J Mol Med (2007) 85:1351–1359
DOI 10.1007/s00109-007-0229-7

REVIEW

IDO expression in the brain: a double-edged sword

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Received: 22 January 2007 / Revised: 6 April 2007 / Accepted: 11 May 2007 / Published online: 27 June 2007

Abstract The tryptophan-catabolizing enzyme indoleamine-2,3-dioxygenase (IDO) initiates the first and rate-limiting step of the kynurenine pathway. It is induced by proinflammatory cytokines such as interferon-β and interferon-γ and has established effects in the control of intracellular parasites. The recent detection of its decisive function in immune tolerance at the maternal–fetal interface stimulated various studies unraveling its regulatory effect on T cells in many pathologies. In the brain, IDO can be induced in microglia by interferon-γ-producing T helper (Th) 1 cells, thereby initiating a negative feedback loop which downmodulates neuroinflammation in experimental autoimmune encephalomyelitis (EAE), the animal model of multiple sclerosis (MS). This protective effect could to be counteracted by the production of neurotoxic metabolites of the kynurenine pathway such as quinolinic acid, which are produced upon IDO induction. Some metabolites of the kynurenine pathway can pass the blood–brain barrier and thus could act as neurotoxins, e.g., during systemic infection. In this paper, we give a brief overview on established immune regulatory functions of IDO, review recent data on IDO expression in the brain, and propose that autoimmune neuroinflammation and the increasingly appreciated neuronal damage in MS are linked by Th1-mediated IDO induction through subsequent synthesis of toxic metabolites of tryptophan.

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Keywords Indoleamine-2 · 3-dioxygenase · Interferon · Tryptophan

Introduction

Mammals have two different oxygenases for the degradation of the essential amino acid tryptophan (Trp). The tryptophan dioxygenase (TDO), which is primarily

expressed within the liver, catabolizes the main part of dietary Trp for the maintenance of serum levels. The second enzyme is the indoleamine 2,3-dioxygenase (IDO), which represents the first and rate-limiting enzyme of the kynurenine pathway in extrahepatic tissues. This enzyme was first described by Higuchi et al. [1]. IDO is a heme-containing enzyme that catalyzes the oxidative cleavage of the Trp pyrrol ring, thereby producing *N*-formyl-kynurenine, which is then further degraded along the kynurenine pathway (Fig. 1).

IDO expression is inducible by the proinflammatory cytokine interferon-γ (IFN-γ) and to a lower extent by interferon-β (IFN-β) in several cell types including macrophages, dendritic cells (DC), and fibroblasts [2–5]. In the brain, murine and human microglia have been shown to express IDO upon treatment with IFN-γ [6, 7]. In peripheral tissues, IDO expression is a common mechanism to suppress the proliferation of infectious parasites such as *Chlamydia trachomatis* [8] and *Toxoplasma gondii* [9, 10] through Trp depletion. Moreover, metabolites of the kynurenine pathway also exhibit immune modulatory functions, e.g., during tumor maintenance [11] and allograft acceptance/rejection [12, 13].

During experimental autoimmune encephalomyelitis (EAE), IDO induction has been shown to downmodulate neuroinflammation [14–16]. However, the induction of IDO in the central nervous system (CNS) is delicate because several metabolites of the kynurenine pathway have well-established neurotoxic effects [17]. Given that multiple sclerosis (MS) is characterized by the massive influx of activated T helper (Th) 1 cells and loss of neurons, an increasingly appreciated hallmark of this disease [18, 19], we propose that neuroinflammation and neurodegeneration are linked by IFN-γ-mediated IDO induction and the accompanying production of toxic Trp metabolites.

