Published in final edited form as:
Trends Immunol. 2013 March ; 34(3): 137–143. doi:10.1016/j.it.2012.10.001.

Indoleamine 2,3 dioxygenase and metabolic control of immune responses

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Abstract

Sustained access to nutrients is a fundamental biological need, especially for proliferating cells, and controlling nutrient supply is an ancient strategy to regulate cellular responses to stimuli. By catabolizing the essential amino acid tryptophan, cells expressing the enzyme indoleamine 2,3 dioxygenase (IDO) can mediate potent local effects on innate and adaptive immune responses to inflammatory insults. Here, we discuss recent progress in elucidating how IDO activity promotes local metabolic changes that impact cellular and systemic responses to inflammatory and immunologic signals. These recent developments identify potential new targets for therapy in a range of clinical settings, including cancer, chronic infections, autoimmune and allergic syndromes, and transplantation.

The IDO pathway and immune regulation

Uncontrolled immune activation can be lethal, and so the immune system is tightly regulated, in part by metabolic pathways responsive to inflammation that modify immune cell functions [1,2]. For example, evolutionarily ancient metabolic pathways shape immune responses by controlling access to nutrients such as glucose and amino acids, and by producing new metabolic products and creating local hypoxia. Here we focus on the indoleamine 2,3-dioxygenase (IDO) pathway. IDO contributes to ‘metabolic immune regulation’ by catalyzing oxidative catabolism of the essential amino acid tryptophan (TRP) along the kynurenine (KYN) pathway (Figure 1). IDO modifies immune responses in two ways: by producing KYN, a natural ligand for the aryl hydrocarbon receptor (AhR); and by depleting TRP to trigger amino-acid sensing signal-transduction pathways. IDO has also been reported to act as a direct intracellular signaling molecule in DCs that express it [3]. This signaling function was independent of the enzymatic activity of IDO and occurred via recruitment of SHP-1/SHP-2 phosphatases to ITIM binding motifs in the IDO molecule; in addition, the IDO-SHP complex was necessary for the sustained tolerogenic effect of TGFβ on the phenotype of murine plasmacytoid DCs [3].

Although various cell types can potentially express IDO, amongst professional APCs (DCs, macrophages, B cells) the expression of IDO is often restricted to certain specific APC

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subsets (see some examples below) that appear specialized for rapid, high-level upregulation of IDO in response to inflammatory stimuli. Even in these “IDO-competent” cells, the expression of IDO is tightly regulated by exogenous signals. At the mRNA level, IDO transcription is promoted by factors such as Foxo3 and IRF-8, and is suppressed by DAP12 [4]; while at the post-translational level, the regulatory factor SOCS3 binds to IDO and targets the IDO protein for ubiquitinylation and rapid degradation [5]. Thus, under most circumstances only certain APCs express IDO, and then only in response to specific environmental cues.

As IDO enzymes are intracellular and not secreted, the metabolic effects of IDO begin as inherently local signals. However, the immunologic effects of IDO are not confined only to the cells expressing IDO, as neighboring cells may sense and respond to secreted KYN metabolites, and to the reduced access to TRP. Thus, professional APCs expressing IDO can affect both the APC itself and also neighboring T cells that interact with APCs. In a similar fashion, the unrelated enzyme TRP dioxygenase (TDO) also catalyzes oxidative TRP catabolism and production of KYN, and tumor cells expressing either IDO or TDO can create local immune regulation that suppresses anti-tumor immunity [6,7].

