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Joanna Witoszyńska-Sobkowiak, Dorota Sikorska, Włodzimierz Samborski

Department of Rheumatology, Rehabilitation and Internal Medicine, Poznan University of Medical Sciences, Poznan, Poland

Influence of inflammation on tryptophan metabolism in chronic rheumatic diseases: the role of the kynurenine pathway in an interferon-dependent mechanism in systemic lupus erythematosus and primary Sjögren's syndrome — a literature review

ABSTRACT

Under physiological conditions, the metabolism of tryptophan (TRP), an endogenous amino acid, leads to the formation of the neurotransmitters regulating mood and sleep and wakefulness patterns – serotonin and melatonin, among others. In inflammation, it is metabolised predominantly along the kynurenine pathway. This is caused by activation by pro-inflammatory cytokines [e.g. interferon (IFN) or tumour necrosis factor alpha (TNF-α)] of one of the enzymes: indoleamine 2,3-dioxygenase (IDO), which catabolises the synthesis of kynurenine (KYN) from TRP. Products of the kynurenine pathway, such as KYN, kynurenic acid, 3-hydroxykynurenine and quinolinic acid, are neuroactive and immunomodulatory substances. Elevated IFN levels and increased IDO activity are characteristic of chronic autoimmune diseases, including systemic lupus erythematosus and Sjögren's syndrome. This article reports on the role of the kynurenine pathway in the above diseases.

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Key words: tryptophan metabolism; kynurenine pathway; interferons; systemic lupus erythematosus; Sjögren's syndrome

INTRODUCTION

The central role of the kynurenine pathway, through its effects on the immune system, is to inhibit inflammatory processes and prevent the development of autoimmunity. The most potent activators of indoleamine 2,3-dioxygenase (IDO), a key enzyme of the kynurenine pathway, are interferons (IFNs), especially interferon gamma (IFN-γ). In rheumatic diseases, systemic lupus erythematosus (SLE) and Sjögren's syndrome, in which IFNs play a significant role in the disease pathogenesis, IDO expression is elevated simultaneously. An association was also observed between overactivation of the kynurenine pathway and the disease's immune activity, with increased levels of pro-inflammatory cytokines, antinuclear antibodies and hypocomplementaemia. Hence, the question is posed of how the activation of IDO and the metabolites of the kynurenine pathway affect the clinical picture in the above diseases. According to the authors, this article is the first publication summarising the effects of the IFN-activated kynurenine pathway on both the immune sys-

Address for correspondence:
Joanna Witoszyńska-Sobkowiak, MD, Department of Rheumatology, Rehabilitation and Internal Medicine, Poznan University of Medical Sciences, ul. 28 Czerwca 1956 r. 135/147, 61–545 Poznań, e-mail: jwitoszynska@orsk.pl

tem and organ lesions in patients with SLE and Sjögren's syndrome.

INTERFERONS

To date, three types of IFN have been described: type I, type II and type III. In rheumatic diseases, type I — alpha and beta — IFNs are most important [1]. Type I IFNs, via the interferon-α/β receptor (IFNAR), induce autophosphorylation of Janus kinase 1 (JAK1) and tyrosine kinase 2 (TYK2), which then leads to activation of signal transducers and activators of transcription (STAT) 1 and 2 [1, 2]. Subsequent binding to IFN gene regulatory factors (IRFs) results in the formation of interferon-stimulated gene factor 3 (ISGF3). ISGF3 activates the transcription of IFN-stimulated genes and the synthesis of antiviral and antitumour proteins [1, 2]. IFNs exert a number of different immunomodulatory effects: inducing B-cell activating factor (BAFF), immunoglobulin switching, increasing antigen presentation and T-cell and natural killer (NK) cell cytotoxicity [1]. They facilitate the influx of immune cells to inflammation sites by increasing the expression of cell adhesion molecules [1].

Type I interferon, which is divided into five classes (IFN-α, β, ε, κ and ω), is produced by immune cells, mainly plasmacytoid dendritic cells, as a response to viral infections and complexes containing nucleic acids from the host [2]. Plasmacytoid dendritic cells have increased expression of Toll-like receptors (TLRs) TLR7 and TLR9, making them susceptible to stimulation by endogenous and exogenous factors, e.g. single-stranded RNA or unmethylated DNA, which, by binding to the receptors, strongly induce the secretion of type I IFN, which plays a vital role in autoimmune diseases [1].

