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Review

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Antiviral activity of interferon-γ involved in impaired immune function in infectious diseases

Abstract: Pro-inflammatory cytokines like interferon-γ (IFN-γ) play dominant roles in pathophysiologic conditions like infections, cardiovascular and neurodegenerative disorders and autoimmune syndromes. As part of its antimicrobial and immunomodulatory armature, the tryptophan-degrading enzyme indoleamine (2,3)-dioxygenase (IDO) is mainly up-regulated in dendritic cells (DCs) and phagocytes by pro-inflammatory stimuli, most notably IFN-γ. By the breakdown of the essential amino acid L-tryptophan along the kynurenine pathway, IDO plays a key role in the inhibition of cell proliferation including that of activated T cells, thereby supporting immune tolerance in mammalian pregnancy, tumor development, allergic inflammation and allotransplantation. IFN-γ-induced tryptophan deprivation also seems to be involved in the pathogenesis of anemia and cachexia when erythroid progenitor cells suffer from insufficient amino acid supply or when protein biosynthesis of the organism is restricted by diminished tryptophan availability. This biochemical cascade seems also to be involved in the production of potentially neurotoxic tryptophan catabolites such as quinolinic acid, which ultimately leads to the development of neuropsychiatric symptoms like cognitive impairment and depression especially in patients suffering from severe and chronic infections.

Keywords: IFN-γ; indoleamin 2,3 dioxygenase; infection.

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Introduction

Within immune response against viral infections, large amounts of pro-inflammatory cytokines like interferon-γ (IFN-γ) are produced by activated T lymphocytes and natural killer (NK) cells. IFN-γ stimulates several antiproliferative biochemical pathways in fibroblasts, macrophages, endothelial cells and tumor cells. These include the inducible nitric oxide synthase (iNOS) as well as the kynurenine pathway, which is inter alia catalyzed by the immunomodulatory enzyme indoleamine (2,3)-dioxygenase (IDO). IDO is widely expressed in human tissues and cell subsets, and it degrades the essential amino acid L-tryptophan to ultimately form kynurenine derivatives and reactive oxygen species (ROS), thereby regulating T-cell proliferation and survival [1, 2]. In the early 1980s, it was demonstrated that tryptophan depletion due to IDO activity is crucial for the IFN-γ-induced growth restriction of *Toxoplasma gondii* in infected fibroblasts [3] (Figure 1). Later activation of IDO was also discovered as an effective antitumoral strategy during the Th1-type (=cellular) immune response [4, 5]. Deprivation of the essential amino acid tryptophan slows down protein biosynthesis and prevents cellular development and proliferation, and induction of IDO was primarily considered as an important part of the antimicrobial and tumoricidal activities of IFN-γ, which restricts cell metabolism, when growth of pathogens and malignant cells is halted by tryptophan starvation.

More recently, it has been recognized that activation of IDO also affects normal host cells like T lymphocytes and, in this way, can contribute to the development of immunotolerance and immunodeficiency [6]. Especially the activated and IDO-expressing dendritic cells (DC) appear to be important to induce regulatory T cells, which slow down T-cell responsiveness [7, 8]. Thus, IDO is considered as a critical factor in host response, directing whether immune activation is successful in controlling an infection or whether persistent infection is developing.

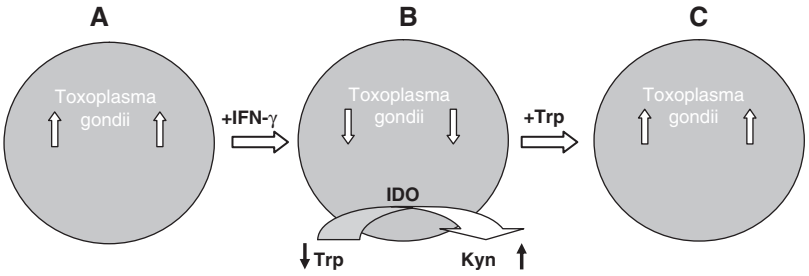

Figure 1 Fibroblasts are susceptible to infection with *Toxoplasma gondii* (A). Interferon-γ (IFN-γ) induces several microbicidal pathways in fibroblasts including the breakdown of tryptophan by indoleamine (2,3)-dioxygenase (IDO). In IFN-γ-treated fibroblasts, tryptophan concentrations decline and its catabolites like kynurenine accumulate. At the same time, growth of *T. gondii* is halted (B). Adding back tryptophan to cultures (C) allows *T. gondii* to grow again, which confirms a most important role of activated IDO to restrict the infectious process, and solely the deprivation of tryptophan is important rather than the production of toxic products within the kynurenine pathway of tryptophan conversion (see Ref. [1]).

Of late, a novel gene with homology to IDO has been reported and then subsequently demonstrated to encode an enzyme that catabolizes tryptophan [9, 10]. On the basis of its structural similarity, this enzyme has been referred to IDO as IDO-2. However, recent data have shown that IDO and IDO-2 may have a differential spectrum of expression and they may have different responses to IDO inhibitors [11].

In the last few years, it has been reported that IFN-γ-induced IDO activity in the development of immunosuppression is well in line with observations made from clinical studies in which tryptophan breakdown was found to be accelerated in infections with *Streptococcus pyogenes* and HIV-1 but also in autoimmune syndromes and in cancer [12–15]. In such patients, a higher degree of immune activation and IDO expression as well as lower serum tryptophan concentrations is detectable. Preferentially, in patients with a progressed disease, high tryptophan metabolism is associated with more rapid disease progression and worse survival expectations [16, 17]. Thus, activated IDO appears as a two-edged sword, on the one hand representing an effective strategy of immune response to restrict, e.g., growth of pathogens, and, on the other hand, down-modulating functional immune response. Accordingly, in infectious diseases, IDO could represent a critical factor in host response, directing whether immune activation is successful in controlling the infection or whether T-cell responsiveness is hampered, and, consequently, persistent infection develops [18].

