Indoleamine 2,3-Dioxygenase in Primary Biliary Cholangitis: A Comprehensive Review of its Role, Clinical Applications, and Regulatory Mechanisms

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Abstract- Primary Biliary Cholangitis (PBC), a common autoimmune liver disease, is characterized by persistent inflammation of the small bile ducts. The disease's pathophysiology is multifaceted, encompassing immune dysregulation, genetic and epigenetic factors, influences from the gut-liver axis, biliary epithelial cell damage, and environmental exposure. A key player in the development of PBC is Indoleamine 2,3-dioxygenase (IDO), an essential enzyme involved in the degradation of tryptophan (Trp) via the kynurenine pathway. This review delves into the diverse roles of IDO in various diseases, including infections, autoimmune diseases, and cholestatic liver diseases, underscoring its potential applications in PBC and its role in the IDO pathway in cancer. IDO proteins predominantly function intracellularly, with other enzymes such as IDO-2, IDO-like protein, and proto-IDO, also capable of degrading Trp. The study proposes potential therapeutic interventions using IDO inhibitors and anticancer drugs, which could yield significant antitumor effects. This review accentuates the pivotal role of IDO in PBC and its wider applications in various diseases, underscoring the need for further research and potential therapeutic advancements.

Index Terms- Indoleamine 2,3-dioxygenase (IDO); interferon gamma (IFNγ); primary biliary cholangitis (PBC); interleukin (IL)-4; localized inflammation

I. Introduction

IDO is an important enzyme that contains heme and plays a crucial role in the initiation of Trp catabolism through the kynurenine pathway by catalyzing the rate-limiting and initial stages of the process [1], [2]. The IDO pathway has been linked to various diseases, such as autoimmune disorders, infections, and cancer. Research suggests that disruptions in the IDO pathway may contribute to the development of PBC, a liver condition that involves bile duct damage, inflammation, portal fibrosis, cholestasis, and cirrhosis [3], [4]. The Indo, which encodes the IDO protein, is a naturally occurring apoenzyme that is conserved across different species. Indo (15 kb) is located on chromosome 8 in the human genome [5]. A limited number of inflammatory mediators control the transcription of this gene. Multiple sequence regions in the promoter of the INDO react differently to various interferon types, particularly interferon gamma [5]. IFN-γ is crucial for the interaction between IRF1 and STAT1, which leads to the activation of IDO through the induction of inducible cytokine-dependent oxidase [6], [7]. Although IFN-γ is the primary inducer of IDO expression, IFN-induced IDO expression surpasses that induced by IFN-α or IFN-β. The sensitivity of IDO cells to H_2O_2, production via an interferon gamma-independent mechanism involving tumor necrosis factor (TNF) and lipopolysaccharides (LPS), and the ability of H_2O_2 to be generated through both interferon-dependent and interferon-independent mechanisms under specific conditions have also been explored (Table 1) [8], [9]. In addition, IDO expression is modulated by interferons, interleukin-4 (IL-4), and transforming growth factor (TGF) [10]–[12]. This comprehensive understanding not only sheds light on the role of IDO in PBC but also underscores its intricate regulation and potential influence in other pathological contexts.

Table 1. Immunomodulatory Factors—Direct and Indirect Inducers and Inhibitors of Gene Expression

	Inducer	Inhibitor
Direct	IFN-α, IFN-β, IFN-γ, LPS, CTLA-4, IL-2, IL-18	TGF-β
Indirect	TNF-α, IL-1, IL-2, IL-4, IL-13, Corticosteroid PGE-2, Estrogen Prolactin, Bacteria Viruses	IL-6, Atorvastatin, Acetylsalicylic acid, Brassinin, Vitamin C, Vitamin E, Sodium sulfate, Sorbic acid, Anti-inflammatory plant extracts