Type I interferon plays a significant role in the pathogenesis of SLE. Its high levels are associated with higher disease activity, greater susceptibility to renal involvement, skin and mucosal symptoms, arthritis and the emergence of autoantibodies such as anti-Sjögren's syndrome-related antigen A (anti-SS-A/Ro), anti-Smith (anti-Sm) or anti-double stranded DNA (anti-dsDNA) [3]. In SLE, IFN secretion is further stimulated by endogenous stimuli, such as autoantibody-mediated immune complexes arising from cell apoptosis or neutrophil extracellular traps (NETs), which release nuclear material (DNA, histones) when activated [2, 3]. Also, in primary Sjögren's syndrome (pSS), IFNs are recognised as key cytokines in the pathogenesis of this disease [1]. Overexpression of type I IFN, the so-called type I IFN signature, has been shown to be present in peripheral blood mononuclear cells and, as in SLE, is associated with the development of systemic extraglandular manifestations, e.g. from the joints, kidneys, lungs or peripheral nervous system, and significant production of autoantibodies and inflammatory cytokines [1].

At the same time, IFN-γ, through stimulation of transcription of the IDO gene, an enzyme of the kynurenine pathway, causes a reduction in T-cell activation and proliferation and stimulation of regulatory T cells, leading to the development of immunotolerance and immunosuppression. In addition, it exerts other effects dependent on the activation of the kynurenine pathway and its metabolites [4].

KYNURENINE PATHWAY AND ITS METABOLITES

Tryptophan (TRP), an exogenous amino acid, undergoes two main transformations. It can provide a substrate for producing serotonin (5-hydroxytryptamine, 5-HT) and melatonin, and 4% are used for protein synthesis [5, 6]. However, 90–95% of it is metabolised via the kynurenine pathway, leading to the formation of several active metabolites. The final product is nicotinamide adenine dinucleotide (NAD+), an important source of energy for cells [5].

The first stage of the kynurenine pathway is the metabolism of TRP to N-formyl-kynurenine, which is then converted to kynurenine (KYN) [5]. Two enzymes are involved in this reaction: tryptophan 2,3-dioxygenase (TDO), which is expressed mainly in the liver, and IDO, which is found in peripheral tissues and the central nervous system [6]. Inflammatory factors such as IFN-γ, tumour necrosis factor alpha (TNF-α) and pro-inflammatory interleukins (ILs) cause excessive IDO activation [7]. The metabolism of KYN may take place via three routes and lead to the formation of kynurenic acid (KYNA), 3-hydroxykynurenine (3-HKA) and anthranilic acid (AA). KYNA is synthesised by kynurenine aminotransferases (KATs), 3-HKA by kynurenine 3-monooxygenase (KMO) and AA by kynureninase [5]. In addition to the irreversible transamination of kynurenine to KYNA, KATs

can also catabolise the conversion of 3-HKA to xanthurenic acid (XA) [5]. Furthermore, 3-HKA and AA can be converted to 3-hydroxyanthranilic acid (3-HAA), which, via an unstable intermediate, becomes quinolinic acid (QUIN) [5]. As mentioned, QUIN is converted into NAD+, the main cofactor for electron transport in the mitochondrial respiratory chain [5, 6]. 3-HAA can also, via 2-amino-3-carboxymuconate semialdehyde, be metabolised to picolinic acid (PIC) [8].

It was initially thought that the kynurenine pathway's main function was to produce energy for cells. However, increasing attention is now being paid to the importance of metabolites of the kynurenine pathway, called kynurenines, as compounds with neuroactive properties that also affect the endocrine and immune systems [9]. It is worth noting that the various metabolites of the kynurenine pathway exhibit opposing properties: neurotoxic, neuroprotective, oxidative and antioxidative [5, 8], and their effects depend on the balance between the activities of the pathway's enzymes that prevail under physiological conditions. IDO activity and certain metabolites of the kynurenine pathway directly affect immune function. The key role of the kynurenine pathway, through its effect on regulatory T cells, is to produce immunotolerance, i.e. inhibition of the response to one's own antigens, thereby preventing the development of autoimmunity.