The IDO pathway comprises two related but distinct enzymes encoded by two linked genes, IDO1 and IDO2 [8,9], which can be expressed by professional APCs in the immune system (macrophages and DCs), as well as epithelial cells, vascular endothelium, and tumor cells. Originally, TRP degradation was described as a innate immune mechanism of host defense against infection [10]. Subsequently, the IDO pathway was shown to be active in multiple additional immunologic contexts. For example, IDO contributes to maternal tolerance to semi-allogeneic fetal tissues and transplanted organs, inhibits local tissue inflammation and autoimmunity, and suppresses immunity to cancer and chronic infections. A common theme in these diverse immunologic settings is that IDO contributes to immune regulation via local metabolic changes in the immediate microenvironment and local tissue milieu, and these local changes may ultimately impact the development of systemic immune tolerance. Here we discuss the molecular mechanisms that mediate the local effects of the IDO pathway, and describe the subsequent downstream pathways that may result in systemic immune regulation. In many cases, we will refer collectively to the “IDO pathway” because most studies in the literature have not distinguished between separate effects of IDO1 and IDO2. Although functional differences between the two enzymes have been reported [9,11], their precise contributions to immune regulation is not yet fully understood, in part because available inhibitors of IDO do not discriminate between IDO1 and IDO2 enzymes. Also, while IDO1-deficient mice have clear immune defects, studies on IDO-2-deficient mice have not been reported. Thus, much of the existing literature does not discriminate between IDO1 and IDO2 and refers to them collectively as ‘IDO’. In this review, we will continue to refer to IDO and the IDO pathway with the caveat that there may be differential roles for these two enzymes in some settings.

Mechanisms of immune regulation by the IDO pathway

Regulation of metabolic pathways

TRP catabolism catalyzed by IDO enzymes generates KYN-pathway metabolites that are biologically active, both as natural immunologically-active ligands for the aryl hydrocarbon receptor (AhR) [12] and [in the case of central nervous system (CNS) inflammation] as excitatory neurotoxins [13]. The AhR is a ligand-activated transcription factor, originally identified as a receptor for xenotoxins such as dioxin. The immunologic effects of the AhR are complex because different endogenous and exogenous ligands may have different (even opposing) effects on T cell subsets depending on their affinity for the AhR, duration of signaling and other factors [14]. However, in the case of KYN-pathway metabolites, the

effect on the AhR appears immunosuppressive, promoting differentiation of Foxp3+ Tregs [12,15], suppression of anti-tumor immune responses [6,7], and decrease in the immunogenicity of DCs [15]. In one report, AhR signaling in DCs was also required to induce the expression of functional IDO [15], suggesting crosstalk between the two pathways. Therapeutically, administration of natural or synthetic KYN compounds can promote tolerance that protects transplanted tissues, and reduces collateral tissue injury caused by pathogen infection [16–18].

A second effect of IDO is the rapid consumption of TRP from the local microenvironment. TRP depletion can act as a potent regulatory signal via molecular stress-response pathways such as GCN2 kinase and the mammalian target of rapamycin (mTOR) that respond to amino-acid withdrawal. The GCN2 molecule contains a kinase domain plus an allosteric regulatory site that responds to the presence of tRNA in the uncharged configuration (i.e., tRNA lacking its cognate amino acid) (reviewed in ref. [19]). Insufficiency of any amino acid thus activates GCN2 kinase activity, leading to phosphorylation of its downstream target, eukaryotic initiation factor 2 (eIF2α). Phosphorylated eIF2α blocks the ribosomal translation of most mRNA species, but it selectively enhances the translation of a small number of transcripts. One example of GCN2-inducible translation is the transcription factor ATF4 [20]. ATF4 mRNA contains two short upstream open reading frames (uORFs), the second of which competes with the ATF4 coding sequence for translation initiation. When eIF2α is phosphorylated by GCN2, this second uORF is bypassed and ATF4 translation is markedly enhanced. Other mRNA species have a specific IRES motif that is favored by phosphorylated eIF2α, with analogous results.

