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Joanna Witoszyńska-Sobkowiak, Dorota Sikorska, Włodzimierz Samborski

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

# Tryptophan metabolism *via* the kynurenine pathway in selected rheumatic diseases: A review of the literature

## ABSTRACT

In chronic inflammatory diseases, as a result of pro-inflammatory cytokines, the enzyme indoleamine 2,3-dioxygenase (IDO) is excessively activated, resulting in increased tryptophan metabolism *via* the kynurenine pathway (KP). Both IDO and metabolites of the KP affect cells of the immune system, mainly T lymphocytes. In this way, they exert an immunosuppressive effect, reducing inflammation. Also in rheumatic diseases such as rheumatoid arthritis (RA), osteoporosis, osteoarthritis and ankylosing spondylitis, there is excessive activation of the KP. This publication reports on disorders of tryptophan metabolism found in the above-mentioned disease entities.

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**KEY WORDS: tryptophan metabolism; kynurenine pathway; rheumatic diseases; inflammation**

## INTRODUCTION

Indoleamine 2,3-dioxygenase (IDO) is the first enzyme of the kynurenine pathway (KP) that metabolises tryptophan (TRP) to kynurenine (KYN). The IDO enzyme has 2 isoforms: IDO1 present in the brain and peripheral tissues and IDO2 found in the liver, kidneys and antigen-presenting cells (APCs) [1]. In a further step, KYN can be converted to kynurenic acid (KYNA), 3-hydroxykynurenine (3-HKA) or anthranilic acid (AA), and the final product of the kynurenic pathway is nicotinamide adenine dinucleotide (NAD+) [2].

Initially, disorders of tryptophan metabolism — with trypophan being a precursor to neurotransmitter, serotonin, that is involved in mood regulation — were mainly linked to the development of depressive disorders. However, further studies proved the activation of the KP, not only in the pathogenesis of depressive disorders but also in other neuropsychiatric conditions such as bipolar affective disorder and schizophrenia [3] as well as in neurodegenerative diseases such as Alzheimer's disease, amyotrophic lateral sclerosis [4], Parkinson's disease and Huntington's disease [5] and multiple sclerosis [6]. Hence, the KP, whose stimulation was also described in many inflammatory diseases, has been of increasing interest to researchers. This is caused by excessive activation of IDO by pro-inflammatory cytokines, e.g., interferons alpha and gamma (IFN-$\alpha$, IFN-$\gamma$), interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-$\alpha$) [1]. Imbalance among metabolites of the KP was found in sepsis, inflammatory bowel disease, cancers, type 2 diabetes, and chronic kidney disease, among others [4, 7, 8]. Overactivation of KP enzymes also occurs in rheumatic diseases such as rheumatoid arthritis (RA) [7], seronegative spondyloarthropathies (SpAs) [9], systemic lupus erythematosus [10] and Sjögren's syndrome [11]. The main role of the KP, by reducing the activation and proliferation of effector T cells and stimulating regulatory T cells, is to develop immunotolerance and prevent the development of autoinflammatory processes [1]. Although there are numerous reports on the role of IDO in autoimmune di-

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

seases, the results of many of them are based on animal models and are often inconclusive, as presented in this article. Hence, the role of disorders of tryptophan metabolism in rheumatic diseases needs to be further explored, which currently places the KP as a focus of numerous studies.