RELATIONSHIPS BETWEEN INTERFERONS, THE KYNURENINE PATHWAY AND INFLAMMATORY DISEASES

In addition to their antiviral effect, first described in 1957 (Isaacs and Lindenmann) [10], IFNs also play an important role in cancer, inflammation and autoimmune processes [11]. Both SLE and pSS are autoimmune diseases showing a marked overexpression of genes regulated by type I IFN, referred to as the IFN signature [12]. However, elevated serum IFN levels have also been found in other rheumatic disorders: rheumatoid arthritis, systemic sclerosis, myositis, mixed and undifferentiated connective tissue disease [11]. Interestingly, an increase in IFN levels in SLE is, on the one hand, associated with high disease activity, severity of symptoms, particularly mucocutaneous and joint symptoms, and a higher risk of relapse [11]; on the other hand, it activates the kynurenine pathway, which reduces the inflammatory response and inhibits the development of autoimmune processes. IFN is the main inducer of IDO in many cell types, including fibroblasts, endothelial cells, tumour cells, monocyte-derived macrophages, mesenchymal stromal cells and dendritic cells [13]. Plasmacytoid dendritic cells, the primary source of type 1 IFN production, are also highly capable of producing IDO [14].

Both the IDO enzyme and some metabolites of the kynurenine pathway affect the immune system. IDO has the ability to inhibit NK cell and Th17 cell proliferation, reduce plasma cell numbers and stimulate IFN release by dendritic cells [13]. KYNA alters tumour necrosis factor-stimulated gene 6 (TSG-6) expression and thus inhibits TNF-α production [5]. KYN inhibits the antigen-specific T-cell response and induces apoptosis of Th1 cells while stimulating Th2 cells, resulting in a shift of the Th1/Th2 ratio in favour of Th2 cells [5]. As a ligand for the aryl hydrocarbon receptor (AhR), it causes T-cell polarisation to Foxp3+ regulatory T cells, which promotes systemic anergy towards the presented antigens [14]. Forkhead box protein 3 (Foxp3) is a transcription factor that plays an important role in the regulation of the immune response, as it is responsible for the formation of regulatory T cells, i.e. cells with suppressive properties. Foxp3 induces the differentiation of CD4+ T cells into CD4+CD25+Foxp3+ regulatory T (Treg) cells, which are capable of inhibiting other CD4+ cells and cytotoxic T cells, such as CD8+ T cells and NK cells [15]. IDO expression can also change the phenotype of CD4+ helper T cells from Th1 or Th17 to Foxp3+ regulatory T cells [14], further enhancing the immunosuppressive effects of the kynurenine pathway. The most potent inducer of the IDO enzyme is IFN-γ, a type II IFN [1, 5]. IFN-γ, produced mainly by T cells and NK cells [2], binds to STAT1, the nuclear factor-kappa B (NF-κB) and IFN regulatory factor 1 (IRF1), thereby regulating the IDO gene [5]. A number of other pro-inflammatory cytokines and inflammatory mediators, such as TNF-α, have a less potent stimulatory effect. IFN-γ is a key cytokine for Th1 responses, including those to intracellular pathogens and tumours [14]. By activating IDO, it simultaneously reduces the inflammatory response.

Thus, it appears that the balance between type I (α and β) and type II (γ) IFNs in autoimmune diseases determines the intensity of the immune response, including through effects on kynurenine pathway activation. Type

I IFNs are associated with high inflammatory activity (higher autoantibody titres and inflammatory cell activity), IFN-γ is associated with stronger activation of the kynurenine pathway, whose role is to suppress the inflammation that stimulates it, weaken the immune response and mitigate the autoinflammatory process [1]. Both type I and type II IFNs are involved in the pathogenesis of rheumatic diseases, which appears to influence the diversity of symptoms of these diseases, as discussed using SLE and pSS as examples [16].