II. IDO and Related Enzymes: Roles and Therapeutic Implications

IDO proteins primarily function intracellularly and have not been detected in their extracellular or secreted form. Notably, constitutive IDO activity has been observed in trophoblast cells at the fetal-maternal interface [13]. Recent discoveries have led to a significant change in the way this field is understood, particularly with the identification of genes related to IDO [14]. Three groups of enzymes, such as IDO, encode Trp: IDO-2, INDOL1, and proto-IDO [15]. Notably, IDO2 expressed in intact mammalian cells catabolizes Trp [16]. Additionally, selective inhibition of IDO1 activity is achieved using 1-methyl-L-Trp, whereas 1-methyl D-Trp selectively inhibits IDO-2 [16]. Further investigations have demonstrated that the combination of IDO inhibitors and anticancer medications yields significant antitumor effects [17]. Interestingly, the expression of IDO2 in dendritic cells (DCs) and its resistance to inhibition suggest a potential role for the IDO2 enzyme in immune evasion within the context of cancer [16].

III. The Trp Paradox: A Key Player in Immunological Dynamics

A. Trp Metabolism: A Critical Pathway in Biological Processes

Trp, an essential amino acid, undergoes one of three processes: incorporation into proteins, conversion into serotonin, or degradation via the kynurenine pathway. The Trp metabolic pathway is a complex network of enzymatic reactions that converts Trp into various metabolites. The main pathway for Trp metabolism is the kynurenine pathway, which produces kynurenine, kynurenic acid, quinolinic acid, and NAD+. The serotonin pathway produces serotonin, melatonin, and 5-hydroxyindoleacetic acid (5-HIAA). The tryptamine pathway produces tryptamine, N-acetyltryptamine, and melatonin. For instance, increased Trp catabolism can impede cell growth and lead to antimicrobial and immunomodulatory effects [18]. This pathway is closely involved in several biological processes, including maternal-fetal immune tolerance, immune modulation, and the development of neurological disorders, such as cerebral malaria and AIDS-related dementia [19]. Trp is an indispensable amino acid that is vital for protein synthesis and various essential metabolic processes in all living organisms. Mammals that cannot synthesize Trp from simple compounds must be obtained from dietary sources. Primary producers play a crucial role in sustaining the flow of tryptophan in the food chain by converting molecules such as phosphoenolpyruvate into Trp. This amino acid is subsequently transported to the liver, where it follows one of two metabolic pathways: entry into the bloodstream for cellular utilization or degradation via the kynurenine pathway. Trp serves as a fundamental building block for protein synthesis and a precursor for the synthesis of crucial compounds [18], [20]–[22].

B. Trp Catabolism: TDO and IDO

Trp metabolism is regulated by two specific enzymes, tryptophan 2,3-dioxygenase (TDO) and IDO. TDO, which is found mainly in the liver, has a high specificity for Trp and is activated by Trp and metabolic hormones [23], [24]. The enzyme indoleamine 2,3-dioxygenase (IDO) is expressed in various organs and is induced by interferon-gamma (IFN-gamma) during the immune response, unlike its localized expression in the placenta. IFN-γ, which is secreted by activated T cells and other immune cells, promotes the production of reactive oxygen species (ROS) and nitrogen species (NO) in macrophages and neutrophils. This finding suggested that IFN-γ-mediated Trp degradation is a biostatic mechanism that limits the local availability of Trp to pathogens, intracellular parasites, and cancer cells. Researchers have recently shown interest in the therapeutic potential of Trp deprivation for combating pathogens and cancer, as this approach may provide an effective strategy for combating these diseases. This approach harnesses the antimicrobial and anticancer effects resulting from the disruption of Trp availability [23], [25]–[27].

