

ELEVATED SERUM LEVELS OF TNF- α AND IL-17 IN PSORIATIC AND RHEUMATOID ARTHRITIS

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Abstract. *Psoriatic arthritis (PsA) and rheumatoid arthritis (RA) are chronic inflammatory immune-mediated rheumatic diseases, in which cytokine dysregulation is key for pathogenesis. In terms of the specific processes involved in predominantly enthesopathic inflammation and predominantly synovial inflammation, PsA and RA are distinct disease entities. The aim of the present study was to investigate the serum cytokine expression profiles of TNF- α and IL-17 in the two inflammatory arthropathies, discussing their role in the context of disease activity assessed by means of DAS28-CRP, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). The study included 32 patients with PsA, 30 with RA and 20 healthy subjects. In patients with RA and PsA, higher serum levels of both cytokines were measured compared to healthy controls, with the difference being significant, except for TNF- α for patients with PsA, whose concentration was numerically but not significantly higher compared to healthy individuals. We also recorded a significant increase in circulating TNF- α in RA versus PsA, with no difference for IL-17 in the two inflammatory joint diseases. The two studied cytokines did not show a significant difference in serum concentrations according to the state of the disease activity (DAS28-CRP < 3.2 vs. DAS28-CRP $\geq$ 3.2) in both PsA and RA, as well as association with clinical and laboratory parameters of activity from correlation analyses, supporting the claim that they are not useful markers for its assessment. In conclusion, both cytokines are clearly abundant in the circulation in conditions of both inflammatory arthropathies. The TNF- α and IL-17 pathways are important links and an active participant in these types of rheumatic inflammation.*

Key words: psoriatic arthritis, rheumatoid arthritis, TNF- α , IL-17

INTRODUCTION

Cytokines are signaling proteins that regulate a wide spectrum of biological functions including innate and acquired immunity, and inflammation mainly through extracellularly signaling. They are secreted by many cell types in high local concentrations and participate in intercellular interactions, influencing cells located in close proximity, on the cell itself from which they originate, and also have a systemic effect realized at a distance through the secretion of soluble substances in the circulation [1]. The effects of cytokines are pleiotropic and involve both synergistic and antagonistic interactions between them [2].

Exercising their biological activity by binding to specific receptors, they activate certain signaling pathways in the cytoplasm and cell nucleus, which leads to the transcriptional and post-transcriptional activation of numerous factors, including other cytokines. This makes them participants in a wide range of immunological processes, in important inflammatory responses, including those leading to autoimmune inflammatory diseases [1]. Advances in molecular and immunological research has enriched

our knowledge for immune-mediated diseases and the role of cytokine dysregulation in their pathophysiology [3-5]. Cytokines are key effectors in the pathogenesis of a number of human immune-mediated inflammatory diseases, such as their propensity for synergistic interactions makes them intriguing therapeutic targets.

Psoriatic arthritis (PsA) is an inflammatory disease characterized by significant heterogeneity in its clinical presentation and variable involvement of the skin, synovial joints, tendons, entheses and axial skeleton [6]. It is a representative of spondyloarthritis (SpA) and, in particular, is a prototype of the subgroup of peripheral SpA (pSpA), for which modern knowledge supports the hypothesis that the primary focus of inflammation occurs at the border between the tendons or ligaments with the bone, in the area of the entheses. In this regard, enthesitis is among the main events in the development of these diseases [7]. On the other hand, rheumatoid arthritis (RA) is a chronic inflammatory arthropathy with predominantly synovial inflammation and hyperplasia, with accumulation of inflammatory cells in the synovium

and subsequent development of progressive destructive arthritis [8].

As chronic inflammatory diseases, the pathogenesis of PsA and RA involves numerous cytokines with predominantly pro-inflammatory effects, well-known key mediators of chronic tissue inflammation, such as subtype 1 T helper (Th1) and tumor necrosis factor- α (TNF- α). Furthermore, Th17 immune responses, characterized by the production of interleukin 17 (IL-17) (as well as other proinflammatory cytokines) and dependent to a significant extent on IL-23, which is responsible for expanding and maintaining their phenotype, underlie the IL-17/23 immune axis concept. The study of type 17 immunity has led to the identification of the crucial role of the IL-23/Th17 pathway in the pathogenesis of chronic tissue inflammation, including that underlying arthritis [9, 10].

