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Original study article

Role of TLR7 in the immunopathogenesis of psoriasis and psoriatic arthritis

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ABSTRACT

BACKGROUND: Toll-like receptor 7 (TLR7) plays a significant role in the development of inflammation in psoriasis. However, there are very few data on the role of different polymorphic markers of the *TLR7* gene in psoriasis and psoriatic arthritis.

AIM: Study of the role of polymorphic marker rs179009 of *TLR7* gene in patients with severe psoriasis.

MATERIALS AND METHODS: The study was conducted during the period of 2016–2024. The analysis of innate immunity indicators in the study group was performed by obtaining RNA in peripheral venous blood and polymorphisms of the gene recognizing marker rs179009 of the TLR7 receptor were investigated by polymerase chain reaction with TaqMan probes. To assess the area and severity of psoriatic lesions of the skin process, we used a standardised method of assessment — determination of the PASI index.

RESULTS: The main group consisted of 168 patients (100%) with psoriasis. Of these, 45 (26.8%) were women and 123 men (73.2%). The average age of the patients was 54.0±14.0 years. The mean duration of psoriasis course was 11.8±0.6 years. The mean psoriasis area and severity index (PASI) value was 17.7±7.2. When analyzing the genotypes of polymorphic marker rs179009 in the *TLR7* gene in patients with psoriasis of different severity, it was revealed that heterozygote CT was significantly more frequent in patients with mild psoriasis, and homozygote CC and homozygote TT were registered at PASI >10 (p <0.05). The C allele of the studied marker was significantly more frequent in patients with late psoriasis debut and late development of psoriatic arthritis (p <0.01). In contrast, the T allele was significantly more frequent in patients with early debut of psoriasis and psoriatic arthritis (p <0.01). When analyzing the genotypes of polymorphic marker rs179009 in the *TLR7* gene, the occurrence of homozygous CC and TT genotypes was also found to have statistically significant differences. The CC genotype was more frequently registered in patients with late onset of psoriasis and late onset of arthritis (p <0.05). In contrast, the TT genotype was significantly more frequently registered in patients with the debut of skin and joint process before 40 years of age (p <0.05).

CONCLUSION: In our study it was found that homozygous carriage of CC and TT genotypes of polymorphic marker rs179009 in the TLR7 gene predisposes to a more severe course of the skin process in psoriasis. Also, the presence in the patient of allele C or homozygote CC of marker rs179009 in the *TLR7* gene is a predictor of late onset of the skin process and the development of arthritis. While the presence of the T allele or TT homozygote statistically significantly predisposes to early onset of psoriasis and early onset of joint symptoms with the development of psoriatic arthritis.

Keywords: psoriasis; psoriatic arthritis; toll-like receptors; polymorphic marker rs179009 of the *TLR7* gene.

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Оригинальное исследование

Роль TLR7 в иммунопатогенезе псориаза и псориатического артрита

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АННОТАЦИЯ

Обоснование. Толл-подобный рецептор 7 (TLR7) играет значимую роль в развитии воспаления при псориазе, однако крайне мало данных о роли различных полиморфных маркеров гена *TLR7* при псориазе и псориатическом артрите.

Цель исследования — изучение роли полиморфного маркера rs179009 гена *TLR7* у больных тяжёлыми формами псориаза.

Материалы и методы. Анализ показателей врождённого иммунитета у участников исследования проводился путём получения РНК из периферической венозной крови; методом полимеразной цепной реакции с TaqMan зондами исследовались полиморфизмы гена *TLR7* (rs179009). Для оценки площади и тяжести псориатических поражений кожного процесса использован стандартизованный метод оценки — определение индекса PASI.

Результаты. Основную группу составили 168 больных псориазом, из них женщин 45 (26,8%), мужчин — 123 (73,2%). Средний возраст пациентов 54,0±14,0 года. Средняя длительность течения псориаза 11,8±0,6 года. Среднее значение индекса площади и тяжести псориатических поражений PASI 17,7±7,2. При анализе генотипов полиморфного маркера rs179009 в гене *TLR7* выявлено, что гетерозигота CT значимо чаще встречалась у пациентов с лёгкой степенью течения псориаза, а гомозиготы CC и TT регистрировались при PASI >10 (p <0,05). Аллель C изучаемого маркера достоверно чаще встречался у пациентов с поздним дебютом псориаза и поздним развитием псориатического артрита (p <0,01), аллель T, напротив, — достоверно чаще у пациентов с ранним дебютом псориаза и ранним развитием псориатического артрита (p <0,01). Анализ генотипов полиморфного маркера rs179009 в гене *TLR7* показал, что встречаемость гомозиготных генотипов CC и TT также имеет статистически значимые различия. Генотип CC чаще регистрировался у больных с поздним дебютом псориаза и поздним присоединением артрита (p <0,05), генотип TT, напротив, достоверно чаще регистрировался у больных с дебютом кожного и суставного процесса до 40 лет (p <0,05).

Заключение. В нашем исследовании обнаружено, что гомозиготное носительство генотипов CC и TT полиморфного маркера rs179009 в гене *TLR7* предрасполагает к более тяжёлому течению кожного процесса при псориазе. Наличие у больного аллеля C или гомозиготы CC маркера rs179009 в гене *TLR7* является предиктором позднего начала кожного процесса и развития артрита, в то время как наличие аллеля T или гомозиготы TT статистически значимо предрасполагает к раннему дебюту псориаза и раннему присоединению суставной симптоматики с развитием псориатического артрита.

Ключевые слова: псориаз; псориатический артрит; толл-рецепторы; полиморфный маркер rs179009 гена *TLR7*.

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BACKGROUND

Psoriasis is a chronic disease of multifactorial nature, with a predominant genetic component. It is characterized by accelerated proliferation and impaired differentiation of keratinocytes, and an imbalance between pro-inflammatory and anti-inflammatory cytokines, leading to frequent pathologic changes in the musculoskeletal system [1]. Currently, psoriasis is the most common chronic dermatosis, affecting 1%–2% of the population in developed countries.

The molecular mechanisms underlying the pathogenesis of psoriasis remain to be elucidated. The functions of various components of the innate immune system in the development of psoriasis, particularly the role of toll-like receptors (TLRs), are subjects of active research. TLRs represent a class of receptors within the innate immune system that identify pathogen-associated molecular patterns, thereby activating the immune response. Therefore, TLRs serve as critical sensors of diverse viral and bacterial infections. In addition, TLRs detect molecular markers associated with damage of endogenous origin [2]. Several studies demonstrated that TLRs may function as effectors of psoriasis. TLRs were observed to recruit adaptor proteins and activate transcription factors, which in turn produce inflammatory cytokines that contribute to the initiation of adaptive immune responses [3].

