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The role of mediators in the formation of leading pathological processes in psoriatic arthritis

Pogonchenkova D.A., Chetvernya L.V., Vasilyeva O.A., Kononova T.E., Poletika V.S., Abramov V.K., Chumakova S.P., Eliseeva L.V., Urazova O.I.

Siberian State Medical University
2, Moscow Trakt, Tomsk, 634050, Russian Federation

ABSTRACT

The lecture analyzes the results of research on the role of humoral and cellular mediators, their interaction, as well as the imbalance of angiogenic factors in psoriatic arthritis. The information is presented with identification of the leading typical pathological processes: inflammation and microcirculation disorders, formed due to the activation of protein cascades and interaction of molecular proinflammatory mediators and angiogenic factors. It is known that the clinical phenotypes of psoriatic arthritis are diverse. A deeper understanding of the pathogenesis and changes in the predominant pathological process can become the basis for the development of a personalized treatment strategy based on the pathogenesis to minimize iatrogenic complications and economic costs, as well as for the introduction of modern diagnostic methods for verification, differentiation, and monitoring of psoriatic arthritis in order to timely correct drug treatment.

Keywords: psoriatic arthritis, inflammation, microcirculation, humoral mediators, C-reactive protein, complement system, bradykinin, eicosanoids, cytokines, angiogenic factors

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Роль медиаторов в формировании ведущих патологических процессов при псориатическом артрите

Погонченкова Д.А., Четверня Л.В., Васильева О.А., Кононова Т.Е., Полетика В.С., Абрамов В.К., Чумакова С.П., Елисеева Л.В., Уразова О.И.

Сибирский государственный медицинский университет (СибГМУ)
Россия, 634050, г. Томск, Московский тракт, 2

РЕЗЮМЕ

В лекции проанализированы результаты исследований, касающихся роли гуморальных и клеточных медиаторов, их взаимодействия, а также дисбаланса ангиогенных факторов при псориатическом артрите. Информация структурирована в соответствии с выделением ведущих типовых патологических процессов: воспаления и нарушений микроциркуляции, формирующихся за счет активации белковых каскадов и

✉ *Pogonchenkova Darya A.,* pogonchenkova.da@ssmu.ru

взаимодействия молекулярных провоспалительных медиаторов и ангиогенных факторов. Известно, что клинические фенотипы псориатического артрита многообразны. Глубокое понимание патогенеза и динамики изменений в преобладании одного патологического процесса над другим может стать основой для разработки персонифицированного патогенетически обоснованного терапевтического подхода с минимизацией ятрогенных осложнений и экономических издержек, а также внедрения современных диагностических методов для верификации, дифференциации и мониторинга активности псориатического артрита с целью своевременной коррекции медикаментозной стратегии.

Ключевые слова: псориатический артрит, воспаление, микроциркуляция, гуморальные медиаторы, С-реактивный белок, система комплемента, брадикинин, эйкозаноиды, цитокины, ангиогенные факторы

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

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INTRODUCTION

Psoriatic arthritis is an autoimmune, multifactorial, systemic disease associated with psoriasis [1]. The clinical progression of psoriatic arthritis is heterogeneous, ranging from isolated joint involvement (distal interphalangeal arthritis with a relatively benign course or mutilating arthritis, characterized by malignant progression with osteolysis of bone tissue and bone ankylosis) [2, 3] to combinations of articular syndrome with lesions of the axial skeleton (sacroiliitis, spondylitis) [4], musculoskeletal patterns (enthesitis, dactylitis, tenosynovitis) [5–7], or extraskeletal extra-articular manifestations (anterior uveitis, chorioretinitis, nonspecific colitis, etc.) [8, 9]. Despite the generally accepted terminology, in the scientific literature one can come across the synonym "psoriatic disease", which emphasizes the systemic nature of this pathology [10].

Lack of specific laboratory markers and pathognomonic symptoms of psoriatic arthritis can make the diagnosis difficult to establish. The diagnosis is confirmed if the clinical, test, and radiological signs match with the CASPAR (Classification of Psoriatic Arthritis) classification criteria. It should be noted that the CASPAR criteria have significant limitations in the differential diagnosis of early arthritis [11].