Interferon-γ

Interferons are divided into type I interferons (IFN-α and IFN-β) and the immune type II or IFN-γ subtype. IFN-γ is one of the most versatile players of the immune response and belongs to a family of glycosylated polypeptides of 143 and 134 amino acids [19]. The main source of IFN-γ in humans is restricted only to a limited number of cell types that include natural killer (NK) cells and certain subsets of T lymphocytes such as $CD4^+$ and $CD8^+$ T cells [20, 21]. In NK cells, IFN-γ production is stimulated by cytokines, especially tumor necrosis factor-α (TNF-α) and IL-12, and via an autocrine loop by IFN-γ itself [22]. In T cells, the main inducer of IFN-γ is engagement of the T-cell receptor complex with its certain target antigen [23]. To exert effector functions, IFN-γ interacts with a specific cell surface receptor, which is ubiquitously expressed on all nucleated cells. This IFN-γ receptor consists of two subunits, a 90-kDa α-chain (IFNGR1), exhibiting the high affinity for ligand binding, and the 62-kDa β-chain (IFNGR2), which is primarily required for signaling [24]. Direct transcriptional activation of a number of genes referred to as the primary IFN-γ response, because it does not require the synthesis of new transcription factors, is initiated following activation of the JAK-STAT pathway. Thereby, tyrosine phosphorylation of specific Janus kinases (JAK1 and JAK2) and signal transducers and activators of transcription (STATs) STAT1α takes place. Cytosolic STAT1α subunits are then translocated to the nucleus as transcriptionally active homodimers, also called IFN-γ activation factor (GAF), that bind γ-activated site (GAS) elements in the promoter region of primary IFN-γ response genes and initiate transcription [25]. In terms of its immunologic functions in host responses, IFN-γ stimulates innate cell-mediated immunity through NK cells, specific cytotoxic immunity via the recognition of antigens expressed in association with major histocompatibility complex (MHC) molecules and, above all, the microbicidal and cytocidal activities of macrophages. Experimental infection studies with intracellular pathogens such as *Leishmania* and *Toxoplasma*

have shown that interference with the production or action of IFN-γ prevented primary immune clearance of these pathogens [26].

IFN-γ is an important mediator of innate and adaptive immune responses that play many critical roles in promoting both protective immune responses and immunopathologic processes and influences a remarkable range of distinct cellular programs [27]. During adaptive immune responses, both $CD8^+$ and $CD4^+$ T cells produce IFN-γ and are probably complementary in warranting protective levels of this cytokine. IFN-γ stimulates MHC class I and II expression; primes T cells towards a Th1-type cytokine pattern; inhibits Th2-type cytokine expression; stimulates intercellular adhesion molecules (ICAM-1), costimulatory signal (B7) and chemokine (e.g., CXCL9, CXCL10, CXCL11) expression; and modulates the immunoglobulin production of B-cells to orchestrate a complete immune response [28]. In addition to its forward-regulatory role in T-cell activation, within Th1-type immune response IFN-γ initiates several antimicrobial and antitumoral biochemical pathways in certain target cells. For example, in various cells, but especially in monocyte-derived macrophages, IFN-γ, together with TNF-α, induces enzymes like nitric oxide synthase (iNOS), GCH and IDO, and triggers the formation of ROS (Figure 2) [29–31]. iNOS produces nitric oxide that, upon reaction with superoxide anion, produces highly toxic peroxynitrite. IDO converts the essential amino acid tryptophan into kynurenine and subsequent degradation products in various cells [30]. Thereby, growth of microbes and tumor cells is affected, because tryptophan deprivation limits protein biosynthesis. Increased IDO activity is indicated by an elevated ratio of kynurenine to tryptophan concentrations (kyn/trp) [32]. Activation of GCH in human macrophages leads to the increased formation of biopterin derivatives such as 5,6,7,8-tetrahydrobiopterin (BH4), the necessary cofactor of iNOS. Human monocyte-derived macrophages and DC are deficient in the subsequent enzyme of BH4 biosynthesis, pyruvoyltetrahydropterinsynthase (PTPS), and thus produce excessive amounts of neopterin at the expense of BH4 upon activation with IFN-γ [33]. This scenario explains why neopterin production can serve as a reliable marker of Th1-type immune activation in humans and non-human primates but less so in other species [29]. Furthermore, this biochemical background helps to understand why there is an intrinsic defect in human macrophages to be stimulated for high output of nitric oxide by IFN-γ, due to the absence of BH4, iNOS function is improper. Neopterin itself accelerates oxidative capacity, e.g., it induces ROS formation in certain cells and may hence be regarded as an indicator for oxidative stress [29]. So it appears that the deficient production of BH4 in human macrophages can be compensated, at least partly, by the pro-oxidative property of neopterin. Surprisingly enough, humans with genetic inability to produce BH4, e.g., PTPS deficiency, do not necessarily present with an increased risk of infections [34], even though their iNOS has to suffer from the absence of BH4 cofactor.

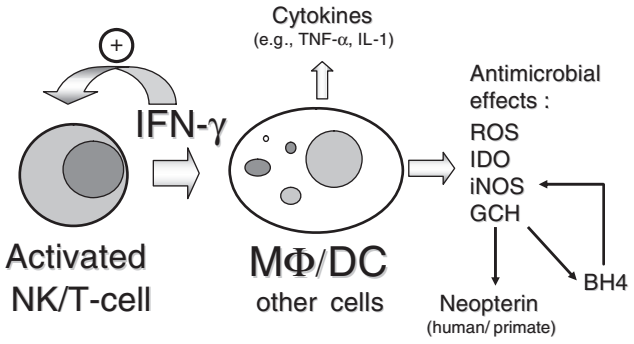

Figure 2 Within the cellular immune response (=Th1-type immune response) T cells and natural killer (NK) cells release pro-inflammatory cytokines like interferon-γ (IFN-γ). IFN-γ, on the one hand, is required for the development of an optimal T-cell response and, on the other hand, induces several antimicrobial and antitumoral (=antiproliferative) biochemical pathways in target cells that include the formation of reactive oxygen species (ROS) and enzymes like indoleamine (2,3)-dioxygenase (IDO), nitric oxide synthase (iNOS) and GTP-cyclohydrolase I (GCH). Because of the intrinsic deficiency of subsequent enzymes, GCH in human and primate macrophages (MΦ) and dendritic cells (DC) form neopterin at the expense of 5,6,7,8-tetrahydrobiopterin (BH4), the necessary cofactor of iNOS. Therefore, iNOS in human and primate MΦ and DC has impaired ability to achieve high output of nitric oxide (NO).

Like IDO activity, several other IFN-γ-mediated biochemical effects are aimed at suppressing the growth of cells carrying non-self-surface structures after infection with viruses, parasites or mycobacteria, or after malignant transformation. In sum, available data have given rise to the generally accepted concept that IFN-γ is critically involved and plays a physiologically relevant role in promoting host resistance to microbial infection and also to tumor development and progression.