SYSTEMIC LUPUS ERYTHEMATOSUS

SLE is a chronic autoimmune disease of varying severity, usually with periods of exacerbation and remission [17]. It is defined by a wide variety of symptoms and the presence of antinuclear antibodies (ANA) [18]. Although joint and skin symptoms and haematological abnormalities are the most common [19], many systems and organs can be involved in the course of SLE, including the cardiovascular, respiratory, renal and central nervous systems. Lupus nephritis and neuropsychiatric lupus are considered the most severe manifestations of the disease, resulting in a shortened life span for patients [18]. Due to the heterogeneous clinical picture, the diagnosis of SLE might cause difficulties. Also, the aetiology of the disease is complex and results from the interaction of genetic, epigenetic and environmental factors (UV light, viral infections, drugs) [18]. The prevalence of SLE is variable, depending on ethnicity (it is more common in people of African and Asian descent) and ranges from 40 to 200 per 100,000 population. It more often affects women with a female-to-male ratio 9:1 [18].

Both innate and adaptive immune responses, with overactivation of T and B cells, impaired immune tolerance, and decreased ability to remove immune complexes and apoptotic cells, are involved in the pathogenesis of SLE [17, 18]. As a result of impaired apoptosis, abnormal release of intracellular antigens occurs, leading to increased production of autoantibodies by B cells. Deposition of immune complexes in tissues results in activation of the complement system, recruitment of inflammatory cells and subsequent organ damage. Innate immune cells produce pro-inflammatory cytokines such as IFN-α, TNF and IL-1, which is accompanied by an abnormal regulation of type I IFN [18]. Levels of type I IFN, an inducer of the IDO enzyme in the KYN/TRP pathway, are therefore higher in SLE patients than in healthy individuals [20]. In addition, metabolic profiling of SLE patients has shown low TRP levels. Therefore, it can be considered a potential biomarker for the disease, differentiating patients with SLE not only from controls but also from patients with Sjögren's syndrome and systemic sclerosis [21]. Abnormalities in TRP metabolism and an increase in IDO activity under the influence of inflammatory factors in the course of SLE were observed more than 20 years ago and regarded as potentially linked to neuropsychiatric disorders in this patient group (Widner et al.) [22, 23].

The prevalence of depressive disorders in patients with autoimmune diseases is higher than in the general population. It is up to six times higher in SLE patients than in healthy individuals [24] and occurs in approximately 11–39% of patients [25]. For this reason, several papers have been published recently on the role of the kynurenine pathway in mood disorders, cognitive impairment or the link to chronic fatigue in SLE patients. Akesson et al. (2017) confirmed increased kynurenine pathway activation in patients with SLE. Compared to controls, SLE patients had higher plasma levels of KYN and QUIN and a higher plasma ratio of KYN to TRP, which measures IDO activity. Interestingly, these observations included patients with both active and inactive disease as measured by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). In contrast, TRP levels were significantly higher in the control group compared to the patient group with active SLE. The study established a correlation between levels of pro-inflammatory cytokines [IP-10 (IFN-γ inducible protein of 10kDa), TNF-α, IL-16] and KYN, QUIN and the KYN/TRP ratio, but not with TRP levels and, in the case of IFN-γ, only with QUIN levels. Thus, it demonstrates the importance of pro-inflammatory cytokines in activating IDO and its potential role in the pathogenesis of SLE. Aside from IDO, the glucocorticoid-induced enzyme TDO is also involved in the metabolism of TRP to KYN. However, a comparison of the KYN/TRP ratio in patients treated with prednisone and without steroid therapy showed no significant difference in the above study. However, contrary to assumptions about the role of the kynurenine pathway in the pathogenesis of depressive disorders, re-

sulting from a decrease in serotonin synthesis from TRP in inflammatory processes, no correlation between kynurenine pathway metabolite levels and depression was demonstrated. However, a weak correlation with fatigue was observed [25]. A recent study (Anderson et al. 2021) also provides similar conclusions. Activation of the kynurenine pathway as measured by elevated serum KYN/TRP and QUIN/KYNA ratios compared to controls was confirmed in SLE patients but was not associated with disease activity as measured by the SLEDAI. However, significantly higher QUIN/KYNA ratios were found in those with elevated anti-dsDNA antibody levels and hypocomplementaemia, i.e. with high immune activity. Although patients with SLE and an elevated QUIN/KYNA ratio were slightly more likely to be depressed, this was not statistically significant. Nonetheless, an association was found between the QUIN/KYNA ratio and poorer cognitive performance as assessed by match-to-sample (MTS) test assessing working memory and visuospatial processing [26]. Elevated QUIN levels in serum and CSF have also been shown in patients with neuropsychiatric manifestations of SLE [27], which may be explained by its neurotoxic effects on the central nervous system through enhanced oxidative stress and glutaminergic excitotoxicity.