## EFFECTS OF THE KP ON THE IMMUNE SYSTEM

Under physiological conditions, the expression of IDO by antigen-presenting cells is necessary to generate tolerance of the transplanted organ, an immunosuppressive environment in the gastrointestinal tract to foreign antigens ingested with food or inhibition of autoimmune processes [12]. The presence of IDO, also found in syncytiotrophoblast cells, provides an inhibitory effect of the KP on maternal T lymphocyte proliferation to prevent immune rejection of the fetus [13]. The immunosuppressive effect of IDO was initially thought to be due to a decrease in tryptophan availability, which was confirmed in infections. The IDO activation induced decrease in the amount of tryptophan needed for the development of bacteria inhibited their growth and multiplication. However, it is now known that the immunosuppressive properties of the KP metabolites are due to their ability to inhibit T-lymphocyte reactivity. The main effect of both IDO and KP metabolites, called kynurenines, on the immune system is to stimulate the differentiation and activation of regulatory T cells and thereby reduce the inflammatory response. Moreover, IDO activity inhibits the function of effector T cells, which are additionally more sensitive to Fas-mediated apoptosis in an environment with reduced tryptophan availability [14]. Reduced tryptophan levels result in the activation of general control nonderepressible 2 (GCN2) kinase in T cells, which is a stress signalling pathway that leads to the inhibition of proliferation of effector T cells in the G1 phase of the cell cycle [7, 14]. The activation of GCN2 kinase results in the down-regulation of the CD3 zeta (ζ) chain in CD8+ T lymphocytes, inhibition of Th17 cell differentiation and activation of resting CD4+ regulatory T lymphocytes [12]. IDO activation may also stimulate dendritic cells to produce anti-inflammatory cytokines such as transforming growth factor β and interleukin-10 (IL-10) [1] and reduces the production of pro-inflammatory interleukin-6 (IL-6) [15], further enhancing immune suppression. By inhibiting NK cell proliferation and function and enhancing NK cell apoptosis, the KP affects not only the adaptive but also the innate immune response [5]. Also, individual metabolites of the KP have direct effects on the immune system. *In vitro* studies on inflammatory cell lines, e.g., induced by administration of bacterial lipopolysaccharide, revealed the effect of KYNA on decreased TNF-$\alpha$ expression and secretion in leukocytes, decreased secretion of high mobility group box 1 protein in monocytes or human alpha-defensins (HNP1–3) in granulocyte cultures [4]. Furthermore, kynurenines induce apoptosis of type 1 (Th1) helper lymphocytes that secrete the pro-inflammatory cytokine IFN-$\gamma$, while stimulating type 2 (Th2) helper lymphocytes that produce the anti-inflammatory IL-10, thereby shifting the Th1/Th2 ratio in favour of Th2 lymphocytes and demonstrating the role of the KP in promoting Th2 responses [5, 16]. An anti-inflammatory role is also attributed to anthranilic acid, which can inhibit pro-inflammatory IFN-$\gamma$ and T- and B-lymphocyte proliferation [1]. Interestingly, AA is a precursor of some non-steroidal anti-inflammatory drugs (NSAIDs) such as mefenamic acid and diclofenac [1]. The immunomodulatory effects of metabolites of the kynurenic pathway occur, among other things, *via* G protein-coupled receptors 35 (GPR35). GPR35 receptors are expressed in many cells of the immune system and are present in human CD14+ monocytes, T lymphocytes, neutrophils and dendritic cells [5]. Kynurenic acid, as a GPR35 receptor agonist, can inhibit the phosphoinositide 3-kinase/protein kinase B (Akt) and mitogen-activated protein kinase pathways, resulting in reduced inflammation. Binding to the GPR35 receptor is responsible for an inhibitory effect on the IL-23/IL-17 cytokine axis and a reduction in the release of pro-inflammatory cytokines [4]. Metabolites of the kynurenine pathway, e.g. KYN, KYNA and xanthurenic acid, can regulate the immune system response to maintain immune tolerance, also through the aryl hydrocarbon receptor (AhR) of which they are ligands [5]. The aryl hydrocarbon receptor is a transcription factor that influences gene expression during the differentiation of immune cells such as dendritic cells, regulatory T lymphocytes and Th17 cells [17, 18]. Hence, activation of IDO1 and upregulation of its product, KYN, *via* the AhR receptor may regulate the inflammatory response [19].

## IMPORTANCE OF THE KP IN SELECTED RHEUMATIC DISEASES

### THE ROLE OF IDO IN THE PATHOGENESIS OF RA IN PRECLINICAL MODELS OF THE DISEASE

Rheumatoid arthritis is a chronic inflammatory disease with a predominant Th1/Th17 immune response [7]. Th17 cells, in the early stages of RA, recruit neutrophils, activate B cells and stimulate osteoclast differentiation. In contrast, Th1 lymphocytes — through inflammatory cytokines such as IL-2, IFN-$\gamma$, TNF-$\alpha$ — influence immune cells, causing activation of macrophages and B lymphocytes and thereby perpetuating the inflammatory response in the synovial membrane [20].