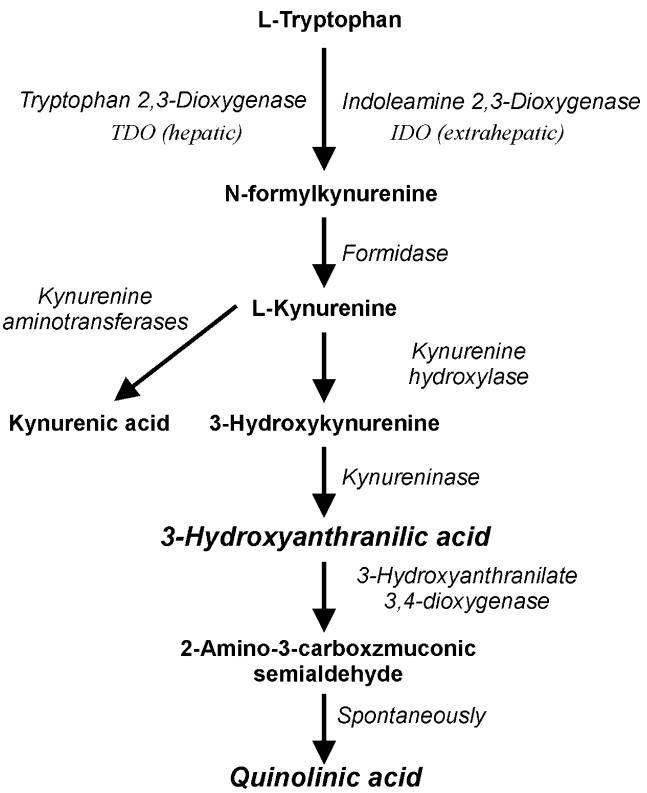

Fig. 1 The kynurenine pathway. Enzymatic degradation of tryptophan to kynurenic acid or quinolinic acid via the kynurenine pathway. Neurotoxic metabolites are labeled in *italics*

IDO in infection

Over the last decades, many studies with human cells showed that IFN-γ-induced IDO expression represents an important mechanism of antimicrobial resistance to parasites [9, 20, 21] and bacteria [8, 22, 23]. In all these cases, the functional expression of IDO and the subsequent degradation of Trp were identified as the effector mechanisms of microbial suppression. Induction of the kynurenine pathway was recently shown to be involved in downmodulation of a fungal infection of the gastrointestinal tract with *Candida albicans* [24]. In vivo, inhibition of IDO exacerbated the infection and its associated inflammatory pathology. In extension of previous studies, Montagnoli et al. [25] demonstrated a reduced number of $CD4^+$ $CD25^+$regulatory T cells (Tregs) in *C. albicans*-infected animals after IDO inhibition. This cell type is capable of downmodulating inflammatory and antifungal Th1 immunity in *C. albicans*-infected mice. In fact, the strain of *C. albicans* used in these experiments was Trp prototrophic. Therefore, the antifungal effect of IDO expression is likely to be mediated through the modification of the host's T cell.

Recent data demonstrate that IDO also plays a role in viral infections. The replication of cytomegalovirus and herpes simplex type I and II has been shown to be restricted by IFN-γ-induced IDO expression [26–28]. Opposite effects have been observed in the course of CNS infection with the human immunodeficiency virus (HIV). IDO activity is also increased in response to this virus [29], but IDO inhibition by 1-methyl Trp does not increase but rather decrease the viral burden. Remarkably, IDO inhibition amplified the number of HIV-specific cytotoxic T cells in HIV-infected severe combined immunodeficiency mice [30]. The HIV virus-infected cells seem to protect themselves from killer cell-mediated lysis by immunomodulation, thereby providing a niche hiding the virus from the immune system. Thus, during infection, IDO induction can exert divergent effects: On the one hand, it limits growth of infectious agents but also the strength of the immune response. The latter may be important to limit loss of infected cells in organs of poor regenerative capacity at the prize of viral persistence [31, 32].

Possible mechanisms of IDO-mediated tolerance induction

In contrast to the liver, Trp degradation is restricted to pathologic conditions in all other organs. The functional expression of IDO initiates the kynurenine pathway during which the degradation progresses along several enzymatic reactions (Fig. 1). Intermediates such as kynurenic acid (KA), quinolinic acid (QUIN) and 3-hydroxyanthranilic acid (3-HAA) have strong effects on many cell types including lymphocytes and antigen-presenting cells (APC). Munn et al. [33] were the first to demonstrate that blocking the IDO during pregnancy in mice causes tolerance breakdown and fetus rejection. Since then, several studies have confirmed a major role of IDO in the maintenance of immune tolerance [16, 34]. Two mechanisms have been proposed to explain the downmodulatory effect of IDO activation on T cells:

1) Munn et al. [33] hypothesized that in analogy of its function during infection, IDO activity creates a Trp-depleted microenvironment limiting the proliferation of T cells.
2) Fallarino et al. [4] showed that Trp degradation products enhance the susceptibility of T cell to apoptosis.

