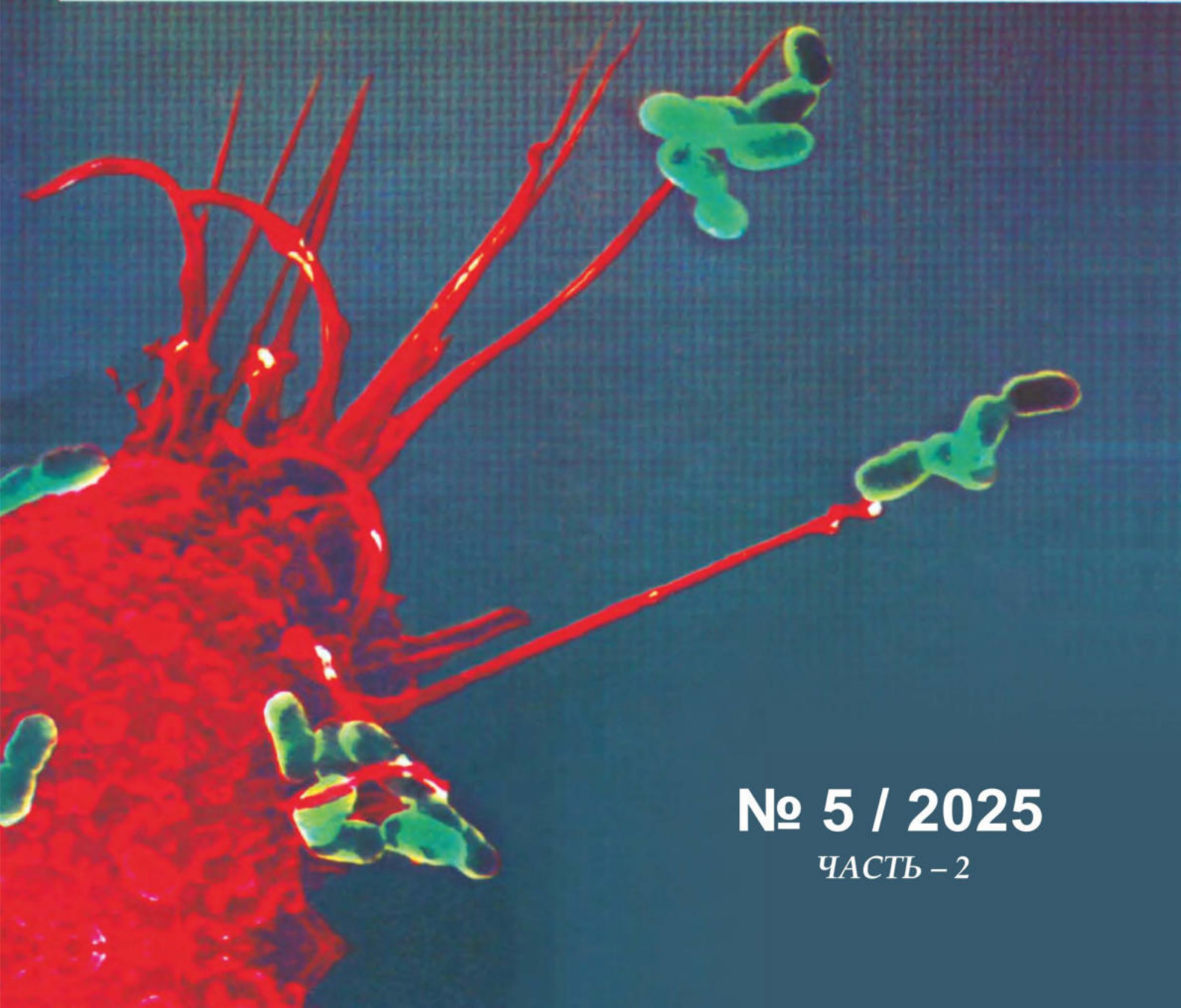
ISSN 2181-5534

ИНФЕКЦИЯ, ИММУНИТЕТ и ФАРМАКОЛОГИЯ



№ 5 / 2025

ЧАСТЬ – 2

ИНФЕКЦИЯ, ИММУНИТЕТ и ФАРМАКОЛОГИЯ

Научно-практический журнал

5/2025

Журнал основан в 1999 г.

Часть – 2

Ташкент – 2025

УДК: 616-053.2: 616.72-002.772

CONTEMPORARY ASPECTS OF THE MECHANISMS OF PATHOGENESIS OF JUVENILE IDIOPATHIC ARTHRITIS

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Key words: Juvenile idiopathic arthritis, etiology, pathogenesis

Juvenile rheumatoid arthritis (JRA) or Juvenile idiopathic arthritis (JIA) represents the most prevalent chronic systemic autoimmune inflammatory disorder of unidentified etiology, occurring in individuals younger than 16 years and persisting for at least six weeks [3,34]. This condition encompasses all forms of chronic childhood arthritis, involving not only the joints but also extra-articular structures such as the eyes, skin, and internal organs, which may ultimately result in disability or even mortality [1,15].