Due to the immunomodulatory effects of the KP, many studies have investigated its role in RA, confirming its involvement in the pathogenesis of this disease entity. RA patients were found to have lower serum tryptophan levels and elevated serum KYN/tryptophan ratio [21], increased IDO activity in the synovial membrane [22] and a relationship between reduced serum tryptophan levels and increased disease progression [23]. However, most conclusions regarding the role of IDO, a key enzyme of the KP, in chronic arthritis were provided by animal models of the disease. One example is collagen-induced arthritis (CIA), in which type II collagen injected into DBA/1 mice induces chronic arthritis, with a clinical picture resembling human RA [7]. In this experimental model of RA, administration of the IDO inhibitor — 1-methyl tryptophan (1-MT) — increased the frequency and severity of arthritis symptoms, depending on the Th1 immune response [24]. Also, IDO1 deletion increased the severity of arthritis and tissue damage, and the administration of adenoviral vectors encoding IDO1 to CIA mice alleviated disease symptoms [19]. Similarly, Criado et al. [25] described greater susceptibility to CIA and more severe RA in IDO-deficient mice. An increase in IDO expression, after immunisation with collagen, was found in dendritic cells of draining lymph nodes. High disease activity in IDO-deficient mice was related to increased production of pro-inflammatory cytokines by T lymphocytes: IFN-$\gamma$ and IL-17 in lymph nodes and the accumulation of Th1 and Th17 cells in inflamed joints, confirming the inhibitory effect of IDO on T lymphocytes [25]. In contrast, administration of L-kynurenine reduced clinical and histological signs of inflammation in a dose-dependent manner [25], demonstrating that not only the reduction in IDO activity is responsible for the severity of arthritis symptoms but also the decrease in the levels of its metabolites. These findings prove the protective role of the KP in the pathogenesis of arthritis.

However, there are contrary reports on the effect of the KP in other disease models. An example is the K/BxN arthritis model, in which deletion of IDO2 caused a decrease in autoantibody production and reduced disease activity [26]. K/BxN transgenic mice develop inflammatory joint disease, similar to human RA, characterised by cellular infiltration, the presence of pro-inflammatory cytokines, autoantibodies, and joint destruction [27]. The K/BxN model differs from the CIA model in that arthritis develops spontaneously, without the need for immunisation with adjuvants [27]. In contrast to the results obtained in the CIA model, the K/BxN model of RA showed that the administration of 1-MT resulted in the relief of arthritis. Inhibition of IDO, following 1-MT treatment, led to lower titres of autoantibodies and levels of inflammatory cytokines, due to a reduced autoreactive B-cell response [28]. The results of the above-mentioned studies reveal that the IDO enzyme, associated with its immunosuppressive effects, may increase autoimmunity under certain conditions by affecting B lymphocytes, and its role in arthritis still needs to be better understood.

### DISORDER OF THE KP AND THE DEVELOPMENT OF RA

In rheumatic diseases, the main role of IDO is to maintain tolerance to own antigens and prevent autoimmunity processes. The KP thus provides a protective mechanism against abnormal immune responses, however, this mechanism is sometimes insufficient to prevent disease progression. Synovial fibroblasts were found to have high IDO activity and thus have the ability to suppress Th lymphocytes and reduce inflammatory processes in the joints [19]. Tykocinski et al. [29] revealed that synovial fibroblasts inhibit Th1 cell proliferation in an IDO1-dependent mechanism. A decrease in tryptophan levels — caused by IDO activation — activates the GCN2 kinase pathway, resulting in phosphorylation of the alpha-subunit of eukaryotic initiation factor 2 (Eif2$\alpha$). As a result, there is impaired translation, down-regulation of the TCR receptor zeta ($\zeta$) chain in lymphocytes and inhibition of Th cell proliferation and IFN-$\gamma$ secretion.

This results in reduced immune responses and prevents excessive T-cell responses [29]. High IDO activity is also found in dendritic cells derived from the synovial membrane of RA patients, which reveal higher IDO expression than in healthy individuals [30]. Mature plasmacytoid dendritic cells from low-activity RA patients show high IDO expression and promote the differentiation of CD4+CD25– T cells into regulatory T cells that secrete the anti-inflammatory IL-10 [7]. RA patients also showed the presence of KYNA in synovial fluid and its ability to inhibit synoviocyte proliferation in vitro, thus preventing the synoviocyte hyperplasia that is a feature of RA [31]. Therefore, the results of the above-mentioned studies point to a protective function of IDO, whose role is to reduce the inflammatory process. This raises the question of why over-activation of the pathway, with potential immunosuppressive effects, does not always prevent autoimmunity and the development of arthritis.