In fact, IDO activity depletes Trp from the culture medium of human macrophages and activated T cells cultured in such medium arrest in a late G1 phase [35]. This Trp starvation-mediated arrest has been shown to be caused in part by the stress-activated GCN2 kinase [36]. However, T cells not only stop proliferation when they are kept under Trp-depleted conditions, they also become highly sensitive to CD95L (FasL)-induced apoptosis [37]. CD95L-mediated deletion of activated T cells is a common mechanism of self-limitation of inflammation [38] and important to minimize inflammation-mediated damage in sensitive tissues such as the brain and the eye [39].

While IDO is inducible in many cell types, its regulation in DC turns out to be decisive for shifting the balance between tolerance and immunity. DC are professional APC. The type of DC presenting an antigen determines the T cell-polarizing signals and thus the T cell differentiation into Th1, Th2, or Treg. In the case of tolerance induction, the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) plays a crucial role. CTLA-4 blocks the CD28-B7 costimulatory signaling, which is essential for functional T cell activation [40]. CTLA-4 immonoglobulin (CTLA-4-Ig) induces IFN-γ expression in DC and thereby an auto- or paracrine induction of IDO expression in the local microenvironment, providing the conditions for long-term survival of allogeneic islet transplants [41]. In cell cultures, DC expressing B220 or CD8α upregulate IDO expression when they are cocultured with CTLA-4-expressing T cells [42].

IDO-expressing DC inhibit T cell proliferation in vitro even when Trp is still available in the medium [43]. This effect is caused by kynurenine, 3-hydroxyanthranilin, and 3-HAA, which are all Trp metabolites produced downstream of the kynurenine pathway [44]. Moreover, 3-HAA and QUIN induce CD95L-independent apoptosis via caspase 8 in activated Th1 but not Th2 cells [4]. This effect can be increased by lowering Trp concentrations in cell cultures [43]. The restriction of these effects to Th1 cells may represent an IDO-dependent mechanism of immune deviation during inflammation.

Interestingly, in $CD123^{+}$DC, IDO expression is induced by interleukine 10 (IL-10), an anti-inflammatory cytokine expressed by Treg cells [45]. While in most investigated in vitro models, IFN-γ is the main inducer of IDO in macrophages, DC, fibroblasts, and microglia [2–5, 46], its expression can also be triggered by lipopolysaccharide (LPS) through an IFN-γ-independent mechanism [47]. The induction of IDO expression without IFN-γ signaling is not dependent on signal transducer and activator of transcription 1α and interferon regulatory factor-1 but requires p38 mitogen-activated protein kinase and nuclear factor-κB [48]. Thus, IDO induction is not restricted to Th1 cells secreting INF-γ but alternate triggers involving IL-10 and LPS. This is in line with the observation that Th2-mediated experimental asthma is also abrogated by functional expression of IDO [49].

An undesirable case of tolerance induction is the manifestation of tumors. The first recognition of tumor antigens by T cells occurs in the tumor draining lymph nodes. Within such lymph nodes, there is a population of plasmocytoid DC (PDC) expressing B220, CD11c, and CD19. These PDC induce T cell anergy and immunosuppression in vivo by the constitutive expression of IDO [50]. $CD19^{+}$PDC are also found in neighboring lymph nodes and spleen, but in contrast to the PDC from tumor draining sentinal lymph nodes, they do not express IDO constitutively. The tumor itself is therefore likely to trigger IDO expression in draining lymph nodes by an as yet unknown mechanism. One possible way of induction could be the binding of CTLA-4 expressed by Tregs, which have been shown to induce IDO expression in DC in vitro [44, 51]. The adoptive transfer of IDO expressing PDC in vivo induces not only a systemic unresponsiveness to antigens [52] but also antigen-specific anergy of T cells within lymph nodes [50].

Tolerogenic mechanisms are not only active in sentinal lymph nodes but were also found within the tumor itself, and IDO expression may represent one of such mechanisms [34]. In fact, the tumor cell line P815 becomes resistant against immunological deletion when the cells were trans-

fected for constitutive IDO expression. In ovarian and colorectal cancer, IDO expression within the tumors correlates to malignancy [53]. In support of this concept, colorectal tumors exhibiting a high IDO activity have a significantly reduced number of $CD3^+$ infiltrating T cells and show an increased frequency of metastases [54]. Thus, determining IDO expression in tumors may be used for clinical prognostic in the future. Moreover, IDO inhibitors could increase the success of antitumor treatment [11].