IV. Exploring the Roles of Kynurenines in Neuroprotection, Immunoregulation, and Disease

Kynurenic acid, a neuroprotective compound found in trace amounts within the brain, functions as an inhibitor of the N-methyl-D-aspartate (NMDA) receptor, particularly at the glycine modulatory site [26], [28]. Furthermore, it has been shown to inhibit alpha 7 nicotinic acetylcholine receptors and selectively activate the G protein-coupled receptor GPR35. At higher concentrations, it also affects glutamate sites and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptors [29]–[31]. In contrast, 3-hydroxyanthranilic acid, a neurotoxic compound, is involved in immunoregulation [32]. It can be generated through the oxidation of anthranilic acid or hydrolysis of 3-hydroxykynurenine. Copper in the system generates free radicals, such as hydrogen peroxide and superoxide [33]. Interestingly, copper can also act as a more effective antioxidant than other antioxidants, such as Trolox or ascorbic acid. This compound triggers apoptosis in T helper 1 cells (Th1) and murine thymocytes through mechanisms that include the release of cytochrome c from the mitochondria and the activation of caspase-8 [25], [26], [34]. Importantly, these effects occur at significantly lower doses than those that result in macrophage death or neurotoxicity. This finding underscores the immunoregulatory function of this compound in diverse disease conditions. Picolinic acid, another compound of interest, exhibits neuroprotective effects and serves as a chelating agent for zinc and iron. Classed as monocarboxylic acid [35], [36], picolinic acid also functions as a growth regulator with antiviral, antifungal, and anticancer properties. It induces cell cycle arrest in the G1 phase through the alteration of NAD+ function, a state that can be readily reversed

by the addition of nicotinamide. Finally, quinolinic acid, previously reported as an amino acid by [37], exhibits increased levels and IDO-1 activity during central or systemic immune responses. Nevertheless, the implications of these changes remain unclear. In the presence of inflammation, infiltrating macrophages, dendritic cells, and microglia represent the primary sources of quinolinic acid synthesized in the brain, as demonstrated by [38].

V. Kynurenine Pathway Metabolites: Immunomodulation and Their Implications in Diverse Disease States

Since the mid-1990s, researchers have extensively investigated the immunological functions of various kynurenine metabolites. A pivotal discovery by Mellor and Munn in 1998 highlighted the central role of IDO in preserving pregnancy and preventing allogeneic fetal rejection [39]. These findings revealed that every metabolite within the kynurenine pathway precisely regulates the immune system, exhibiting effective concentrations ranging from micromolar to picomolar levels. With a focus on IDO activity, researchers have explored the potential of Trp replenishment to counteract its effects, as initially suggested by the Trp depletion theory. However, as investigations have delved deeper into IDO induction across diverse experimental contexts, anomalies have emerged that cannot be fully explained by this theory [40]–[42]. In murine lung cancer, reduced IDO activity is associated with delayed tumor development, which is a noteworthy finding [43]. Significantly, metabolites of the kynurenine pathway, such as kynurenine, 3-hydroxykynurenine, and 3-hydroxyanthranilate, potently inhibited T-cell activation, with lasting inhibitory effects mediated through apoptotic cell death. These findings open doors to explore the potential use of kynurenine pathway metabolites for the elimination of B and natural killer cells. Intriguingly, DCs exhibited resistance to apoptosis induced by these metabolites. Furthermore, elevated levels of Trp breakdown and kynurenine in the serum have been observed in various clinical scenarios, often culminating in quinolinic acid production. The kynurenine pathway is upregulated in infectious diseases such as HIV, HCV, and HPV; neurological disorders such as AD and ALS; malignancies such as hematological neoplasia and colorectal cancer; and autoimmune conditions such as rheumatoid arthritis and MS. Notably, substantial increases in Trp levels have been observed in breast and lung cancers [44], [45].

VI. IDO: A Multifaceted Player in Immunology, Disease, and Cancer

IDO no longer stands as a mere participant in the host's immune response to infections, as is traditionally perceived [46], [47]. Instead, they have emerged as pivotal components of the immune system, particularly in the battle against various pathogens. While the efficacy of IDO in inhibiting pathogen proliferation in vitro is well documented, its precise role in regulating infections in vivo remains unclear. It is conceivable that IDO may confer more advantages to pathogens than to the host [48], [49]. The molecular mechanisms underpinning the capacity of IDO to create an immunosuppressive environment are the subject of active investigation. Trp depletion, initially identified as the primary mode of IDO action, has been found to be reversible when excess Trp is introduced into the culture medium. Further research has shown that additional injections of Trp can reverse IDO-mediated T-cell suppression. Nevertheless, IDO metabolites, such as 3-hydroxy-anthranilic acid and quinolinic acid, possess toxic and immunosuppressive properties that affect human T cells [50]. However, the exact influence of downstream kynurenine pathway metabolites on T cells and the mechanisms governing their effects have not been fully elucidated [50], [51]. The molecular signaling pathways through which T cells perceive and respond to the local conditions imposed by IDO have not been fully elucidated. These include the GCN2 stress-kinase pathway and the mTOR signaling pathway, which are triggered and inhibited by amino acid withdrawal, respectively [52], [53]. The role of IDO extends beyond immunosuppression. It may play a causal role in diseases in which the protective responses of the immune system are compromised, leading to the development of pathological tolerance and chronic conditions. Notably, IDO expression is frequently observed in various cancer types and serves as a resistance mechanism against tumor-infiltrating activated effector T cells. This results in an immunosuppressive microenvironment. Elevated levels of Trp catabolites in the urine of cancer patients have been documented, and surgical tumor reduction has been shown to reverse this effect. Multiple studies have suggested a link between IDO overexpression and poor prognosis, with IDO positivity in various tissues correlating with decreased survival and an increased incidence of liver metastasis (Figure 1) [54].

