Opposing Biological Functions of Tryptophan Catabolizing Enzymes During Intracellular Infection

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Recent studies have underscored physiological and pathophysiological roles for the tryptophan-degrading enzyme indolamine 2,3-dioxygenase (IDO) in immune counterregulation. However, IDO was first recognized as an antimicrobial effector, restricting tryptophan availability to Toxoplasma gondii and other pathogens in vitro. The biological relevance of these findings came under question when infectious phenotypes were not forthcoming in IDO-deficient mice. The recent discovery of an IDO homolog, IDO-2, suggested that the issue deserved reexamination. IDO inhibition during murine toxoplasmosis led to 100% mortality, with increased parasite burdens and no evident effects on the immune response. Similar studies revealed a counterregulatory role for IDO during leishmaniasis (restraining effector immune responses and parasite clearance), and no evident role for IDO in herpes simplex virus type 1 (HSV-1) infection. Thus, IDO plays biologically important roles in the host response to diverse intracellular infections, but the dominant nature of this role—antimicrobial or immunoregulatory—is pathogen-specific.

Oxidative degradation of tryptophan to kynurenine is catalyzed by at least 2 structurally distinct classes of enzymes in mammals: a homeostatic enzyme, tryptophan 2,3-dioxygenase, expressed by the liver; and indolamine 2,3-dioxygenase (IDO), whose expression is regulated in diverse cell types by pathogen- and host-derived inflammatory signals, including proinflammatory cytokines (paradigmatically, interferon-γ [IFN-γ]), Toll-like receptor ligands (eg, lipopolysaccharide), and interactions between immune cells (eg, the engagement of costimulatory molecules on antigen-presenting cells by cytotoxic T-lymphocyte antigen-4) [1]. IDO has recently been shown to serve important immunoregulatory functions. Tryptophan catabolism by IDO functions as a counterregulatory pathway, mediating potent modulation of T-cell responses in vitro and in vivo [1]. The molecular mechanisms remain to be fully defined. Both localized tryptophan deprivation (inhibiting mammalian target of rapamycin signaling and upregulating the GCN2 kinase stress response pathway, leading to arrest of T-cell proliferation and anergy) and the production of bioactive tryptophan metabolites (facilitating the generation of regulatory T cells, inhibiting the generation of T-helper 17 cells, and driving T-cell apoptosis) have been implicated in various systems [1–7]. Modulation of T-cell responses by IDO-expressing dendritic cells is thought to play an important physiological role in suppressing the development
expression of autoimmune and allergic diseases [1]. Similarly, inhibition of allogeneic T-cell responses by IDO-expressing trophoblast cells is thought to facilitate maternal/fetal tolerance [1]. Pathophysiological roles for IDO-mediated immunosuppression have also been described. IDO is expressed by many tumors, as well as by a subpopulation of dendritic cells in tumor-draining lymph nodes; IDO inhibition can rescue anergic, tumor antigen–specific T-cell effector function, inhibiting tumor growth in mouse models [8–10]. Sustained IDO activation is also thought to be an important cause of immunosuppression in human immunodeficiency virus (HIV) infection [11]. The potential for therapeutic exploitation of physiological IDO activity (in autoimmune disease and transplantation) and therapeutic targeting of pathophysiological IDO activity (in cancer and HIV) are currently under active exploration.

More than 2 decades ago, however, IDO was described as an antimicrobial defense mechanism. The original reports were with Toxoplasma gondii, a ubiquitous protozoan that causes severe disease in immunocompromised hosts. Treatment of T. gondii–infected human cells with IFN-γ upregulated IDO expression and activity, leading to restriction of parasite replication—something reversible by the addition of exogenous tryptophan [12–15]. The tryptophan auxotrophy of T. gondii provided a clear biological rationale for the targeting of this organism by immune-driven IDO activity. Subsequently, similar studies reported that IFN-γ induction of IDO played a role in restricting the replication of a range of intracellular pathogens, including bacterial tryptophan auxotrophs (notably, Chlamydia species [14, 16, 17]) and diverse viruses [18–22]). Despite this extensive in vitro literature, the generation of IDO–deficient mice was not followed by published evidence of an important in vivo role for IDO in host defense—something that cast doubt on the biological relevance of these in vitro observations. Indeed, despite the fact that acute murine toxoplasmosis leads to induction of IDO expression and activity [23, 24], we found that the course of infection with T. gondii was unaltered in IDO–deficient mice, on either C57BL/6 or BALB/c backgrounds, compared with wild-type controls (data not shown). The recent discovery of a gene closely related to IDO(-1), IDO-2 [25, 26], suggested an obvious potential reason for this apparent lack of phenotype in IDO-1 knockout mice. This, together with the practical availability of 1-MT, an in vivo inhibitor of IDO-1 and -2, led to us to reexamine the role of IDO in the host response to infection with intracellular pathogens.

