СРАВНИТЕЛЬНЫЙ АНАЛИЗ ЭКСПРЕССИИ РАСТВОРИМОЙ ФОРМЫ РЕЦЕПТОРА IL-7 У ПАЦИЕНТОВ С АРТРОПАТИЕЙ

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Резюме. Артропатии являются одними из самых распространенных заболеваний, в основе которых лежит деструкция и ремоделирование хрящевой и костной ткани. Предшествующее деструкции воспаление может быть вызвано механической нагрузкой на суставы, аутоиммунными реакциями. В последнее время IL-7 рассматривают как один из ключевых цитокинов, способствующих продукции матриксных металлопротеиназ, катаболических ферментов, Т-клеточноопосредованной активации моноцитов, созреванию остеокластов. Растворимая форма рецептора к IL-7 может способствовать увеличению продолжительности жизни IL-7 и тем самым обеспечивать биодоступность цитокина и опосредовать эффект IL-7 на клетки. Целью данного исследования стало определение растворимой формы рецептора к IL-7 (sIL-7R) в плазме крови пациентов с ревматоидным артритом (RA), остеоартритом (OA), псориатическим артритом (PsA) и вульгарным псориазом (PS), а также здоровых индивидуумов. Пациенты с RA, вошедшие в исследование, имели умеренную и высокую активность заболевания согласно индексу DAS28. Пациенты с PsA преимущественно имели умеренную и низкую активность заболевания (DAS28) и характеризовались легкой и средней степенью тяжести заболевания (PASI). В соответствии с индексом PASI в исследование были включены пациенты с PS с легким и тяжелым течением заболевания. У всех пациентов с OA был метаболический фенотип, который сопровождается повышенным индексом массы тела.

sIL-7R определяли в плазме крови методом иммуноферментного анализа. Было обнаружено, что у пациентов с артропатией повышен уровень растворимой формы IL-7 относительно здоровых индивидуумов, исключение составила группа пациентов с PsA. Также высокая концентрация sIL-7R наблюдалась у пациентов с PS. Проведя анализ с учетом клинических характеристик пациентов, мы

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установили, что уровень sIL-7R повышался у пациентов с RA и PsA с высокой активностью заболевания по DAS28. Кроме того, были выявлены положительные корреляционные связи между концентрацией sIL-7R и DAS28 при RA и PsA. У пациентов с PsA со средне-тяжелой степенью тяжести (PASI) концентрация sIL-7R также была повышена относительно донорских значений. Напротив, у пациентов с PS высокий уровень sIL-7R фиксировался вне зависимости от степени тяжести заболевания. У пациентов с OA не было выявлено взаимосвязей между уровнем sIL-7R и клиническими параметрами.

Таким образом, повышенный уровень sIL-7R у пациентов с артропатией может говорить о вовлеченности IL-7 и его рецепторной системы в патогенез суставных заболеваний. Рецептор IL-7 может стать перспективной мишенью как в терапии заболеваний суставов, так и других аутоиммунных заболеваний, включая псориаз.

Ключевые слова: растворимый рецептор IL-7, иммуноферментный анализ, псориатический артрит, псориаз, ревматоидный артрит, остеоартрит

COMPARATIVE ANALYSIS OF THE EXPRESSION OF THE SOLUBLE IL-7 RECEPTOR IN PATIENTS WITH ARTHROPATHY

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Abstract. Arthropathy is one of the most prevalent diseases, which are based on the destruction and remodeling of cartilage and bone tissue. The inflammation that precedes destruction can be caused by mechanical stress on the joints, or by autoimmune reactions. Recently, IL-7 is considered as one of the key cytokines that promote the production of matrix metalloproteinases, catabolic enzymes, T cell-mediated activation of monocytes, and maturation of osteoclasts. The soluble form of the IL-7 receptor can help prolong the lifespan of IL-7 and thereby it ensures the bioavailability of the cytokine and mediates effect of IL-7 on cells. The aim of this study was to determine the soluble form of the IL-7 receptor (sIL-7R) in the blood plasma of patients with rheumatoid arthritis (RA), osteoarthritis (OA), psoriatic arthritis (PsA) and psoriasis vulgaris (PS), as well as healthy individuals. The RA patients included in the study had moderate to high disease activity according to the DAS28 index. Patients with PsA predominantly had moderate and low disease activity (DAS28) and were characterized by mild to moderate disease severity (PASI). In accordance with the PASI index, patients with PS with mild and severe severity of the disease were included in the study. All patients with OA had a metabolic phenotype that is accompanied by an elevated body mass index.