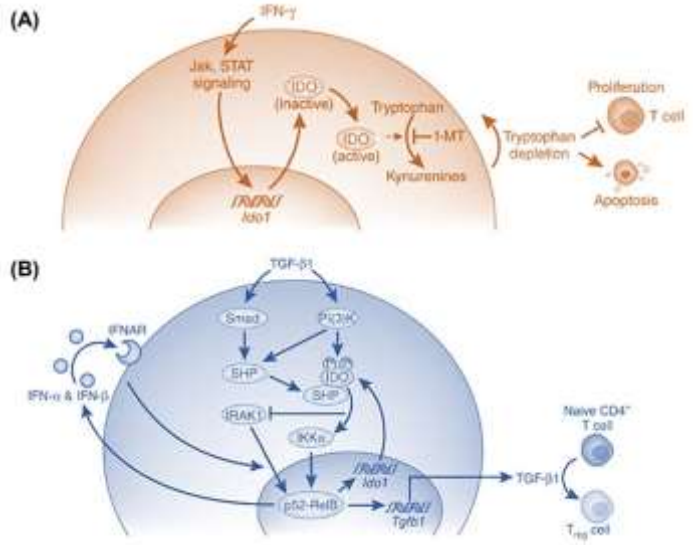

Figure 1: Distinct Roles of IDO in Plasmacytoid Dendritic Cells (pDCs) in Response to IFN-γ or TGF-β (a) IFN-γ signaling and T-cell regulation: The

illustration demonstrates the mechanism by which IFN-γ, through JAK kinases and STAT transcription factors, induces the production of indoleamine 2,3-dioxygenase (IDO) in pDCs. This active IDO then catalyzes the conversion of tryptophan to kynurenine, leading to the depletion of tryptophan within pDCs and T cells, which results in the inhibition of T-cell proliferation and increased apoptosis. The role of 1-methyltryptophan (1-MT) in modulating this process is highlighted. (b) TGF-β1 signaling pathway and immune tolerance: The figure shows the impact of TGF-β1 on IDO activation through a non-Smad signaling pathway involving PI(K)3 and Fyn-dependent phosphorylation. Additionally, TGF-β1 induces the expression of SHP-1 and SHP-2 via both Smad- and PI(K)3-dependent pathways. IDO's function in recruiting SHP-1 and SHP-2 is crucial for selectively activating the noncanonical NF-kB pathway, which results in the phosphorylation of IKKα and nuclear translocation of p52-RelB to target genes, potentially involving interleukin-1 receptor-associated kinase 1 (IRAK1) inhibition. This cascade leads to the expression of genes encoding IDO, TGF-β, and interferon-alpha/beta (IFN-α–IFN-β). Additionally, TGF-β produced by pDCs stimulates the generation of Foxp3+ regulatory T cells (Tregs) from naive CD4+ T cells, thereby promoting immune tolerance. The complex interplay between the IFN-γ and TGF-β1 pathways holds clinical significance for immune regulation and long-term immune tolerance, with the interferon-alpha/beta receptor (IFNAR) serving as a central component.