**MATERIALS AND METHODS**

**Infection Models**

*Toxoplasmosis*

Female C57BL/6 mice were infected by the intraperitoneal injection of 20 T. gondii cysts (ME49 strain) recovered from brain homogenates of chronically infected mice [27]. T. gondii cysts were counted in brain homogenates by microscopy [27]. Systemic cytokine production over 18 hours was quantified by the cytokine capture assay (CCA) assay [28].

*Cutaneous Leishmaniasis*

Infective-stage metacyclic promastigotes (10^5) of Leishmania major clone V1 (MHOM/IL/80/Friedlin) were inoculated intradermally into the ears of female C57BL/6 mice [29]. Lesion size was quantified with vernier calipers [29]. Parasite burden was quantified as described [29]. Intradermal lymphocytes were isolated as described [29]. Cells were subsequently analyzed by flow cytometry for surface markers and intracellular forkhead box p3 (Foxp3) expression. Cells isolated from lymph nodes draining lesions were stimulated with L. major promastigote lysates; cytokines were quantified by enzyme-linked immunosorbent assay (ELISA) in culture supernatants harvested 48 hours later. Systemic cytokine production over 18 hours was quantified by the CCA assay. Lesional mRNA expression was quantified by quantitative reverse transcription–polymerase chain reaction (qRT-PCR).

*Herpes Simplex Virus Type 1 Infection*

Male Swiss Webster or C57BL/6 mice were inoculated on scarified corneas with 2 × 10^5 plaque-forming units (pfu) of wild-type herpes simplex virus type 1 (HSV-1) strain 17syn+ [30]. The infectious viral burden in eyes and trigeminal ganglia was quantified 4 days after infection by plaque assay [30]. The burden of latent infection was measured by real-time PCR [31]. The reactivation competency of latent genomes was tested by explant of trigeminal ganglia in the presence of acyclovir for 3 days, followed by quantification of lytic viral proteins by immunohistochemistry. During infection, animals were observed for signs of encephalitis, death, and reactivation of virus in eye swabs. Standard histological analysis of the central nervous system and periocular areas was performed.

Animal care was provided in accordance with National Institutes of Health guidelines; studies were approved by the Cincinnati Children’s Hospital Medical Center Institutional Animal Care and Use Committee.

**IDO Inhibition**

Mice were treated orally with the D isomer of 1-MT (D1-MT; Sigma-Aldrich), prepared as described [2], in their drinking water (2 mg/mL solution, sweetened with Nutrasweet; controls: Nutrasweet alone). To analyze effects of 1-MT on acute infection, mice were pretreated for 1 week prior to infectious challenge. The volume of water consumed by the animals was monitored. No difference in the volume of water consumed was observed between 1-MT-treated and control-treated animals. Consistent with the lack of toxicity reported in preclinical toxicological studies [32], administration of D1-MT for 101 days to unininfected mice led to no evident adverse effects (data not shown). In some experiments, the effects of
treating mice with the L isomer of 1-MT (Sigma-Aldrich), handled in the same fashion, was compared with that of treating mice with D1-MT.

Reagents
The following PCR primers were used: IFN-γ 5’ TGGCTGTTTCTGGCTGTTACTG, 3’ ACGCTTATGTTGTTGGATGG; tumor necrosis factor (TNF)-α 5’ CCAGACCCTCA-CACTCAGATCA, 3’ CACTTGGTGGTTTGCTACGAC; interleukin (IL)-12/23p40 5’ GGAAGCACGGCAGCAGAATA, 3’ GAACTTGAGGGAGAAGTAGGAATGG; IL-10 5’ GAAGCATGGCCGGAATCA, 3’ TGCTCCACTGCCTTGCTCTT; IDO-1 5’ GTGGGCAGCTTTTCAACTTC, 3’ GGGCTTTGCTCTACCACATC; IDO-2 5’ TGCCTGATGGCCTATAACCAGTGT, 3’ TGCAGGATGGACCTCTACGCT; β-actin 5’ GGCCCAGAGCAAGAGAGGTA, 3’ GGTTGGCCT TAGGGTTCAGG; HSV-1 5’ CTTAACCAGGCTAGGCTAGG; 3’ CAAAGGTGGGAGT.