In humans, the TLR family comprises 10 types of receptors that are expressed on the cell surface and within the cell. Intracellular TLRs, particularly TLR3, TLR7, TLR8, and TLR9, are capable of recognizing nucleic acids [4]. TLR7 was shown to detect single-stranded RNA and subsequently facilitate its transportation to endosomes [5]. Several recent scientific studies have indicated that TLR7 activation may contribute to the development of psoriasis [6]. However, the exact mechanisms of such activation are not fully understood. The *TLR7* gene is responsible for encoding a transmembrane protein which consists of 1049 amino acids. The gene is located in the region of chromosome X 12.87-12.89 and contains one exon [7]. TLR7 is capable of recognizing single-stranded RNAs (ssRNAs), including those found in some viruses. TLR7 activation may lead to the activation of various immune cells, such as dendritic cells and macrophages, resulting in the release of pro-inflammatory cytokines. Pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin (IL) 6, are potential stimulants for keratinocytes, leading to their proliferation and accelerated differentiation [6–8].

The fact that TLR7 activation may contribute to joint inflammation through activation of synovial macrophages and dendritic cells is important in understanding the pathogenesis of psoriasis and PsA. This results in the release of pro-inflammatory cytokines, which can stimulate joint inflammation and lead to joint tissue damage [9]. TLR7 activation may occur in response to environmental conditions and biophysical factors, often influenced by genetic predispositions. This reaction of innate and adaptive immune response leads to increased secretion of various cytokines such as IL-1, IL-6, TNF-α, IL-17, and IL-23 [10–12]. Furthermore, the activation of T cells and macrophages is regarded as a prerequisite for the initiation of inflammatory and destructive processes in joints. The pathogenesis of joint inflammation in PsA is outlined as follows: dendritic cells induce T cell differentiation by presenting antigens and secreting various pro-inflammatory cytokines. An increased expression of TLR-2 was detected in immature dendritic cells of patients with PsA [13]. Patients diagnosed with PsA exhibit an elevated proportion of immature myeloid dendritic cells in the synovial fluid compared with plasmacytoid dendritic cells. In PsA, the stimulation of TLRs leads to the polarization of T cells toward the Th1 subpopulation, which subsequently increases the production of interferon gamma (IFN-γ), TNF-α, and IL-2. Plasmacytoid dendritic cells, in turn, generate cytokines such as IFN-γ, TNF-α, IL-12, and IL-23, which subsequently act as signals for clonal proliferation of both CD4+ and CD8+ T cells. Activated macrophages are involved in several proinflammatory processes in the synovial membrane of joints. For example, skin inflammation induced by TLR-7 ligand in mouse models was associated with infiltration of CD68+ macrophages and stimulation of inflammatory cytokine expression in joints. This study demonstrated that macrophages may contribute to the inflammatory process in PsA and may be a critical factor in the transition of inflammation from skin to joints [9]. In contrast, TLR-7 activation was shown to increase the ratio of pro-inflammatory (M1) to anti-inflammatory (M2) macrophages in psoriatic skin lesions [14]. Macrophages with an M1 phenotype in PsA secrete pro-inflammatory cytokines that activate T and B cells through antigen presentation and stimulate bone resorption [15]. Mast cells, located in the synovial membrane of joints, were shown to induce angiogenesis, neutrophil recruitment, and synovial fibroblast proliferation, indicating that these cells may actively contribute to inflammatory arthritis. In the synovial membrane of peripheral spondyloarthritis, mast cells are the predominant source of IL-17A [16].

TLR7 induces the production of the membrane-bound chemokine CXCL16 by dendritic cells, which is expressed on their surface. Lu et al. [17] demonstrated that this chemokine is overexpressed in skin lesions of pustular psoriasis and that neutrophils express a receptor for this chemokine. CXCL16 is known to activate the secretion of inflammatory factors IL-8 and TNF-α by neutrophils.

The co-culture of neutrophils with dendritic cells that were treated with a TLR7 inhibitor or TLR7 agonist demonstrated that TLR7 plays a regulatory role in the activation, migration, and apoptosis of neutrophils. Based on these studies, the authors suggested that TLR7 may influence the release of CXCL16 by dendritic cells and the pro-inflammatory effects of neutrophils by interfering with the signaling pathway of the myeloid differentiation primary response gene 88 (MyD88).

Activation of the TLR7-MyD88-DC-CXCL16 pathway results in neutrophil migration to skin lesions, their activation, and the inflammatory response in pustular psoriasis.

Accordingly, the analysis of recent Russian and foreign studies indicate that TLR7 plays a significant role in the development of inflammation in psoriasis and PsA. However, there is limited data on the role of various polymorphic markers of the *TLR7* gene.

In this study, the polymorphic marker rs179009 in the *TLR7* gene was examined, along with its association with psoriasis of varying severity.

The role of TLR7 markers in various diseases has been a subject of active investigation in Russia and abroad [18–20]. In particular, Galimova et al. [7] analyzed the association of polymorphic variants (rs179003, rs179008, rs179020, rs850632, and rs12013728) of the *TLR7* gene with the risk of psoriasis in individuals of Tatar ethnicity and demonstrated that, among all the studied polymorphic variants of the *TLR7* gene, only rs179008 significantly correlated with the risk of psoriasis. However, studies of the polymorphic marker rs179009 in the *TLR7* gene and its associations in patients with psoriasis and PsA have not yet been conducted.

The aim of the study was to investigate the role of the polymorphic marker rs179009 in the *TLR7* gene in patients with severe psoriasis.

MATERIALS AND METHODS

Study design

A case-control study was conducted.

The primary endpoint was to detect differences in alleles and genotypes of the polymorphic marker rs179009 in the *TLR7* gene in patients with psoriasis and PsA according to severity and time of disease onset. There were no interim endpoints.

Eligibility criteria

Inclusion criteria: first or previously diagnosed psoriasis; age 18 years and older; patients of different sexes.

Non-inclusion criteria: failure to meet the inclusion criteria; severe comorbidities or other autoimmune diseases in the patient's history; patient's unwillingness to participate in the study for any reason.

Exclusion criteria: patient's willingness to discontinue participation in the study.

Study setting

The study was conducted in the Branch No. 8 of the Burdenko Main Military Clinical Hospital of the Ministry of Defense of the Russian Federation; the European Medical Center; and the Korolenko Clinic of the State Budgetary Healthcare Institution Moscow Scientific and Practical Center of Dermatovenereology and Cosmetology of the Moscow Healthcare Department.

Study duration

The study was conducted between 2016 and 2023.

Intervention description

All patients underwent a comprehensive clinical and laboratory evaluation, including family and medical history, physical examination, clinical blood count, urinalysis, and blood biochemistry.

The assessment of the area and severity of psoriatic lesions was conducted using the PASI (Psoriasis Area and Severity Index), a standardized assessment method. According to clinical guidelines [1], a PASI of ⩽10 points indicates a relatively mild disease, a PASI of 10–19 points indicates a moderate disease, and a PASI of >20 points indicates a severe psoriatic disease.

The analysis of innate immunity indicators in the study group was performed by obtaining RNA from peripheral venous blood using the kit for RNA isolation from clinical material (Interlabservice, Russia). Polymorphisms of the TLR7 gene (rs179009) were investigated by polymerase chain reaction (PCR) with TaqMan probes. The reverse transcription reaction was performed using the Reverse Transcription Kit (Syntol, Russia) according to the manufacturer's instructions. Subsequently, real-time PCR (RT-PCR) was conducted using SYBR Green dye (DT-96), with the primers and reagents for the PCR being synthesized by Syntol (Russia).

