Review Article

A narrative review of the roles of indoleamine 2,3-dioxygenase and tryptophan-2,3-dioxygenase in liver diseases

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Abstract: Indoleamine 2,3-dioxygenase (IDO) and tryptophan-2,3-dioxygenase (TDO) are induced by several immune factors, such as interferon-γ, and act as intracellular enzymes that catabolize essential amino acid tryptophan into kynurenine and other downstream metabolites, including kynurenic acid (KYNA), xanthurenic acid (XA) and so on. IDO and TDO work as a double-edge sword. On one hand, they exert the immunomodulatory effects, especially immunosuppressive effects on the microenvironment including infections, pregnancy, tumor cells escape and transplantation. TDO plays the major role under basal conditions, while IDO comes into play under different circumstances of immune activation, thus IDO has a wider spectrum of immune regulation. On the other hand, these enzymes also inhibit pathogens such as Chlamydia pneumoniae, Staphylococcus aureus, Toxoplasma gondii and so on. Moreover, IDO regulates metabolic health through shaping intestinal microbiota. Recently, these enzymes have attracted more and more attention in liver diseases. Several studies have indicated that IDO and TDO can modulate viral hepatitis, autoimmune liver diseases, non-alcoholic fatty liver disease (NAFLD), liver cirrhosis, liver cancer even liver transplantation. Targeting them or their antagonists may provide novel therapeutic treatments for liver diseases. In this review, we will discuss the exact roles that IDO and TDO play in diverse hepatic diseases.

Keywords: Indoleamine 2,3-dioxygenase (IDO); viral hepatitis; autoimmune liver diseases; liver fibrosis and cirrhosis; liver tumors

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Introduction

Kynurenine pathway (KP) accounts for 95% of the metabolic process of degradation of the essential amino acid L-tryptophan (Trp), which mainly occurs in the liver (1). The process is rate limited by tryptophan-2,3-dioxygenase (TDO, also known as tryptophan pyrrolase) in the liver and indoleamine 2,3-dioxygenase (IDO) outside of the liver, especially in mucosal tissues and the immune system (2), including lung, placenta and immune cells (1). L-Trp is first converted into N-formylkynurenine, which is mediated by IDO or TDO, and then into L-kynurenine (3). L-Kynurenine is mainly metabolized into 3-hydroxykynurenine (3-HK) by kynurenine-3-monooxygenase (KMO) and then further converted into 3-hydroxyanthranilic acid (3-HAA) by kynureninase (KYNU). 3-HAA is catabolized into quinolinic acid (QuinA) by 3-hydroxyanthranilate 3,4-dioxygenase (HAAO) and then processed into end product nicotinamide adenine dinucleotide (NAD+) by quinolinic acid phosphoribosyltransferase (QPRT). The catabolism of 3-HK into xanthurenic acid (XA) by kynurenine aminotransferases (KATs) and the metabolism of L-kynurenine into anthranilic acid (AA) and kynurenic acid (KYNA) are the minor L-Kynurenine metabolism pathways (4,5) (*Figure 1*). TDO responds to Trp in meals and hormones such as glucocorticoids (5). Two forms of IDO, IDO1 and IDO2 are constitutively and locally expressed, respectively (1). The capacity of IDO2 to metabolize Trp is much smaller than that of IDO1, so we mainly focus on IDO1, and use IDO instead (IDO in the following article all refers to IDO1). IDO can be induced by interferon-γ (IFN-γ), tumor necrotic factor (TNF-α), lipopolysaccharide (LPS), and other proinflammatory cytokines in epithelial cells, dendritic cells (DCs) and macrophages (1,6-8). The combination of cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and CD80/CD86 molecules can also promote IDO expression (3). Moreover, anti-inflammatory cytokines hamper IDO expression (1,9,10). The capacity of TDO in the liver to catalyze Trp is much stronger than that of IDO under basal conditions. However, IDO expressed in the extrahepatic tissues is markedly induced by the abovementioned cytokines under some pathophysiological circumstances of immune activation including bacterial and viral infections in the liver, as well as nonpathogenic inflammation including autoimmune liver diseases, liver tumors and liver transplantation, which means IDO has a wider range of effects. That is the reason why IDO could play a role in the liver diseases (1,5). IDO has received more attention for its anti-infection and tumor-promoting activities (11).