Antibodies for flow cytometric analysis were from eBiosciences. Immunohistochemical analysis of IDO-1 in formalin-fixed tissue was performed with rabbit anti-IDO-1 polyclonal antibodies, as previously described [8]. ELISA reagents for CCA analysis (of IL-10, TNF, IFN-γ and IL-4) and for IL-17A/F were from eBiosciences; those for quantification of in vitro IL-10 and IFN-γ production were from BD Bioscience.

Statistical Analysis
Data were analyzed by Mantel–Cox test (survival analysis) and analysis of variance (ANOVA), followed by Tukey multiple comparison test or unpaired Student t test, as appropriate. For kinetic lesion size analysis during Leishmania infection, the assumption of normality was tested using a normal quantile-quantile (Q-Q) plot or by multivariate analysis of variation (MANOVA), to reject the null hypothesis. Leishmania numbers were log-transformed before analysis.

Figure 1. IDO inhibition during acute toxoplasmosis leads to an inability to control infection. C57BL/6 mice were infected intraperitoneally with T. gondii (ME49 strain), in the presence and absence of IDO inhibition with D1-MT. A, Survival analysis (n = 8 mice/group; closed symbols, 1-MT; open symbols, control). **P < .0001 (Mantel-Cox test). Representative of 3 independent experiments (100% vs 0% mortality in the 2 not pictured). B, Parasite burden. T. gondii cysts were counted in brain homogenates of mice sacrificed 30 days after infection. Values shown are means ± standard error (SE) of 22 mice/group, pooled from 2 separate experiments. *P < .03 (Student t test). C–E, Systemic cytokine production was quantified by the CCA assay [28] 30 days after infection. Values shown are means ± SE of 8 mice/group. C, Serum IFN-γ. D, Serum TNF-α. E, Serum IL-10. F–I, Cytokine mRNA was quantified in brain by qRT-PCR 30 days after infection. Values shown are means ± SE of data normalized for β-actin mRNA expression of 8 infected mice/treatment, and 3 uninfected mice. F, IL-12/23p40 mRNA. G, IFN-γ mRNA. H, TNF-α mRNA. I, IL-10 mRNA.
RESULTS

IDO Is Necessary for Control of Acute and Latent Toxoplasmosis

We infected mice intraperitoneally with *T. gondii* in the presence and absence of IDO inhibition with D1-MT. As shown in Figure 1A, IDO inhibition rendered mice incapable of surviving *T. gondii* infection. Similar to previous reports in NOS2-deficient mice [33, 34], death did not occur during early infection, but at a time when latent infection has been normally achieved in wild-type mice in this model. *T. gondii* is able to replicate in most nucleated cells. In the immunocompetent, serious disease is averted by a vigorous immune response, dominated by IFN-γ production, which leads to parasite killing and the transformation of remaining parasites into the dormant (bradyzoite; cyst) form, largely in the central nervous system [35]. This systemic immune response is, perforce, kept under tight control. Neither genetic deficiency of mediators driving the protective immune response (eg, IFN-γ) nor of mediators that restrain this response (eg, IL-10) is compatible with survival during toxoplasmosis [35]. Mice with the former deficiency die with increased parasite burdens; with the latter, of unrestrained production of proinflammatory mediators and decreased parasite burdens [35]. Thus, the mortality observed with IDO inhibition during toxoplasmosis was compatible with an inability to control either the parasite or the immune response to the parasite. Of note, IDO inhibition was associated with significantly increased parasite burdens (Figure 1B). Such inhibition did not alter serum levels of critical pro- and anti-inflammatory cytokines (IFN-γ, TNF-α, IL-10; Figure 1C–E), something mirrored by a lack of biologically important changes in the expression levels of mRNA for IL-12/23p40, IFN-γ, TNF-α or IL-10 in the central nervous system (Figure 1F–I). Thus, IDO inhibition throughout the course of toxoplasmosis is associated with a late failure to control parasite replication, in the absence of evident effects on the immune response.