Main study outcome

The primary outcome of the study was to detect differences in allele and genotype frequencies of the polymorphic marker rs179009 in the *TLR7* gene in patients with psoriasis and PsA.

There were no other study outcomes.

Subgroup analysis

The study group comprised 168 patients (100%) with moderate to severe psoriasis, including 45 women (26.8%) and 123 men (73.2%), with a mean age of 54.0±14.0 years. The diagnosis of PsA was confirmed in 31 (18.5%) cases using CASPAR (Classification Criteria for Psoriatic Arthritis) criteria. Consequently, the study group was divided into two subgroups. Subgroup 1 comprised patients with skin manifestations of psoriasis exclusively (n=137), while subgroup 2 consisted of patients with PsA (n=31).

Methods for registration of outcomes

Peripheral blood samples were obtained from all patients, from which RNA was extracted, and polymorphisms of the TLR7 recognition receptor gene were studied by PCR using TaqMan probes. After RT-PCR, the dependence of fluorescence intensity on the number of amplification cycles was obtained. The growth of the curve indicated the accumulation of amplificate. The data obtained after PCR amplification for each of the genes studied were recalculated by the ΔΔCt method relative to the housekeeping β-actin gene.

The level of gene expression was determined relative to the reference sample using the $2^{-\Delta\Delta Ct}$ method. The results were expressed in relative units, indicating how many times the gene expression changed in the test sample compared to the reference sample. The β-actin gene, which is a housekeeping gene with a stable expression level in different cells regardless of conditions, was used as an internal control.

Ethical review

The study was approved by the Ethics Committee of the Medical Institute of the Federal State Autonomous Educational Institution of Higher Education Patrice Lumumba People's Friendship University of Russia (Protocol No. 13 dated December 15, 2022).

Statistical analysis

Statistical analysis and visualization of the obtained data were performed using the R 4.3.0 statistical computing environment (R Foundation for Statistical Computing, Vienna, Austria) and the Microsoft Excel program of the Microsoft Office 2016 package.

The following descriptive statistics were presented: the number of observations (relative frequency) for categorical variables, the mean (± standard deviation) and the median (1st and 3rd quartiles) for quantitative variables. The Mann–Whitney test was used to compare groups with respect to quantitative variables, and the Fisher's exact test was used for categorical variables. When examining intergroup differences, the mean differences were estimated with corresponding 95% confidence intervals (95% CI) for quantitative variables, odds ratios (OR) were estimated with corresponding 95% CI for binary variables, and proportional OR were estimated with corresponding 95% CI (using ordinal regression) for ordinal variables. Two-factor linear, logistic, and regression models were used to obtain these estimates adjusted for disease duration.

The analysis of allele and genotype frequencies in the studied groups was calculated using the χ^2 test. If the expected value in any of the cells was <10, the χ^2 test was calculated using the Yates's correction. If the expected value was <5, the Fisher's exact test was used for analysis. The OR and 95% CI were calculated to quantify the association between PsA and carriage of an adverse polymorphic marker.

Results with p <0.05 were considered statistically significant.

RESULTS

Participant characteristics

The study group (n=168, 100%) was divided into two subgroups. Subgroup 1 included 137 patients with skin manifestations of psoriasis only, while subgroup 2 included 31 patients with PsA. The mean age of patients was 54.0±14.0 years, ranging from 53.8±14.4 years for subgroup 1 to 54.7±12.5 years for subgroup 2. The mean duration of psoriasis was 25.7±16.6 years, and the mean duration of PsA was 8.3±9.5 years. Table 1 presents the sex and age characteristics of the study participants. Comparative analysis showed that PsA was statistically significantly more frequently diagnosed in women than in men (OR 3.34; 95% CI: 1.48–7.59; p=0.006). Thus, 30 (66.7%) out of 45 women in the study group were diagnosed with psoriasis and 15 out of 45 (33.3%) were diagnosed with PsA. In men, psoriasis was diagnosed in 107 (87.0%) of 123 cases and PsA in 16 (13%) of 123 patients. Therefore, PsA was diagnosed 3-fold more frequently in women than in men (p <0.05). The groups were comparable in age.

The mean PASI was 17.7±7.2, indicating a severe course of psoriasis in all patients of the study group. In patients with only skin manifestations of psoriasis, the mean PASI was 17.3±7.2. In patients with PsA, the mean PASI was 19.5±6.9, indicating a more severe skin condition. The distribution of patients in the study group according to the severity of skin involvement is shown in Figure 1. As illustrated, 49.4% of patients in the study group exhibited a PASI ranging from 20 to 30, indicating a severe psoriasis. In subgroup 1, the distribution was as follows: PASI <10 in 24.8%, PASI 10–20 in 25.5%, and PASI 20–30 in 47.4% of patients. Consequently, in subgroup 1, which exclusively comprised skin manifestations

Table 1. Distribution of patients by sex and age (n=168)

Characteristics	Patients			p
	n=168	Subgroup 1 n=137	Subgroup 2 n=31	
Sex: • Female • Male	 45 123	 30 (66.7%) 107 (87.0%)	 15 (33.3%) 16 (13.0%)	 0.006
Age, years	54.0±14.0 55 (43–65)	53.8±14.4 55 (43–65)	54.7±12.5 54 (44–67)	0.925

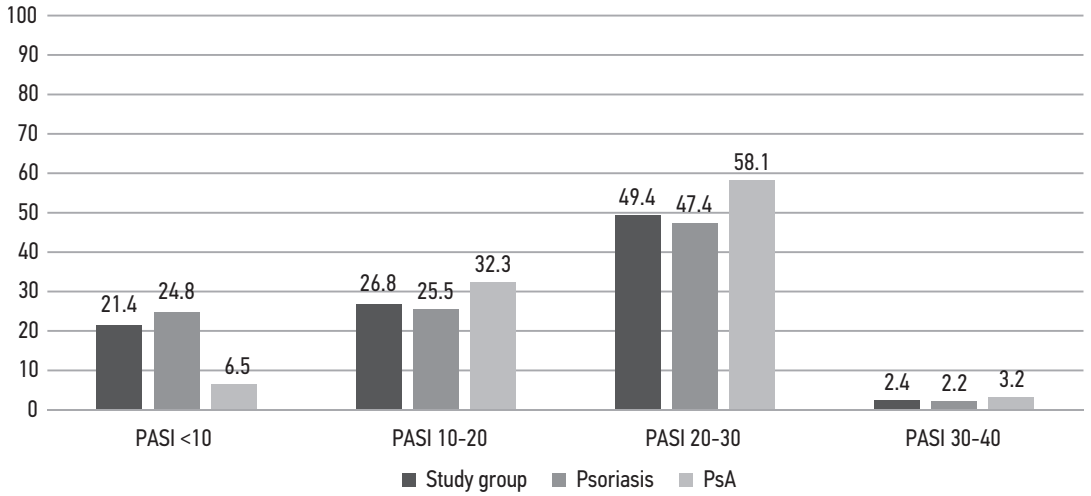

Fig. 1. Distribution of patients depending on the severity of the skin process (*n*=168, %). ПсА — psoriatic arthritis.

of psoriasis, the majority of patients exhibited a medium to severe skin condition. In subgroup 2 (PsA), patients were distributed by severity as follows: PASI <10 in 6.5%, PASI 10–20 in 32.3%, and PASI 20–30 in 58.1% of patients. Therefore, in subgroup 2, as well as subgroup 1, the majority of patients exhibited moderate to severe skin condition. Notably, only 4 patients (2.4%) in the study group had PASI >30 and were excluded from further comparative analysis due to the limited number of cases.