In addition to neurological and psychiatric symptoms, nephritis is a frequent clinical manifestation of SLE, occurring in up to 50% of patients [28]. In the histopathologic classification of lupus glomerulopathy according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003, there are six classes that differ in course, prognosis and treatment. Class I includes minimal mesangial lesions, II — mesangial proliferative lesions, III — focal lesions, IV — diffuse proliferative lesions, V — membranous lesions, VI — advanced glomerular sclerosis [29]. Also in lupus nephropathy, abnormalities of TRP metabolism were found to be associated with disease manifestation and activity. Stimulation of IDO activity by type I IFN leads to increased TRP metabolism in the kynurenine pathway, reducing the availability of TRP for serotonin synthesis. Lood et al. (2015) demonstrated decreased levels of serotonin in the serum and platelets in SLE patients and their association with the presence of anti-dsDNA antibodies and nephritis, and thus with a more severe disease course [30]. Although the role of metabolites in the kynurenine pathway in the pathogenesis of chronic kidney disease was postulated earlier [31], an article on their role in SLE nephritis has only recently been published. In a study published in 2021, Anekthanakul et al. identify the PIC/TRP ratio as a potential biomarker for the diagnosis of lupus nephropathy. Patients, compared to controls, showed significantly higher levels of 3-HKA and reduced PIC. The kynurenine 3-monooxygenase enzyme, which is responsible for the synthesis of the metabolite 3-HKA that has the ability to generate reactive oxygen species and impair mitochondrial function, is located, among others, in podocytes, whose damage may lead to the development of class V lesions in the kidneys. Therefore, the PIC/TRP ratio appears to be particularly useful for differentiating membranous forms (class V) from proliferative forms (class III–IV) of lupus nephritis. Perhaps its use in clinical practice will enable therapeutic decision-making and treatment monitoring without the need for repeated renal biopsies [32].

Increased IDO activity found in SLE patients and associated with immune system activation was also considered as a predictor of exacerbation risk. As solar radiation is one of the factors that cause disease exacerbation, the variability of IDO activity was studied during three seasons — winter, spring and summer. A significant correlation was found between IDO activity and disease activity, as assessed by the European Consensus Lupus Activity Measurement (ECLAM) scale, both in spring and summer. High IDO activity in the winter was found to be a predictor of SLE activation during the sunny period. The authors of the article (Pertovaara et al.) explain this relationship with the inhibitory effect of IDO on T cells and its immunosuppressive effect, which becomes insufficient to suppress disease symptoms after additional stimuli such as ultraviolet radiation [33].

In recent times, increasing attention has been given to the role of disruption of the gut microbiome in the pathogenesis of many rheumatic diseases, such as SLE, but also rheumatoid arthritis and seronegative spondyloarthropathies. A study of mice genetically susceptible to lupus showed that one of the mechanisms that increase immunisation is the effect of bacterial flora on TRP metabolism. In animals with gut dysbiosis, a high-tryptophan diet resulting in elevated levels of KYN exacerbated the disease.

Hence, the authors of the study concluded that the interplay of an abnormal gut microbiota and impaired TRP metabolism overlapping with a genetic predisposition could lead to the development of autoimmunity and the onset of the disease [34].

SJÖGREN'S SYNDROME

Primary Sjögren's syndrome (pSS) is a chronic systemic autoimmune rheumatic disease that is marked by lymphocyte infiltration of the exocrine glands, particularly the salivary and lacrimal glands, leading to dry eyes (*keratoconjunctivitis sicca*), dry mouth (xerostomia) and a range of extra-glandular symptoms including joint, lung and renal involvement [1, 35, 36]. Immunologically, the disease is indicated by hypergammaglobulinemia, the presence of ANA (anti-SS-A/Ro, SS-B/La), rheumatoid factor (RF), and IFN production [37].