sIL-7R was determined in blood plasma by enzyme-linked immunosorbent assay. It was found that in patients with arthropathy, the level of soluble form of IL-7 was increased relative to healthy individuals, with the exception of the group of patients with PsA. Also, a high concentration of sIL-7R was observed in patients with PS. Analyzing the clinical characteristics of the patients, we found that sIL-7R levels were elevated in RA and PsA patients with high disease activity by DAS28. In addition, positive correlations were found between the concentration of sIL-7R and DAS28 in RA and PsA. In patients with PsA with moderate severity of the disease (PASI), the concentration of sIL-7R was also increased relative to donor's values. On the contrary, in patients with PS, a high level of sIL-7R was noted regardless of the severity of the disease. In patients with OA, no relationship was found between sIL-7R levels and clinical parameters.

Thus, an elevated level of sIL-7R in patients with arthropathy may indicate the involvement of IL-7 and its receptor system in the pathogenesis of joint diseases. The IL-7 receptor may become a promising target both in the treatment of joint diseases and other autoimmune diseases, including psoriasis.

Keywords: soluble IL-7 receptor, enzyme-linked immunosorbent assay, psoriatic arthritis, psoriasis, rheumatoid arthritis, osteoarthritis

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Introduction

Arthropathy is one of the most prevalent diseases, and it often irrevocably changes the quality of patient life [7]. It is believed that osteoarthritis (OA) is based on inflammation caused by inappropriate mechanical stress on the joints, rheumatoid arthritis (RA) is based on autoimmune inflammation, while in psoriatic arthritis (PsA) there is no relatively well-formed pathogenetic concept. In addition, the common feature of the three diseases is the destruction and remodeling of bone tissue and cartilage.

IL-7 is an important cytokine for the generation, development, maintenance and function of human T lymphocytes [11]. In addition to its role as a T cell homeostatic factor, it also promotes the production of IFN and IL-17, which adversely affects the course of Th1- and Th17-mediated diseases, including joint diseases.

It is known that IL-7 is produced not only by immune cells, but also by keratinocytes and chondrocytes. At the same time, cytokine production by chondrocytes is enhanced in response to stimulation by fibronectin filaments, IL-1 and IL-6. Through its receptor (IL-7R), IL-7 induces the production of matrix metalloproteinase-13 associated with the release of proteoglycans from cartilage. It can be assumed that IL-7 is indirectly involved in the destruction of joint tissue through autoimmune mechanisms [7]. IL-7 induces T cell-mediated activation of monocytes, and also increases the production of TNFα, which is an inhibitor of cartilage matrix synthesis and an inducer of cartilage degradation through an increase in the activity of fibroblasts that produce catabolic factors. IL-7 promotes the maturation of osteoclasts from monocytes through the induction of TNFα and an increase in RANKL expression [12], which may have an aggravating effect on the condition of the joints in OA, RA, and PsA. IL-7 expression is increased in OA [6]. In this disease, IL-7 has been found to mediate destruction of joint tissue through osteoclast activation as well as through its action on IL-7R$^+$ chondrocytes. Blockade of IL-7R led to a decrease in the intensity of cartilage tissue destruction *in vitro* and *in vivo* [8].

Soluble forms of receptors can be formed from the extracellular portion of a membrane-bound protein or as a result of alternative splicing. They are able to trigger the development of various immunological reactions through binding to the appropriate ligands, however, the effect may differ from the result of activation of the signaling pathway of a similar membrane-bound receptor [1]. The reason for this difference is the activation of different signaling pathways upon binding of cytokines to soluble and membrane forms of receptors [13].