Primary findings

A comparison of the frequency of occurrence of alleles and genotypes of the rs179009 marker in the *TLR7* gene revealed that C and T alleles of the studied marker were found in psoriasis and PsA with approximately equal frequency, with the T allele occurring less frequently in psoriasis than in PsA (0.446 and 0.556, respectively; OR 1.55; 95% CI: 0.76–3.18; p >0.05). In contrast, the C allele was reported more frequently in psoriasis than in PsA (0.554 and 0.444, respectively; OR 1.55; 95% CI: 0.76–3.18; p >0.05) (Fig. 2). Genotype analysis of the polymorphic marker rs179009 in the *TLR7* gene revealed that the CC homozygote was more prevalent in patients with psoriasis than in patients with PsA (0.344 and 0.222, respectively; OR 1.83; 95% CI: 0.56–6.04; p >0.05). Conversely, the TT homozygote was detected less frequently in patients with psoriasis than in those with PsA (0.237 and 0.333, respectively; OR 0.62; 95% CI: 0.21–1.84; p >0.05) (Fig. 2). As illustrated, there is a tendency to detect the C allele and the CC homozygote in patients with psoriasis, while the detection of the T allele and the TT homozygote is more frequent in patients with PsA.

Furthermore, the distribution of the polymorphic marker rs179009 in the *TLR7* gene was examined in relation to the severity of skin condition in patients with psoriasis (see Fig. 3). Figure 3 shows that the C and T alleles of the studied marker occur with approximately equal frequency across various severity of the skin condition. Furthermore, the analysis of the genotypes of the polymorphic marker rs179009 in the *TLR7* gene revealed that the CT heterozygote was found to be significantly more prevalent in patients with mild psoriasis (0.567 cases; OR 2.94; 95% CI: 0.98–8.86). CC and TT homozygotes were predominantly observed in patients with moderate to severe psoriasis. CC homozygotes were identified in only 0.267 cases with PASI <10 and 0.708 cases with PASI >10 (p <0.05). The TT homozygote was recorded in 0.167 cases with PASI <10 and 0.686 cases with PASI >10 (p <0.05). These findings suggest that homozygous carriage of the CC and TT genotypes of the polymorphic marker rs179009 in the *TLR7* gene may predispose individuals to a more severe course of skin psoriasis.

The age of disease onset may vary according to the specific type of psoriasis. Type I psoriasis, for example, is associated with the human leukocyte antigen (HLA) system, specifically HLA Cw6, HLA B13, and HLA B17. This type of psoriasis was observed to manifest in 65% of patients and is characterized by its early onset, occurring between the ages of 18 and 25. In contrast, type II psoriasis, which is not associated with the HLA antigen system, manifests at a later age, typically after 40 [21]. The mean age of psoriasis onset in the present study was 45 (31–58) years, with a minimum age of 11 years and a maximum age of 79 years. Furthermore, more than half of the patients (57.1%) had psoriasis duration of more than a year, and no statistically significant differences were found regarding the age of psoriasis onset between the groups of patients with psoriasis and PsA. The mean age of PsA onset was 52 (35–57) years, with a minimum age of 22 years and a maximum age of 69 years. Notably, 21 (67.7%) patients had PsA at the time of disease onset.

The association between the presence of the polymorphic marker rs179009 in the *TLR7* gene and the age of psoriasis onset was analyzed to assess the influence of the *TLR7* gene on the age of psoriasis onset (Fig. 4). The results demonstrated that the C allele of the studied marker was significantly more

prevalent in patients with late-onset psoriasis. Specifically, in patients with psoriasis onset before and after the age of 40, the frequency of the C allele was 0.400 and 0.632, respectively (OR 0.38; 95% CI: 0.2–0.74; p <0.01). In contrast, the T allele was found to be significantly more prevalent in patients with early-onset psoriasis. Specifically, the T allele was observed at a frequency of 0.600 and 0.368 in patients with psoriasis onset before and after the age of 40, respectively (OR 0.38; 95% CI: 0.2–0.74; p <0.01). In the analysis of the genotypes of the polymorphic marker rs179009 in the *TLR7* gene, the occurrence of homozygous CC and TT genotypes was found to be statistically significant. The CC genotype manifested at a frequency of 0.175 in patients with early-onset psoriasis and 0.395 in patients with late-onset psoriasis (OR 0.32; 95% CI: 0.11–0.92; p <0.05). In contrast, the TT genotype was found to be significantly more prevalent in patients with skin disease onset before the age of 40 compared to those with the onset after the age of 40, with 0.375 and 0.132 cases, respectively (OR 3.96; 95% CI: 1.27–12.35; p <0.05). Thus, the presence of the C allele or homozygous CC marker rs179009 in the *TLR7* gene in a patient is indicative of the late-onset skin disease, while the presence of the T allele or TT homozygote is a statistically significant predictor of the early-onset disease.

Furthermore, a comparative analysis of the frequency of alleles and genotypes of polymorphic marker rs179009 in the *TLR7* gene in patients with PsA revealed significant differences depending on the age of arthritis onset (Fig. 5). Specifically, the T allele was observed to be more prevalent in patients with PsA and early-onset arthritis compared to those with psoriasis and late-onset arthritis, with a frequency of 0.75 and 0.25, respectively (OR 0.11; 95% CI: 0.02–0.58; p < 0.05). The C allele was associated with late-onset arthritis in comparison with the group of patients with psoriasis and early-onset arthritis, with frequencies of 0.75 and 0.25, respectively (OR 0.11; 95% CI: 0.02–0.58; p <0.05). Furthermore, an analysis of the genotypes of the polymorphic marker rs179009 in the *TLR7* gene, depending on the age of disease onset, revealed a trend toward a higher frequency of the TT homozygote in patients with early-onset PsA. CC homozygotes and CT heterozygotes were more prevalent among patients with psoriasis who experienced a late onset of joint symptoms. Specifically, CC homozygotes were observed in 0.1 cases of early-onset PsA and 0.5 cases of late-onset PsA (OR 0.11; 95% CI: 0.01–1.52; p <0.05). Conversely, the CT homozygote was observed in 0.3 cases of early-onset PsA and 0.5 cases of late-onset PsA (OR 0.42; 95% CI: 0.05–3.48; p <0.05).