As in SLE, IDO overexpression was also found in pSS [38]. Blood analysis of patients diagnosed with pSS showed higher IDO-1 expression in dendritic cells compared to healthy subjects, and increased IDO activity in T cells and monocytes [1]. Therefore, the question of the potential influence of metabolites in the kynurenine pathway on the course of the disease and, in particular, the occurrence of dryness symptoms was also raised in this disease entity.

In an animal model, the presence of serum L-kynurenine (L-KYN) was investigated as a marker to differentiate patients with autoimmune-related symptoms, such as Sjögren's syndrome, from patients with dryness syndrome of other origin. SATB1 conditional knockout mice (SATB1cKO mice) were used for this purpose. Special AT-rich sequence-binding protein-1 (SATB1) is a chromatin organiser that regulates the expression of various genes and is found in many haematopoietic cell types, particularly T cells. SATB1cKO mice develop impaired immune tolerance and develop the symptoms typical of Sjögren's syndrome — immune cell infiltration and destruction of salivary glands with the presence of anti-SS-A and anti-SS-B antibodies. The IFN-γ-dependent increase in IDO levels in the salivary and lacrimal glands found in these mice occurs earlier than the symptoms of pSS. In SATB1cKO mice, serum L-KYN is detected as early as four weeks after birth; immune factors such as anti-SS-A or anti-SS-B antibodies were not found until four weeks later. The authors of this study postulate a role for L-KYN as an early, non-invasive biomarker of the disease that can be determined before the onset of clinical symptoms of dryness [39]. In 2020, Sardenberg et al. published results confirming the association of adipose infiltration present in the labial salivary gland biopsy of pSS patients, not only with IFN-γ activation but also with the presence of metabolites in the kynurenine pathway. In patients with present adipose infiltration, which is a late histological sign of inflammation, there were higher levels of kynurenines. In addition, they were more likely to show concomitant dysfunction of lacrimal glands (Schirmer's test $\leq$ 5 mm/5 min, 69.2% in patients with adipose infiltration *vs.* 41% without infiltration). The results of the above study thus show an association of the kynurenine pathway and its metabolites with greater damage to both salivary and lacrimal glands in pSS [40].

There are also reports on the effect of another TRP metabolite, serotonin, on ophthalmic symptoms in patients without a diagnosis of pSS and a correlation between serotonin levels in tears and dry eye symptoms [41]. This was experimentally confirmed by feeding mice a TRP-deficient diet, which resulted in a decrease in blood serotonin levels and a reduction in tear secretion due to impaired hormonal regulation mediated by the serotonin type 3a receptor (5-HT3aR) [42].

In pSS patients, activation of the kynurenine pathway was also analysed as a cause of chronic fatigue, which occurs in approximately 70% of this patient group [1]. Elevated IFN-induced expression of the *IDO-1* gene was confirmed in pSS patients, resulting in decreased synthesis of serotonin and melatonin from TRP. These substances are responsible for sleep, mood, and the feeling of fatigue. Interestingly, in pSS patients – contrary to SLE patients – there was no confirmed correlation between *IDO-1* expression and fatigue [16].

It has also been hypothesised that IDO activation plays a role in the induction of neurological symptoms — including hyperalgesia — in the course of Sjögren's syndrome, especially in patients with milder symptoms of dryness [38]. Stimulation of the kynurenine pathway also affects glutamatergic neurotransmission responsible, via the MNDA receptor, for pain perception [9]. This is supported by the fact that IDO activation was found in patients with chronic pain, including fibromyalgia [1]. However, some findings contradict

this relationship. In a study by Valim et al., IDO activity measured by the KYN/TRP ratio correlated positively with disease activity: elevated levels of C-reactive protein (CRP), hypergammaglobulinemia, reduced C3 and C4 complement components and glandular symptoms, but negatively with pain [43].