The functions of the KP are usually as follows: (I) protection from excess Trp, which is exclusive to liver-expressed TDO; (II) c onservation of plasma Trp validity by TDO under normal conditions and by IDO under immune activation status; (III) production of kynurenine metabolites that take part in neuronal and immune responses (1). IDO is a double-edged sword. It plays the role of immunosuppressor in circumstances including infections, pregnancy, tumor cells escape and transplantation (3,12). Indeed, it is both the depletion of Trp and the production of kynurenine and other metabolites that play the roles in immune regulation. Firstly, catabolizing Trp itself in the local microenvironment triggers amino acid-sensing signal transduction pathways. Secondly, the downstream metabolites of Trp reduce activities of innate cells like natural killer (NK) cells, DCs and macrophages, inhibit Th1 cell proliferation while promoting Th2-phenotype polarization, and induce transforming growth factor-β (TGF-β) production and subsequent regulatory T cell (Treg) differentiation. Tregs activate myeloid-derived suppressor cells (MDSCs), leading to T cell inhibition. The metabolites also act to block the differentiation of type 17 T helper (Th17) cells (5,12-19) (*Figure 2*). IDO also inhibits intracellular pathogens like *Chlamydia pneumoniae* and bacteria like group B streptococci and mycobacteria (6,8). TDO expressed on HeLa cells is able to suppress *Staphylococcus aureus*, *Toxoplasma gondii* and *herpes simplex virus* (18). However, IDO may have opposite antimicrobial effect when excessive Trp is available. Lepiller *et al.* (19) showed IDO promoted HIV persistence. Moreover, genetic deficiency of IDO could promote the metabolic health through shaping the intestinal microbiota. Depletion of microbiota in the high fat diet (HFD)-fed wildtype (WT) and IDO-knockout (KO) mice discarded the body weight difference between these two groups of mice in which IDO-KO mice were protected from metabolic complications. Co-housing these two groups of mice made the phenotype of WT mice similar to IDO-KO mice in the separated cages. What's more, feeding the WT mice with the feces from L-1methyl tryptophan (1MT)-treated ob/ob mice made the WT mice gain less body weight. The bacterial components of feces indicated that the decrease of *Clostridiales Lachnospiraceae* may be beneficial to control inflammation in the HFD-fed IDO-KO and 1MT-treated ob/ob mice. All these phenomena demonstrated that the intestinal microbiota of IDO-KO mice indeed