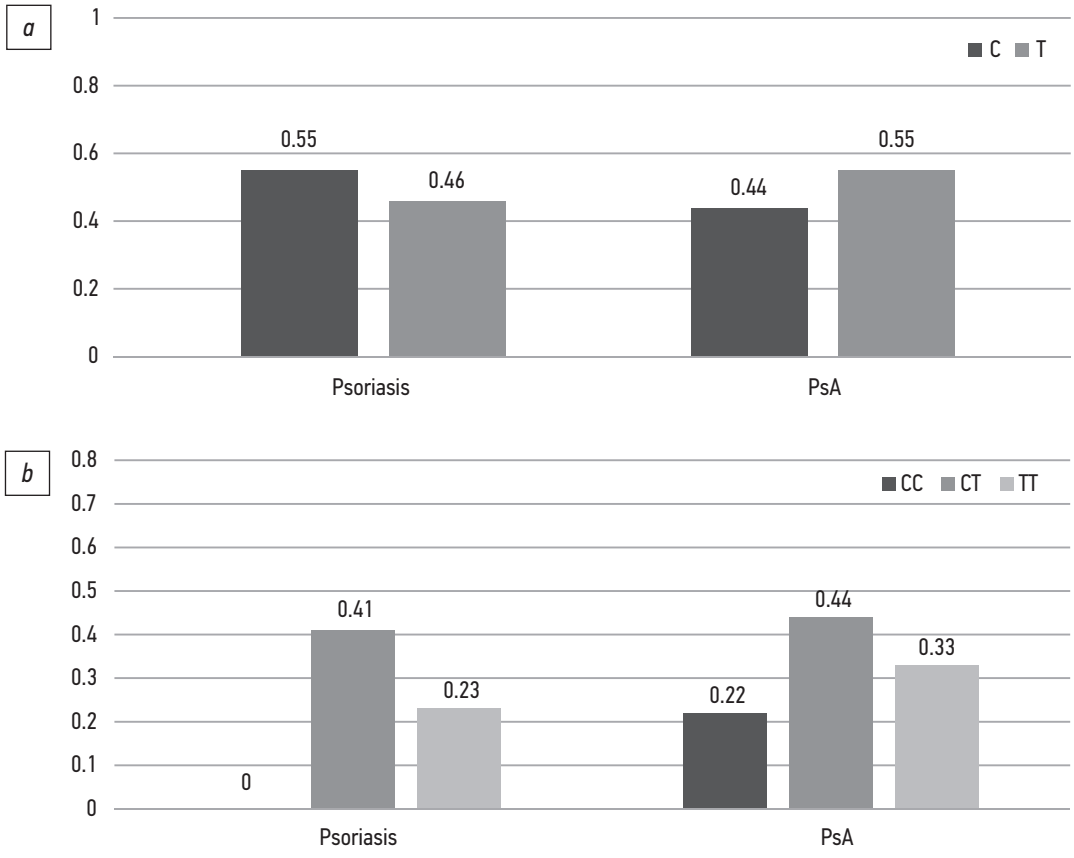

Fig. 2. Distribution of allele (*a*) and genotype (*b*) frequencies of polymorphic marker rs179009 in *TLR7* gene in patients with psoriasis and psoriatic arthritis (n=168). The abscissa axis represents the studied groups, the ordinate axis represents the frequency (p >0.05). ПсА — psoriatic arthritis.

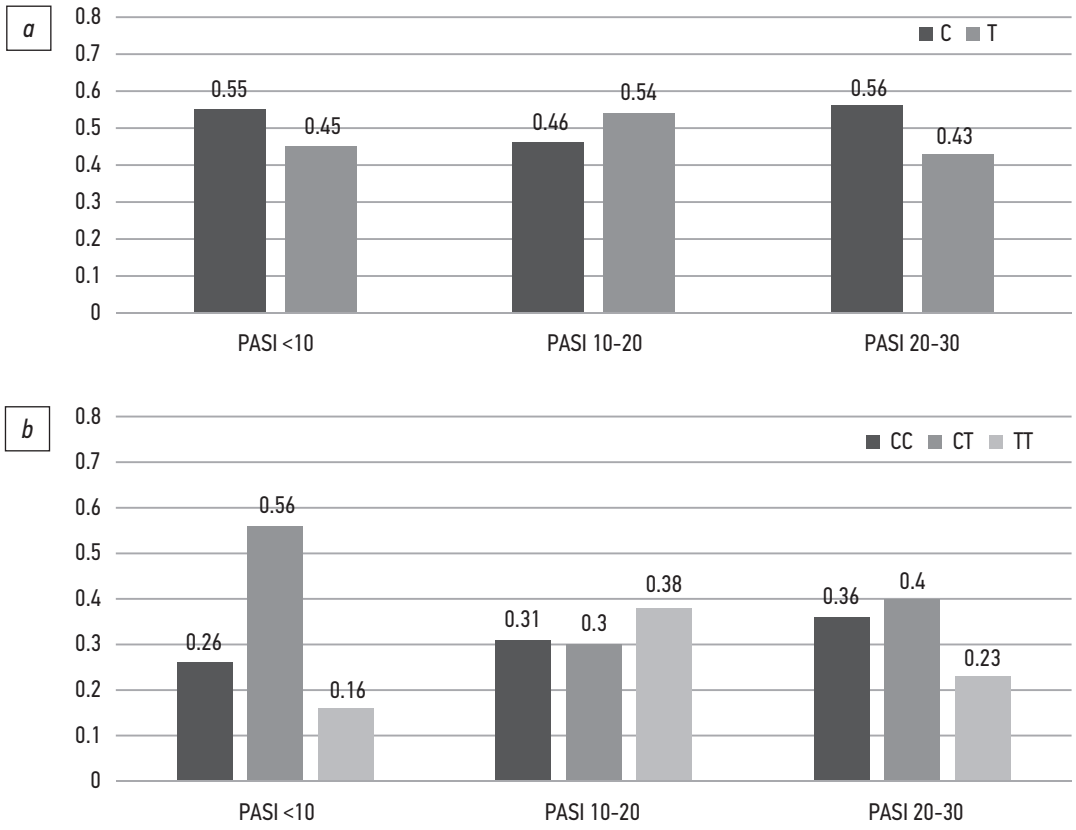

Fig. 3. Distribution of allele (*a*) and genotype (*b*) frequencies of polymorphic marker rs179009 in the *TLR7* gene in psoriasis patients depending on the severity of the skin process (*n*=164). The abscissa axis represents the studied groups, the ordinate axis represents the frequency (p >0.05).