*T. gondii* infection leads to sustained upregulation of IDO-1 and IDO-2 mRNA expression in the brain (Figure 2A and 2B). Immunohistochemical analysis revealed expression of IDO-1 by glial and other cells (Figure 2C–F). In order to analyze the effect of IDO inhibition on latent *T. gondii* infection, we treated mice with D1-MT beginning 30 days after infection. Notably, IDO inhibition led to reactivation of disease and mortality (Figure 3A), associated with increased parasite burdens (Figure 3B), but without evident effects on either local or systemic production of inflammatory mediators (Figure 3C–I).

IDO Plays a Role in Immune Counterregulation During Cutaneous Leishmaniasis

Like *Toxoplasma, Leishmania* are tryptophan auxotrophs [36]. Cutaneous leishmaniasis has additional similarities with
toxoplasmosis. Parasite replication is restricted by an immune response in which IFN-\(\gamma\) plays a central role, and immune counterregulation is key to the outcome of infection. In the case of \(L.\) major infection, IL-10 production is critical to the negotiation of latency between host and parasite; neutralization of IL-10 leads not to latency, but to sterile cure \([29, 37]\). Given these similarities, we analyzed the effect of IDO inhibition on the course of cutaneous leishmaniasis. We infected C57BL/6 mice intradermally with \(L.\) major (V1 strain), in the presence and absence of IDO inhibition with D1-MT. As expected, \(L.\) major infection induced lesional expression of IDO-1 and IDO-2 mRNA (Figure 4A and 4B). Immunohistochemical analysis revealed that the majority of lesional IDO-1 immunoreactivity was associated with granulocytes, while lymph-node immunoreactivity was restricted to mononuclear inflammatory cells (likely, both macrophages and dendritic cells) (Figure 4C–F).

Inhibition of IDO led to significant decreases in lesion size during the phase of parasite clearance (Figure 5A), along with a significantly better control of parasite load (Figure 5B). During the early phase of parasite clearance, D1-MT treatment was associated with significantly increased serum IFN-\(\gamma\) and decreased serum IL-10 concentrations, (Figure 5C and 5D), without changes in serum IL-4 concentrations (data not shown)—findings that mirrored \(Leishmania\) antigen-driven IFN-\(\gamma\) and IL-10 production by T cells isolated from lymph nodes draining the sites of cutaneous infection (Figure 5E and 5F). D1-MT treatment was also associated with a trend toward increased lymph node T-cell production of IL-17F (Figure 5G) and IL-17A production (data not shown) in response to leishmanial antigens. At this same time, IDO inhibition was associated with a significant increase in the lesional ratio of effector to regulatory CD4\(^+\) T cells (Figure 5H). Thus, in
contrast to its role in toxoplasmosis, IDO plays a modest role in immune counterregulation in leishmaniasis, restraining both the immune response and pathogen clearance.

**IDO Inhibition Fails to Alter the Pathobiology of HSV-1 Infection**

Protective immunity against the neurotropic virus HSV-1 depends on IFN-γ [38, 39]. HSV-1 is also prototypical of viruses reported to undergo IDO-mediated restriction of replication in vitro [19]. We thus inoculated C57BL/6 mice with 2 × 10⁵ pfu of HSV-1 strain 17syn+ [30] on scarified corneas, in the presence and absence of IDO inhibition with D1-MT (begun 3 days prior to infection). The acute phase of infection was monitored by evaluating viral titers in the eyes and trigeminal ganglia 4 days after inoculation—the time of peak viral replication [19]—in a subset of mice. As shown in Figure 6A, IDO inhibition had no effect on acute viral replication. Further, IDO inhibition had no effect on mortality (Figure 6B), did not alter the burden of latent infection (Figure 6C), and failed to affect the reactivation competency of latent genomes (Figure 6D). Thus, inhibition of IDO during HSV-1 infection failed to alter viral replication, virulence, or the induction of latency. Similar results were seen with IDO inhibition during HSV-1 infection of Swiss Webster mice (8/group). Treatment was continued for an additional 45 days, during which time animals were observed for signs of encephalitis, death, or reactivation of virus in eye swabs. Of note, no animals died, none became sick, and no infectious virus was detected in eye swabs (data not shown). Histological examination of the central nervous system and trigeminal ganglia showed no differences between groups (data not shown). Thus, IDO inhibition during latent infection does not result in uncontrolled reactivation and spread of latent HSV in the nervous system. Taken together, these studies indicate that IDO does not play a biologically important role in restricting HSV-1 replication or latency.