VII. Mechanisms and Local Effects of IDO-Mediated Bystander Suppression in T-cell Responses

Ongoing investigations into the mechanisms underlying the impact of IDO on immune responses have revealed several possibilities, including direct effects on T cells, the influence of IDO on antigen-presenting cells (APCs), and the interplay between these mechanisms. These mechanisms function in tandem and activate multiple pathways. Although in vitro experiments have demonstrated these effects, their in vivo implications remain speculative. At the molecular level, how T cells sense and respond to local conditions influenced by IDO has not been determined. Additionally, IDO may modify the behavior of IDO-expressing APCs, rendering them tolerogenic, and bystander suppression, observed both in vivo and in vitro, dominantly inhibits T-cell responses to antigens presented by neighboring IDO− APCs. The specific mechanisms for dominant (bystander) suppression may involve the local effects of IDO, such as Trp depletion, or the production of diffusible soluble factors, such as toxic Trp metabolites or immunoregulatory cytokines. Despite several possible explanations, no published data favor any one mechanism, emphasizing the importance of considering all potential mechanisms that directly regulate IDO, given our limited understanding of the remarkable immunosuppressive potency of IDO+ DCs (Figure 2).

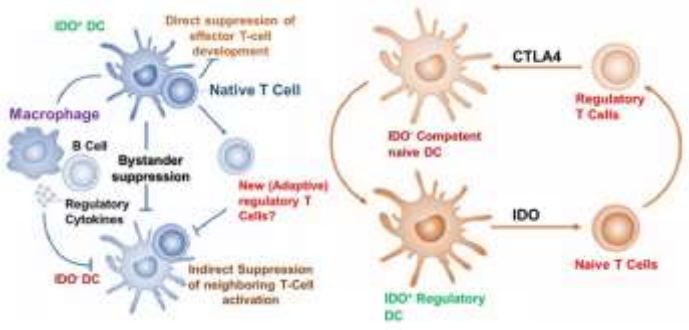

Figure 2. Illuminates the intricate mechanisms underlying the function of indoleamine 2,3-dioxygenase (IDO) within immune cells, particularly in panel (a), revealing the 'bystander' effects initiated by IDO-expressing cells, where a minor population of these cells can exert considerable suppressive influences on neighboring immune cells. This effect stems from various mechanisms, such as the generation of detrimental substances, depletion of a vital nutrient (tryptophan), or the release of IDO-induced regulatory cytokines. These mechanisms collectively contribute to the establishment of a tolerogenic environment, even for antigens presented by immunogenic antigen-presenting cells. Panel (b) shows a self-amplifying regulatory network model involving interactions between IDO-competent dendritic cells and regulatory T cells (Tregs). These findings suggest that the ability of IDO to induce the generation of Tregs can, in turn, stimulate the development of other tolerogenic dendritic cells, potentially elucidating the concept of 'infectious' tolerance. These insights emphasize the critical role of IDO in regulating immune responses and maintaining immune tolerance, with implications for clinical applications.

VIII. IDO in Immunity, Disease, and Cancer: A Complex Role in Immunomodulation

In numerous malignant tumors, the production of transforming growth factor-beta (TGF-β) directly inhibits the proliferation of cancer cells during the early stages of tumor growth [55], [56]. Paradoxically, while this suppression of TGF-mediated proliferation may initially impede tumor growth, it can lead to the development of cancer cells harboring mutations in the TGF receptor, TGF-β, and downstream signaling proteins, such as Smad receptors. Consequently, patients with metastatic or advanced malignancies may experience severe immunosuppression, which is a consequence of cancer cells becoming resistant to TGF-β owing to its overexpression[57]–[60]. Resistance is a hallmark of profound immunosuppression [55], [56]. Numerous studies have explored the regulatory role of T cells in the context of TGF-β and its influence on the immune response to tumors. Early research focused primarily on the direct effect of TGF-β on CD8+ cytotoxic T lymphocytes (CTLs) because TGF-β was found to inhibit IL-2 production and CTL activation [61]–[64]. In tumor cells transfected with TGF-β, CTL activity was inhibited both in vitro and in vivo [65]. TGF-β also influences the differentiation of CD4+ T helper cells [66], [67]. Additionally, TGF-β has been reported to inhibit TH1 responses by suppressing IFN-γ production by natural killer cells and limiting the maturation and activation of DCs [68]–[70]. This impairs their capacity to present antigens and drives T-cell proliferation. The role of TGF-β in the context of T-regulatory cells is not fully understood, despite the use of neutralizing antibodies against TGF-β to alleviate immune suppression in various inflammatory settings [71], [72]. Recent studies have highlighted the significance of TGF-β in the peripheral expansion of T-regulatory cells. Furthermore, in vitro treatment of CD4+ CD25– cells with TGF-β has been shown to enhance FOXP3 expression, leading to differentiation toward a T-regulatory phenotype capable of suppressing CD4+ T-cell activation and cytokine production [73]–[76]. Given the complex effects of TGF-β on tumor growth and its potential implications for the immune system, researchers have explored various strategies for developing TGF-β pathway inhibitors. Chronic cholestatic liver diseases, such as PBC, primarily affect women, with a male-to-female ratio of approximately 1:10. PBC affects middle-aged