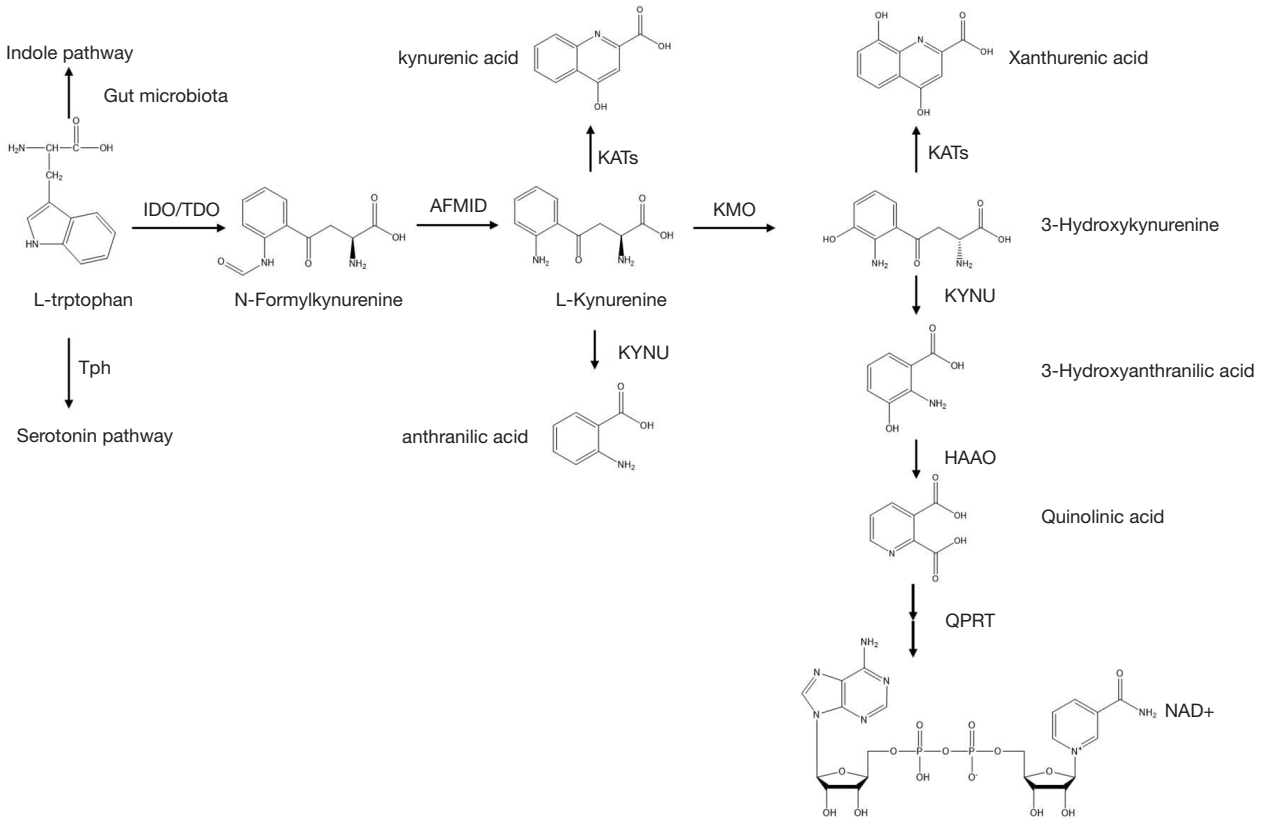

Figure 1 Degradation of tryptophan in kynurenine pathway. L-Trp is first converted into N-formylkynurenine, which is mediated by IDO or TDO, and then into L-kynurenine (3). L-Kynurenine is mainly metabolized into 3-hydroxykynurenine by KMO and then further converted into 3-hydroxyanthranilic acid by KYNU. 3-hydroxyanthranilic acid is catabolized into quinolinic acid by HAAO and then processed into end product NAD+ by QPRT. The catabolism of 3-hydroxykynurenine into xanthurenic acid by KATs and the metabolism of L-kynurenine into anthranilic acid and kynurenic acid are the minor L-kynurenine metabolism pathways. IDO, indoleamine 2,3-dioxygenase; TDO, tryptophan 2,3-dioxygenase; AFMID, kynurenine formamidase (arylformamidase); KMO, kynurenine-3-monooxygenase; KYNU, kynureninase; HAAO, 3-hydroxyanthranilate 3,4-dioxygenase; NAD+, nicotinamide adenine dinucleotide; QPRT, quinolinic aacid phosphoribosyltransferase; KATs, kynurenine aminotransferases.

protected the mice against obesity (20). In addition to the abovementioned effects, crucial roles for these enzymes in hepatic inflammation, fibrosis and cancers have also been suggested by a few studies. Herein, we provide an overview of the IDO/TDO in various hepatic diseases (*Table 1*).

We present the following article in accordance with the Narrative Review reporting checklist (available at: http://dx.doi.org/10.21037/atm-20-3594).

IDO/TDO in liver diseases

IDO/TDO in viral hepatitis

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are often regarded as the most common causes of viral hepatitis. Activated HBV and HCV-specific cytotoxic T lymphocytes (CTLs) produced IFN-γ which acted on hepatocytes, making the hepatocytes express IDO in patients with the corresponding type of viral hepatitis (21,22). IDO has dual roles in antiviral responses; although IDO inhibited HBV replication, Trp consumption mediated by IDO suppressed the killing infected hepatocytes by CTLs (23). An increased level of IDO, together with chemokine (C-X-C motif) ligand (CXCL) 9, CXCL10 and CXCL11 expression, was the marker of HBV clearance in patients with acute hepatitis B (AHB) (6). Whereas, the anti-HBV role of IDO was lost in IDO-knockout (KO) cells (6). Moreover, the anti-HBV activity was enhanced