In terms of the specific processes involved in predominantly enthesopathic inflammation and predominantly synovial inflammation, PsA and RA are distinct disease states. The aim of the present study was to investigate comparatively the serum cytokine expression profiles of TNF- α and IL-17 in the two inflammatory arthropathies, discussing their role in the context of disease activity.

PATIENTS AND METHODS

Examined patients

The study is cross-sectional. In it, we included 32 consecutive patients with PsA (11 men and 21 women), and 30 with RA (7 men and 23 women). We compared them with 20 randomly selected healthy individuals with no prior history of infectious, neoplastic, or autoimmune disease.

The inclusion criteria were: Men and women over the age of 18 years; confirmed diagnosis of PsA according to CASPAR classification criteria (2006), [11] and diagnosis of RA on the base on the ACR/EULAR 2010 RA classification criteria [12]; different duration and activity of the disease; patients treated with different therapeutic regimens according to the standard of care for the respective disease.

Exclusion criteria: Current active acute or chronic infection, including acute or chronic viral hepatitis B and C, HIV infection or tuberculosis; history of malignant disease; diagnosed inflammatory disease other than PsA and RA, including but not limited to sarcoidosis, systemic lupus erythematosus, and reactive arthritis (individuals with diagnosed chronic ulcerative colitis or Crohn's disease were permitted to participate in the study); significant comorbidity (car-

diovascular, neurological, renal, hepatic, metabolic, gastrointestinal, hematological, immunological, etc.) – unstable or uncontrolled acute or chronic disease; other diseases, including mental ones, which, in the opinion of the researcher, are inappropriate for the inclusion of the patient in the study.

Data were collected on the demographic characteristics of the patients, clinical manifestations, indicators related to the activity of the disease and the therapy carried out.

Patients with PsA were aged (mean $\pm$ SD) 51 ± 12 years, ranging from 32 to 70 years. Mean ($\pm$ SD) disease duration was 11 ± 10 years (range 0.5 to 36 years). Mean age of the RA subgroup 51 ± 9 years (range 24-63 years) and disease duration 10 ± 10 years (range 0.5-42 years).

The gender and age distribution of the healthy subjects included in the control group was 5 men (25%) and 15 women (75%), with a mean age ($\pm$ SD) of 46 ± 12 years (range 28–65 years). Patients with both inflammatory arthropathies and healthy individuals were matched in age ($\chi^2 = 2.086$, $p = 0.35$) and gender ($\chi^2 = 1.044$, $p = 0.59$).

Clinical assessment

With the state on the disease activity in the two subgroups of patients with PsA and RA we rated them by means of the index DAS28-CRP, containing the following items: number of painful and swollen joints (0-28), C-reactive protein (mg/l) and the patient's assessment of general health on a visual analogue scale (mm), calculated using an electronic calculator (<https://www.das-score.nl/das28/DAScalculators/dasculators.html>).

We also examined indicators of the acute phase response – erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Elevated inflammatory biomarkers were accepted for ESR > 28 mm/h, and for CRP > 6 mg/l.

Determination of the serum concentration of cytokines

Patient and control sera were stored at -80°C until testing. Quantitative measurement of the studied pro-inflammatory cytokines was performed with a solid-phase immunoenzymatic method and commercial ELISA kits (Diacclone Human TNF α ELISA Kit and Diacclone Human IL-17A ELISA Kit), following the manufacturer's instructions. Individual values of each of the cytokines were calculated after constructing a standard curve of 6 concentrations of the respective cytokine standard and expressed in picograms per milliliter (pg/ml). The minimum detectability of cytokines indicated by the manufacturer is:

for TNF- α ELISA kit 8 pg/ml, ranging from 25 to 800 pg/ml and for IL-17 ELISA kit – 2.3 pg/ml (range from 3.125 to 1000 pg/ml), respectively. Serum samples of cases and controls were analyzed together in the same analytical lot, in order to avoid within-run and day-to-day variations in the analysis of specific cytokines.