Difficulties may arise in patients without manifestations of skin psoriasis or with a symmetric rheumatoid-like subtype of psoriatic arthritis, as well as in individuals with mono- or oligoarthritis, with positive rheumatoid factor (RF) test and / or anti-cyclic-citrullinated peptide (CCP) antibody and minimal skin manifestations, which often causes misdiagnosis [12]. Additionally, the DAPSA (Disease Activity index for Psoriatic Arthritis) activity scales used in real clinical practice often evoke reasonable criticism for their limited reproducibility and low prognostic sensitivity [13]. Diagnostic and therapeutic approaches for psoriatic arthritis require reevaluation, taking into consideration modern fundamental knowledge in the field of proteomics and molecular cell biology.

Accordingly, the aim of this lecture was to summarize and systematize relevant data on the role of key humoral and cellular mediators and their interaction during the initiation of the inflammatory process and microcirculatory disorders in psoriatic arthritis.

HUMORAL INFLAMMATORY MEDIATORS IN PSORIATIC ARTHRITIS

Currently, a large amount of scientific data indicates that, in addition to general patterns, the inflammatory process in psoriatic arthritis has specific characteristics related to the mediators, which justifies the isolation of this disease into an independent nosological unit. The clinical phenotypes of psoriatic arthritis depend on the multitudinous and cross-inducible expression of mediators, the order of mediator network formation, the duration and location (systemic or limited to a topographic location) of the mediator-induced effect, and the degree of the imbalance of proinflammatory and anti-inflammatory regulators [14, 15].

C-reactive protein (CRP) is a mediator of the acute phase of inflammation and a leading marker

of choice in assessing the activity of psoriatic arthritis [16]. CRP activates early components of the complement system via the classical pathway while inhibiting the alternative pathway, preventing the formation of the membrane attack complex (MAC) [17, 18]. The functions of CRP are not limited to humoral effects, as it is involved in the formation of the humoral-cellular proinflammatory networks. By interacting with the Fcγ receptor on the membranes of myeloid cells, CRP modulates the production of interleukin (IL) 1® and tumor necrosis factor (TNF) α. In addition, CRP stimulates the synthesis of reactive oxygen species [19].

The role of CRP in the pathogenesis of psoriatic arthritis requires clarification. The studies whose results have been implemented in clinical practice compared the levels of total and high-sensitivity CRP with the activity of the inflammatory process, without considering the influence of different peptide isoforms. It should be noted that CRP isoforms may exhibit opposite biological effects [20, 21]. For example, monomeric CRP (mCRP) can accumulate in tissues and enhance local inflammation, whereas the native isoform of CRP (nCRP) mostly remains within the systemic circulation [22]. The accumulation of mCRP in the cells of the synovial membrane was demonstrated in the model of rheumatoid arthritis [23], while no similar studies have been carried out focusing on psoriatic arthritis. Native isoform of CRP also opsonizes apoptotic cells, triggering their phagocytosis [24].

The complement system is crucial in initiating and maintaining inflammation in psoriatic arthritis [25]. Displaying an additive effect with other mediators, the complement system participates in forming a molecular basis for the clinical manifestation of the disease. An increased concentration of the components C3 and C4 in the blood and C3 in the synovial fluid triggers the activation of phagocytes in the vascular bed and stimulation of effector cells incorporated into the synovial membrane. The recruitment of innate and adaptive immune cells from the bloodstream into target organs is realized with the assistance of light chain fragments C3a and C4a, which act as chemoattractants and display kinin-like activity [26].

Fragments C3b attach to the surface of the synovial membranes, representing opsonized targets to effector cells [28]. According to the classical model of inflammation, the complex formed by C5b-C9, when integrated into cell membranes, forms a channel for hydrogen ions, sodium ions, and water to flow into target cells [27]. However, the degree of involvement of this mechanism in psoriatic arthritis is not fully understood. While the proteins of the C5b-C9 complex present in a liquid medium lack the capacity for lysis, an increase in their concentration positively correlates with the activity of psoriatic arthritis and may represent an indirect indicator of tissue destruction [28]. It is evident that the complement system in psoriatic arthritis has lost its biologically determined protective function. The components C3, C4, and C5b-C9 do not have selective histological affinity [27].