The soluble form of the IL-7 receptor (sIL-7R) increases the bioavailability of IL-7 and enhances proliferative activity caused by activation of the membrane receptor signaling pathway [4]. An association of serum sIL-7R levels with the development of autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, and Schegen's syndrome, has been established [2, 5]. At the same time, in RA, a high level of sIL-7R is associated with a lack of response to non-steroidal anti-inflammatory drug therapy and systemic glucocorticosteroids, and with a poor prognosis for the patient. In addition, in RA, fibroblasts produced sIL-7R in response to TNFα, IL-1β, and IL-17. All of this indicates the need to study the role of sIL-7R in the development of joint diseases [9]. The aim of this study was to determine the soluble form of the IL-7 receptor (IL-7R) in the blood plasma of patients with rheumatoid arthritis (RA), osteoarthritis (OA), psoriatic arthritis (PsA) and psoriasis vulgaris (PS), as well as healthy individuals.

Materials and methods

Object of investigation

The study included patients with rheumatoid arthritis (RA, n = 14), osteoarthritis (OA, n = 16), psoriatic arthritis (PsA, n = 26), psoriasis vulgaris (PS, n = 12) and healthy individuals (n = 16). The recruitment of patients with rheumatoid arthritis and osteoarthritis was carried out on the Department of Rheumatology, Clinic of Immunopathology of RIFCI (Novosibirsk) with the participation of rheumatologists. The recruitment of patients with psoriatic arthritis was carried out on the State Budgetary Health Institution of the Novosibirsk Region "City Hospital No. 3" (Novosibirsk) with the participation of rheumatologists and dermatologists. The recruitment of patients with psoriasis was carried out on the Clinic "Allergo-city" (Novosibirsk) with the participation of dermatologist. Written informed consent was obtained from all participants included in the study prior to collection of peripheral blood samples. Peripheral blood samples were collected in the 6 mL vacuum tubes, containing K_2EDTA.

Characteristics of persons included in the study, are presented in Table 1. Thirteen patients with OA had an obesity: body mass index was more than 30; 3 patients had body mass index more than 25 and less than 30. Patents with RA characterized by moderate and high activity of the disease, Rg-stage II-IV. Patients with PsA had predominantly moderate and low activity of the disease (DAS28), mild and moderate severity (PASI). The group of psoriasis was presented by patients with mild and severe severity of the disease, according to PASI.

TABLE 1. CHARACTERISTICS OF PERSONS INCLUDED IN THE STUDY

	Healthy control (n = 16)	Psoriasis (n = 12)	Psoriatic arthritis (n = 26)	Rheumatoid arthritis (n = 14)	Osteoarthritis (n = 16)
Age, years	41.30±3.26	38.00±3.62	55.10±2.66	45.90±3.95	65.3±2.1
Gender: m/f (%)	6/10 (37.5/62.5)	6/6 (50/50)	11/15 (42.3/57.7)	0/14 (0/100)	0/16 (0/100)
PASI **Severity:** **– mild** **– moderate** **o severe** **– severe**	–	23.30±5.78 – 5 patients – 0 patients – 7 patients	8.70±0.89 – 19 patients – 7 patients – 0 patients	–	–
DAS28 **Activity of the disease:** **– low** **– moderate** **– high**	–	–	3.75±0.21 – 7 patients – 14 patients – 3 patients	5.00±0.35 – 0 patients – 7 patients – 7 patients	–
VAS (mm) **BMI (kg/m²)**	–	–	–	–	65.40±4.87 32.70±0.97
Rg-stage: **– II** **– III** **– IV**				– 6 patients – 6 patients – 2 patients	– 6 patients – 10 patients – 0 patients

Note. VAS, Visual Analogue Scale of pain; BMI, body mass index. The data are presented as Mean±Standard error.

Evaluation of soluble IL-7 receptor

Vacuum tubes with blood were performed centrifugation on 3000 rpm during 20 minutes to obtain plasma. Samples of plasma were collected and frozen. Prior to enzyme-linked immunosorbent assay, samples were rethawed and diluted in 5 times by 0,01M PBS (pH 7.0).

We used the ELISA kit for IL-7 receptor (Cloud-Clone Corp., USA), that is a sandwich enzyme immunoassay, to quantitatively measure human IL-7 receptor in the plasma samples, acting accordingly to the instruction. Measurement of absorbance of the enzyme-substrate reaction was performed at a wavelength of 450 nm with reference at a wavelength of 620 nm by a spectrophotometer Infinite F50 (Tecan, Austria). The concentration of IL-7 receptor in the samples was determined by counting the optical density of the samples to the standard curve (0.156-10 ng/mL) and multiplying the dilution factor.