Increased IDO-mediated tryptophan catabolism due to IFN-γ stimulation

The release of IFN-γ during infectious disease is the main stimulus for activating IDO in monocyte-derived macrophages, DCs, fibroblasts and various other cell types [35–37]. However, other cytokines like IFN-α, IFN-β and

TNF-α or lipopolysaccharides are also able to induce IDO, although to a much lesser extent [38]. IDO, a 42-kDa heme-containing enzyme, degrades the essential amino acid L-tryptophan to form *N*-formyl kynurenine that, depending on cell type and enzymatic repertoires, is subsequently converted to its final form, niacin and nicotinamide/adenine dinucleotides NAD and NADH (Figure 3). This process involves the cleavage of the five-membered indole ring. Once cleaved, the indole ring cannot be resynthesized by human metabolism. L-Tryptophan is therefore an essential amino acid, which is required for the biosynthesis of proteins and is the precursor for several biologically important compounds such as neurotransmitter 5-hydroxytryptamine (5HT, serotonin), formed by tryptophan (5)-hydroxylase followed by decarboxylation, and melatonin.

Increased IFN-γ concentrations during immune responses have been shown to lead to robust and sustained tryptophan depletion [39]. Recently, a clear association has been made between tryptophan catabolism and inflammatory reactions in a wide array of different diseases, with much of the focus centering on the kynurenine pathway of tryptophan breakdown occurring in the immune system.

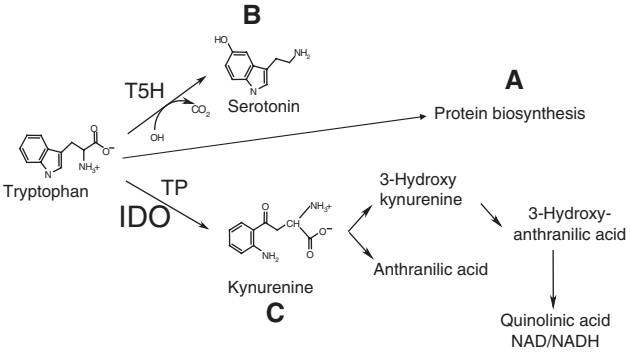

Figure 3 Essential amino acid tryptophan is required for three biosynthetic activities of cells: (A) tryptophan is an essential component of proteins, (B) tryptophan is a precursor for the biosynthesis of neurotransmitter 5-hydroxytryptamine (serotonin) by tryptophan 5-hydroxylase (T5H) and (C) tryptophan is a precursor for the biosynthesis of *N*-formylkynurenine by hepatic tryptophan 2,3-dioxygenase (TDO, tryptophan pyrrolase) and cytokine-inducible indoleamine (2,3)-dioxygenase (IDO). *N*-Formylkynurenine is hydrolyzed to kynurenine and, depending on the enzymatic repertoire of cells, can be further converted to products like kynurenic acid, quinolinic acid and/or the end products nicotinic acid adenosine dinucleotides NAD/NADH.

Interferon-γ induced IDO activity can limit cellular growth via tryptophan deprivation

IFN-γ-mediated tryptophan breakdown acts to reduce substrate availability for certain intracellular pathogens, bacteria or cancer cells, and contributes substantially to its antimicrobial and antitumor response [40]. Consequently, tryptophan depletion is regarded as a natural defence mechanism of immunocompetent cells, which is induced by IFN-γ during immune response. However, local tryptophan depletion has recently been hypothesized to represent also a mechanism for suppressing T-cell responses. Activation of IDO inhibits responsiveness of T cells to mitogenic stimulation *in vitro* and *in vivo* [7, 35, 41]. This is especially true when the enzyme is induced by IFN-γ in macrophages and DCs. It appears that not only tryptophan deprivation is important to arrest T cells within the G1 phase of the cell cycle, but also the pro-apoptotic effect of certain tryptophan catabolites like kynurenine is of relevance [6]. A report from Fallarino et al. [42] recently showed that 3-hydroxyanthranilate and quinolinate suppress T-cell proliferation, with apoptosis of Th1 cells being the proposed mechanism. Refaeli et al. showed that IFN-γ regulates T-cell survival by promoting apoptosis in activated T cells through a caspase-8-mediated mechanism [43]. It appears possible that this effect of tryptophan catabolites is achieved via their redox-manipulating character [44, 45].

Tryptophan depletion is also critically involved in DC functions. DCs are known as APCs that prime T helper cells and are also involved in tolerance induction towards self- and non-pathogenic foreign antigens [46]. Dependent on the state of DC maturation, these cells can activate lymphocytes to respond to a certain antigen or to induce tolerance to the presented antigen [47]. All these observations together support the view that activation of IDO together with other biochemical pathways induced by IFN-γ is an important anti-proliferative mechanism of monocyte-derived macrophages and DCs that, however, can also decrease the responsiveness of stimulated T cells and thus contribute to the development of immunodeficiency [48]. In general, IFN-γ-mediated metabolic activation of IDO during prolonged disease stages can be regarded as harmful to the host by slowing down T-cell responses.

Interferon-γ measurement

Measurement of circulating levels of IFN-γ in the serum or plasma of patients is hampered by the fact that cytokines, once released, usually bind very rapidly to target cells or

soluble receptors. Furthermore, the kinetics of cytokine production is tightly regulated. Significant production of IFN-γ can be detected *in vitro* following antigen- or mitogen-stimulated T-cell activation. In patients, measurement of IFN-γ concentrations may reveal positive results when done at the right time and place following a sufficiently significant insult [48]. Unfortunately, the sensitivity of assays very often turns out to be too low for broader application *in vivo*. Alternatively, measurements of biochemical products of IFN-γ activity can be undertaken to indirectly monitor the production of cytokines. This approach has the inherent advantage that it allows conclusions about the biological activity of cytokines, because it directly reflects the biochemical changes that were induced by IFN-γ in certain target cells. The monitoring of neopterin production and tryptophan breakdown is well suited for this purpose [29]. As mentioned above, both biochemical events are rather specifically induced by IFN-γ, and the measurement of neopterin, kynurenine and tryptophan concentrations is reliable in meeting the standards for laboratory diagnostic applications. Serum neopterin may be determined by immunoassays in an easy way, with neopterin concentrations averaging 5.3±2.7 nmol/L in the serum/plasma of healthy adults [49]. Because of the fact that neopterin is constantly distributed in body fluids, alternative or additional measurement of neopterin concentrations in urine specimens can be performed [50]. Tryptophan measurement in serum, plasma and other body fluids can be achieved by employing high-performance liquid chromatography (HPLC) on reversed-phase C18 columns [51]. Tryptophan is most sensitively monitored by its natural fluorescence at an excitation of 285 nm and an emission of 365 nm of wavelength. To assess the rate of tryptophan breakdown, it is, however, necessary to analyze the concentration of the first product of IDO reaction, namely, kynurenine, in parallel to tryptophan.