The kynurenine-pathway and neurotoxic metabolites in the brain

Two Trp degradation products, QUIN and 3-HAA, exhibit neurotoxic properties. QUIN is an endogen *N*-methyl-D-aspartate (NMDA) receptor agonist [55]. At micromolar concentrations, the excitotoxic effect of QUIN can be mimicked in primary cortical neuronal cell cultures [56]. The same effect is found in vivo where intracerebral injection of QUIN induces excitotoxic lesions [17]. The second neurotoxic Trp metabolite is 3-HAA, which is unstable under physiological conditions. Upon spontaneous auto-oxidation, 3-HAA produces reactive radical species, which in turn induce oxidative stress and apoptosis in neurons [57–59].

In a dead end side branch of the kynurenine pathway, KA is synthesized by kynurenine aminotransferases (KATs). KA is known as a noncompetitive NMDA receptor antagonist [60]. Therefore, KA might counteract the neurotoxic effect of QUIN. Indeed, blocking of the kynurenine pathway at the kynurenine hydroxylase stage reduced the neuronal damage after cerebral ischemia in vivo [61] and postischemic neuronal death in slice cultures [62].

As anticipated, such treatment forced Trp degradation to the KA branch [59, 63]. To analyze the biological role of KA, Yu et al. [64] created a knockout mouse deficient for KAT2 expression. KAT2 is the aminotransferase substantially contributing to the KA formation in the CNS [65]. These mice exhibit a decreased KA formation within the CNS for the first 3 weeks of life, which afterward returns to control levels as seen in wild-type mice. No significant differences in the production of QUIN or 3-HAA were observed at any age [64]. The delayed compensation was assumed to be caused by the alternative KAT1 enzyme or by other enzymes that exhibit KAT activity. To analyze a neuroprotective effect of endogenous KA in vivo, Sapko et al. [66] induced excitotoxic lesions by the injection of QUIN in 14-day-old $KAT2^{-/-}$ mice. In comparison to wild-type mice, the lesion volumes were significantly increased in the knockout. If the same experiment was performed in 2-month-old mice, the lesion volumes were similar in knockout and wild-type animals. This suggests that the CNS-specific synthesis of KA by KATs represents a neuroprotective mechanism, which at least in part counteracts the neurotoxic effects of QUIN.

The neurotoxic effects caused by chronical induction of the kynurenine pathway have been analyzed in several diseases. Mackay et al. [67] reported an increased Trp katabolism to kynurenine but not to QUIN in the serum from patients with brain injuries even several years after injury. They proposed that this might be a result of increased activity of IDO and/or TDO. QUIN accumulates within the cerebrospinal fluid (CSF) of humans after traumatic brain injuries [68] and is increased in the CNS but not in the blood of gerbils after cerebral ischemia [69]. It is therefore tempting to speculate that trauma-induced IDO activation induces secondary neuronal damage via accumulation of neurotoxic metabolites. First evidence for this hypothesis derives from studies of spinal cord injury. Inhibition of 3-HAA oxygenase attenuated QUIN accumulation after spinal cord injury and reduced the severity of injury-related functional deficits [70, 71]. A similar mechanism may also be active in HIV encephalopathy. HIV-infected macrophages within the CNS express IDO. The way of its induction by the virus is currently not clear, but it is plausible that IFN-γ or even virus particles themselves trigger it [72]. However, HIV-1 is known to persist within the CNS [73], and as discussed above, its persistence seems to involve IDO-mediated immune deviation [30]. Thus, the chronic production of neurotoxic substances such as QUIN may cause part of the damage leading to HIV dementia [74].

Increasing data show the involvement of the kynurenine pathway in several neurodegenerative diseases such as Parkinson's, Huntington's, and Alzheimer's disease, epilepsy, and amyotrophic lateral sclerosis and in mental disorders such as schizophrenia and depression [75]. It is remarkable that even an acute injury of the brain induces long-lasting alterations in Trp degradation with a shift toward detrimental metabolites [67]. The respective enzymes thus are promising therapeutic targets for the future. However, it is noteworthy that many human cells respond to stimulation with IFN-γ, Tumor necrosis factor-α (TNF-α), and LPS by much higher IDO activities than their murine counterparts. On the other hand, only the latter synthesize high amounts of reactive nitrogen species via inducible nitric oxide synthase induction in response to stimulation [76] rendering it difficult to transfer results from animal models to the human situation.