Statistical analysis

Statistical data processing was carried out using the software "Statistica 6.0" (StatSoft, USA) and "GraphPadPrism 9.0" (GraphPad, USA), using nonparametric statistics methods (Mann–Whitney U test). For correlation analysis, the Spearman correlation coefficient was used. Differences were considered statistically significant at $p < 0.05$.

Results and discussion

We found that the concentration of the soluble IL-7 receptor was increased in patients with arthropathy compared to healthy individuals, excluding patients with PsA (Table 2, p1). Nevertheless, content of the soluble IL-7 receptor in plasma of patients with PS was significantly higher than that in healthy individuals and patients with PsA. Patients with RA had a large concentration of the soluble IL-7 receptor; it significantly differed from values of patients with PsA. We suggested that observed differences may be linked to the severity and the activity of the diseases.

In the next step, we analyzed the soluble IL-7 receptor concentration in patients with PS, PsA and RA depending on the PASI and DAS28. It turned out that IL-7 receptor level was elevated in patients with PsA, having moderate to severe severity (Figure 1A) and high activity of the disease (Figure 1C) relatively donor's values.

Similar results were found for patients with RA: significant increasing of the soluble IL-7 receptor concentration was observed in patients with high activity of the disease (Figure 1D). On the contrary, the concentration of the soluble IL-7 receptor was increased in patients with PS regardless of the severity of the disease (Figure 1B). Moreover, IL-7 receptor level was strongly correlated with DAS28 values in

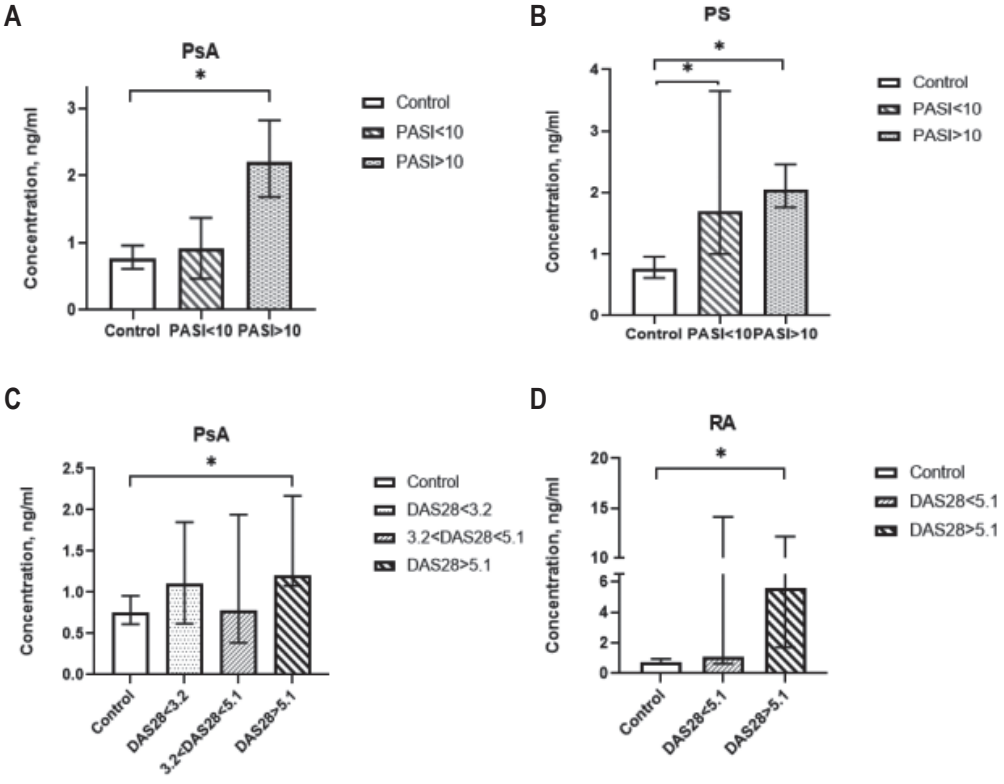

Figure 1. Concentration of the soluble IL-7 receptor depending on the severity and activity of the disease

Note. (A) Concentration of the soluble IL-7 receptor depending on PASI in psoriatic arthritis. (B) Concentration of the soluble IL-7 receptor depending on PASI in psoriasis. (C) Concentration of the soluble IL-7 receptor depending on DAS28 in psoriatic arthritis. (D) Concentration of the soluble IL-7 receptor depending on DAS28 in rheumatoid arthritis. *, significant differences, $p < 0.05$ (Mann–Whitney U test).

group of patients with RA ($R = 0.84$, $p < 0.05$). In patients with PsA, it was observed direct relationship between content of IL-7 receptor in plasma and PASI ($R = 0.48$, $p < 0.05$). No relationship has been found between clinical parameters (BMI, VAS pain) and concentration of IL-7 receptor in the plasma of patients with osteoarthritis.