Local effects of IDO on T cells and Tregs

In CD8+ T cells, IDO-induced activation of GCN2 leads to cell-cycle arrest and functional anergy [21]. In CD4+ T cells, activation of GCN2 blocks TH17 differentiation [22,23] and promotes *de novo* Treg differentiation and activation of functional suppressor activity in mature Tregs [24,25]. As TRP depletion would first occur in the IDO-expressing APCs themselves, it seems likely that the GCN2 pathway is also activated in these cells. However, less is known about the cell-autonomous effects of the IDO and GCN2 pathways [26]. GCN2 responds to other amino acids besides TRP. Reduced local arginine concentration, resulting from Arginase-I enzyme activity in macrophages or myeloid-derived suppressor cells, also activates GCN2, which leads to similar cell-cycle inhibitory effects on activated T cells [27]. Overall, GCN2 appears to enhance Treg activity, and inhibit T effector cells.

Amino acid withdrawal can also affect the nutrient-sensing mTOR pathway [28]. mTOR activity is inhibited in inflammatory settings in which amino acids are catabolized by IDO, arginase, tryptophan-hydroxylase and other enzymes [29,30]. Although direct effects of IDO on the mTOR pathway have not been described, it seems likely that mTOR is a downstream pathways affected by IDO. Given the potent effects of mTOR on Treg and effector T cell functions [28], further research is needed to establish the effects of IDO on mTOR signaling and immune regulation.

The IDO pathway contributes to regulation of Foxp3+ Treg lineage commitment and function. In vitro, TRP deprivation (sensed by GCN2) acts synergistically with KYN metabolites to drive de novo differentiation of Foxp3+ Tregs from uncommitted CD4+ T cells [24,31,32]. *In vivo*, IDO inhibitors or genetically ablation of IDO1 genes prevents the normal differentiation of antigen-specific Tregs in response to mucosal antigen challenge [33,34]. In the case of pre-existing, mature Tregs, co-culture with DCs expressing IDO during Treg activation enhances their suppressive functions [25], and blocks inflammation-induced destabilization of the regulatory Treg phenotype [35–37]. Finally, several models show that the IDO pathway and its downstream KYN metabolites selectively suppress the

pro-inflammatory TH17 pathway [38,39], thus tipping the balance of Tregs/TH17 cells in favor of Tregs. This shift may control excessive inflammation and prevent immune-mediated pathology, but may be undesirable in settings such as HIV infection, where inflammation and T cell responses would be beneficial [40].

Systemic regulation of immunity by IDO

Acquired peripheral tolerance – defined as a functional state of immunologic unresponsiveness to antigenic challenge – is a continuous process that prevents innocuous, non-self antigens from stimulating excessive immunity leading to tissue damage. IDO1-deficient mice do not develop the spontaneous lethal autoimmune disorders that are seen in *Foxp3* or *Ctla4*-deficient mice, indicating that IDO is not crucial for self-tolerance during tissue homeostasis. However, inhibiting IDO leads to defects in acquired tolerance to new antigens, for example in response to transplanted tissues [41,42] or antigens presented at mucosal surfaces [33,34]. Moreover, disruption of *Ido1* leads to lupus-like syndromes after chronic systemic exposure to apoptotic cells [43], and administration of a pharmacologic IDO-inhibitor (1-methyl-TRP, 1MT) accelerates lupus onset in the MRL-lpr mouse model of spontaneous lupus disease [43]. Conversely, transfer of recombinant IDO genes into tissue allografts creates de novo systemic tolerance to the transplanted organ, without any other immunosuppression [44,45]. Taken together, these models suggest that the IDO pathway restrains progressive breakdown of peripheral self-tolerance in settings of chronic inflammation, and creates systemic tolerance to auto- and allo-antigens in settings of autoimmunity and transplantation.