While the detrimental effects of QUIN and 3-HAA to neurons are well described, the cell types producing these metabolites under pathologic conditions are ill defined. In primary cell cultures, microglia, astrocytes,

and neurons have been shown to express IDO upon IFN-γ stimulation. Mass spectrometry of QUIN in these cultures revealed its degradation by astrocytes and neurons, suggesting that they do not contribute to neurotoxicity but to neuroprotection. On the other hand, stimulated microglia synthesize high amounts of QUIN [46]. This in vitro observation is in line with the immune histological identification of IDO-positive microglia/macrophages in EAE and viral encephalitis [15, 72]. Unfortunately, no marker exists to differentiate between intrinsic microglia and recruited macrophages. In activated macrophages, the kynurenine pathway is much more effective than in activated microglia [6, 46], and therefore, macrophages may provide significantly more harm for neurons.

Under physiological conditions, most Trp metabolites of the brain are primarily produced outside of the CNS. The first substrate for the kynurenine pathway, Trp, is transported into the CNS by large neutral amino acid transporters [77]. However, in the absence of local inflammatory signals, the vast majority of Trp is not degradative to neurotoxic substances [78]. L-Kynurenine is also imported into the CNS by large neutral amino acid transporters and subsequently taken up by astrocytes and maybe microglia [79]. 3-Hydroxykynurenine is incorporated in the same way as L-kynurenine. Both substrates are then degradative depending on the distribution of downstream enzymes and the glial subtype.

Activated microglia secrete high amounts of neurotoxic 3-HAA and QUIN, while astrocytes synthesize but do not release significant quantities of QUIN [46]. In cell culture of human astrocytes, IFN-γ induces not only the degradation of neurotoxic 3-HAA and QUIN but also enhances the production of neuroprotective KA. [46]. Thus, astrocytes might counteract the production of neurotoxins by microglia.

In the CNS of gerbils, 85% of extracellular QUIN is imported from the blood into the brain under normal conditions, while almost all (96%) QUIN is produced within the CNS after intracerebral LPS stimulation. After systemic immune activation, almost all QUIN within the CNS is imported from the blood raising the intriguing question of whether peripheral QUIN production, e.g., during infection, may provide harm to the brain [78].

In summary, kynurenines produced in the periphery can enter the CNS through the blood–brain barrier, where they can be taken up and degraded by glial cells in an IDO-independent way. It is currently unclear whether this capacity of glial cells can fully protect neurons under all conditions of peripheral pathology. In case of local damage, astrocytes seem to eliminate neurotoxins produced by microglia. If this delicate balance is deranged by infiltrating macrophages remains to be evaluated.

The kynurenine pathway in EAE and MS

Like many autoimmune diseases, MS is characterized by waxing and waning inflammation in the target organ. What initiates the onset of individual attacks is poorly understood, but there is some insight from animal models into what drives their termination and what cause tissue damage. In EAE, the animal model for MS, autoimmunity to myelin epitopes is induced by immunization with myelin epitopes or transfer of myelin-specific Th1 cells. Subsequently, leukocytes accumulate in perivascular cuffs around brain blood vessels. Many of these cells are Th1 lymphocytes, but there is also a high percentage (depending on the model, approx. 50%) of macrophages [80]. As a result of this inflammation, myelin is phagocytosed by macrophages and activated microglia. In addition, there is a significant degeneration of axons and neurons, which for long has been neglected [18, 19].

During the acute phase of EAE, tissue levels of the neurotoxin QUIN are increased in the lumbar and sacral parts of the spinal cord. Interestingly, the clinical disease severity and the QUIN concentration in the cervicolumbar spinal cord correlate well [81]. Immunohistochemical studies have shown that enzymes of the kynurenine pathway such as the IDO and kynurenine 3-mono-xygenase are mainly expressed by infiltrating macrophages/activated microglia in the perivascular/juxtavascular area during the acute phase of EAE [15, 56]. IDO expression and activity is increased in the acute and remission phase of EAE. The main inducer of IDO, the proinflammatory cytokine IFN-γ, is the key cytokine of encephalitogenic Th1 cells. TNF-α is also secreted by these Th1 cells and acts synergistically