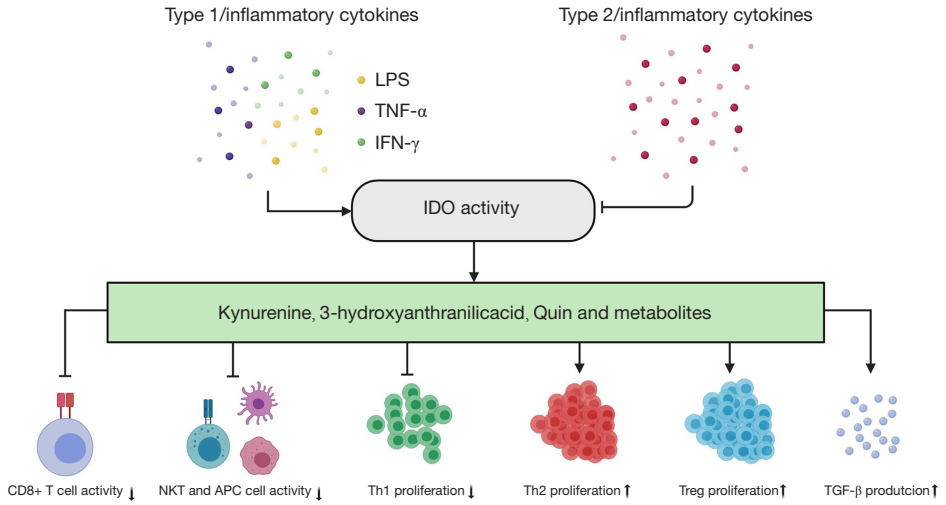

Figure 2 Modulation of kynurenine pathway in extrahepatic immune system. The activity of IDO can be stimulated by inflammatory cytokines and blocked by anti-inflammatory cytokines. The metabolites of KP catabolized by IDO play the suppressive role in the immune responses. They reduce activities of CD8+T cells and innate cells such as NKT cells, DCs and macrophages. They also inhibit Th1 cell proliferation. However, They promote Th2-phenotype polarization and Treg differentiation, as well as TGF-βproduction.

Table 1 Role of IDO/TDO in liver diseases

Liver diseases	Roles of IDO/TDO
Viral hepatitis	Inhibition of HBV replication; Exacerbation of liver injury
Autoimmune liver diseases	Protection against immune overactivation
Non-alcoholic fatty liver disease	Protection against liver inflammation; Promotion of liver steatosis
Liver fibrosis and cirrhosis	Aggravation or attenuation of liver lesions
Liver tumors	Promotion of tumor progression
Hepatectomy and liver transplantation	Suppression of liver regeneration; Protection against immune rejection

by NK cells and plasmacytoid dendritic cells (pDC) by driving the production of IFN-γ in HBV-positive Huh7 cells (6). Mao *et al.* (23) also demonstrated that IDO, one of 37 IFN-stimulated genes (ISGs), was able to dose-dependently inhibit intracellular HBV DNA replication in HepG2 cell lines but not RNA transcription. However, IDO was also a double-edged sword. Among chronic HBV infection, especially HBeAg(+) patients, persistent infection and immune tolerance might be mediated by MDSCs through expression of IDO, thus leading to HBsAg-specific T cells suppression (24). IDO exacerbated liver injury in the mice model of acute hepatitis injected with HBV-specific CTLs, and liver injury was eased when the mice were treated with its antagonist 1-methyl-D-tryptophan (1-MT) (25). In fulminant viral hepatitis, the activity of IDO and metabolites of KP were positively correlated with liver injury (25).

In regard to patients with HCV infection, the expression of IFN-γ and IDO was induced (26). It was reported that the hepatic mRNA expression of IDO was upregulated when chimpanzees were acutely infected and remained chronically high (19). Moreover, the enhanced IDO activity was positively correlated with severity of hepatic inflammation and fibrosis (27). Similar to the functions of IDO in HBV infection, IDO also played an important role in anti-HCV and immunoregulation in different phases of HCV infection. For instance, upregulated expression of IDO in the early stage inhibited HCV replication, while IDO might induce immune tolerance in the later time (19). One of mechanisms underlying the immune tolerance

can be attributed to the functions of IDO expressed by DCs mediated through the suppression of activated T cell and induction of Tregs (27). The key question of how the antiviral effect is balanced with its immunosuppressive role can be answered by evaluating the levels of Trp (19).