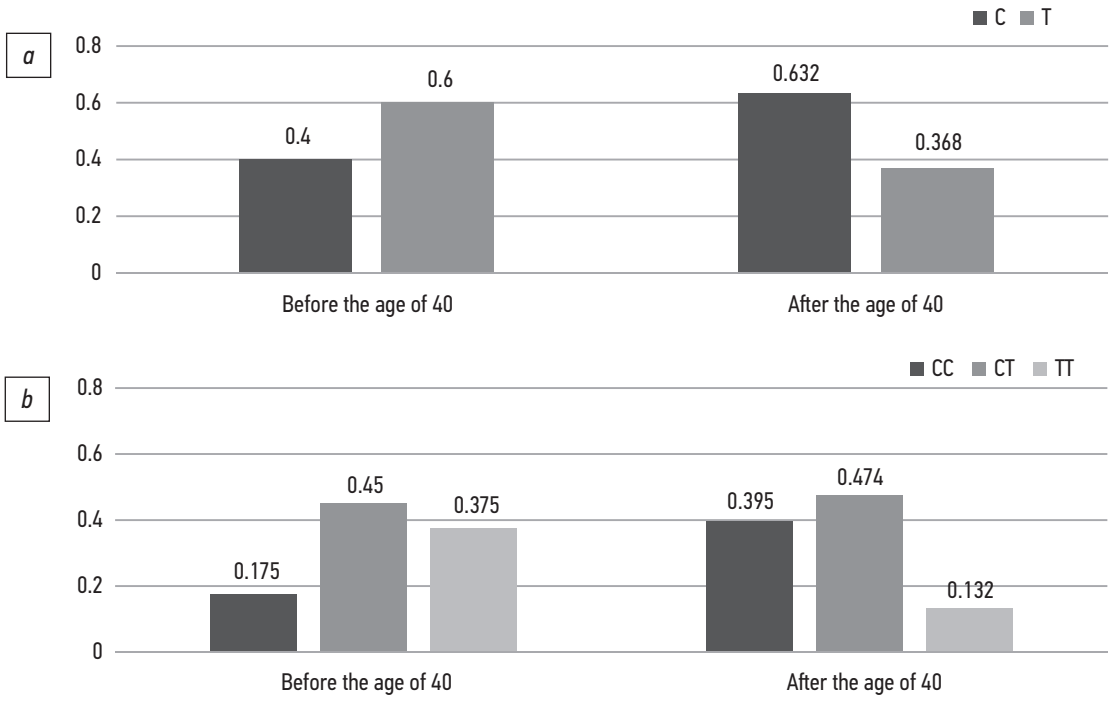

Fig. 4. Distribution of allele (*a*) and genotype (*b*) frequencies of polymorphic marker rs179009 in the *TLR7* gene in psoriasis patients depending on the age of psoriasis debut (*n*=168). The abscissa axis represents the studied groups, the ordinate axis represents the frequency (p <0.05).

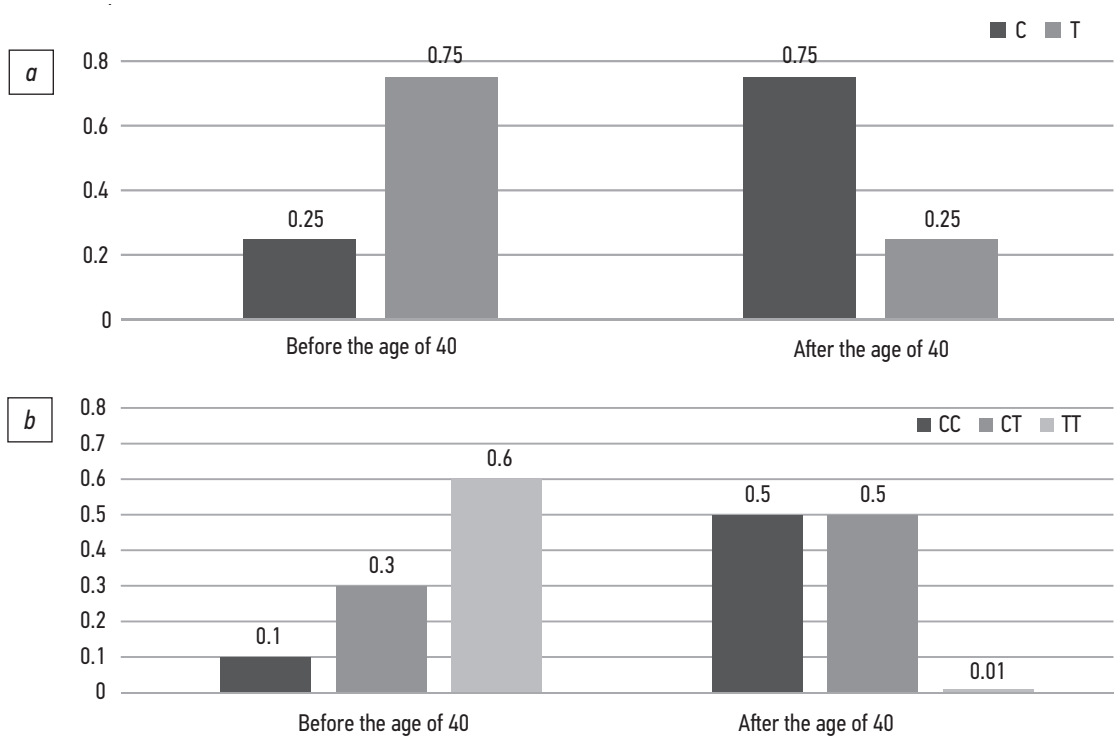

Fig. 5. Distribution of allele (*a*) and genotype (*b*) frequencies of polymorphic marker rs179009 in *TLR7* gene in patients with psoriatic arthritis depending on the age of psoriasis debut (n=31). The abscissa axis represents the studied groups, the ordinate axis represents the frequency (p <0.05).

Adverse events

No adverse events were reported.

DISCUSSION

Summary of the primary study results

This study was the first to analyze the frequency of occurrence of alleles and genotypes of the rs179009 marker of the *TLR7* gene in patients with psoriasis and PsA. The study indicates that the T allele and the TT homozygote are not only more prevalent in patients with psoriasis and PsA compared to healthy individuals, but they also predominate in patients with PsA. In other words, the presence of the TT homozygote in patients with PsA significantly increases the risk of a more severe course of psoriasis and frequently results in triggering synovial inflammation in joints.

Discussion of the primary study results

Activated TLR7 is known to be able to stimulate dendritic cells and macrophages, which in turn leads to the release of pro-inflammatory cytokines (TNF-α, IL-6). These cytokines, in turn, stimulate the proliferation and accelerated differentiation of keratinocytes [6–8]. Furthermore, TLR7 activation may contribute to the triggering of joint inflammation through the activation of synovial macrophages and dendritic cells, leading to the release of pro-inflammatory cytokines that can stimulate joint inflammation and result in joint tissue damage [9]. Consequently, TLR7 activation plays a pivotal role in the onset and exacerbation of psoriatic process.

The role of the TLR7 receptor in various infectious and immune-mediated diseases, including hepatitis C, human immunodeficiency virus infection, systemic lupus erythematosus, and bronchial asthma, has been a subject of recent study [18, 20]. Galimova et al. [7] demonstrated a significant correlation between the polymorphic variant rs179008 of the *TLR7* gene and the risk of psoriasis. Specifically, the presence of the T allele (rs179008) in the *TLR7* gene significantly increases the risk of the disease and predisposes to the late onset of skin condition. However, current literature lacks evidence regarding the association of polymorphic marker rs179009 in the *TLR7* gene with psoriasis and PsA.

When analyzing the occurrence of the polymorphic marker rs179009 in the *TLR7* gene in relation to the severity of the skin condition in patients with psoriasis, a significant association of CC and TT homozygotes with the severe course of skin condition was found. Thus, CT heterozygous carriage predisposes to a mild course of psoriasis with the formation of psoriatic lesions of a severity corresponding to PASI <10. On the contrary, homozygous CC and TT carriage was a significant marker for moderate and severe psoriasis with psoriatic lesion severity corresponding to PASI >10.