Certainly, the complement system is involved in the initiation of acute inflammation at the onset of the disease, maintaining and enhancing local inflammatory process during periods of exacerbation, potentiating the mechanisms leading to the alteration of articular tissues. The production of humoral mediators can be a precursor of comorbidity, with a high probability of complications whose etiology will not be related to psoriatic arthritis. An increase in C3 levels in the bloodstream in the context of psoriatic arthritis represents a synergistic cardiometabolic effect, which contributes to an increase in cardiovascular risk [29–31].

To date, the role of the kallikrein – kinin system in the pathogenesis of psoriatic arthritis has not been sufficiently studied. Several studies have explored the correlation between the progression of cutaneous psoriasis, the levels of bradykinin, and the overexpression of B1 and B2-kinin receptors [32, 33]. Vasoactive amines, in particular bradykinin, regulate the diameter and permeability of the microvasculature. They also stimulate the migration of T lymphocytes and neutrophils, enhancing the inflammatory process. Thus, the blockade of bradykinin receptors is able to reduce the activity of psoriasis [34].

Moreover, bradykinin acts as an inducer of the inflammatory pain, which is the leading clinical symptom of psoriatic arthritis [35–37]. Despite the common nature of the autoimmune process in cutaneous psoriasis and arthritis, and a high theoretical probability of a similar role of bradykinin receptors and ligands, it is still too early to extrapolate the available data due to the lack of objective evidence for receptor overexpression in articular tissues, tendons, or entheses. At the same time, it would be unwise to ignore the role of the kallikrein – kinin system in the pathogenesis of psoriatic arthritis. An increase in the level of kallikreins in the synovial fluid and blood was demonstrated in rheumatoid arthritis, which is also characterized by inflammatory arthralgia [38–40].

According to the literature, psoriatic arthritis is associated with dysregulation of the hemostatic system, characterized by an imbalance in procoagulant factors. This includes the activation of Hageman factor, an imbalance of plasminogen activator-1 inhibitor (PAI-1) and tissue plasminogen activator (t-PA), decreased levels of natural anticoagulants (proteins C and S, antithrombin III), and elevated fibrinogen and D-dimer levels in the blood [41–44].

CELLULAR MEDIATORS OF INFLAMMATION IN PSORIATIC ARTHRITIS

Lipid and protein cellular mediators are key signaling molecules in the initiation of an autoimmune inflammatory process. In patients with psoriatic arthritis, there is an increase in the plasma levels of lipid mediators (endocannabinoids and certain eicosanoids), which are produced as a result of lipid peroxidation within cell membranes and the metabolism of arachidonic acid [45, 46].

Free 4-hydroxynonenal (4-HNE) is a secondary messenger and a reactive biomarker associated with lipid peroxidation. The effector potential of free 4-HNE depends on its concentration. Through its capacity to modulate the expression of specific receptors on the membranes of immunocompetent cells, free 4-HNE effectively neutralizes the effects of endocannabinoids, stimulates the selection of lymphocytes with a proinflammatory phenotype, and participates in the activation of intracellular enzyme systems that trigger apoptosis of injured cells [47].

Prostaglandin E_2 is a lipid mediator with pronounced pyrogenic activity. This eicosanoid has a kinin-like effect, modulates dilation of the microvasculature, and, while lacking a direct affinity for pain receptors (nociceptors), indirectly leads to hyperalgesia by causing hypersensitization to bradykinin [48–50]. In the context of the inflammatory process, 8-Isoprostaglandin F_{2a} (8-isoPGF_{2a}) acts as a signaling molecule activating TNFα synthesis [51].

Hepoxilin B3 (HXB3) is a bioactive substance that promotes exudation by increasing the permeability of the vascular wall. It interacts with TrpV1 and TRPA1 receptors, inducing the inflammatory pain in psoriatic arthritis [52].