Statistical analysis

Data were analyzed using SPSS version 22 (SPSS Inc., Chicago, IL, USA). Means with SDs and percentages were calculated to describe the clinical and laboratory characteristics of the studied individuals. Intergroup comparisons were performed using the analysis of variance (Kruskal–Wallis test) and the Mann–Whitney U test. Proportional differences were tested using χ -square (χ^2) and Fisher's exact test. Spearman correlation coefficients were calculated to assess the univariate correlation between the different parameters studied. In all analyses, results having a significance level of $p < 0.05$ were considered statistically significant.

RESULTS

Clinical features of the studied patients

A total of 62 patients, 32 with PsA and 30 with RA (all positive for anti-CCP and 75% positive for RF) were included in the study. During the course of the disease, all patients with PsA have pronounced peripheral arthritis. At the time of inclusion in the study, 13 of the patients with PsA (40.6%) had inactive disease/ low disease activity, and 19 (59.4%) had moderate/ high disease activity according to DAS28-CRP (DAS28-CRP < 3.2 versus ≥ 3.2). The mean ($\pm$ SD) of the disease activity index DAS28-CRP was 3.8 ± 1.2 (range 1.5 to 6.0). There were 26 RA patients with moderate/ high disease activity based on DAS28-CRP ≥ 3.2 (86.7%), and 4 patients with inactive disease (DAS28-CRP < 3.2) (13.3%), mean ($\pm$ SD) of index 4.2 ± 1.0 (range 1.9 to 6.2). PsA patients had elevated mean plasma CRP levels of 10.51 ± 22.8 mg/l and borderline high values of ESR 27 ± 21 mm/h. In the RA subgroup, a slight increase in CRP was also recorded at 8.18 ± 9.2 mg/L, while the mean values of ESR 25 ± 15 mm/h were normal.

Regarding the pharmacological therapy conducted, 13 patients with PsA

(40.6%) were treated with a biological disease-modifying antirheumatic drug (bDMARD), 3 (9.3%) in combination with methotrexate and 10 (31.2%) were treated with methotrexate alone. In the RA subgroup, 9 patients (30%) were treated with bDMARDs, in 5 of whom biological therapy was combined with methotrexate, 16 patients (53.3%) were treated with methotrexate alone.

Demographic, laboratory and the clinical characteristics of the studied patients are presented in Table 1.

Serum levels of the investigated cytokines in patients with PsA, RA and healthy individuals

The serum concentrations of the investigated cytokines and the comparison between the groups – patients with PsA, RA and healthy controls is presented in Table 2.

Patients with RA had significantly higher serum levels (mean $\pm$ SD) of TNF- α – 11.14 ± 24.69 pg/ml compared to healthy controls (4.11 ± 13.79 pg/ml, $p = 0.005$) and the patients with PsA (8.53 ± 32.47 pg/ml, $p = 0.002$). Among patients with PsA, the levels of this cytokine were numerically but not significantly higher compared to healthy subjects ($p = 0.569$). Mean serum concentrations of IL-17 in pa-

