excessive type I interferon response (IFN-α/β) can paradoxically promote immune suppression, limiting macrophage activation and reducing bacterial clearance [14]. This imbalance in interferon signaling contributes to the establishment of chronic infection, characterized by sustained low-grade inflammation and clinical features such as joint damage and hepatosplenomegaly in long-term brucellosis cases [15,16].

Macrophages display functional plasticity and can differentiate into either classically activated M1 or alternatively activated M2 phenotypes depending on the surrounding immune environment. Although M1 polarization supports pathogen elimination, *Brucella* infection simultaneously drives M2 polarization, which suppresses effective immune responses. In patients with chronic brucellosis, an M2-dominant immune profile is commonly observed and is associated with persistent infection and reduced therapeutic response [17,18]. Therefore, targeting the balance between M1 and M2 macrophage polarization represents a promising approach for improving vaccine strategies and developing host-directed immunotherapies.

ADAPTIVE IMMUNE RESPONSES IN BRUCELLOSIS

Adaptive immunity, especially Th1-type responses, is essential for controlling *Brucella* infection [19]. CD4+ T cells contribute to host defense by activating macrophages through the secretion of IFN-γ and TNF-α, while CD8+ T cells eliminate infected host cells. However, *Brucella* has evolved mechanisms to escape adaptive immune recognition, including interference with antigen presentation. Through its Type IV secretion system, the bacterium can disrupt antigen processing pathways and reduce MHC class I and II expression [20]. This immune evasion skews T-cell differentiation toward Th2 and regulatory T responses, which are less effective for intracellular bacterial clearance.

Although *Brucella* is primarily an intracellular pathogen, it also induces humoral immunity, leading to the production of IgM and IgG antibodies that support opsonization and phagocytosis. Nevertheless, antibody-mediated protection may decline in chronic infection due to impaired immune efficiency [21]. Neutrophils, while classically part of the innate immune system, can also indirectly modulate adaptive immunity by competing for antigen availability or releasing suppressive mediators that alter T-cell responses [12].

In chronic brucellosis, immune checkpoint pathways such as PD-1/PD-L1 and CTLA-4 become upregulated, contributing to T-cell exhaustion and reduced effector function. Increased PD-1 expression on T cells is associated with decreased cytokine production and impaired proliferation, thereby facilitating persistent infection and immune evasion. Experimental studies indicate that blockade of PD-1/PD-L1 or CTLA-4 pathways may restore T-cell activity and enhance bacterial clearance, particularly when used alongside antibiotic therapy.

In addition, vaccine strategies incorporating checkpoint inhibition or novel adjuvants have demonstrated improved induction of memory T-cell responses and long-term protective immunity. Emerging therapeutic approaches targeting *Brucella* immune evasion include adjuvant-enhanced

vaccines, nanoparticle-based delivery systems, and immune checkpoint inhibitors designed to strengthen cellular immunity and reverse immune suppression [13–15].

GLOBAL EPIDEMIOLOGICAL STATUS OF BRUCELLOSIS

Brucellosis is a widely distributed zoonotic disease, with the highest burden reported in Africa, Asia, and the Middle East [18]. The World Health Organization classifies it as a neglected tropical disease, largely due to its underdiagnosis, limited surveillance systems, and significant public health impact. As a result, the true global incidence is likely underestimated.

Endemic transmission is particularly common in Central Asia, North and Sub-Saharan Africa, and several regions of Latin America. In China, the highest incidence is observed in the northern provinces, although sporadic cases are increasingly reported in southern areas as well. In recent years, an upward trend has also been noted in regions where brucellosis was previously rare or poorly recognized, including parts of Southeast Asia and Eastern Europe.

TRANSMISSION ROUTES AND RISK FACTORS OF BRUCELLOSIS

Brucellosis is transmitted through several routes, including direct contact, ingestion, and occupational exposure [19]. The risk of infection is particularly high during animal birthing, milking, or slaughtering processes, when contact with infected tissues and secretions is most frequent [10]. A major source of human infection is the consumption of unpasteurized dairy products or undercooked meat [11]. Individuals working closely with animals, such as veterinarians, farmers, and slaughterhouse workers, are considered high-risk groups due to repeated exposure. Disease transmission is further influenced by environmental contamination of soil and water, as well as the movement and migration of infected animals. The interaction between humans, domestic animals, wildlife, and the environment maintains a continuous cycle of transmission, with both wild and domestic species acting as reservoirs of infection. *Brucella* species can persist in the environment for extended periods, allowing indirect exposure through contaminated materials. The epidemiology of brucellosis is increasingly shaped by emerging risk factors, particularly urbanization and climate change. Expansion of urban areas into peri-urban and rural zones increases human–animal contact, while climate variability may alter animal migration patterns, pathogen survival in the environment, and ecological conditions that support transmission [12].