Eicosanoids, possessing ty for PPARδ receptors, suppress antioxidant protection of cells (by inhibiting the production of superoxide dismutase and heme oxygenase), provoking oxidative stress, which leads to the chronification of the disease [46]. When discussing the role of eicosanoids in the onset and progression of psoriatic arthritis, it should be emphasized that, in addition to the overproduction of proinflammatory signaling molecules, the imbalance of proinflammatory and anti-inflammatory lipid mediators plays a significant role in the pathogenesis of the disease. A decrease in resolvins, which deactivate arachidonic acid derivatives, has been demonstrated [45]. The deficiency of resolvins inhibits the feedback mechanisms, leading to overproduction of proinflammatory cytokines and thromboxanes, an increase in platelet aggregation and leukocyte chemotaxis, stimulation of neoangiogenesis in inflamed tissues, and accumulation of superoxide anion radicals, which contributes to the local resorption of periarticular bone tissue [53].

Protein cellular mediators (cytokines) are molecules whose main function is to organize intercellular crosstalk [54]. The leading role in the pathogenesis of psoriatic arthritis is attributed to cytokines that stimulate the recruitment of immune cells into tissues to initiate and maintain the inflammatory process. The trigger for cross-overproduction of IL-1, IL-6, and IL-8 in psoriatic arthritis is the interaction between the soluble form of TNFα and the CD120b receptor on cells of mesenchymal origin.

Notably, TNFα should be considered a mediator, which is a regulator and an effector at the same time. During the onset of the disease, high concentrations of TNFα trigger activation of intracellular signaling, resulting in cells producing TNFα and forming a vicious circle of cytokine overproduction. At the molecular and cellular level, the mechanisms responsible for self-limitation of the TNFα production fail to eliminate it effectively, preventing the remission of the disease and reconvalescence at the body level. It is important to note that the inflammatory response depends on the concentration of TNFα [55–57]. In psoriatic arthritis, overproduction of proinflammatory cytokines IL-1β and IL-6 can result in a self-sustaining pathological process if constitutive expression of TNFα is present [58]. The IL-23/IL-17A axis is another example of cross cytokine expression. Acting as a ligand, IL-23 modulates the activation of T-helper lymphocytes (Th) type 17 that synthesize IL-17A, as well as IL-21, IL-22, and TNFα [59].

Similarly, IL-1β activates signaling pathways that are responsible for the overproduction of IL-17A or IL-36. The proinflammatory potential of IL-36 has been observed in skin psoriasis. According to a number of studies, IL-36 can maintain inflammation in psoriatic arthritis as a regulator of cross-inflammatory

expression [60]. IL-17A activates transcription factors and kinases, mediates cross-inducible secretion of IL-1, IL-6, TNFα, and chemokines, and modulates the expression of TNFα receptor type 2 [61].

On the one hand, the ability of cytokines to duplicate each other's biological functions ensures the maintenance of the pathological process and justifies the status of psoriatic arthritis as a chronic disease [54]. On the other hand, the diversity of the effector potential of each individual mediator and the absence of a strictly determined structure of the mediator network per unit of time underlie the heterogeneous phenotype of the disease.

As previously mentioned, TNFα realizes its proinflammatory potential in a concentration-dependent manner, polarizes monocytes and macrophages, and enhances their migration, stimulates Th1-lymphocytes, and mediates Th17-cells, aggravates the course of arthritis, and participates in the pathogenesis of joint erosion [54, 66–68].

IL-6, a pyrogen and a cytokine with a pronounced systemic effect, stimulates the production of acute-phase proteins (CRP, fibrinogen) by hepatocytes, polarizes the maturation of macrophages towards the proinflammatory M1-phenotype, and activates the STAT3-mediated signal transduction pathway in inflammatory cells [54, 62–64]. IL-23 induces the formation of psoriatic plaques, tendonitis, and enthesitis but exerts a protective effect towards the intestinal mucosa at physiological concentrations.