When it comes to other hepatitis virus infections, blockage of TDO and IDO lead to different outcomes. In a study of mouse hepatitis virus (MHV-A59) model, blocking TDO with LM10, a derivative of 3-[2-(pyridyl) ethenyl] indole, decreased the level of anti-MHV antibody and inhibited autoimmune responses, indicating that TDO may be a new perspective and target to treat certain kind of viral infection (28). Nevertheless, Duhalde Vega *et al.* (29) expressed the opposite opinion, indicating that application of L-MT, which blocked IDO without affecting TDO, did not protect the mice from MHV infection but instead augmented detrimental effects of the virus action, including hypergammaglobulinemia, anti-MHV Ab and uric acid release, as well as liver fibrosis.

IDO in autoimmune liver diseases

Autoimmune liver diseases are chronic liver diseases caused by immune dysfunction. In a model of α-galactosylceramide (α-GalCer)—induced hepatitis that resembles pathogenesis of autoimmune liver disease, IDO acted as liver protector against immune overactivation (3). Among patients with primary biliary cirrhosis (PBC), there was high degree of kynurenine metabolized from tryptophan and it increased the proportion of Tregs (30). Although few studies have been published, the role of IDO in autoimmune liver diseases cannot be ignored.

IDO in non-alcoholic fatty liver disease (NAFLD)

NAFLD is one of the metabolic diseases with high prevalence among contemporary humans. It was reported that IDO-KO mice were more prone to liver inflammation and fibrosis induced by a HFD compared to IDO-WT, suggesting that IDO may be beneficial in NAFLD (31). Moreover, a study conducted among obese women showed that the increased activity of IDO in the liver and adipose tissue was inversely correlated with balance of Th17 relative to Treg in subcutaneous fat (32). However, Laurans *et al.* (20) demonstrated that upregulated activity of IDO was correlated with obesity. They found that lack of IDO ameliorated the state of insulin resistance, improved the intestinal permeability, and protected mice from liver steatosis. In addition, another study demonstrated that kynurenine, the metabolite of Trp by IDO, was a known aryl hydrocarbon receptor (AhR) agonist and resulted in obesity. Blocking IDO or AhR prevented longer-term, diet-induced liver steatosis (33). Moreover, a HFD which facilitated proinflammatory environment suppressed the activity of TDO in the liver, but enhanced the extrahepatic metabolism of Trp by IDO (34). Therefore, IDO plays different roles in the NAFLD which needs further research.

IDO in liver fibrosis and cirrhosis

Liver fibrosis, which may progress to liver cirrhosis as the disease continues to advance, is characterized by extracellular matrix (ECM) component accumulation. IDO is found to be associated with liver fibrosis and cirrhosis. Zhong *et al.* (9) demonstrated that the serum level of IDO was positively related to liver lesions, regardless of hepatic function or liver stiffness, in liver cirrhosis patients and mice. Asghar *et al.* (35) found that it was more highly expressed in HCV-infected patients than in healthy subjects, which contributed to HCV-related liver cirrhosis. Another study showed that IFN-γ along with IDO inhibitor 1-MT induced hepatic stellate cells (HSCs) apoptosis, leading to amelioration of liver fibrosis (36). In addition, IDO-KO mice were protected from liver fibrosis with a reduced level of IL-17A and an increased level of TDO. These findings suggested that IDO might be a sign of liver cirrhosis. However, Ogiso *et al.* (37) came to the opposite conclusion, reporting that liver inflammation and fibrosis were intensified in IDO-KO mice treated with carbon tetrachloride (CCL_4) for 6 weeks. In a study which focused on utilizing mesenchymal stem cells (MSC) to mitigate liver fibrosis, Milosavljevic *et al.* (38) demonstrated that IDO was required to restrain IL-17 production by Th17 cells, thus attenuating liver fibrosis. Taken together, the opposite effects of IDO on liver fibrosis were associated with different circumstances. It exacerbated liver fibrosis and cirrhosis in some cases, and in other cases, it ameliorated the lesions.