An evaluation of the association of alleles and polymorphisms of the *TLR7* gene with the age of psoriasis onset revealed that the C allele and the CC genotype were

statistically significantly associated with late-onset psoriasis (after 40 years of age). In contrast, the presence of the T allele or the TT homozygote was statistically significantly associated with early-onset psoriasis (before 40 years of age). A similar correlation was observed in the analysis of the dependence of different alleles and genotypes of the polymorphic marker rs179009 in the *TLR7* gene in patients with the age of PsA onset. In this case, the TT homozygote was more prevalent in patients with early-onset arthritis (before 40 years of age), while the CC homozygote and the CT heterozygote were significantly more prevalent in patients with psoriasis and late-onset joint symptoms (after 40 years of age).

Thus, our study was the first to demonstrate the association of the polymorphic variant rs179009 in the *TLR7* gene with PsA in patients with psoriasis, and to identify the genotypes correlated with early-onset psoriasis and PsA, as well as with the severe course of the skin condition.

CONCLUSION

The immunological patterns described in this study underscore the significance of *TLR7* genes located on the X chromosome in psoriasis and contribute to the understanding of the etiopathogenesis of this disease. The present study identified an association between specific TLR7 rs179009 alleles and genotypes and an earlier and more severe psoriasis. This finding strengthens the existing concept of the role of TLRs in psoriasis and PsA, suggesting that it may serve as a foundation for the development of diagnostic tools aimed at predicting the onset and early diagnosis of PsA in patients with psoriasis. Such tools could facilitate the timely adjustment of treatment regimens in these patients.

ADDITIONAL INFORMATION

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Author's contribution. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work. N.V. Batkaeva — writing an article, literature review, statistical processing, analysis of study groups; M.M. Gitinova — conducting TLR7 rs179009 research methods in the laboratory (sequencing, polymerase chain reaction), critical analysis of the study, interpretation and evaluation of the results; O.Yu. Olisova — critical analysis of the study, observation of patients with psoriasis and psoriatic artritis, analysis of study groups, article editing.

REFERENCES

1. Clinical guidelines. *Psoriasis. 2023-2024-2025 (10.02.2023).* Approved by the Ministry of Health of the Russian Federation. (In Russ.) Available from: http://disuria.ru/_ld/12/1261_kr23L40MZ.pdf. Accessed: 15.07.2024.

2. Bryant CE, Gay NJ, Heymans S, et al. Advances in toll-like receptor biology: Modes of activation by diverse stimuli. *Crit Rev Biochem Mol Biol.* 2015;50(5):359–379. EDN: VEYRFD doi: 10.3109/10409238.2015.1033511

3. Newman ZR, Young JM, Ingolia NT, Barton GM. Differences in codon bias and GC content contribute to the balanced expression of TLR7 and TLR9. *Proc Natl Acad Sci USA.* 2016;113(10):E1362–1371. doi: 10.1073/pnas.1518976113

4. Blasius AL, Beutler B. Intracellular toll-like receptors. *Immunity.* 2010;32(3):305–315. doi: 10.1016/j.immuni.2010.03.012

5. Wang A, Bai Y. Dendritic cells: The driver of psoriasis. *J Dermatol.* 2020;47(2):104–113. doi: 10.1111/1346-8138.15184

6. Zhu Y, Wu Z, Yan W, et al. Allosteric inhibition of SHP2 uncovers aberrant TLR7 trafficking in aggravating psoriasis. *EMBO Mol Med.* 2022;14(3):e14455. EDN: YQQECY doi: 10.15252/emmm.202114455

7. Galimova ES, Kingo K, Koks S. Toll-like receptor 7 gene gln11leu missense-mutation and susceptibility to psoriasis. *Medical Immunology = Meditsinskaya immunologiya.* 2017;19(3):267–274. EDN: YTDOKJ doi: 10.15789/1563-0625-2017-3-267-27

8. Sorokina EV, Kalinichenko EO, Bisheva IV, Stolpnikova VN. Langerhans cells and gamma delta т-lymphocytes in the pathogenesis of psoriasis. *Vestnik dermatologii i venerologii.* 2024;100(1):31–37. EDN: YAMGGM doi: 10.25208/vdv14875

9. Van Raemdonck K, Umar S, Palasiewicz K, et al. TLR7 endogenous ligands remodel glycolytic macrophages and trigger skin-to-joint crosstalk in psoriatic arthritis. *Eur J Immunol.* 2021;51(3):714–720. doi: 10.1002/eji.202048690

10. Matushevskaya EV, Konovalova MV, Vladimirova EV, Svirshchevskaya EV. Pathogenesis and therapy of psoriasis and psoriatic arthritis. *Russ J Clin Dermatol Venereol.* 2019;18(5):634–643. EDN: NIXGCJ doi: 10.17116/klinderma201918051634

11. Azuaga AB, Ramírez J, Cañete JD. Psoriatic arthritis: Pathogenesis and targeted therapies. *Int J Mol Sci.* 2023;24(5):4901. EDN: YOMGUQ doi: 10.3390/ijms24054901

12. Lee BW, Moon SJ. Inflammatory cytokines in psoriatic arthritis: Understanding pathogenesis and implications for treatment. *Int J Mol Sci.* 2023;24(14):11662. EDN: UQJFYS doi: 10.3390/ijms241411662

13. Candia L, Marquez J, Hernandez C, et al. Toll-like receptor-2 expression is upregulated in antigen-presenting cells from patients with psoriatic arthritis: A pathogenic role for innate immunity? *J Rheumatol.* 2007;34(2):374–379.

14. Lu CH, Lai CY, Yeh DW, et al. Involvement of m1 macrophage polarization in endosomal toll-like receptors activated psoriatic inflammation. *Mediators Inflamm.* 2018;2018:3523642. doi: 10.1155/2018/3523642

15. Zhguleva AS, Zementova MS, Selkov SA, Sokolov DI. M1/M2 macrophages: Origin, phenotype, methods of production, interaction with natural killer cells and trophoblast. *Medical Immunology = Meditsinskaya immunologiya.* 2024;26(3):425–448. EDN: LYFSSE doi: 10.15789/1563-0625-MMO-2877

16. Chen S, Noordenbos T, Blijdorp I, et al. Histologic evidence that mast cells contribute to local tissue inflammation in peripheral spondyloarthritis by regulating interleukin-17A content. *Rheumatology.* 2019;58(4):617–627. EDN: PZLDHL doi: 10.1093/rheumatology/key331
17. Lu J, Zhong X, Guo C, et al. TLR7-MyD88-DC-CXCL16 axis results neutrophil activation to elicit inflammatory response in pustular psoriasis. *Cell Death Dis.* 2023;14(5):315. EDN: TGULWO doi: 10.1038/s41419-023-05815-y
18. Sleptsova SS, Bilyukina IF, Malov SI, et al. Polymorphism of genes localized on the x-chromosome as a marker of predisposition to infectious process chronicity at hepatitis c in the ethnic group of male Yakuts. *Yakut Med J.* 2019;(2):64–66. EDN: VQPDQO doi: 10.25789/YMJ.2019.66.19
19. Singh H, Samani D, Aggarwal S. TLR7 polymorphism (rs179008 and rs179009) in HIV-infected individual Naïve to ART. *Mediators Inflamm.* 2020;2020:6702169. doi: 10.1155/2020/6702169
20. Mishra H, Schlack-Leigers C, Lim EL, et al. Disrupted degradative sorting of TLR7 is associated with human lupus. *Sci Immunol.* 2024;9(92):eadi9575. EDN: HDXRZU doi: 10.1126/sciimmunol.adi9575
21. Vladimirov VV, Menshikova LV. Modern ideas about psoriasis and methods of its treatment. *Russkii medicinskii zhurnal.* 1998;(20):1318–1323. (In Russ.)