Although considerable progress has been made in elucidating the mechanisms underlying local and systemic inflammation in JRA, the primary initiating triggers of the disease process remain largely unidentified. The pronounced heterogeneity of JRA subtypes poses substantial challenges to investigating its etiology and pathogenic pathways, leaving the initiating factors unresolved [12,19,35]. Current evidence suggests that the onset of JRA is shaped by a combination of genetic, epigenetic, and environmental influences, including infectious agents, vaccinations, antibiotic exposure, vitamin D deficiency, psychological stress, and physical trauma, among others [7,18,29].

The genetic background of JRA demonstrates subtype-specific variability and is generally classified into two principal categories: HLA-associated genes and non-HLA genes. For most JRA subtypes, a pronounced association has been established with HLA loci, which are fundamentally involved in the regulation of antigen-dependent immune mechanisms [6,9].

Accumulating evidence indicates that non-HLA genetic predisposition plays a pivotal role in the initiation of inflammatory responses culminating in tissue damage. A range of genes has been implicated in the pathogenesis of JRA, including those encoding cytokines (TNF, IL2, IL10, IL6), macrophage migration inhibitory factor (MIF), protein tyrosine phosphatase (PTPN22), signal transducer and activator of transcription-4 (STAT4), solute carrier family 11 member 1 (SLC11A1, also known as NRAMP1), and WNT1-inducible signaling pathway protein 3 (WISP3) [9]. Furthermore, polymorphisms in genes encoding endoplasmic reticulum aminopeptidases (ERAP1 and ERAP2) have

been associated with a predisposition to enthesitis-related arthritis (ERA), whereas variants in IL1, IL6, IL10, and MIF genes confer an elevated risk for systemic JRA (sJRA), a subtype considered genetically distinct from other JRA forms [19].

According to current evidence, genetic factors explain only a limited proportion (10–25%) of disease causation, while environmental influences of unknown nature are considered the primary contributors [26]. Certain studies have demonstrated that prenatal exposure to environmental toxins is associated with the early programming and subsequent development of childhood diseases [17].

Multiple investigations have examined the relationship between exposure to environmental pollutants and the development of rheumatic diseases in pediatric populations [11,32].

Twin studies involving monozygotic and dizygotic pairs have underscored the role of environmental antigens and HLA-associated immune mechanisms in the pathogenesis of JRA [31]. Identification of potential environmental risk factors is considered essential for the development of preventive strategies against JRA.

It is hypothesized that microbial antigens, upon contact with mucosal surfaces, contribute to the early programming of immune responses [25].

According to M. Aslan et al., infectious agents represent the most critical environmental determinants; however, psychological stress and physical trauma are likewise regarded as relevant factors in the disease etiology [2].

The relationship between mucosal microbiota and mucosal immune responses in JRA remains insufficiently characterized. Certain mucosal alterations observed in JRA mirror those described in type 1 diabetes mellitus (T1DM) and Crohn's disease, including HLA-DR expression within intestinal crypts and enhanced intestinal permeability [8,24]. Furthermore, the risk of developing Crohn's disease and T1DM has been associated with prior exposure to antibacterial agents [28,35].

The postnatal period represents a critical window during which the immune system is programmed to establish tolerance toward microbial and dietary antigens [22]. Colonization of the neonatal mucosa by commensal bacteria during this phase facilitates the induction of intestinal tolerance. Disruption of this process, however, may occur through exposure to agents such as antibiotics, which perturb mucosal homeostasis and induce long-term alterations in commensal microbial composition. Such modifications of the fecal microbiota have been associated with the development of polyarticular JRA as well as rheumatoid arthritis (RA) [14].

However, research examining the link between childhood rheumatic diseases and exposure to inhaled pollutants during pregnancy and the period from birth to diagnosis is still scarce [28].

The concept that various microbes colonizing or infecting not only mucosal surfaces such as the oral cavity but also the respiratory tract and intestines can trigger autoimmune processes leading to chronic arthritis and JRA was first formulated at the beginning of the last century [8].

Barr virus, parvovirus B, rubivirus, hepatitis B virus) and bacteria (Salmonella spp., Shigella spp., Campylobacter

spp., S. pyogenes, B. henselae, M. pneumoniae, Chlamydophila pneumonia) have been reported as causative factors provoking JRA [29,30].

RR Mistry found that gastrointestinal infection, which leads to loss of gut microbiome diversity and disruption of tryptophan metabolism, increases the risk of ERA [22].