Constitutive expression of IDO is found primarily in mucosal tissues, but the IDO pathway is induced in many tissues during inflammation because IDO gene expression is induced by interferons (IFNs). Thus, IDO pathway activation often manifests in concert with local production of pro-inflammatory cytokines associated with immune activation, particularly when inflammation is sustained. In certain settings the choice between immunity versus tolerance appears to depend on local factors that affect the balance between the immunosuppressive activity of the IDO pathway versus local pro-inflammatory signals (Figure 2). For example, treating transplanted mice with CTLA-4-Ig or CD40-Ig, induces protective tolerance, but if IDO is blocked, there is robust graft rejection despite CTLA4-Ig or CD40-Ig treatment [41,42]. IDO can be induced in non-hematopoietic (epithelial/endothelial, fibroblast) and hematopoietic (myeloid, not lymphoid) cell types in inflamed tissues and associated lymphoid tissues. IDO can confer tolerogenic phenotypes on professional APCs (e.g., DCs and macrophages), while IDO expression by non-immune (stromal) cell types can inhibit immune effector processes in tissues to limit collateral damage (e.g., in transplanted or chronically-infected lungs [38,46], or in graft-versus-host disease [47]). Acquisition of IDO-dependent tolerogenic phenotypes may be associated with specific, specialized subsets of APCs. In mice for example, we have described a discrete DC subset with attributes of both B cells and DCs (CD19+ DCs). These cells expressed IDO in lymph nodes draining sites of melanoma growth, and in spleen in response to B7 (CTLA4Ig) and TLR9 ligands (CpGs) [48,49]. CD19+ DCs have been seen in other models: e.g., elevated numbers of splenic DCs expressing CD19 and producing high levels of IL-10 and IFNαβ were present in spleens of lupus-prone Nba2 mice, suggesting that CD19+ DCs may play an important role in this setting (although this study did not test whether these CD19+ DCs expressed IDO) [50]. In the case of CpG-induced IDO, the effect was dependent both on the route (intravenous) and dose of CpGs administered, such that low CpG doses enhanced classic Th1 effector responses, whereas high CpG doses became immunosuppressive due to induction of counter-regulatory IDO. Signals from TGF-β, CTLA-4 and PD-1 were essential for induction of immunosuppressive IDO by CpGs, and the effect of IDO was to potently activate Treg-mediated suppressive activity [37]. In a

different model in which mice were challenged with intravenous apoptotic cells, the normal tolerogenic responses were also IDO-dependent, as inhibiting IDO activity or ablating IDO1 genes led to increased susceptibility to onset of lupus-like syndromes after chronic exposure to apoptotic cells [43]. In this case marginal zone MOMA1+ metallophilic macrophages expressing Sigleg1/CD169 were critical for mediating tolerogenic responses via IDO [43]. In both the CpG model and the apoptotic-cell model, small populations of rare but discrete innate immune cell types, in both cases located in the splenic marginal zone created functional systemic tolerance. These cells mediated dominant regulatory responses to defined inflammatory insults via the IDO pathway.

In vivo, IDO often appears to participate as part of a network of tolerogenic signals. For example, analyses of stable tolerant states ('infectious tolerance') to skin allografts revealed increased local catabolism of several essential amino acids, including IDO-induced TRP catabolism [30], with consequent effects on both the GCN2 and mTOR pathways. In other models, elevated IDO activity was required for tolerance to solid-organ allografts following CD40 blockade [41,51], or treatment with CTLA-4-Ig [42]. Conversely, the immunosuppressant drug, halofuginone, mimics the effects of amino acid withdrawal by inhibiting prolyl-tRNA synthetase activity, which activates GCN2 and blocks effector TH17 responses [22,23]. While sustained IDO activity suppresses T cell immunity and slows disease progression at sites of chronic inflammation, immune-mediated tissue injury may still occur over time. For example, effector T cells may acquire increased resistance to IDO-mediated suppression by over-expressing TRP-tRNA synthetase (WRS), enabling T cells to access TRP even when IDO is active [52]. In summary, IDO and its downstream pathways can be pivotal factors that shape the nature and outcome of an immune response at sites of chronic inflammation.