One reason for the impaired immunosuppressive effect of the KP is the abnormal methylation of the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) gene promoter found in RA patients. Ligation of the B7 complex on dendritic cells with CTLA-4, which is expressed in the membranes of regulatory T cells, results in the activation of IDO1 in dendritic cells, which contributes to the maintenance of immunotolerance. Abnormal DNA methylation in the CTLA-4 promoter results in loss of IDO activation and reduced regulatory T cell function, limiting the anti-inflammatory role of the KP [19, 32]. A single-nucleotide polymorphism in the gene encoding IDO1 was also described in RA patients [19], which may also contribute to its dysfunction and the development of arthritis symptoms. It should also be mentioned that synovial fibroblasts inhibited, *via* tryptophan metabolism, the proliferation of Th1 cells without affecting Th2 and Th17 cells. Meanwhile, Th17 cells that do not show IDO1-mediated suppression are also involved in the pathogenesis of RA [29]. Although synovial fibroblasts, in RA patients, can inhibit Th cell proliferation, their effect is weaker than in osteoarthritis [29]. Similarly, dendritic cells from RA patients revealed higher IDO1 expression than dendritic cells from healthy subjects, however, did not inhibit the proliferation of autoreactive T cells from RA patients [27]. The reason for the resistance of T cells to IDO-induced tryptophan depletion is the increase, under the influence of pro-inflammatory cytokines (IFN-$\gamma$, TNF-$\alpha$), of the functionally active tryptophanyl-tRNA synthetase (TTS) in T cells from the synovial membrane of RA patients [27]. TTS is a cytoplasmic enzyme that mediates the binding of tryptophan to its specific t-RNA, and overexpression of TTS in T cells leads to increased tryptophan storage, providing a reserve for protein synthesis [7]. Therefore, RA is an autoimmune disease with abnormal IDO activity and impaired synthesis of KP metabolites, including KYN, a compound with immunomodulatory properties, and defective function of T lymphocytes, which impairs the immunosuppressive effects of the KP [33].

## OSTEOARTHRITIS

In the first step of the KP, the metabolism of tryptophan to KYN — in addition to pro-inflammatory cytokine-activated IDO — may also occur *via* tryptophan 2,3-dioxygenase, which is present in the liver and is stimulated by glucocorticosteroids [1]. Therefore, it appears that due to the increased levels of pro-inflammatory cytokines and the steroid therapy that is often used in this group of patients, activation of the KP in RA should be more expressed than in osteoarthritis. Meanwhile, IDO1 expression in synovial fibroblasts of RA patients was found to be lower than in osteoarthritis [29], and KYNA levels were higher in synovial fluid of patients with osteoarthritis than in patients with RA and SpAs, and it was related to pain scores and morning stiffness [30]. Overexpression of IDO1 was also found in the joint fluid of osteoarthritis patients compared to healthy controls [34]. IDO1 activity directly inhibits chondrocyte proliferation and type II collagen production, increasing cartilage degeneration. It has been suggested that IDO1 — through the expression of the tumor necrosis factor-stimulated gene 6 — stimulates chondrocytes to secrete matrix metalloproteinase 13, causing type II collagen degradation. Hence, the KP, being involved in immune processes that inhibit chondrogenesis, may play an important role in the early development of osteoarthritis [34]. On the other hand, however, the high expression of IDO — an enzyme with immunosuppressive effects — in synovial fibroblasts in the course of osteoarthritis may be an explanation for the less severe joint inflammation found in this disease, compared to RA [16].

## OSTEOPOROSIS

Osteoporosis is a systemic skeletal disease characterised by low bone mineral density, abnormal bone architecture and increased susceptibility to fractures, leading to reduced

quality of life, disability and premature death [35]. Also in osteoporosis, disruption of the KP and its association with bone metabolism was confirmed. An increased ratio of KYN to tryptophan, indicative of IDO activation, was found to be inversely correlated with bone mineral density [16]. An age-related significant decrease in tryptophan levels was also described, accompanied by an increase in KYN levels, which corresponds to a higher incidence of osteoporosis in the elderly [16].