**1-MT Isomers Have Similar Effects on Intracellular Infection**

The stereoisomers of 1-MT may have somewhat different biological properties. The L isomer has been reported to be more potent at inhibiting purified IDO-1 enzyme in cell-free systems or recombinant IDO-1 expressed in cell lines, and may preferentially inhibit IDO in tumor cells [40]. However, the D isomer appears more effective in reversing the suppression of T cells by IDO-1-expressing dendritic cells in both human and mouse systems [40]. This may be due to lower nonspecific toxicity, since the DL mixture appears to have off-target toxic effects on antigen-presenting cells when used at high concentrations [41]. It is also possible that the D isomer is more effective at inhibiting...
the activity of IDO-2 [26]. Whatever the mechanism, the D isomer has been shown to be effective in vivo in mice [2, 40], and in vitro using IDO-expressing antigen-presenting cells from both mice and humans [8, 42, 43]. Notably, parallel experiments employing D1-MT and L1-MT led to identical results in mouse models of experimental toxoplasmosis (mortality; Figure 7A), cutaneous leishmaniasis (lesion size; Figure 7B), and HSV-1 infection (acute viral replication, mortality, viral latency, and viral reactivation competence—data not shown).

**DISCUSSION**

The data presented here demonstrate that IDO, recently recognized to play key physiological and pathophysiological roles in immune counterregulation, play biologically important, contradictory roles during intracellular protozoal infection—facilitating (*T. gondii*) or suppressing (*L. major*) microbial clearance in a pathogen-specific manner. Our finding of an important antimicrobial role for IDO in toxoplasmosis, in the absence of demonstrable effects on the immune response, provides in vivo validation of an extensive in vitro literature going back more than 20 years. As for other protozoa, IDO has also recently been shown to play a critical role in host resistance against *Trypanosoma cruzi* in mouse models. In the case of *T. cruzi*, the antimicrobial effects of IDO appear to be mediated by kynurenines [44]. On the other hand, IDO inhibition has been reported to lead to increased effector T-cell responses in the absence of any robust effects on disease course in a mouse model of malaria [45].

Despite an extensive in vitro literature on viruses and IDO, viruses are not marked by tryptophan auxotrophy. The mechanisms by which tryptophan restriction leads to suppression of in vitro viral replication have thus not been entirely
straightforward. Tryptophan starvation stresses mammalian cells and inhibits their proliferation [46]. It is perhaps not surprising that such stress renders cells less efficient as hosts for viral replication, whether or not this is actually exploited as an antiviral defense mechanism in vivo. The lack of an evident role for IDO in restricting HSV-1 replication in vivo suggests that such in vitro studies may be misleading and that in vivo studies will be needed to determine whether IDO modulates the course of infection with particular viruses. Indeed, consonant with the hypothesis that IDO activation plays an immunosuppressive role in HIV infection, blockade of IDO during retroviral infection of mice (LP-BM5) and rhesus macaques (simian immunodeficiency virus) led to decreased viral burdens [47, 48].

As for other classes of pathogens, despite an in vitro literature on IDO-mediated restriction of Chlamydiae replication, our preliminary experiments have suggested that IDO inhibition fails to alter pulmonary bacterial burden during lung infection with Chlamydophila pneumoniae (data not shown).

IDO in restricting HSV-1 replication in vivo suggests that such in vitro studies may be misleading and that in vivo studies will be needed to determine whether IDO modulates the course of infection with particular viruses. Indeed, consonant with the hypothesis that IDO activation plays an immunosuppressive role in HIV infection, blockade of IDO during retroviral infection of mice (LP-BM5) and rhesus macaques (simian immunodeficiency virus) led to decreased viral burdens [47, 48].

As for other classes of pathogens, despite an in vitro literature on IDO-mediated restriction of Chlamydiae replication, our preliminary experiments have suggested that IDO inhibition fails to alter pulmonary bacterial burden during lung infection with Chlamydophila pneumoniae (data not shown). In the case of fungi, the immunoregulatory properties of IDO appear to be essential to limit inflammatory responses to Aspergillus and Candida, which, in the absence of such restraint, compromise the hosts’ ability to eradicate infection [6]. Similar findings have been reported in mouse models of tuberculosis [49]. Immunohistochemical analysis revealed that infection of mice with Mycobacterium tuberculosis is associated with dramatic upregulation of IDO-1 expression [49], something that we have replicated and found to be true in human disease as well (data not shown). Elegant studies employing bone marrow chimeric mice indicate that IDO