IDO and cancer

IDO is expressed in many human cancers, and high IDO expression is associated with poor prognosis in a variety of cancer types (reviewed in ref. [53]). One unanswered question is whether the major site of IDO expression is the tumor cells themselves, or host accessory cells such as IDO-expressing DCs found in tumors or tumor-draining lymph nodes [54]. Within the tumor itself, expression of IDO by tumor cells (or TDO, if the tumor expresses TDO) would contribute to local immune suppression within the tumor microenvironment[6,7,55,56]. This doubtless plays a role in suppressing immune responses in the tumor. However, several potent immunologic functions of IDO, such as systemic activation of Tregs and creation of systemic tolerance, normally occur when IDO is expressed in specialized, professional APCs. Thus, upregulation of IDO by host APCs in response to local tumor growth may also be crucial for the ability of IDO to contribute to systemic immune suppression and tolerance toward tumors.

Mouse models suggest that developing tumors actively recruit IDO-expressing cells [57] and induce IDO upregulation by DCs in tumor-draining LNs [49]. In prostate cancer (both in humans and in mouse models), IDO induction in DCs is dependent on the transcription factor Foxo3 [58]. It is not known which factors in the tumor and tumor-draining LN trigger Foxo3 activation and consequent IDO induction. One candidate is CTLA-4-expressing Tregs, because surface CTLA-4 expressed by Tregs can bind B7 molecules on DCs to induce IDO expression [59], and this "back-signaling" from CTLA-4 to B7 is likely mediated via Foxo3 [60]. Under this model, tumor-infiltrating Tregs would be causally linked to IDO induction in the tumor milieu. Reciprocally, IDO can activate Tregs via the GCN2 and AhR pathways, as discussed above [12,24,25]. Thus, there is potential for a mutually-reinforcing, positive-feedback loop between IDO and suppressive Tregs in the

tumor microenvironment. If such immunosuppression occurs it would be highly undesirable; hence the interest in blocking IDO as an adjunct to cancer immunotherapy.

Several IDO-inhibitor drugs [61,62] are now in Phase I clinical trials as immunomodulators in cancer. Based on preclinical animal models, settings in which IDO-inhibitors might be useful include administration in combination with chemotherapy [63] or with vaccines [35,36]. As already mentioned, the IDO pathway is linked to the CTLA-4 pathway (which is also an important checkpoint in cancer, targeted clinically via ipilimumab and other agents). In a recent study, patients with higher IDO expression in host stromal cells in the tumor were more likely to respond to therapy with the CTLA4 blocking antibody ipilimumab [64], suggesting that the between these two checkpoint pathways may be clinically relevant.

IDO and infectious disease

IDO can have opposing roles in host defense against infection. IDO can play a dominant role in directly suppressing pathogen replication (for example during toxoplasmosis or chlamydial infections [65,66], or by limiting the spread of virus infection [67]); however, IDO can also dampen protective host immunity, thus indirectly leading to increased pathogen burdens (e.g., as occurs during leishmaniasis [65,68]). In mice infected with murine leukemia virus (MuLV), IDO was found to be highly expressed and ablation of IDO enhanced control of viral replication and increased survival [69]. IDO may be pivotal in controlling the degree and type of pathogen-induced lung inflammation in respiratory infections such as TB and influenza [38,70]; in one model of influenza infection, the immunosuppressive effects of IDO could predisposed lungs to secondary bacterial infection [70]. IDO is highly expressed in gut mucosa during initial HIV infection, where it may alter the local ratio of Tregs/TH17 cells by promoting Tregs and attenuating protective TH17 responses [40].

Pathogen-derived TLR ligands trigger release of immunostimulatory cytokines. TLR ligands can also induce IDO expression in certain APCs, which then acquire immunosuppressive activity providing a possible mechanism for feedback counter-regulation. Thus, the initial host immune response to pathogens may be attenuated by TLR-mediated upregulation of IDO in APCs, For example, *E. coli* infection induces an immunoregulatory phenotype in human myeloid DCs that is associated with increased IDO and IL-10 expression [71]. More speculatively, pathogen associated TLR ligands that induce IDO (e.g. via type I IFNs) in some APCs might explain why Treg expansion and increased Treg-mediated regulation manifests in some chronic infections [72]. From a therapeutic perspective, the ability of TLR ligands to induce counter-regulatory IDO expression might impact the biology of certain vaccine adjuvants (which often include TLR ligands): thus if counter-regulatory IDO is inadvertently induced by an adjuvant compound it might attenuate the desired response to vaccine.