Interferon-γ and immunodeficiency

Immunodeficiency with reduced cell-mediated immune response occurs in a number of chronic infectious diseases, including tuberculosis, leishmaniasis and HIV-1 infection [52]. More recently, it has become increasingly apparent that cellular immunity is also suppressed in virtually all malignant diseases, including melanoma, colorectal and prostate cancer, and this becomes even more evident as the disease progresses [53]. However, the mechanisms underlying the immune defects noticed in cancer patients have not been fully elucidated [54]. In patients with HIV-1 infection, like in cancer patients, higher neopterin concentrations and kyn/trp predict a more rapid disease progression and shorter survival time, and both clinical conditions are associated with the development of immunodeficiency. The correlation between an increased kyn/trp and the concentrations of immune activation markers like neopterin (Figure 4) was able to confirm the involvement of IDO rather than TDO in tryptophan breakdown. Enhanced breakdown of tryptophan has been demonstrated earlier in several diseases, which go hand-in-hand with or are even characterized by acquired immunodeficiency. This is especially true for patients with HIV-1 infection, but also for various other mostly chronic diseases like autoimmune disorders, in which immunodeficiency develops as disease progresses and is a sign of poor prognosis [55]. Acquired immunodeficiency is the hallmark of progressing HIV-1 infection. In parallel, activation of several immune compartments has been observed including activation of B-cells, T cells and macrophages. Several parameters of immune activation were found to predict disease development in patients with HIV-1 infection [56–58], and data show that immune activation coexists with immune deficiency in such patients [58]. Notably, significant associations were observed between IFN-γ and

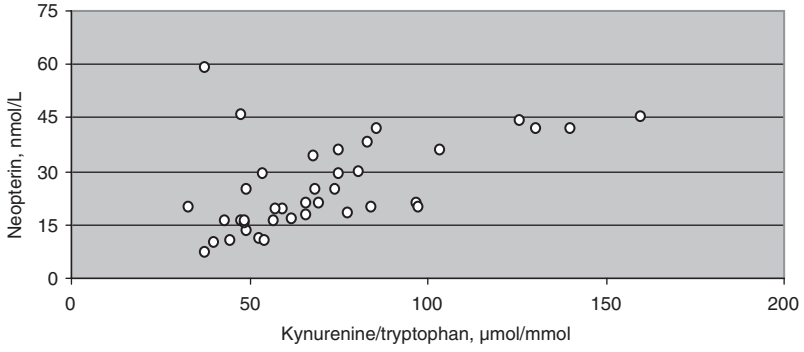

Figure 4 In patients with HIV-1 infection, a close association exists between the degree of tryptophan breakdown as is expressed by the kynurenine-to-tryptophan ratio (kyn/trp) and the concentrations of neopterin (n=38; rs=0.571, p<0.0001), which confirms their immunobiological background in common, namely, Th1-type immune response and interferon-γ (for comparison, see ref. [7]).

neopterin concentrations in the serum of patients with HIV-1 infection and with the rate of tryptophan breakdown [12]. Activation of IDO by IFN-γ could be involved in diminishing T-cell responsiveness in patients with HIV-1 infection, and reduced T-cell proliferative response to soluble antigens *in vitro* has been found to be associated with the immune activation status in these patients [59].

IFN-γ is involved in cachexia, anemia, organ failure and depression of infectious diseases

The majority of advanced-stage cancer patients, and also patients with chronic infections, often experience a wasting syndrome called cachexia, in which metabolic changes occur in the host leading to loss of adipose tissue and of skeletal muscle mass, as well as anemia is developing [60]. The process appears to be mediated by a broad range of pro-inflammatory cytokines acting either alone or in concert with certain cytokines such as IFN-γ [61]. No effective treatment is currently available for this cachexia syndrome and it must therefore be regarded as a strong independent risk factor [62]. As previously mentioned, tryptophan is essential for many cellular functions, including protein biosynthesis and cell proliferation, and an intracellular tryptophan deficiency alters these cellular functions substantially. Increased neopterin levels and kyn/trp were found to be associated with cachexia and weight loss [63] as well as with anemia [64]. Enhanced tryptophan breakdown appears to be involved in the development of these symptoms as well. Likewise, in patients with hematological neoplasias, low tryptophan concentrations were found to be associated with low serum albumin concentrations and weight loss [65]; this association was apparent at study entry and during patient follow-up. IFN-γ-mediated tryptophan deprivation may be the underlying mechanism that causes a slowdown of protein biosynthesis and, in turn, accelerates the breakdown of muscle proteins. Cytokines affect the homeostatic loop of body weight regulation in patients either by their involvement in the brain's serotonergic system (see IDO and mood changes) or by mimicking leptin, a member of the helical cytokine family [66] and one of the key targets for neuropeptidergic effector molecules that regulate food intake and energy expenditure via the sympathetic nervous system [67]. More direct evidence of cytokine involvement comes from experiments in which specific neutralization of cytokines can relieve cachexia in experimental animal models [68]. Examples are the anti-TNF-α, anti-IL-1 and anti-IFN-γ antibodies, although no single antibody could reverse all of the features of cachexia [69]. These studies revealed that cachexia is associated with cytokine activation and other cachectic factors that are orchestrated to induce major metabolic abnormalities [70, 71].

Anemia is another frequent complication in patients suffering from infections, especially in a chronic situation. In a considerable number of patients, no cause other than the infection itself can be implicated. Infection-related anemia is similar to the anemia observed in other chronic diseases, characterized by a hyporegenerative, normocytic, normochromic anemia associated with reduced serum iron and transferrin saturation. Recently, accelerated catabolism of tryptophan may play a role in the pathogenesis of anemia in states of chronic inflammation [64]. It is currently well established that pro-inflammatory cytokines IFN-γ and TNF-α suppress the growth and differentiation of erythroid progenitor cells [59], and these cytokines are crucially important in the pathogenesis of anemia. Notably, before its molecular characterization TNF-α was even denominated as "cachectin". Thus, IFN-γ-induced tryptophan deprivation appears to be involved in hematopoietic suppression in patients with, e.g., virus infections or tuberculosis, and the limitation of tryptophan availability may be a key mechanism in cytokine-mediated inhibition of erythroid progenitor cells. Indeed, such patients with increased tryptophan breakdown or neopterin production are more likely to present with anemia at the same time (Figure 5) [57, 65].