women, and the preponderance of this disease in females may provide insights into its etiology. PBC is a chronic inflammatory autoimmune disease that primarily affects the interlobular bile ducts of the liver. Without intervention, patients often progress to cirrhosis and eventually to liver failure within 10–20 years. The disease manifests as the destruction of biliary epithelial cells (BECs) lining the small intrahepatic bile ducts, accompanied by significant infiltration of inflammatory portal tract T cells, B cells, natural killer cells, eosinophils, and macrophages. Recent research has highlighted the immunological aspects of this disease, including the identification of autoantibodies in the serum of patients with PBC. This discovery represents one of the initial steps in characterizing autoreactive responses in terms of antigen specificity [3], [77]–[79].

IX. Pathological Factors in PBC

PBC is characterized by the breakdown of immunological self-tolerance toward highly conserved mitochondrial and nuclear antigens. The initial autoimmune response observed in PBC involves the production of antibodies targeting antigens on the inner mitochondrial membrane, referred to as antimitochondrial antibodies. Moreover, autoreactive T-cell responses, specifically CD4 and CD8 responses, to the self-pyruvate dehydrogenase complex (PDC-E2) have been identified [80]–[82]. In PBC, there is straightforward evidence of heightened TGF-β signaling in the liver, which amplifies the release of IL-6 partially through the action of hydrophobic bile salts. Furthermore, PBC is associated with a reduction in the T-regulatory (T-reg) CD4+ CD25+ FoxP3+ compartment [83]. IDO plays a critical role in shaping the induction and regulation of T-lymphocyte proliferation [84]. Notably, TGF-β levels are elevated in PBC [85], and TGF-β acts as an inhibitor of IDO transcription. Several stimuli collectively contribute to increased TGF-β production [86].

X. Immunoregulatory Mechanisms in Patients with Chronic Hepatitis C Virus Infection: Insights into Adaptive Immune Initiation and Immune Response Coordination

Hepatitis C virus (HCV), a member of the hepacivirus genus within the flavivirus family [87], affects approximately 3% of the global population, with approximately one-third of those infected progressing to end-stage liver disease. Treatment for HCV-related hepatitis often involves antiviral medications, such as protease inhibitors (e.g., boceprevir and telaprevir). However, the interaction between HCV and hepatocytes is complex and influences the development of fibrosis and hepatocellular cancer. Understanding the pathogenesis of the virus, particularly its interaction with hepatocytes, requires multiple investigative approaches. The innate immune response plays a pivotal role in the response to invading pathogens and can progress through two phases: initiation and response. Pattern recognition receptors on the cell surface, in endosomes, and in the cytoplasm are responsible for identifying pathogens and initiating interferon-stimulated gene expression [88], [89]. Combating HCV, like many other viruses, necessitates a coordinated effort between innate and adaptive immune responses. Lymphocyte responses, including CD4+ and CD8+ responses, are critical for pathogen elimination and eventual recovery [90]–[92]. Nonetheless, understanding the intricacies of adaptive immune initiation in chronic HCV infection is challenging, as a prevalent decrease in CD4+ and CD8+ cells occurs [93], [94]. T-regulatory cells (Tregs) have been implicated in HCV infection, hampering HCV-specific immunity and contributing to disease progression (Figure 3).