IDO and vascular biology

IDO has recently been found to participate in several aspects of vascular biology. KYN produced by endothelial-derived IDO acts as a vascular relaxing factor contributing to vasodilatation in septic shock [73], and pharmacologic inhibition of IDO improved survival in a mouse septic-shock model [74]. This was unexpected, and exactly how these vascular effects of IDO relate to its immune effects still requires clarification. However, several studies imply that IDO expression by vascular endothelium may be immunologically important, as shown by the fact that the IDO expressed in tolerized solid-organ allografts was primarily localized to vascular endothelial cells [41,75].

IDO is also highly expressed in human atherosclerotic plaques [76] where it has been suggested to play a beneficial role in atherosclerosis by suppressing local inflammation. This is supported by a recent report that in mice the beneficial effect of omega-3 fatty acids on regression of atherosclerotic lesions is mediated largely via IDO induction in the lesions [77]. The role of IDO in vascular biology warrants further investigation.

IDO and neurologic function

Chronic inflammatory syndromes are frequently accompanied by comorbidities of heightened pain (nociception) and affective depression. The fact that IDO activity in the CNS is elevated in such syndromes provides a novel perspective on this correlation, because IDO can have direct effects on pain and neurologic depression. Elevated plasma KYN has been reported in patients with chronic pain or depression [78], and chronic stress stimulates IDO1 expression and depressive behavior in rats [79]. In mice, genetic IDO1 ablation or pharmacologic IDO inhibition eliminated behavioral changes linked to 'sickness-induced' depression in a model of chronic mycobacterial infection [80], and pharmacologic and genetic IDO ablation attenuated brain hippocampal nociceptive and depressive behavior [79]. These findings suggest that increased IDO activity in chronic inflammatory syndromes contributes to pain perception and depressive complications. This possibly results from reduced serotonin levels (due to depletion of TRP, the substrate for serotonin synthesis) and/or release of neurotoxic TRP catabolites. It is currently unclear if IDO activity in specific areas in the brain exclusively mediates these neurologic effects, or if IDO activity elsewhere in the body can mediate these effects at a distance (e.g. due to TRP catabolites entering the CNS). Speculatively, neurotoxic IDO activity in brain might also contribute to the neuropathogenesis of dementia in patients chronically infected with IDO-inducing pathogens such as malaria, West Nile Virus and HIV [13], and possibly even neurodegenerative disorders such as Alzheimer's disease [81,82]. If experimentally verified, this could have implications for use of IDO inhibitors in these clinical settings.

Concluding remarks

IDO has diverse biologic roles. It participates in both innate and adaptive immune responses. When expressed by professional APCs, IDO is centrally positioned to link these two arms to create local immune suppression, and to promote systemic tolerance by activating Tregs. IDO also has effects outside the immune system, in sites such as blood vessels and in the brain. The diverse biologic roles of IDO may reflect the fact that it is part of an ancient pathway, conserved throughout vertebrate evolution and back to invertebrates. As with other evolutionarily ancient pathways such as nitric oxide and prostaglandins, IDO may have had a long time to acquire its diversity of regulatory functions. IDO functions at the level of metabolic regulation, enlisting several fundamental, highly conserved downstream cellular control pathways such as GCN2, mTOR and AhR. And – precisely because it is primarily a straightforward catalytic enzyme and a metabolic regulator, rather than a complicated signaling receptor – IDO can be readily targeted with small-molecule inhibitors and simple pharmacologic inducers. This makes IDO an attractive target for therapeutic manipulation in the clinic.