IL-17A realizes its proinflammatory potential in cooperation with other cytokines (TNFα, IL-1, and IL-6), links factors of innate and adaptive immunity, promotes recruitment of Th17 cells, innate lymphoid cells (ILC) 3, and neutrophils, increases the procoagulant potential of the blood, and participates in the initiation and maintenance of cutaneous manifestations of psoriasis, enthesitis, and tendonitis [65].

IL-36α produced by B lymphocytes and plasmocytes promotes the proliferation of synovial fibroblasts and stimulates the production of IL-6 and IL-8, which enhance local inflammation [60, 69–71].

Microcirculatory disorders in psoriatic arthritis: the role of lipid and cellular mediators

True inflammatory hyperemia of tissues, which arises due to impaired rheological properties of blood and changes in the vascular wall and perivascular tissues, as well as exudation, are the crucial components of the pathogenesis of psoriatic arthritis. The activity of the disease and the presence of a particular complex of symptoms depend on the spectrum of signaling molecules that modulate the effects of immunocompetent cells, perivascular cells, and microvasculature.

In psoriatic arthritis, the severity of exudation depends on the permeability of venules and capillaries. Humoral mediators with a direct effect on blood vessels include bradykinin and proteins of the complement system, C3a and C5a, which can modulate the contraction of endotheliocytes [72, 73]. CRP can potentially affect the permeability of the vascular wall as well. It has been shown that the mCRP isoform induces the expansion of microcirculatory vessels by activating local overproduction of nitric oxide. The nCRP isoform has the opposite effect, provoking vasoconstriction and leukocyte adhesion [22]. At present, there is no comprehensive understanding of the relationship between the variability of the level of individual CRP isoforms in the blood and synovial fluid and the activity of psoriatic arthritis.

Cellular mediators can influence the architecture of the microvasculature, increasing exudation through cell-mediated damage to the vascular wall or defective cellular contact between pericytes and endothelial cells. Psoriatic arthritis is characterized by an increase in the number of immature vessels. TNFα and IL-1 can trigger cross-expression of angiogenic factors, such as vascular endothelial growth factor (VEGF). In turn, IL-17 stimulates the recruitment of endothelial cells during the formation of new vessels [74, 75].

Angiogenic factors in the pathogenesis of microcirculation disorders in psoriatic arthritis

In psoriatic arthritis, an imbalance of angiogenic mediators stimulates the development of microangiopathies with specific signs. The synovial membrane is characterized by the presence of elongated, bushy, and tortuous capillaries, is hypervascularized due to an increase in the number of functioning capillaries, accompanied by neoangiogenesis and impaired rheological properties of blood due to the aggregation of blood cells [76, 77]. Microangiopathy of the nail bed in patients with psoriatic arthritis is manifested by the presence of avascular zones, hemorrhages, the appearance of giant capillaries, and an increase in the number of tortuous and twisted capillaries. A number of researchers note a decrease in the linear density of capillaries, while other authors describe an increase in the density of capillaries [78–80]. Dermal microangiopathy occurs prior to the clinical manifestation of cutaneous psoriasis and is characterized by capillary dilation

and increased endothelial permeability, leading to exudation and edema [81, 82]. Important angiogenic factors include VEGF, platelet-derived growth factor (PDGF), angiopoietin, and transforming growth factor (TGF) β.

VEGF has regenerative potential, being a key factor in the process of neoangiogenesis. In psoriatic arthritis, a local increase in VEGF expression is detected in the synovial membrane of the joint [83–85]. However, the data on the diagnostic and prognostic significance of an increase in the concentration of VEGF in the blood plasma of patients with psoriatic arthritis remains inconclusive.

PDGF is a growth factor that ensures the migration of pericytes to the area of vascular sprouts [85]. Angiopoietin, another growth factor, is overexpressed in the synovial membrane, while its isoform, Ang2, plays the key biological role. In inflammation, Ang2 enters the bloodstream via endothelial cells, increases the permeability of the vascular wall, and stimulates the recruitment of endothelial cells into new tissue niches, promoting neoangiogenesis. It should be noted that the proangiogenic potential of angiopoietin is realized in the presence of VEGF [86, 87].