Table 1. Main characteristics of patients with PsA and RA

Characteristics	PsA (n = 32)	RA (n = 30)	Value of r
Age (years) mean $\pm$ SD (range)	51 $\pm$ 12 (32-70)	51 $\pm$ 9 (24 -63)	0.767
gender men n (%) women n (%)	11 (34.4) 21 (65.6)	7 (23.3) 23 (76.7)	0.408
Duration of illness (years) mean $\pm$ SD (range)	11 $\pm$ 10 (0-36)	10 $\pm$ 10 (0-42)	0.553
DAS28-CRP mean $\pm$ SD (range) ≥ 3.2 n (%) < 3.2 n (%)	3.8 $\pm$ 1.2 (1.5-6.0) 19 (59.4) 13 (40.6)	4.2 $\pm$ 1.0 (1.9-6.2) 26 (86.7) 4 (13.3)	0.335
ESR mm/h mean $\pm$ SD (range)	27 $\pm$ 21 (2-79)	25 $\pm$ 15 (2-70)	0.994
CRP mg/l mean $\pm$ SD (range)	10.51 $\pm$ 22.8 (0.1-96.0)	8.18 $\pm$ 9.2 (0.2-38.0)	0.275
Therapy CS n (%) MTX n (%) bDMARD n (%)	10 (31.2) 10 (31.2) 13 (40.6)	18 (60.0) 16 (53.3) 9 (30.0)	0.042 0.119 0.467

DAS 28-CRP = Ankylosing Spondylitis Disease Activity Score calculated with C-reactive protein; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; CS = corticosteroids; MTX = methotrexate; bDMARD = biological disease-modifying antirheumatic drugs

Mann-Whitney U test, χ^2 Fisher's exact test

Table 2. Serum concentrations of the studied cytokines in patients with PsA, RA and healthy controls

Cytokines	PsA (n = 32)	RA (n = 30)	Healthy controls (n = 20)	P
TNF- α (pg/ml)				
mean $\pm$ SD	8.53 $\pm$ 32.47	11.14 $\pm$ 24.69	4.11 $\pm$ 13.79	0.001
(range)	(0.97–172.25)	(0.97–127.01)	(0.97–62.71)	
% above 95th percentile (n) *	6.3% (2)	33.3% (10)	5% (1)	0.006
IL-17 (pg /ml)				
mean $\pm$ SD	7.89 $\pm$ 6.71	9.37 $\pm$ 6.90	4.56 $\pm$ 3.81	0.023
(range)	(0.33–36.04)	(0.01–24.20)	(0.01–12.76)	
% above 95th percentile (n) *	12.5% (4)	23.3% (7)	5% (1)	0.185

TNF- α = Tumor Necrosis Factor α ; IL = Interleukin

* Percentage of patients and controls with values of: TNF- α > 5.97 pg/ml, IL-17 > 12.76 pg/ml

Kruskal–Wallis test

tients with PsA (7.89 $\pm$ 6.71) and RA (9.37 $\pm$ 6.90) also showed significantly higher values compared to healthy subjects (4.56 $\pm$ 3.81) (p = 0.039 and 0.008, respectively), in the absence of a significant difference between the two inflammatory arthropathies (p = 0.398). Both in patients with both inflammatory joint diseases and in healthy individuals in general, serum concentrations of the two cytokines showed an irregular distribution, varying widely in individual blood samples. When patients and controls were divided into subgroups based on the 95th percentile of mean cytokine values in healthy controls, 33.3% of RA patients and 6.3% of those with PsA had TNF- α values greater than the 95th percentile vs. 5% of healthy subjects (p = 0.006), 23.3% of RA patients and 12.5% of those with PsA had IL-17 values great-

er than the 95th percentile vs. 5% of healthy subjects (p = 0.185).

For better understanding, the ratio of the mean serum concentrations of cytokines in patients with PsA and RA compared to healthy individuals is presented as an index/number ratio (Fig. 1).

Comparison of serum cytokine concentrations according to the level of clinical disease activity (DAS28 – CRP $\geq$ 3.2 versus < 3.2)

The two investigated cytokines did not show a significant difference in serum concentrations according to the state of disease activity – inactive disease or low disease activity (DAS28-CRP < 3.2) versus moderate and high disease activity (DAS28-CRP $\geq$ 3.2) both in PsA and RA (Table 3).