IFN-γ has been furthermore implicated in the pathogenesis of bone marrow failure. *In vitro*, bone marrow stromal cells genetically engineered to constitutively express IFN-γ markedly suppressed the proliferative capacity of

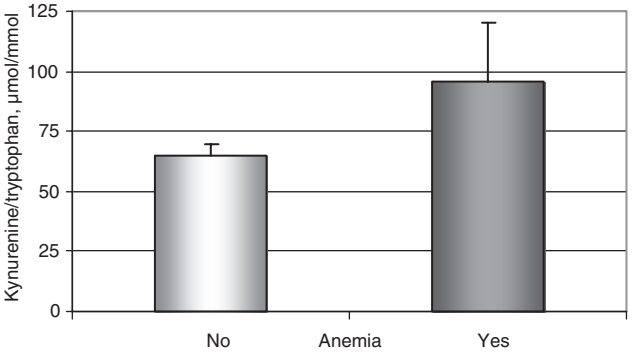

Figure 5 Tryptophan breakdown rate as is expressed by the kynurenine-to-tryptophan ratio relates to the risk of developing subnormal hemoglobin concentrations and anemia. The data show the results obtained from 39 patients with HIV-1 infection (for comparison, see ref. [59]).

erythrocyte, granulocyte and monocyte precursors [72]. Such impaired bone marrow function may also contribute to the development of multiple-organ dysfunction syndrome and multiple-organ failure in patients with infections.

Other distressing symptoms that debilitate patients with chronic infections and contribute to their profound fatigue are severe mood changes, subtle cognitive changes and depression. Insufficient availability of tryptophan reduces the biosynthesis of neurotransmitter 5-hydroxytryptamine (serotonin), which, in turn, can increase the susceptibility to develop mood disturbances and depression and which may also impair cognitive function [73]. Furthermore, downstream products of the tryptophan-kynurenine degradation pathway such as 3-hydroxyanthranilic acid and quinolinic acid can cause neuronal damage and dysfunction [74]. The latter is a potent neurotoxin, which interferes with the *N*-methyl-D-aspartate (NMDA) receptor and may thereby influence the neuroendocrine system in addition to the neuropathologic effects of tryptophan deprivation. Immune-mediated tryptophan breakdown by means of IDO may thus elicit neuropsychiatric symptoms when the availability of tryptophan is insufficient for normal serotonin biosynthesis (Figure 6) [75]. In patients with major depression, decreased serum tryptophan concentrations are found, correlating with increased concentrations of immune activation markers [76]. On the one hand, reduced concentrations of 5-hydroxyindoleacetic acid, the main catabolite of serotonin, are observed and confirm the insufficient availability of serotonin. On the other hand, treatment with selective serotonin-reuptake inhibitors (SSRIs) can be very effective in patients with depression. Similarly, enhanced breakdown of tryptophan due to immune stimulation could underlie the increased risk for the development of mood disturbances and susceptibility to depression in patients with chronic infections, especially when undergoing prolonged disease. Interestingly also, in patients with Alzheimer's and with Huntington's disease there exists an association between tryptophan breakdown and cognitive ability in the late phase [77, 78]. Aside from infections, in patients with advanced colorectal cancer enhanced breakdown of tryptophan was found to coincide with impaired quality of life [79]. Moreover, during treatment with IFN-α, a relationship between lower tryptophan levels and increased susceptibility of depression was reported recently in malignant melanoma patients [80]. Animal model system data are able to further substantiate these relationships: in a murine animal model system, IDO activity with increased kyn/trp after a single intraperitoneal injection of bacille Calmette-Guérin was found to precipitate the development of depressive-like behaviors as detected by the changes in the forced swim test and tail suspension test only in wild-type but not in IDO-/- knock-out mice [81]. Thus, it is apparently becoming clear that increased and sustained IFN-γ levels in the course of chronic infectious diseases are an integral mechanism in initiating the long-term, aforementioned side-effects of chronic immune activation that subsequently impair quality of life and aggravate the severity of tumor burden in this patient population.

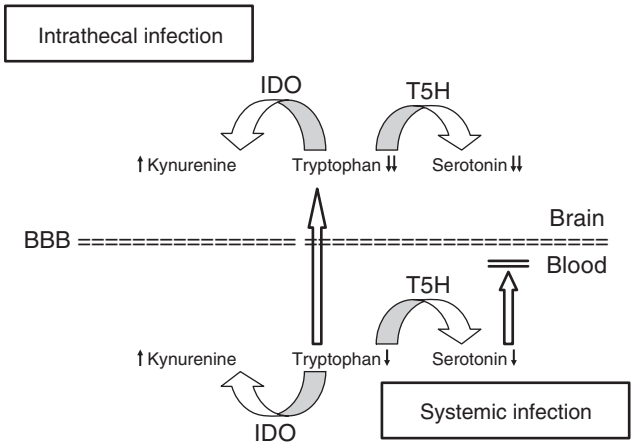

Figure 6 Cytokine-induced tryptophan breakdown is one important aspect for the increased susceptibility for depressive mood in patients suffering from chronic immune activation syndromes such as virus infections. In systemic infections (e.g., HIV-1 infection and sepsis), activation of indoleamine (2,3)-dioxygenase (IDO) results in low serum-free tryptophan concentrations, and accumulation of degradation products like kynurenine and quinolinic acid takes place in the peripheral blood. Low tryptophan levels diminish the availability and the biosynthesis of neurotransmitter 5-hydroxytryptamine (5HT, serotonin) by tryptophan 5-hydroxylase (T5H). Unlike serotonin, which does not cross the blood-brain barrier, the lowered blood tryptophan levels affect tryptophan supply in the brain. Low tryptophan availability in the brain then leads to subnormal brain serotonin concentrations, which increase the risk of depression in such patients. In case of cerebral infections (e.g., neuroborreliosis but also HIV-1-associated encephalitis/meningitis), IDO induction in the brain destroys tryptophan; in some cases, the levels reach concentrations <0.1 μmol/L, and breakdown products accumulate (for comparison, see ref. [59]). In addition, IDO activity in the brain is able to degrade serotonin as well, which is a substrate for IDO, albeit with lower efficacy than tryptophan.