TGFβ is also highly expressed within the synovial membrane, especially in patients with erosive psoriatic arthritis [88]. TGFβ regulates the composition and quantity of the vascular matrix by preserving and stimulating neoangiogenesis [89].

CONCLUSION

At the current stage, research of psoriatic arthritis is markedly focused on the role of individual cytokines, which does not allow for formulating a generalized model of pathogenesis that would reflect the mechanisms of interaction between humoral and cellular mediators. In addition, there is no clear understanding of the hierarchy of various mediators of different origins and their combinations within the pathogenesis of psoriatic arthritis, with relation to the activity of the disease and its clinical phenotype. The priority is to determine the dominant pathological process during the evolution of the disease in a particular patient. Absolute reciprocal relationship between inflammation and microcirculation disorders has not been proven. Given the generally accepted paradigm in which tissue inflammation is the primary event, the hypothesis that microcirculation disorders can be the initiating process in the pathogenesis may seem revolutionary. Evidently, the contribution of vascular bed pathology to the development of psoriatic arthritis has not yet been sufficiently studied and is a promising area of research.

It is important to acknowledge that incomplete understanding of the pathogenesis of psoriatic arthritis renders the practical application of therapeutic modalities based on genetic engineering purely empirical. Given the pleiotropic potential of most cytokines, this strategy is comparable to the use of antibiotics without determining microbial susceptibility [90], which discredits the concept of translational medicine and the principles of a rational personalized approach, increasing the burden of non-targeted economic costs in the healthcare system.

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Authors' information

Pogonchenkova Daria A.– Cand. Sci. (Med.), Head of the Rheumatology Unit, Medical Center "Professor", Siberian State Medical University, Tomsk, pogonchenkova.da@ssmu.ru, http://orcid.org/0000-0002-5903-3662

Chetvernya Lada V. – Rheumatologist, Medical Center "Professor", Siberian State Medical University, Tomsk, chetvernya.lv@ssmu.ru, http://orcid.org/0009-0003-0436-5349

Vasilyeva Olga A. – Cand. Sci. (Med.), Associate Professor of the Pathological Physiology Division, Associate Professor of the Biochemistry and Molecular Biology Division with Clinical Laboratory Diagnostics Course, Siberian State Medical University, Tomsk, vasileva.oa@ssmu.ru, http://orcid.org/0000-0002-2882-4533;

Kononova Tatyana E. – Cand. Sci. (Med.), Associate Professor, Pathological Physiology Division, Siberian State Medical University, Tomsk, kononova.te@ssmu.ru, http://orcid.org/0000-0001-8457-9440

Poletika Vadim S. – Cand. Sci. (Med.), Associate Professor, Pathological Physiology Division, Siberian State Medical University, Tomsk, vpoletika@yandex.ru, http://orcid.org/0000-0002-2005-305X

Abramov Vitaly K. – Laboratory Assistant, Pathological Physiology Division, Siberian State Medical University, Tomsk, abramoff.vk@yandex.ru, http://orcid.org/0000-0002-7991-9786;

Chumakova Svetlana P. – Dr. Sci. (Med.), Associate Professor, Professor of the Pathological Physiology Division, Siberian State Medical University, Tomsk, chumakova.sp@ssmu.ru, http://orcid.org/0000-0003-3468-6154

Eliseeva Larisa V. – Cand. Sci. (Med.), Head of the Rheumatology Unit, Assistant of the Intermediate-Level Therapy Division with Clinical Pharmacology Course, Siberian State Medical University, Tomsk, eliseeva.lv@ssmu.ru, http://orcid.org/0000-0001-9089-3321

Urazova Olga I. – Dr. Sci. (Med.), Professor, Corresponding Member of the RAS, Head of the Pathological Physiology Division, Siberian State Medical University, Tomsk, urazova.oi@ssmu.ru, http://orcid.org/0000-0002-9457-8879

(✉) **Pogonchenkova Darya A.,** pogonchenkova.da@ssmu.ru

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