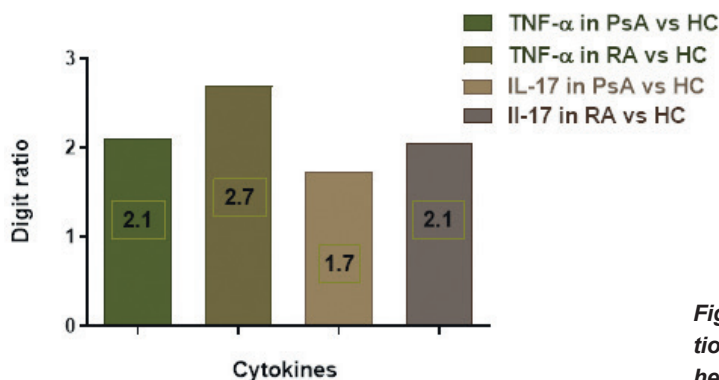


Fig. 1. Numerical ratio of the mean serum concentrations of the two cytokines in PsA and RA compared to healthy subjects

Table 3. Mean serum cytokine concentrations stratified by disease activity

PsA (n = 32)	DAS28-CRP < 3.2	DAS28-CRP $\geq$ 3.2	P value *
	Mean $\pm$ SD	Mean $\pm$ SD	
TNF- α (pg/ml)	1.05 $\pm$ 0.29	14.24 $\pm$ 42.79	0.658
IL-17 (pg /ml)	8.64 $\pm$ 5.20	7.37 $\pm$ 7.67	0.186
RA (n = 30)	DAS28-CRP < 3.2	DAS28-CRP $\geq$ 3.2	P value *
	Mean $\pm$ SD	Mean $\pm$ SD	
TNF- α (pg /ml)	3.56 $\pm$ 5.18	12.30 $\pm$ 26.33	0.361
IL-17 (pg /ml)	11.23 $\pm$ 6.96	9.09 $\pm$ 6.99	0.583

*Mann-Whitney U test

Correlation of the serum concentration of the investigated cytokines with disease activity in PsA and RA

The relationship of changes in circulating cytokine levels with disease activity (DAS28-CRP, ESR, CRP) was investigated. Calculated Spearman correlation coefficients showed no association of TNF- α and IL-17 with any of the disease and inflammatory activity parameters ($p > 0.05$ for all).

DISCUSSION

Despite the appearance of similar clinical symptoms on the part of the peripheral joints and the sometimes difficult distinction between them, psoriatic and rheumatoid arthritis are different disease entities, with their own unique features, including in the pathophysiological aspect. Enthesitis, as focal inflammation of the insertions of ligaments, tendons, or joint capsule to bone, is the primary focus and main feature of the spondyloarthritis to which PsA belongs. Later changes associated with enthesitis include periostitis and osteitis, new bone formation (ossifying enthesitis) and enthesial erosions, inflammation of the synovial membrane and adjacent soft tissues [13]. McGonagle and co-authors maintain that synovitis in spondyloarthritis is secondary, resulting from the release of proinflammatory mediators from the entheses, in contrast to synovitis in rheumatoid arthritis, which is primary [14]. Appel and Braun also state that synovitis in SpA is of minor importance, especially compared to other inflammatory joint diseases such as rheumatoid arthritis [15]. It is firmly established that in RA, the synovium is the primary and main localization of the inflammatory process and left untreated, synovitis leads to irreversible bone-cartilage erosions and destructions and progressive joint deformations, subluxations and ankylosis [16].

Cytokines produced in response to immune activation play a key role in the immunopathogenesis of chronic inflammatory arthritis. The excessive, the lowered, or the abnormal cytokine responses significantly contribute to immune – mediated inflammation. In this regard, the aim of our study was to analyze the serum levels of two key proinflammatory cytokines, TNF- α and IL-17, in the two inflammatory arthropathies that are distinctive in nature.

We found significantly increased levels of circulating TNF- α in RA regardless of the state of disease activity, compared to healthy individuals (2.7 times) and compared to patients with PsA, as 1/3 of patients with RA had TNF- α values higher than the 95th

percentile of the mean values of cytokines in healthy controls. Similar data on increased serum levels of the pro-inflammatory cytokine TNF- α , confirming its pathogenetic role in the local and systemic inflammatory response in RA, have also been presented in previous publications [17]. In psoriatic patients, although not significantly, TNF- α was 2.1 times higher in serum compared to healthy controls and did not differ according to the clinical activity of the disease. Our results are in line with other studies. High levels of TNF- α have been found in both serum and synovial fluid and membrane of patients with PsA [18, 19] and RA [20], suggesting that this cytokine plays an important role in the pathogenesis of these diseases through pro-inflammatory your effect.