IFN-γ-mediated pathways and neuropsychiatric complications in HIV-1 infection

Tryptophan breakdown, but also other IFN-γ-mediated pathways, may be crucially involved in the development

of central nervous system symptoms of HIV-1 infection. Patients with progressive HIV-1 infection tend to have neurologic/psychiatric disorders more often than healthy individuals; furthermore, they often complain about impaired quality of life [82–84]. Many HIV-1-infected individuals suffer from depression, anxiety and sleep disturbances, which importantly affect patients' quality of life [85]. A causal relationship between IFN-γ-mediated pathways and cognitive impairment as well as depression has been suggested. On the one hand, higher neopterin cerebrospinal fluid (CSF) concentrations were found in HIV-1-infected patients with neurologic/psychiatric symptoms in comparison to unaffected patients [86]. On the other hand, enhanced IDO activation within immune response is suggested to affect serotonergic functions [76, 85, 87, 88].

IDO activation could in fact contribute to the development of neuropsychiatric complications in HIV-1 infection. By decreasing tryptophan availability, IDO might impair serotonin metabolism severely (Figure 6): several studies have suggested that enhanced tryptophan catabolism in HIV-1-infected patients may be involved in the development of mood disturbances, AIDS-related dementia and peripheral neuropathy [30, 32, 89, 90]. Decreased tryptophan availability leading to decreased biosynthesis of neurotransmitter serotonin is supposed to increase the susceptibility for depressive disorders [91, 92] and may also impair cognitive function and sleeping [93]: in HIV-1-infected patients, lower tryptophan concentrations were associated with shorter and "less efficient" sleeping time. Sleep disturbances are frequently observed in patients with depression, which is also a major problem in HIV-1-infected patients.

Neopterin is able to penetrate through the blood-brain barrier [94]. The pro-oxidative activities of neopterin derivatives might enhance oxidative stress in the brain and induce/accelerate apoptosis in neuronal cells [95–97]. Recent data show that, in addition to invading monocytic cells, astrocytes can also represent a relevant source of neopterin in the brain [98]. Elevated neopterin concentrations are found in the CSF of HIV-1-infected patients, and strong intrathecal formation of neopterin has been described in HIV-1-associated dementia, with CSF neopterin concentrations being much higher than serum values [86, 99]. In patients with AIDS dementia complex, CSF neopterin concentrations were found to correlate with disease severity. Under treatment with zidovudine, CSF neopterin concentrations decreased with clinical improvement; in parallel also, CSF tryptophan concentrations increased significantly [100].

Recent, so far unpublished data from our group show that a high percentage of HIV-1-infected patients suffer from depression (27% mild depression, 14.5% moderate depression, 9.2% severe depression, according to Beck Depression Inventory scores) and have to take antidepressants. In parallel, many patients complain about impaired quality of life (as assessed by the Multidimensional Quality of Life Questionnaire-HIV/AIDS). Quality of life and mood disturbances were strongly interrelated in our study; however, associations were also observed between the two parameters and immune activation. These data from our cross-sectional study therefore confirm that immune activation might influence the central nervous system symptoms of HIV-1-infected patients; longitudinal studies investigating IFN-γ-mediated biochemical pathways as well as the effects of intervention therapy would certainly provide very interesting data. In that context, it should be mentioned that treatment of patients with interferons often leads to depression [101]. Although comparable studies are thus far not available in IFN-treated patients with HIV-1 infection, it seems noteworthy to mention that, in patients suffering from malignant melanoma, who were treated with IFN-α, tryptophan concentrations decreased and neopterin levels increased in patients developing depressive symptoms [102], confirming the hypothesis that interferons might enforce the development of depression.

IDO and other IFN-γ-mediated pathways in the development of immunodeficiency

Acquired immunodeficiency is characteristic for progressing HIV-1 infection. In patients, strong activation of several immune compartments has been described including activation of B-cells, T cells and macrophages. Several studies have tried to find out which cells are mainly responsible by Steinmann et al. for the development of functional anergy against HIV-1. HIV-1-specific CD8 T-cell responses are established to play an important role in limiting acute viral replication, but inappropriate maturation and impaired cytolytic capacity result in the inability of $CD8^+$ T cells to control viral replication in chronic infection [103]. Antigen-stimulated CD4 cell proliferation in contrast has been described to become impaired early, even in the asymptomatic phase, continuing to impair within the course of disease [104]. The molecular basis for such impaired responses is most likely multifactorial, and the interactions between different immunocompetent cells are complex.

The resulting immune and cytokine cascades are complex and a detailed description would be beyond the scope of this review. Rather the role of key players that are critical for the pathogenesis of HIV-1 disease, in the orchestra of immune response, shall be reviewed: IFN-γ acts as a potent positive regulator of immune reaction via modulation of antigen presentation, as well as of lymphocyte differentiation and proliferation. Along the first wave of cellular immune activation, it increases T cell activity by supporting Th1-type immune response and suppresses Th2-type immune response. However, ongoing and overwhelming activity of the pro-inflammatory cytokine during chronic immune stimulation goes along with the development of immunodeficiency. Due to an "exhausted immune response," HIV-1 can finally take over control. Reduced T-cell proliferation in response to soluble antigens *in vitro* is related to T cell activation status in HIV-1-infected patients [105].

Exhausted immune response is most probably a consequence of chronic exposure of immunocompetent cells to cytokines: cells are overstimulated over a long period of time and cannot react properly to "real" antigen stimulation, resulting in an increased susceptibility to opportunistic infections [106–108]. The failure of T cells to respond properly is, among other factors, a consequence of the reduced capability of peripheral blood mononucleated cells (PBMCs) to release cytokines like interleukin-2 (IL-2) or IFN-γ upon stimulation [33, 109–111]. Determination of antigen-stimulated cytokine formation by lymphocytes has been used as a sensitive *in vitro* test to assess the "quality" of immune response in HIV-1-infected persons [112], and, similarly, lymphocyte proliferation assays have also been used as prognostic markers. Impaired proliferative response of T lymphocytes to antigen stimulation is related to the stage of disease [113–115]; stimulated PBMCs of HIV-1-infected patients produce lower amounts of IL-2 as well as of IFN-γ compared to the PBMC of healthy controls [116]. Interestingly, exogenous substitution of cytokines is able to restore the proliferative response to antigens markedly *in vitro* [117, 118], whereas systemic administration of IFN-γ may rather result in an impaired proliferative response to mitogens [119]. A study performed in 1988 first showed that increased serum neopterin concentrations in HIV-1-infected patients were associated with diminished IFN-γ production of lymphocytes upon stimulation *in vitro* [120]. Similarly, stimulation with soluble antigens and alloantigens also led to diminished *in vitro* IL-2 production by the PBMC of seropositive patients with high neopterin concentrations [105]. Thus, increased systemic immune activation as reflected by elevated IFN-γ and neopterin concentrations in HIV-1-infected patients (i.e., *in vivo*) was recognized early to coincide with a reduced ability of immunocompetent cells to react to *in vitro* stimulation. Highly active antiretroviral therapy is able to improve the functional immune response of patients with HIV-1 infection, and, likewise, the improved immune function concurs with a lowered tryptophan breakdown rate [115].