The effect of the kynurenine pathway on immune cells was also analysed. IDO is an enzyme that inhibits T-cell activity and induces the differentiation of Foxp3+CD4+ regulatory T cells (Tregs) [44]. Under the influence of IDO and KYN, undifferentiated CD4+ T cells are transformed into regulatory T cells, which are necessary to maintain immune tolerance and inhibit the initiation of autoimmune processes. In IFN-positive pSS patients, increased IDO activity was confirmed to correlate with an increased percentage of CD25 cells with high levels of Foxp3+Treg. IDO activity as measured by the KYN/TRP ratio was significantly elevated in pSS patients compared to healthy controls and reached significantly higher values in IFN-positive patients compared to IFN-negative patients. It was also related to the presence of anti-SS-A (anti-Ro-52 and anti-Ro-60), anti-SS-B autoantibodies and the presence of other laboratory parameters of disease activity — RF, CRP or immunoglobulin IgG, IgA, IgM levels [45]. The results of this study are consistent with previous reports of an association between abnormalities of TRP metabolism via the kynurenine pathway and disease manifestation and activity in pSS patients. Pertovaara et al. (2005) also described increased TRP degradation and IDO activity in pSS patients and its association with disease activity. IDO activity correlated with high levels of inflammatory markers (ESR, CRP), beta-2 microglobulin, IgA, and a positive ANA result, indicating its importance in the regulation of the immune response. In addition, IDO-positive dendritic cells can stimulate the synthesis of the anti-inflammatory cytokines: transforming growth factor β (TGFβ) and interleukin 10 (IL-10) and activate B cells, resulting in increased levels of beta-2 microglobulin and ANA titres [46]. Also, Furuzawa-Carballeda et al. (2013), evaluating the immunophenotype of peripheral blood cells by flow cytometry, found a higher percentage of IDO-expressing dendritic cells and IL-10-producing B cells in pSS patients compared to controls. This favours the differentiation of regulatory T cells expressing Foxp3 and capable of controlling organ-specific inflammation [47].

CONCLUSIONS

Overactivation of IDO is found in SLE and Sjögren's syndrome patients with high immunological activity. It is associated with elevated inflammatory parameters, higher levels of pro-inflammatory cytokines and the presence of ANA antibodies, and thus with a more severe disease course and increased risk of organ damage. Previous findings indicating a higher prevalence of anti-dsDNA antibodies in SLE patients with concomitant disturbances in TRP metabolism confirm the association of kynurenine pathway activation with the occurrence of lupus nephropathy in this group of patients. Similarly, in Sjögren's syndrome, IDO activity correlates with the presence of anti-SS-A and anti-SS-B antibodies, which is associated with damage to the salivary and lacrimal glands and thus the occurrence of dryness — the most typical symptom of this disease entity. This demonstrates the influence of the kynurenine pathway on disease manifestations in autoimmune disorders. Interestingly, although chronic inflammatory diseases are associated with reduced levels of TRP, the precursor of neurotransmitters regulating mood and sleep – serotonin and melatonin, no significant risk of depression was confirmed. Correlations with fatigue were observed only in SLE patients. Although the kynurenine pathway plays an immunosuppressive role, its inhibitory effect on the immune system in rheumatic diseases appears to be insufficient to suppress the symptoms of the disease.

POTENTIAL THERAPEUTIC OPTIONS

Currently, an increasing number of drugs affecting IFN — and thus indirectly the kynurenine pathway — have become available. These include JAK kinase inhibitors (tofacitinib, baricitinib, upadacitinib) or monoclonal antibodies against type I IFN (anifrolumab for SLE therapy), and drugs inhibiting plasmacytoid dendritic cells (BIIB059) are in clinical trials [11]. Immunosuppressive effects of the kynurenine pathway are currently being investigated in the treatment of cancer: for example, a selective IDO1 inhibitor, epacadostat in the treatment of melanoma [48]. However, for rheumatic diseases, there is still

a lack of reports on therapeutic options based on direct activation of the IDO enzyme or derivative metabolites with immunosuppressive and immunomodulatory properties. Knowing the role of IDO enzymes in inhibiting autoimmune processes, perhaps these will become the focus of further research.

AUTHOR CONTRIBUTIONS

J.W.S. — participation in the conception and design of the study, collection of literature, preparation of the manuscript and editing of the paper. D.S. — participation in the conception, content supervision, critical appraisal of the manuscript. W.S. — content supervision, critical appraisal of the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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