It is known that sIL-7R enhances the activity of IL-7 and increases IL-7-induced proliferation of T lymphocytes and their survival [4, 7]. Our data also indirectly indicate this: in patients with severe and moderate PsA and RA, a significantly higher content of sIL-7R was observed compared with a mild form of the disease, and a correlation was found with the

TABLE 2. CONCENTRATION OF THE SOLUBLE IL-7 RECEPTOR IN THE PLASMA OF HEALTHY INDIVIDUALS AND PATIENTS WITH ARTHROPATHY, Me ($Q_{0.25}$-$Q_{0.75}$)

Groups	sIL-7R, ng/mL	p_1	p_2	p_3
Healthy control	0.76 (0.61-0.96)	–	0.13	0.0006
Psoriasis	1.89 (1.45-2.41)	0.0001	0.022	0.52
Psoriatic arthritis	1.16 (0.58-1.94)	0.13	–	0.015
Rheumatoid arthritis	2.68 (1.11-12.64)	0.0006	0.015	–
Osteoarthritis	1.33 (1.09-2.61)	0.001	0.103	0.236

Note. sIL-7R, soluble IL-7 receptor; p_1, p values of the difference from group of healthy control; p_2, p values of the difference from group of patients with psoriatic arthritis; p_3, p values of the difference from group of patients with rheumatoid arthritis.

level of sIL-7R and PASI in PsA and with DAS28 in rheumatoid arthritis. Similar data on the relationship between the severity of the course of the disease and the level of sIL-7R in the blood serum were found in systemic lupus erythematosus [3]. Moreover, in this disease, an inverse relationship was also found between the content of the soluble form of the receptor and the level of the complement component C1q.

These data allowed us to consider the content of sIL-7R as a prognostic factor in the course of the disease, which can be done based on our data on PsA and RA. However, for this, in our opinion, it is additionally necessary to evaluate the relationship between the sIL-7R content and laboratory parameters, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and also to evaluate the response to conventional therapy in patients with high and low levels of the receptor in peripheral blood.

Patients with classic psoriasis vulgaris without joint involvement were characterized by significantly higher levels of sIL-7R compared to controls, while no association with disease severity was found. At the same time, the concentration of sIL-7R in psoriasis vulgaris is higher than in patients with the arthropathic form of the disease. It can be assumed that keratinocytes, even in limited forms of the disease, are characterized by a more pronounced ability to produce sIL-7R compared to chondrocytes in the arthropathic form of the disease.

In RA, the highest concentration of sIL-7R in the peripheral blood was observed compared with PsA and OA. It is known that sIL-7R α-chain polymorphism is associated with the development of RA, which indirectly indicates the involvement of the soluble form of the receptor of this cytokine in the development of this disease [9]. Patients with severe RA are generally characterized by a greater shift in CRP, ESR, as well as a more pronounced severity of the course of the disease compared to PsA, which may explain the higher level of sIL-7R in these patients [10].

Conclusion

Thus, an elevated level of sIL-7R in patients with arthropathy may indicate the involvement of IL-7 and its receptor system in the pathogenesis of joint diseases. At the same time, in the case of autoimmune diseases, such as RA and PsA, the level of sIL-7R correlates with the activity of the disease. In the case of diseases without an autoimmune component and presence of metabolic disorders (osteoarthritis), the plasma concentration of sIL-7R is increased compared to donor values, however, it is not associated with either body mass index or VAS pain level. It is possible that sIL-7R reflects the inflammatory background in OA, that needs for further confirmation. A high concentration of sIL-7R in PS is detected even in mild psoriasis, which indicates its involvement in the pathogenesis of the disease at the early stage. Based on the obtained data, the IL-7 receptor can be considered a promising target for targeted therapy of various arthropathies and autoimmune diseases, including psoriasis.

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