Increased tryptophan breakdown in patients with HIV-1 was suggested to be involved in immunosuppression in 1991 [121]; still, despite several clinical studies, no studies were performed comparing the *in vivo* and the *in vitro* situation regarding IDO activity in HIV-1 infection until now. Recent data show that plasma tryptophan catabolism in HIV-1-infected individuals is related to mitogen-induced proliferation to some extent [117], but concentrations of immune activation marker neopterin were much better suited to estimating the proliferative response in response to mitogen concanavalin A or phytohemagglutinin. In fact, plasma neopterin concentration was identified as a strong predictor of impaired proliferative responses *in vitro*. *In vitro* proliferative responses to mitogen stimulation were better, the more IFN-γ was produced by PBMC. In line with these data, IFN-γ-mediated pathways, namely, tryptophan breakdown and neopterin formation, were more sustained in PBMC with better proliferative responses *in vitro*. Thus, these data indicate that immune-mediated tryptophan breakdown *in vivo* is one contributing factor, but not the only determinant of impaired proliferation of PBMC of HIV-1-infected patients. Still, IFN-γ and IDO activation might participate in the development of immunodeficiency by influencing the generation of regulatory T cells (Treg). A recent review proposed that IFN-γ produced rapidly and only transiently by induced Treg cells is crucial to their function *in vivo* [122]. $CD25^+CD4^+$ Treg cells are capable of modulating the tryptophan catabolism of dendritic cells, thereby priming them for tolerance induction [7] (Figure 7). In fact, IDO induction in dendritic cells has been supposed as a common mechanism of deletional tolerance by Treg cells [7]. In HIV-1-infected patients, decreased numbers of Treg cells have been described in the peripheral blood; however, in the tonsils and in the mucosal system, Treg numbers are increased and are positively associated with viral loads [123, 124].

IDO and transplantation

One of nature's most impressive examples of tolerance induction is the way an allogeneic fetus evades immune attack during pregnancy. This is considered a major

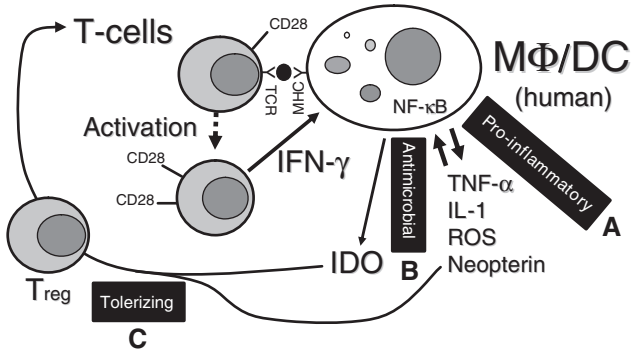

Figure 7 Th1-type immune response and induction of indoleamine (2,3)-dioxygenase (IDO) are substantial components of antimicrobial immune response. However, if the immunocompetent cells fail to destroy the invading pathogen on time, the antiproliferative strategies of cells become deleterious for the immune system itself. Interferon-γ (IFN-γ) released by activated natural killer (NK) cells and T cells induce several antimicrobial effects including specific enzymes, cytokines and reactive oxygen species (ROS), which orchestrate inflammation (A). Tryptophan breakdown by the enzyme indoleamine 2,3-dioxygenase (IDO) is directed to deprive infected cells of essential amino acid, which limits protein biosynthesis and thus growth and development of infected cells (B). As a side effect, the growth of normal human tissues such as T cells (C) and erythroid progenitors are also affected. Moreover, some of the compounds and tryptophan catabolites formed, namely, 3-hydroxyanthranilic acid, quinolinic acid and also neopterin, possess pro-apoptotic activity to counteract infection, which, however, is not selective for infected cells; it may also affect T cells. Finally, expression of IDO by dendritic cells (DC) triggers regulatory T cells (Treg), which counteract the activation of Th1-type immunity (C).

paradox in terms of transplantation immunology wherein the immunomodulatory enzyme IDO plays a vital role [125]. Munn and Mellor [126] were the first to report this IDO-dependent survival of allogeneic fetus. Blockade of tryptophan metabolism with pellets releasing 1-methyl tryptophan (1-MT) resulted in fetal abortion due to the activation of maternal T-cell responses. Furthermore, our own group was able to detect IDO expression in the human placenta as well as tryptophan metabolites in sera of pregnant women [127, 128]. These data suggest that IDO plays a dominant role in murine and human feto-maternal tolerance.

Both *in vitro* and *in vivo* studies have shown that increased IDO activity in transplanted cells has tolerogenic effects [129]. Novel costimulatory blocking agents like the fusion proteins CTLA4-Ig and CD40-Ig have been reported to have protolerogenic effects through the up-regulation of IDO expression in DCs [130]. These cells, furthermore, seem to induce a peripheral tolerogenic pathway via the increase of Tregs [131, 132]. Grohmann et al. reported that pancreatic islet transplantation in fully MHC-mismatched strains is successful upon temporary CTLA4-Ig treatment. In this case, allograft tolerance was halted through the administration of 1-MT, leading to the presumption that IDO was key to tolerance in this model. Subsequent experiments showed that CTLA4-expressing Tregs can exert an immunosuppressive effect via interaction with B7 molecules on DCs, through IDO functional activity [133, 134]. In summary, CTLA4 is a major signaling molecule for Tregs and DCs, and IDO has been implicated to be an important downstream effector for CTLA4-mediated immune tolerance. Although several trials conducted with costimmulatory blockers in humans [135, 136], in this species evidence for a cross-linked interplay of CTLA4 and IDO is still missing.

A large body of evidence suggests that $CD4^+$ $CD25^+$ Tregs play an essential role in the perpetuation of negative control over pathologic as well as physiologic immune responses [137–139]. Fallarino et al. addressed some of the physiologic mechanisms of IDO-mediated immunsuppression by showing that IDO-expressing DCs in mice can suppress $CD8^+$ T cell activity and can induce naïve $CD4^+$ T cells to develop into $Foxp3^+$ Tregs. These effects were mediated through GCN2 kinase signaling, which required tryptophan depletion and production of tryptophan catabolites [140]. These findings are in accord with the belief that $CTLA4^+$ Tregs have the ability to induce IDO-mediated immune suppression through the action of responsive CDs, suggesting the idea that there may be a nonlinear mechanism by which the tolerogenic DCs go on to recruit the development of additional Tregs, which, in turn, recruit more DCs through the action of IDO [141].