TNF- α is one of the most extensively studied cytokines due to its key role in a number of human diseases. It is found in increased amounts in a number of autoimmune lesions, and its dysregulation characterizes many autoimmune diseases. TNF- α is known to be present in higher serum concentrations in RA and PsA patients. The important role of TNF in these diseases is also confirmed by their successful treatment with TNF-antagonists [21]. In cultures from synovial cells from RA patients where TNF- α has a proven dominant role, the inhibition with antibodies significantly reduces production of IL-1, IL-6, IL-8 and granulocyte-macrophage colony-stimulating factor (GM-CSF) [22]. Hence, the blockade of TNF- α in the disease can have a more pronounced effect on the inflammation than the blockade on others cytokines present high concentrations in synovial tissue, such as IL-1. The concept of the central role of TNF- α in a lot of immune-mediated diseases is firmly accepted. In autoimmunity, it is an autocrine stimulator and a strong paracrine inducer of the expression of other pro-inflammatory cytokines and chemokines – IL-1, IL-6, IL-8 and GM-CSF. Induces or enhances the expression of adhesion molecules, by binding to the tumor necrosis factor receptor (TNFR), which is presented on almost all nucleated cells. It also promotes angiogenesis and plays a major role in protecting synovial fibroblasts and suppressing regulatory T cells, as well as in the induction of pain [23-25]. Although most studies have found that levels of this cytokine in PsA are slightly lower than those found in the joints of RA patients, as is our finding regarding serum levels, the overall pattern of cytokine expression is similar, there is some similarity in cytokine status, suggesting that it is a common mediator of joint inflammation and destruction [18, 26].

Levels of the IL-17 cytokine compared to healthy controls both in PsA (1.7-fold) and in RA (2.1-fold),

with a trend toward the higher values, at the expense of only 1/8 of those affected by PsA. In both inflammatory arthropathies, we found no difference in serum IL-17 profiles according to disease activity.

Th17 cells are a stimulator of the inflammatory pathological process in autoimmune diseases. Many, if not most, autoimmune diseases are somehow related to IL-17 or Th17. IL-17 was found to enhance priming of T cells, stimulates different cell types, including fibroblasts, endothelial cells, macrophages and epithelial cells for pro-inflammatory production mediators (IL-1, IL-6, TNF- α , IL-8, inducible NO synthetase, matrix metalloproteinases and chemokines) [27, 28].

There is evidence of the role of IL-17 in unlocking RA. High levels of IL-17 and its receptor have been found in synovial fluid and tissue explants in the disease [29, 30]. Improvement in symptoms and measures of therapeutic response in RA from treatment with monoclonal anti-IL-17A antibodies has been observed, but in some of the clinical trials the primary efficacy endpoint was not achieved, justifying the need for further studies in this direction [31]. It should be kept in mind that studies have been reported suggesting a greater importance of Th1 cells than Th17 cells for RA inflammation [32].

In a study of Benham et al., concentration of IL-17, secreted from stimulated peripheral blood mononuclear cells in the supernatants on patients with PsA and psoriasis is significantly higher than in healthy controls [33]. IL-17 inhibitors have demonstrated efficacy in key clinical domains in PsA [34]. Our present findings of increased circulating levels of IL-17 are consistent with the earlier publications. These data confirm the potential functional importance of this cytokine and that IL-17 mediates effector biological actions associated with the pathology of inflammatory lesions.

Although IL-17 alone possesses the ability to induce pro-inflammatory factors, its activity is greatly enhanced when combined with other cytokines, particularly TNF- α . IL-17 synergizes with TNF- α to stimulate the induction of almost all of its target genes, and in many cases synergy with interferon gamma (IFN- γ) and IL-1 β is also observed [35]. TNF- α and IL-17 remain cardinal, and occupy an important place in the hierarchy structure of cytokines in a wide array of rheumatic diseases.