IDO/TDO in liver tumors

Liver tumors are one of the most common cancers worldwide. Many chronic liver diseases, such as viral infections and alcoholic liver diseases, lead to pathogenesis of liver cancers. IDO acts as immunosuppressors in malignancies (39). A previous study found that the IDO was positively correlated with tumor progression. It has

been demonstrated that hepatocellular carcinoma (HCC) cells and surrounding cells expressed high levels of IDO, which helped tumors escape immune surveillance (40). Monocytes/macrophages also produced proinflammatory cytokines to induce IDO expression upon encountering CD69+T cells, leading to tumor growth (41,42). In addition, the frequency of these monocytes/macrophages in the tumor site was negatively correlated with survival in HCC (41). Apart from monocytes/macrophages, a clinical study also demonstrated an elevated percentage of intratumoral neutrophils infiltration and increased expression of IDO in HCC cells. IDO and intratumoral neutrophils may predict the prognosis of overall survival in HCC (43). IDO participated in the process of tumor antigen tolerance by contributing to the presentation of tumor antigens by host antigen-presenting cells (APCs), the escape from surveillance mediated by immune cells and induction of T cells exhaustion in the tumor microenvironment (8,44). Hypoxia inducible factor-1 α (HIF-1α)-CCL20-IDO pathway promoted tumor metastasis as well (44). Furthermore, in a model of diethylnitrosamine-induced liver carcinogenesis, IDO-KO mice developed fewer hepatic tumor foci and fewer Tregs infiltrated in the liver compared to IDO-WT mice. This finding indicated that inhibiting IDO or reducing the levels of downstream metabolites of KP may be beneficial to HCC treatment (45). Brown *et al.* (46) demonstrated that application of immune checkpoint (IC) inhibitors increased IDO expression in HCC patients, which made the drugs less effective than expected. Brown *et al.* (46) and Li *et al.* (47) suggested that a therapeutic regimen consisting of IC inhibitors and IDO inhibitors may be beneficial in improving treatment efficacy. Not only IDO, but also TDO played the immunosuppressive role in the malignancy (48). Canavese *et al.* (49) supp orted the hypothesis that TDO-Kyn-AhR metabolic pathway led to immunosuppressive effect, thus promoting HCC development. Tumor cells proliferated and escaped immune surveillance in the presence of a high level of kynurenine via two mechanisms (5). First, AhR activated by KP metabolites promoted cell migration by TDO; second, AhR disrupted T cell proliferation (50). TDO inhibition may change an unresponsive tumor immune microenvironment and enhance antitumor ability with minimal harmful effects on a normal cell line, which offered a potential way to treat HCC (48,51). Therefore, IDO helps liver tumor escape the immune surveillance and promotes tumor progression.

IDO in hepatectomy and liver transplantation

IDO also played important roles in hepatectomy and liver transplantation. After partial hepatectomy, IDO deficiency promoted activation of immune cells and broke immunotolerance, thus leading to liver regeneration (52). In regards to liver transplantation, IDO expression is upregulated in the APCs in rat allograft liver (53,54). For instance, the expression of IDO by Kupffer cells (KCs) in tolerance group grew dependently over time (55). Moreover, Sun *et al.* (56) demonstrated that IFN-γ-treated IDO-expressing DCs re-infused rat group showed milder symptoms of acute rejection compared to the control group. These findings indicated that IDO can be used to protect against immune rejection in liver transplantation. In addition, transfusion of IDO accompanied with cytotoxic lymphocyte antigen 4-immunoglobulin (CTLA4-Ig) gene increased survival rate in a rat model of liver transplantation acute rejection (57). Taken together, IDO induces immune tolerance and plays a protective role in liver transplantation.

Conclusions

Overall, the metabolic enzymes IDO or TDO in the KP of trptophan degradation have recently been recognized as important mediators that function as double-edge swords in various liver diseases. We may be able to take advantage of the predicted and therapeutic roles of these enzymes and their antagonists to prevent and treat hepatic diseases in the near future.

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Footnote

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