PATHOPHYSIOLOGICAL MECHANISMS OF BRUCELLOSIS

Brucella improves its ability to survive and spread within host cells by altering immune signaling pathways, which plays a key role in maintaining long-term infection [23,24]. The persistence of brucellosis is mainly linked to its intracellular lifestyle, supported by major virulence factors such as the VirB Type IV secretion system (T4SS). This system injects effector proteins into host cells, disrupting intracellular trafficking and autophagy processes, thereby enhancing bacterial survival. A defining feature of infection is the development of the Brucella-containing vacuole (BCV), a specialized intracellular compartment. Inside macrophages, *Brucella* prevents lysosomal fusion and redirects vesicular transport toward the endoplasmic reticulum, where it establishes a protected niche for replication [25].

Brucellosis is also characterized by organ-specific damage, with the liver being one of the most commonly affected sites. Hepatic infection stimulates hepatic stellate cell activation, increased collagen production, and progressive fibrotic changes. In the musculoskeletal system, the disease causes substantial morbidity through immune-mediated pathways. TLR2 activation promotes cytokine release, which drives osteoclast formation, leading to bone degradation and joint injury. Clinically, sacroiliitis and spondylodiscitis are frequently observed complications and often require long-term antibiotic treatment, with surgery needed in severe cases.

PROGRESS IN IMMUNOTHERAPY FOR BRUCELLOSIS

Immunotherapy for brucellosis remains largely in the experimental stage but has demonstrated promising potential [21]. Because *Brucella* can evade immune elimination,

strengthening host immune responses is considered a key therapeutic strategy. Experimental animal studies have shown that bacteriophage-derived lysates can trigger strong immune activation and significantly reduce bacterial burden in infected cattle. Recent research using murine models has also indicated that nanoparticle-based subunit vaccines can induce robust Th1-type immune responses, leading to improved bacterial clearance and reduced splenic colonization [22]. Although an approved human vaccine is not yet available, live attenuated vaccines used in animals have shown strong immunogenicity, but they are associated with safety concerns, including the risk of abortion in livestock [13]. In parallel, subunit and DNA-based vaccines are under active investigation, with encouraging results in terms of both safety and protective immunity.

A phase I clinical trial evaluating a DNA vaccine targeting *Brucella* outer membrane proteins (OMPs) demonstrated acceptable safety and immunogenicity in healthy volunteers, representing an important step toward human vaccine development [24]. In addition, multi-antigen vaccine approaches are being explored to broaden immune coverage and improve protective efficacy, offering a promising direction for future vaccine design [25].

INDIVIDUAL VARIABILITY IN THE IMMUNE RESPONSE TO BRUCELLOSIS

The clinical heterogeneity seen in brucellosis is largely explained by marked differences in host immune responses [15]. These differences involve variations in humoral and cellular immunity, cytokine production patterns, and immune cell function, all of which are shaped by genetic predisposition and previous exposure to infections. Emerging technologies such as transcriptomic profiling and single-cell sequencing are providing new insights into the biological basis of this variability [26–29]. In most cases, *Brucella* infection induces a humoral immune response dominated by IgG1 and IgG3 antibodies; however, individual antigen recognition patterns vary considerably among patients [20]. Despite the presence of specific antibodies, humoral immunity alone is generally insufficient to eliminate the pathogen. This limitation is primarily due to the intracellular localization of *Brucella*, which allows it to evade antibody-mediated mechanisms.

To persist within the host, *Brucella* employs multiple immune evasion strategies, including inhibition of phagosome–lysosome fusion, suppression of apoptosis in infected cells, and interference with key innate immune pathways such as NF-κB signaling and type I interferon responses. These mechanisms enable long-term intracellular survival and prevent effective immune clearance.

Cell-mediated immunity is central to protection against *Brucella*, particularly Th1 responses characterized by IFN-γ and TNF-α production. However, immune responses vary significantly between individuals, with some patients showing a predominance of Th2 responses or increased regulatory T cell activity [31]. Such shifts can weaken host defense, as Th2- or Treg-dominated immunity suppresses the inflammatory responses required for bacterial elimination. Additional variability arises from differences in innate immune signaling, including altered Toll-like receptor (TLR) expression and downstream pathway activity, which influence the magnitude of inflammatory and adaptive responses. Moreover, host-related factors such as genetic background and mucosal immune integrity further affect susceptibility and vaccine responsiveness. These findings emphasize the importance of individualized approaches in both prevention and treatment strategies for brucellosis.

Conclusion. In conclusion, brucellosis represents a multifaceted infectious disease that requires integrated strategies combining improved diagnostics, innovative immunotherapeutic approaches, effective vaccination, and strengthened epidemiological control. A deeper understanding of its immunopathogenesis is essential for the development of next-generation interventions aimed at achieving long-term disease control and eventual eradication.

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