S. W Bell et al. reported that maternal smoking during pregnancy increases the likelihood of immune imbalance during fetal development, leading to the onset and progression of childhood arthritis [3,4]. In contrast, some beneficial factors such as breastfeeding and having siblings in the family may reduce the risk of developing JRA [13].

Antibiotic use has been found to be associated with JRA [33,36]. E. Kindgren et al. showed that the odds of developing JRA were three times higher in those exposed to antibiotics during the first 3 years of life compared with those who were not (aOR 3.17; 95% CI 1.11–9.03, p = 0.031). The corresponding odds of developing JRA were more than two times higher in those exposed to antibiotics during the first 5 years of life compared with those who were not exposed (aOR 2.18; 95% CI 1.36–3.50, p = 0.001). Furthermore, the odds of developing JRA were 78% higher in those exposed to antibiotics during the first 8 years of life compared with those who were not exposed (aOR 1.78; 95% CI 1.15–2.73, p = 0.009) [16].

It should be noted that many authors believe that systemic JRA differs from other subsets because it recognizes dysregulation of the innate immune response as the predominant pathogenic factor [23].

Patients with JRA present with systemic symptoms associated with macrophage activation syndrome (MAS), a potentially life-threatening condition with histopathological features that include accumulation of terminally differentiated macrophages with high hemophagocytic activity [21,27].

Currently, the limitations of the ILAR classification scheme are relevant and include the lack of association with pathogenesis, molecular pathways and response to therapy [10]. In addition, there is a significant unclassified cohort of patients with JRA onset before 6 years of age and a female predominance, having specific features that include symmetric arthritis, iridocyclitis, ANA and HLA-DR8 positivity [5] .

A recent history of gastrointestinal or urinary tract infection, the presence of bowel inflammation evidenced by elevated fecal calprotectin concentrations, as well as sacroiliitis with spinal inflammatory changes and enthesitis identified by MRI, serve as key diagnostic indicators of ERA [20].

In summary, the etiopathogenesis of juvenile idiopathic arthritis remains multifactorial, controversial, and poorly understood. Genetic predisposition, environmental factors, microbiota, and innate and adaptive immune mechanisms combine to form a complex pathogenetic cascade. A better understanding of the molecular and immunological basis of the disease is crucial for the development of more effective diagnostic criteria and targeted therapies.

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РЕЗЮМЕ
СОВРЕМЕННЫЕ АСПЕКТЫ МЕХАНИЗМОВ ПАТОГЕНЕЗА ЮВЕНИЛЬНОГО ИДИОПАТИЧЕСКОГО АРТРИТА

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Ключевые слова: Ювенильный идиопатический артрит, этиология, патогенез

Ювенильный ревматоидный артрит (ЮРА), более широко обозначаемый термином «ювенильный идиопатический артрит» (ЮИА), является наиболее распространённой хронической ревматической патологией детского возраста, характеризующейся аутоиммунной природой, прогрессирующим течением и риском деструктивных поражений суставов. Согласно современным данным, патогенез заболевания определяется сложным взаимодействием генетических, эпигенетических и факторов внешней среды. Несмотря на значительные достижения в изучении механизмов локального и системного воспаления, исходные триггерные звенья, инициирующие развитие ЮИА, остаются недостаточно выявленными.

RESUME
YUVENIL IDIOPATIK ARTRIT PATOGENEZI MEXANIZMLARINING ZAMONAVIY JIHATLARI

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Kalit so'zlar: Yuvenil idiopatik artrit, etiologiya, patogenez

Yuvenil revmatoid artrit (YURA), shuningdek "yuvenil idiopatik artrit" (YUIA) atamasi bilan ham keng qo'llanilib, bolalar yoshida eng ko'p uchraydigan surunkali revmatik kasallik hisoblanadi. Kasallik autoimmun tabiatga ega bo'lib, progressiv kechuvi va bo'g'imlarda destruktiv o'zgarishlar rivojlanishi xavfi bilan tavsiflanadi. Zamonaviy tadqiqotlar shuni ko'rsatadiki, kasallik patogenezi genetik, epigenetik va tashqi muhit omillarining murakkab o'zaro ta'siri bilan belgilanadi. Mahalliy va tizimli yallig'lanish jarayonlarini o'rganishda katta yutuqlarga erishilganiga qaramay, YuIAning rivojlanishini boshlaydigan asosiy trigger omillar hanuzgacha to'liq aniqlanmagan.

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Научно-практический журнал

5/2025

Часть № 2

Международный стандартный номер издания – ISSN 2181-5534
Лицензия № 0293 выдана Агентством Республики Узбекистан по печати и информации при Администрации Президента Республики Узбекистан от 23.10.2019 г.

Отпечатано в ***ЧП «PULATOV I.N.»***
Подписан к печати 10.10.2025 г.
Формат А4. Объём 300 стр.
Тираж: 60 экз.
Цена договорная.

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Наш сайт: https://infection-immunity.uz
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