In patients diagnosed with osteoporosis, before the implementation of therapy, serum levels of one of the metabolites of the kynurenine pathway — 3-hydroxyanthranilic acid (3-HAA) — were significantly, approximately eight times lower while serum AA levels were 6 times higher compared to healthy subjects. After two-year treatment with a bisphosphonate (etidronate) or a selective oestrogen receptor modulator (raloxifene), these values returned to levels comparable to the control group, accompanied by an increase in bone density in the bisphosphonate-treated group. Tryptophan levels also increased in the treated patients. Given that the tryptophan metabolite — 3-HAA, according to redox conditions, is both an oxidative and an antioxidant compound, it is postulated that the identified imbalance of the KP may cause oxidative stress that exacerbates disease progression [36].

Studies involving animal models revealed that KYN reduces bone mineral density by increasing osteoclastogenesis [37]. An osteoclast is a multinucleated giant cell derived from a haematopoietic stem cell of the myeloid lineage, which requires interaction with cytokines for further differentiation: M-CSF (macrophage colony-stimulating factor) and RANKL (receptor activator of nuclear factor kappa-B-ligand) [38]. RANKL, produced by osteoblasts, is the ligand for the membrane receptor RANK (receptor activator of nuclear factor kB*)* present on the surface of osteoclast precursors. The binding of RANK to RANKL triggers the signalling cascade that is necessary for the differentiation of haematopoietic progenitor cells into osteoclasts and the activation of mature osteoclasts that have bone resorptive activity [39]. In mouse cells, KYN was found to induce osteoclast differentiation *in vitro*. Under the influence of KYN, RANKL-mediated activation of the transcription factors such as c-fos and NFATc1 (nuclear factor of activated T-cells cytoplasmic 1) occurs, increasing the number of tartrate-resistant acid phosphatase (TRAP)-positive osteoclasts and a decrease in bone mineral density [37]. In contrast, the deletion of AhR — the receptor for KYN — in mouse osteoclasts resulted in the inhibition of cell differentiation, reduced bone resorption and increased bone mass [40]. However, the result of a study published in 2021 [18] regarding the effect of KYN on osteoclastogenesis in human cells provided a different conclusion. AhR activation, in this case, inhibited osteoclastogenesis through suppression of the NFATc1 protein — a key transcription factor in osteoclast differentiation. Kynurenine, which is an AhR agonist, caused inhibition of osteoclastogenesis in human cells, particularly at the early stage of osteoclast differentiation, where AhR is highly expressed [18]. These distinct insights into the effect of KYN on osteoclasts may be due not only to the fact that the studies were conducted on human or mouse cells but also due to different signaling cascades resulting from AhR stimulation. AhR induces intracellular signaling *via* both classical genomic pathways, as in the case of the KYN-induced increase in RANKL-mediated osteoclastogenesis, and non-genomic pathways. Activation of the non-genomic pathway causes, among other things, the release of c-Src tyrosine kinase which leads to protein phosphorylation and, *via* E3 ubiquitin ligase, causes proteasomal degradation of NFATc1 and consequently impairs osteoclast formation and function [18]. Moreover, there were positive effects of the KP on stimulating osteoblasts and increasing bone formation, e.g., mice with IDO deletion had reduced osteoblast number and osteopenia [40]. Although most publications portray the role of the KP as promoting osteoclast activation and the development of osteoporosis, the results of the above-mentioned studies show opposing effects of its metabolite — KYN — on bone remodelling. Furthermore, the stimulatory effects of KP metabolites, on both osteoblasts and osteoclasts, highlight the need to better understand their influence on the balance of bone formation and resorption.

## SERONEGATIVE SPONDYLOARTHROPATHIES

Axial SpAs are a group of chronic inflammatory diseases that mainly affect the axial skeleton, which are characterised by sacroiliitis HLA-B27 antigen presence and clinical signs such as inflammatory back pain and morning stiffness. Axial forms of seronegative SpAs include ankylosing spondylitis (AS), in which structural changes in the sacroiliac joints are visible on an X-ray, and the non-radiographic form of SpA [41].