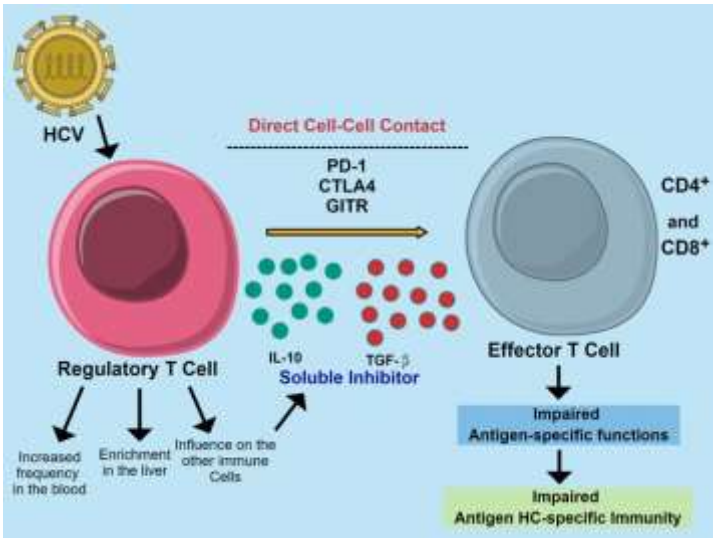

Figure 3. This study demonstrates the essential regulatory function of T-regulatory cells (T-regs) in the context of persistent hepatitis C virus (HCV) infection. Tregs exert both immediate and indirect suppressive effects on HCV-specific immunity, ultimately leading to a reduction in the immune response.

DCs expressing IDO exhibit enhanced regulatory T (Treg) function [95]. However, the mechanisms underlying IDO induction during HCV infection have not been elucidated. Notably, chronic infection has been associated with an increased serum kynurenine-Trp ratio and upregulated IDO expression in the liver. In many cases, this has been linked to viral clearance and patient recovery [96]. Intriguingly, significant IDO expression has been observed in chimpanzees infected with HCV, both when the virus is cleared and when the disease progresses to a chronic form [96]–[98]. In summary, IDO has significant effects on various biological processes and diseases, such as immunological regulation, infections, autoimmune disorders, and cancer. The presence of IDO isoforms underscores the complexity of the kynurenine pathway, suggesting its potential involvement in additional biological functions. IDO exerts its influence by restraining T-cell proliferation through Trp depletion and by generating immunosuppressive Trp metabolites, thus playing a vital role in immune regulation. IDO regulation is intricate and subject to numerous factors, including proinflammatory cytokines, TGF-β, IL-10, and nitric oxide. Its involvement in

diseases such as primary biliary cirrhosis and chronic hepatitis C infection indicates its role in the establishment of autoimmunity and tolerance. Further research is essential to unravel the mechanisms and implications of IDO in immunosuppression, autoimmunity, and tumor immune evasion. Therapeutic strategies aimed at inhibiting IDO may hold promise as adjuvant treatments; however, maintaining a balance between immune suppression and activation is critical. Understanding the interplay between IDO and TGF-β may provide valuable insights into novel immunomodulatory therapies.

XI. Conclusion

IDO has significant implications in several biological processes and diseases, including immunological control, infection, autoimmune disorders, and cancer. The discovery of IDO isoforms highlights the intricate nature of the kynurenine pathway and suggests its potential involvement in additional biological functions. IDO cells modulate immune responses by obstructing T-cell proliferation through Trp depletion and generating immunosuppressive Trp metabolites, thereby playing a crucial role in immune regulation. The regulation of IDO is a complex process influenced by factors such as proinflammatory cytokines, TGF-β, IL-10, and nitric oxide. Its contribution to diseases such as primary biliary cirrhosis and chronic hepatitis C infection suggests its involvement in the establishment of autoimmunity and tolerance. Further research is necessary to elucidate the mechanisms of IDO and the implications of IDO in immunosuppression, autoimmunity, and tumor immune evasion. Therapeutic strategies targeting IDO inhibition may hold promise as adjuvant treatments; however, balancing immunosuppression and activation is critical. Understanding the IDO-TGF-β interplay will provide valuable insights into novel immunomodulatory therapies.

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