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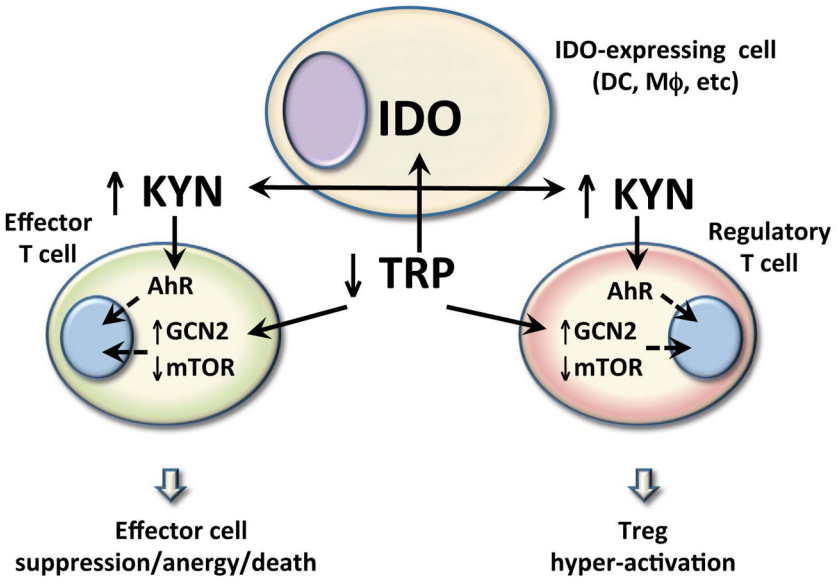

Figure 1. Metabolic control of T cell and Treg responses via IDO

Kyn release and Trp consumption by accessory cells expressing IDO generates signals via AhR and amino-acid sensors (GCN2, mTOR), respectively, that have profound effects on T cell and Treg responses to inflammatory and antigenic signals. IDO activity in APCs also enhances Treg differentiation from naïve CD4 T cells via these metabolic pathways (not shown).

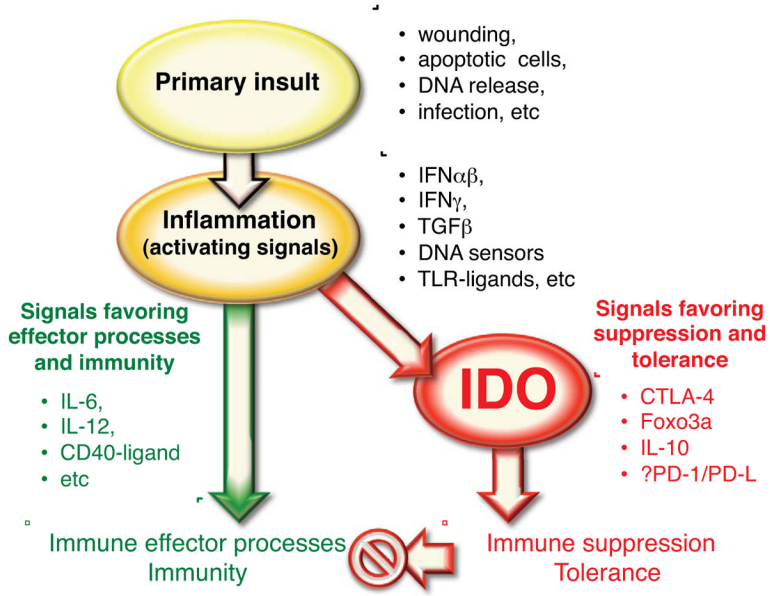

Figure 2. IDO is activated inflammation and helps create conditions that favor immune suppression and tolerance

Primary insults create local inflammation and generalized signals that activate immune cells. However, overall immune outcomes depend on the balance of additional signals that promote either effector and regulatory responses. Thus inflammation drives the immune response, but the specific character depends critically on the overall balance of immune stimulatory and regulatory pathways activated in a particular setting. Inflammatory signals that favor regulatory/suppressor outcomes often activate and/or sustain local IDO enzyme activity.