Our correlation analyzes as well as stratification sub-analyses did not show an association of the two pro-inflammatory cytokines with the clinical and laboratory parameters of activity in the two diseases. This supports the claim that TNF- α and IL-17 do not accu-

rately reflect disease activity in the Bulgarian population of patients with PsA and RA, and are not useful markers for its assessment. It is important to note that in our study, cytokines and disease activity status was assessed at a fixed point in time. Prospective follow-up of the variation of serum cytokine concentrations during the course of the disease could reveal more valuable data. On the other hand, the patients are treated with different pharmacological agents by time on the survey, including anti-TNF therapy, as well and IL-17 inhibitors for those with PsA.

CONCLUSION

Our results suggest that complex interactions between inflammatory lymphocyte T cell subpopulations and monocytes/macrophages help to unlock the pathogenesis of PsA and RA through the cytokines they produce. The TNF- α and IL-17 pathways are important links and an active participant in the full unfolding of these types of rheumatic inflammation. The two cytokines are apparently abundantly present in the circulation in the conditions of both inflammatory arthropathies, which makes them a significant target for biological treatment.

Studying the characteristics of the immune response and the mechanisms of cytokine involvement can contribute to advances in our knowledge of the pathogenesis of PsA and RA.

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Библиография / References

1. Fan CK. Chapter 27 – Cytokines. In: Asthma and COPD (Second Edition), 2009;327-341.
2. Boissier M-C. Cell and cytokine imbalances in rheumatoid synovitis. *Joint Bone Spine* 2011;78(3):230-234.
3. O'Shea JJ, Ma A, Lipsky P. Cytokines and autoimmunity. *Nat Rev Immunol* 2002;2(1):37-45.
4. Veale DJ, Fearon U. The pathogenesis of psoriatic arthritis. *The Lancet* 2018;391(10136):2273-2284.
5. McInnes I, Schett G. Cytokines in the pathogenesis of rheumatoid arthritis. *Nat Rev Immunol* 2007;7:429-442.
6. Ritchlin CT, Colbert RA, Gladman DD. Psoriatic arthritis. *N Engl J Med* 2017;376:2095-2096.
7. Araujo EG, Schett G. Enthesitis in psoriatic arthritis (Part 1): pathophysiology. *Rheumatology (Oxford)* 2020;59(Suppl 1):10-14.
8. Smolen JS, Aleattha D, McInnes IB. Rheumatoid Arthritis. *The Lancet* 2016;388(10055):2023-2038.
9. Miossec P, Korn T, Kuchroo VK. Interleukin-17 and type 17 helper T cells. *N Engl J Med* 2009;361(9):888-898.
10. Korn T, Bettelli E, Oukka M, Kuchroo VK. IL-17 and Th17 Cells. *Annu Rev Immunol* 2009;27:485-517.