Increased tryptophan metabolism was also observed in this disease group. SpA patients were found to have lower tryptophan levels and patients with AS and juvenile idiopathic arthritis had elevated serum KYN levels compared to healthy subjects [42]. Disruption of the KP in AS patients and its association with inflammation has been recently confirmed [9]. Tryptophan, KYNA and 3-HKA levels were lower in AS patients, while KYN and quinolinic acid levels were higher, compared to controls. The increased ratio of KYN to tryptophan found in AS corresponded to IDO activity [9]. Both levels of inflammatory parameters: C-reactive protein (CRP) and IL-6, as well as disease activity as measured by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scale, were negatively correlated with plasma tryptophan levels and positively correlated with KYN levels and the KYN/tryptophan ratio, confirming the role of inflammation in IDO activation [9]. Since AS is characterised by excessive bone formation, along with syndesmophyte formation in the spine, impairment of the KP was analysed by the study authors as one of the causes of abnormal bone remodelling. The KP interacts with osteoblast differentiation and many of its metabolites affect bone remodelling. Bone mass is reduced by 3-HKA through the inhibition of osteoblast activity. The opposite effect is exerted by picolinic acid and 3-HAA whose age-related decrease promotes the development of osteoporosis [43]. Similarly, quinolinic acid — through binding of N-methyl-D-aspartate receptors expressed in osteoblasts and osteoclasts — influences altered bone metabolism in SpA patients [9]. The described imbalance between kynurenines, higher levels of quinolinic acid, which increases bone mineral density, and decreased 3-HKA are considered as one of the causes of excessive bone remodelling in AS [9]. Another of the products of tryptophan metabolism that may regulate bone formation is serotonin, which is an inhibitor of osteoblastogenesis. Serum serotonin levels were found to be significantly lower in AS patients, compared to healthy subjects and RA patients. Furthermore, there was an additional decrease in serotonin levels in AS patients after treatment with TNF-$\alpha$ inhibitor, which was not found in patients with RA — a disease associated with the bone loss [44]. Perhaps the decrease in serotonin levels in SpA patients, after treatment with TNF-$\alpha$ inhibitor, was due to a decrease in the availability of tryptophan, from which serotonin is synthesised. Indeed, the analysis of the effect of the treatment used on the level of metabolites of the KP revealed that both patients who were treated conventionally (NSAIDs and/or disease-modifying antirheumatic drugs) and with TNF-$\alpha$ inhibitors had lower KYN/tryptophan ratio and thus there was inhibition of IDO activity; however, the TNF-$\alpha$ inhibitor-treated group revealed lower levels of tryptophan, KYN, KYNA and quinolinic acid than those receiving standard therapy [9]. On the contrary, the metabolome analysis of serum samples from AS patients who were treated with the Janus kinase inhibitor, upadacitinib, revealed an increase in the level of tryptophan under treatment and its association with disease activity, a decrease in CRP levels and Ankylosing Spondylitis Disease Activity Score (ASDAS-CRP) [45]. Unfortunately, although the above findings indicate an association of IDO activation with inflammation, higher disease activity and abnormal bone remodelling, there are still few reports on the effect of the applied treatment on the metabolites of the KP and the resulting clinical consequences.

## SUMMARY

Tryptophan metabolism *via* the kynurenine pathway, through its effects on immune cells, plays a significant role in regulating the immune response. By reducing the inflammation that activates it, this metabolism provides a counter-regulatory mechanism [4], preventing excessive immune responses and the development of autoimmunity. In chronic inflammatory diseases, which include rheumatic diseases, pro-inflammatory cytokines (e.g., IFN-$\gamma$, TNF-$\alpha$, IL-6, IL-12) and other inflammatory mediators increase IDO enzyme expression, while anti-inflammatory cytokines (IL-10, PD-1) inhibit it. Therefore, it appears that a local balance between pro-inflammatory and anti-inflammatory factors determines IDO activity and maintains immune homeostasis and immunotolerance [5, 46]. Perhaps one of the causes contributing to the development of rheumatic diseases is an abnormality in the activation of the KP or an imbalance between its different metabolites and enzymes, which still requires further research and a better understanding of the abnormal tryptophan metabolism in diseases of autoimmune aetiology.

## CONFLICT OF INTEREST

None declared.

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