Interestingly, IDO does not seem to be involved in the maintenance of immune homeostasis under basal conditions because in IDO-deficient mice, central and peripheral tolerance seems to be not compromised, and these mice do not develop spontaneous autoimmune diseases. However, they fail to master potentially lethal T cell responses after the transfer of allogeneic $CD8^+$ T cells. CTLA4 treatment did not abrogate this effect in IDO-deficient hosts; however, in wild-type hosts, as a consequence of IDO up-regulation, CTLA4 has been shown to be effective in blocking $CD8^+$ T cell expansion [142].

Our own group has recently provided evidence that IDO expression could also serve as a marker for immune activation and allograft rejection. We were able to detect IDO expression only in transplanted kidneys suffering from allograft rejection. Increased serum kyn/trp as an estimate of DO activity was measured using HPLC. Patients who rejected their organs thereby displayed significantly higher serum kynurenine and lower tryptophan concentrations, reflecting IDO activity [143].

Tumor immunosurveillance by IFN-γ-mediated tryptophan catabolism: the role of IDO

The concept that immune escape is a critical gateway to malignancy has emerged over the past decade, and a variety of active mechanisms of immune suppression that are elaborated by tumors to drive this escape of immune attack have become apparent [141]. IFN-γ-induced IDO-mediated tryptophan breakdown is considered as one of the major possible mechanisms of this tumor-driven immune evasion. Cells that may contribute to these crucial escape mechanisms include regulatory DCs and Tregs. In cancer, regulatory DCs are important because they instruct $CD4^+$ T cells through B7 receptor signaling pathways to ultimately propagate immune response/suppression to tumor antigens. Early work in the field identified CD28 as the key T-cell surface receptor that mediates the aforementioned dendritic B7 regulation. "Positive" coregulatory B7 signals therefore instruct a T cell to resist the antigen, whereas "negative" B7 signals instruct the T cell to become tolerant to the antigen [144]. Several important negative B7 receptor signaling pathways have been described in the context of tumor immune escape including the T-cell coreceptor CTLA-4. CTLA-4 and other cell surface molecules like PD-1 and OX-40 present promising therapeutic targets [145], which could be antagonized by monoclonal antibodies. Early clinical work on CTLA-4 antagonists suggests an augmentation of tumor immunity along with the occurrence of a unique profile of immune-related adverse events including colitis, hepatitis and endocrinopathies [144].

Since IFN-γ is one of the strongest inducers of IDO expression and since it has sustained effects on tumor cell proliferation, the cross-linked interplay of IFN-γ and IDO seems to be of greater importance. *In vitro* studies suggest that IFN-γ has sustained effects on murine cancer cell proliferation when IDO expression is increased [146]. L-Tryptophan breakdown through stringent IDO activity has been shown to inhibit tumor cell proliferation effectively. However, these antiproliverative effects can only be reversed by supplementation of this essential amino acid. Similar results were obtained in human malignant cells [147], where IDO expression can be detected [148]. However, the clinical significance is still discussed controversially [149]. Our own group was able to show that IDO had a prognostic value in terms of liver metastasis in patients with colorectal cancer [150]. IDO expression goes along with reduced $CD3^+$ lymphocyte infiltration, suggesting a suppressive function on tumor reactive T cells. In patients with hepatocellular carcinoma, similar findings were reported [151]. Although our own findings did not suggest a correlation for IDO expression and patient survival, another study performed in primary metastatic renal cell carcinomas was able to show a positive correlation between IDO expression in endothelial cells of tumors and long-term patient survival [152]. Apart from IDO, neopterin has been shown to be a reliable prognostic marker for human malignancies [153]. Increased neopterin levels in patients with melanomas, breast cancers, squamous cell carcinomas, gynecological tumors and colorectal carcinomas have been shown to be associated with poor prognostic outcomes [16, 154–157].

Conclusion

In many pathologic conditions like infections, autoimmune syndromes, cardiovascular and neurodegenerative disorders as well as cancer and organ transplantation, immune activation and inflammation are strongly involved. Pro-inflammatory cytokines like IFN-γ play a dominant role in the clearance of infections but also in the development of inflammation. IFN-γ is probably one of the most important cytokines, which is released in large amounts during infections with viruses or intracellular bacteria and parasites. It induces several biochemical pathways and mechanisms in order to stop the growth of such microbes. However, if the immune system is unable to eliminate the infection, immune activation may persist and production of IFN-γ continues.

Whereas in human monocytic cells neopterin production is induced, in various cells, the expression of tryptophan-degrading enzyme IDO is induced by IFN-γ as a part of its antimicrobial activity. Activation of IDO restricts cell metabolism by tryptophan deprivation, and thus growth of pathogens and also of malignant cells is halted. As a side effect, development and proliferation of normal host cells like activated T lymphocytes are also restricted. Accordingly, IDO appears to represent a critical factor in host response, directing whether immune activation is successful in controlling an infection or whether T-cell responsiveness is hampered and, consequently, whether persistent infection is developing. Tryptophan deprivation as a consequence of the microbicidal activity of IFN-γ appears to be involved also in the pathogenesis of anemia when erythroid progenitor cells suffer from insufficient tryptophan supply. Also, weight loss and cachexia are closely linked to inflammatory response when protein biosynthesis of the organism is restricted by diminished

tryptophan availability. In the absence of any ability to synthesize tryptophan, and upon shortage of tryptophan cells begin to degrade cellular protein to sequester tryptophan for production of highly needed proteins. Finally, tryptophan shortage may affect the biosynthesis of neurotransmitter 5-hydroxytryptamine (serotonin) and lead to the production of potentially neurotoxic tryptophan catabolites such as quinolinic acid. Both these biochemical cascades of events seem to be involved in the development of neuropsychiatric symptoms like cognitive impairment and depression, especially in patients suffering from severe and chronic infections. Thus, accelerated tryptophan breakdown by IFN-γ-induced IDO can give rise to an immune activation syndrome in patients suffering from infections, which is characterized by subnormal tryptophan levels and an enhanced susceptibility of patients to develop immunodeficiency, anemia, cachexia and depression. This relationship provides a useful background to better understand the association between enhanced neopterin concentrations in patients suffering from various diseases like infections, autoimmune syndromes and cancer, and the appearance of such symptoms in the course of the diseases.

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