11. Taylor W, Gladman D, Helliwell P, CASPAR Study Group. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum* 2006;54(8):2665-2673.
12. Aletaha D, Neogi T, Silman AJ et al. Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010;62(9):2569-81.
13. McGonagle D, Conaghan P, Emery P. Psoriatic arthritis – a unified concept 20 years on. *Arthritis Rheum* 1999;42:1080-6.
14. McGonagle D, Gibbon W, Emery P. Classification of inflammatory arthritis by enthesitis. *Lancet* 1998;352(9134):1137-40.
15. Appel H, Braun J. Synovitis in Spondyloarthritis. *The Open Rheumatology Journal*, 2011, 5, (Suppl 1:M5) 123-126.
16. Hitchon CA, El-Gabalawy HS. The synovium in rheumatoid arthritis. *Open Rheumatol J*. 2011;5:107-14.
17. Иванова М, Стоилов Р, Ганчева Р, Станилова Сп, Манолова И. Серумно ниво на TNF- α при ревматоиден артрит във връзка с болестната активност и провежданата терапия. *Ревматология* 2013;21(4):31-37.
18. Partsch G, Steiner G, Leeb BF et al. Highly increased levels of tumor necrosis factor- α and other proinflammatory cytokines in psoriatic arthritis synovial fluid. *J Rheumatol* 1997;24:518-23.
19. Ritchlin C, Haas-Smith SA, Hicks D et al. Patterns of cytokine production in psoriatic synovium. *J Rheumatol* 1998;25:1544-52.
20. Wei ST, Sun YH, Zong SH, Xiang YB. Serum Levels of IL-6 and TNF- α May Correlate with Activity and Severity of Rheumatoid Arthritis. *Medical Science Monitor. Int Med J Exp Clin Res*. 2015;21:4030-4038.
21. Jang DI, Lee AH, Shin HY et al. The Role of Tumor Necrosis Factor Alpha (TNF- α) in Autoimmune Disease and Current TNF- α Inhibitors in Therapeutics. *Int J Mol Sci* 2021;22(5):2719.
22. Haworth C, Brennan FM, Chantry D et al. Expression of granulocyte-macrophage colony-stimulating factor in rheumatoid arthritis: regulation by tumor necrosis factor- α . *Eur J Immunol* 1991;21:2575-2579.
23. Butler DM, Maini RN, Feldmann M, Brennan FM. Modulation of proinflammatory cytokine release in rheumatoid synovial membrane cell cultures. Comparison of monoclonal anti TNF- α antibody with the interleukin-1 receptor antagonist. *Eur Cytokine Netw* 1995;6(4):225-230.
24. Feldmann M, Brennan FM, Maini RN. Rheumatoid arthritis. *Cell* 1996; 85: 307-310.
25. Hess A, Axmann R, Rech J et al. Blockade of TNF- α rapidly inhibits pain responses in the central nervous system. *Proc Natl Acad Sci USA* 2011; 108: 3731-3736.
26. Danning CL, Illei GG, Hitchon C et al. Macrophage-derived cytokine and nuclear factor κ B p65 expression in synovial membrane and skin of patients with psoriatic arthritis. *Arthritis Rheum* 2000;43:1244-56.
27. Kolls JK, Linden A. Interleukin-17 family members and inflammation. *Immunity* 2004;21:467-476.
28. Nakae S, Saijo S, Horai R et al. IL-17 production from activated T cells is required for the spontaneous development of destructive arthritis in mice deficient in IL-1 receptor antagonist. *Proc Natl Acad Sci USA* 2003;100:5986-5990.
29. Kotake S, Udagawa N, Takahashi N, et al. IL-17 in synovial fluids from patients with rheumatoid arthritis is a potent stimulator of osteoclastogenesis. *J Clin Invest* 1999;103:1345-1352.
30. Honorati MC, Meliconi R, Pulsatelli L, et al. High in vivo expression of interleukin-17 receptor in synovial endothelial cells and chondrocytes from arthritis patients. *Rheumatology (Oxford)* 2001;40:522-527.
31. Kunwar S, Dahal K, Sharma S. Anti-IL-17 therapy in treatment of rheumatoid arthritis: a systematic literature review and meta-analysis of randomized controlled trials. *Rheumatol Int* 2016;36(8):1065-75.
32. Yamada H, Nakashima Y, Okazaki K, et al. Th1 but not Th17 cells predominate in the joints of patients with rheumatoid arthritis. *Ann Rheum Dis* 2008;67:1299-1304.
33. Benham H, Norris P, Goodall J et al. Th17 and Th22 cells in psoriatic arthritis and psoriasis. *Arthritis Res Ther* 2013;15:R136.
34. Mease PJ, McInnes IB, Kirkham B, et al. Secukinumab inhibition of interleukin-17A in patients with psoriatic arthritis. *N Engl J Med Overseas Ed* 2015;373:1329-39.
35. Shen F, Gaffen S. Structure–function relationships in the IL-17 receptor: implications for signal transduction and therapy. *Cytokine* 2008;41:92-104.

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