СПИСОК ЛИТЕРАТУРЫ

1. Клинические рекомендации. Псориаз. 2023-2024-2025 (10.02.2023). Утверждены Минздравом России. Режим доступа: http://disuria.ru/_ld/12/1261_kr23L40MZ.pdf. Дата обращения: 15.07.2024.
2. Bryant C.E., Gay N.J., Heymans S., et al. Advances in toll-like receptor biology: Modes of activation by diverse stimuli // Crit Rev Biochem Mol Biol. 2015. Vol. 50, N 5. P. 359–379. EDN: VEYRFD doi: 10.3109/10409238.2015.1033511
3. Newman Z.R., Young J.M., Ingolia N.T., Barton G.M. Differences in codon bias and GC content contribute to the balanced expression of TLR7 and TLR9 // Proc Natl Acad Sci USA. 2016. Vol. 113, N 10. P. E1362–1371. doi: 10.1073/pnas.1518976113
4. Blasius A.L., Beutler B. Intracellular toll-like receptors // Immunity. 2010. Vol. 32, N 3. P. 305–315. doi: 10.1016/j.immuni.2010.03.012
5. Wang A., Bai Y. Dendritic cells: The driver of psoriasis // J Dermatol. 2020. Vol. 47, N 2. P. 104–113. doi: 10.1111/1346-8138.15184
6. Zhu Y., Wu Z., Yan W., et al. Allosteric inhibition of SHP2 uncovers aberrant TLR7 trafficking in aggravating psoriasis // EMBO Mol Med. 2022. Vol. 14, N 3. P. e14455. EDN: YQQECY doi: 10.15252/emmm.202114455
7. Галимова Э.С., Кинго К., Кокс С. Миссенс-мутация Gln11Leu гена toll-подобного рецептора 7 и предрасположенность к псориазу // Медицинская иммунология. 2017. Т. 19, № 3. С. 267–274. EDN: YTDOKJ doi: 10.15789/1563-0625-2017-3-267-27
8. Сорокина Е.В., Калиниченко Е.О., Столпникова В.Н., Бишева И.В. Клетки Лангерганса и гамма-дельта Т-лимфоциты в патогенезе псориаза // Вестник дерматологии и венерологии. 2024. Т. 100, № 1. С. 31–37. EDN: YAMGGM doi: 10.25208/vdv14875
9. Van Raemdonck K., Umar S., Palasiewicz K., et al. TLR7 endogenous ligands remodel glycolytic macrophages and trigger skin-to-joint crosstalk in psoriatic arthritis // Eur J Immunol. 2021. Vol. 51, N 3. P. 714–720. doi: 10.1002/eji.202048690
10. Матушевская Е.В., Коновалова М.В., Владимирова Е.В., Свирщевская Е.В. Патогенез и терапия псориаза и псориатического артрита // Клиническая дерматология и венерология. 2019. Т. 18, № 5. С. 634–643. EDN: NIXGCJ doi: 10.17116/klinderma201918051634
11. Azuaga A.B., Ramírez J., Cañete J.D. Psoriatic arthritis: Pathogenesis and targeted therapies // Int J Mol Sci. 2023. Vol. 24, N 5. P. 4901. EDN: YOMGUQ doi: 10.3390/ijms24054901
12. Lee B.W., Moon S.J. Inflammatory cytokines in psoriatic arthritis: Understanding pathogenesis and implications for treatment // Int J Mol Sci. 2023. Vol. 24, N 14. P. 11662. EDN: UQJFYS doi: 10.3390/ijms241411662
13. Candia L., Marquez J., Hernandez C., et al. Toll-like receptor-2 expression is upregulated in antigen-presenting cells from patients with psoriatic arthritis: A pathogenic role for innate immunity? // J Rheumatol. 2007. Vol. 34, N 2. P. 374–379.
14. Lu C.H., Lai C.Y., Yeh D.W., et al. Involvement of m1 macrophage polarization in endosomal toll-like receptors activated psoriatic inflammation // Mediators Inflamm. 2018. Vol. 2018. P. 3523642. doi: 10.1155/2018/3523642
15. Жгулева А.С., Зементова М.С., Сельков С.А., Соколов Д.И. Макрофаги M1/M2: происхождение, фенотип, способы получения, взаимодействие с естественными киллерами и трофобластом // Медицинская иммунология. 2024. Т. 26, № 3. С. 425–448. EDN: LYFSSE doi: 10.15789/1563-0625-MMO-2877
16. Chen S., Noordenbos T., Blijdorp I., et al. Histologic evidence that mast cells contribute to local tissue inflammation in peripheral spondyloarthritis by regulating interleukin-17A content // Rheumatology. 2019. Vol. 58, N 4. P. 617–627. EDN: PZLDHL doi: 10.1093/rheumatology/key331
17. Lu J., Zhong X., Guo C., et al. TLR7-MyD88-DC-CXCL16 axis results neutrophil activation to elicit inflammatory response in pustular psoriasis // Cell Death Dis. 2023. Vol. 14, N 5. P. 315. EDN: TGULWO doi: 10.1038/s41419-023-05815-y
18. Слепцова С.С., Билюкина И.Ф., Малов С.И., и др. Полиморфизм генов, локализованных на Х-хромосоме, как маркер предрасположенности к хронизации инфекционного процесса при гепатите С в этнической группе якутов-мужчин // Якутский медицинский журнал. 2019. № 2. С. 64–66. EDN: VQPDQO doi: 10.25789/YMJ.2019.66.19
19. Singh H., Samani D., Aggarwal S. TLR7 polymorphism (rs179008 and rs179009) in HIV-infected individual Naïve to ART // Mediators Inflamm. 2020. Vol. 2020. P. 6702169. doi: 10.1155/2020/6702169
20. Mishra H., Schlack-Leigers C., Lim E.L., et al. Disrupted degradative sorting of TLR7 is associated with human lupus // Sci Immunol. 2024. Vol. 9, N 92. P. eadi9575. EDN: HDXRZU doi: 10.1126/sciimmunol.adi9575
21. Владимиров В.В., Меньшикова Л.В. Современные представления о псориазе и методы его лечения // Русский медицинский журнал. 1998. № 20. С. 1318–1323.

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