Figure 6. IDO inhibition during HSV-1 infection fails to alter disease or viral dynamics in C57BL/6 mice. Mice were inoculated with $2 \times 10^5$ pfu of HSV-1 strain 17syn+ on scarified corneas, 3 days after beginning treatment with D1-MT or control. A, Acute viral replication (n = 3–7 mice/group). Viral titers in eyes, trigeminal ganglia, and tears were quantified by plaque assay 4 days after infection. B, Survival analysis (n = 9 mice/group). C, Burden of latent viral infection (n = 3–8 mice/group). Latent viral genomes were quantified by quantitative polymerase chain reaction 30 days after infection. D, Reactivation competence of latent HSV-1 genomes (n = 6 mice/group). Immunohistochemical analysis of lytic protein expression in trigeminal ganglia (TG), performed 3 days after explant (on day 45 of infection) in the presence of acyclovir. Representative of 2 independent experiments. Values shown are means + SE; closed symbols, 1-MT; open symbols, control.

Figure 7. 1-MT isomers have similar biological effects on experimental toxoplasmosis and leishmaniasis. A, T. gondii infection, survival analysis. C57BL/6 mice were infected intraperitoneally with T. gondii (ME49 strain) in the presence and absence of IDO inhibition with D1-MT (black circles), L1-MT (black squares), or vehicle control (open circles). n = 6 mice/group; **P < .0001 (Mantel–Cox test). B, L. major infection, lesion size. C57BL/6 mice were infected intradermally with L. major (V1 strain), in the presence and absence of IDO inhibition with D1-MT, L1-MT or vehicle control (symbols as in A). Values shown represent means ± SE of 8 mice/group. MANOVA $P < .025; ^*P < .05; ^{**}P < .01$, ***P < .001 (Student t test).
expression by nonhematopoietic cells in the lung is necessary to limit IL-17 production and harmful neutrophil inflammation during experimental tuberculosis [49].

It will be noted that the biologically antagonistic, pathogen-specific roles played by IDO during infection (restraint of microbial replication, restraint of the host response) are remarkably similar, at least superficially, to the activities of another enzyme exploited by both the innate and adaptive immune systems—inducible nitric oxide synthase [50]. Critical issues remain to be addressed in these and other infection models, including: (1) the relative role of IDO-1 and -2 in immune counterregulation and antimicrobial activity, (2) which IDO-expressing cell types are responsible for these diverse activities, (3) the relative role of tryptophan starvation and tryptophan metabolite production in these activities, and (4) the potential contribution of tryptophan catabolic enzyme expression by pathogens themselves to disease pathogenesis. With regard to the first of these issues, the current studies do not provide much in the way of insight. The fact that IDO-1 and -2 are differentially expressed by distinct cell types at baseline and undergo differential regulation of stimulated expression in vivo suggests that the enzymes are unlikely to be fully functionally redundant [51]. That said, despite the fact that IDO enzymes play opposing biological roles in experimental toxoplasmosis and leishmaniasis, the similar fold-induction of IDO-1 and -2 mRNA expression in these infections in the face of very different levels of baseline IDO-2 mRNA expression in ear and brain do not suggest an obvious hypothesis for enzyme specificity of the observed dominant biological effect. As a caveat, it should be noted that regulation of IDO is quite complex, including the use of alternate promoters and the generation of diverse splice forms, as well as posttranslational modification of enzyme activity [51, 52]. As for the last of these issues, while Basic Local Alignment Search Tool (BLAST) searches suggest that it is unlikely that T. gondii and L. major express IDO homologs, such searches indicate that several bacterial pathogens of human importance—including Pseudomonas aeruginosa and Burkholderia cepacia—do encode IDO homologs (not shown), something that may well be exploitable therapeutically.

While these studies suggest appropriate caution during sustained therapeutic inhibition of IDO (eg, giving secondary chemoprophylaxis to those latently infected with T. gondii), both counterregulatory and antimicrobial activities may provide potential novel therapeutic targets during chronic infection. For infections in which IDO plays a counterregulatory role such as leishmaniasis and HIV, IDO inhibition may be useful as an adjunct to antimicrobial therapy. On the other hand, for latent infections in which IDO plays an antimicrobial role, IDO may also provide a therapeutic target. Eradication of latent infection is hampered by the fact that, in the latent state, pathogens are metabolically inert and thus insensitive to the activity of current antimicrobials. For a latent pathogen against which IDO is an important antimicrobial effector mechanism, IDO inhibition may facilitate pathogen eradication through controlled reactivation, under cover of antibiotics.

Notes

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