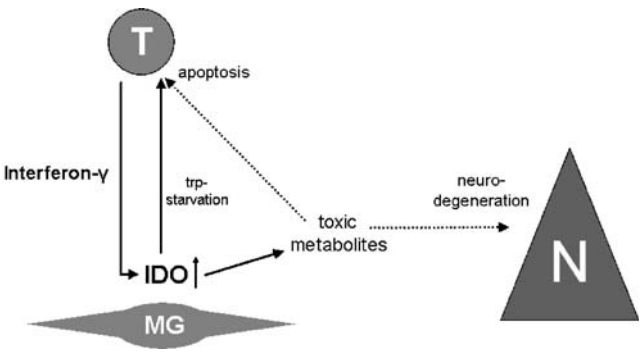

Fig. 2 The dual role of IDO: immune regulation and bystander damage. Immune regulation (*left side*): Infiltrating Th1 cells (*T*) secrete high amounts of interferon-γ inducing IDO expression in microglia (*MG*). Through the subsequent Trp depletion and production of toxic metabolites, T cell growth is inhibited, and apoptosis is supported. This negative feedback loop may underlie the self-limitation of inflammation not only in MS. Bystander damage (*right side*): IDO induction causes enhanced production of neurotoxins such as QUIN and 3-HAA. Excessive production during neuroinflammation is likely to contribute to neurodegeneration

with IFN-γ on the induction of IDO in macrophages and microglia [2, 6].

In analogy to the experiments by Munn et al. [33] in the placenta, the net effect of IDO induction during neuroinflammation has been tested by in vivo inhibition experiments. Daily application of the IDO inhibitor 1-methyl-Trp clearly exacerbated disease development and reduced the clinical recovery [14, 15]. The effects of IDO inhibition were similar when the treatment started in the preclinical phase [14] or at the onset of the acute phase of disease [15]. This observation suggests that the inhibition of IDO in the periphery is not crucial for disease development. Consequently, the local induction of the kynurenine pathway and the accompanying synthesis of Trp metabolites appear to downmodulate autoimmune CNS inflammation.

Recently, the anti-inflammatory effect of the kynurenine pathway reaction products was shown by intraperitoneally injection of 3-HAA and oral administration of its synthesized derivate *N*-3,4-dimethoxycinnamoyl anthranilic acid (DAA). Both substances significantly reduced the relapse phase in immunized SJL mice [16]. Splenocytes from animals that had been treated with 3-HAA or 2,4-DAA showed decreased proliferation of T cells and expression of IFN-γ and TNF-α. Moreover, treatment of immunized mice with 3-HAA or 3,4-DAA also shifted inflammatory lymph node cells to a potentially regulatory cell type with a decreased IFN-γ secretion and an increased production of IL-10 [16].

From all these studies in EAE, one can interpret IDO induction by IFN-γ-secreting Th1 cells as a protective negative feedback loop eventually terminating neuroinflammation [15]. However, this interpretation by no means excludes significant bystander damage through toxic Trp metabolites as the downside of such self-limitation (Fig. 2). Conversely, the apparent tight control over IDO expression in the brain supports this view. Currently, little is known as to the induction of IDO and the subsequent synthesis of bioactive kynurenines within the CNS during MS. Kepplinger et al. [82] described an increase in KA in the CSF of MS patients during relapse, and Barans et al. [83] described low activities of the KA synthesizing enzymes KAT I and KAT II in postmortem MS brains. The latter results were supported by the analysis of CSF probes from MS patients where a decrease in KA was found in the relapse phases [84]. However, changes in the synthesis of KA do not necessarily lead to an alteration in the synthesis of QUIN or 3-HAA. Consequently, modulation of the kynurenine pathway in human MS remains to be further investigated.

The overall beneficial effects of IFN-β treatment in MS are poorly understood but often explained by a shift from Th1 to Th2-mediated immune responses. Interestingly, IFN-β induces the kynurenine pathway and the synthesis of QUIN in human macrophages, although to a lesser extent than IFN-γ [5]. This is in line with the observation that treatment with IFN-β increased the relative IDO activity in blood serum samples (Kyn/Trp) from MS patients [85]. However, increased IDO activity was not found in specimens deriving from patients who received long-term treatment with IFN-β. This is of note, as QUIN and 3-HAA induce secondary degeneration of neurons and potentially of oligodendrocytes [86]. This must be taken into account when testing therapeutical strategies targeting the kynurenine pathway in MS. Moreover, the contribution of Trp metabolites to the increasingly appreciated axonal and neuronal damage in MS [19] must be further explored.

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