Review Article

ROLE OF INDOLAMINE-2,3-DIOXYGENASE IN THE PATHOGENESIS OF CANCER AND HEPATITIS

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Summary

The gene responsible for Indolamine-2,3-dioxygenase (IDO) in humans is located at chromosome 8, it controls the tryptophan breakdown via the kynurenine pathway. IDO is actively expressed in epithelial cells, monocytes, tumor cells, macrophages, and the vascular endothelium. This enzyme exclusively converts L-tryptophan to L-kynurenine. Normally, it is produced in lower concentration. But overexpression of IDO suppresses the immune system of the body by reducing the metabolic fuel, tryptophan, required for immune activity. The function of the immune system can be suppressed by the upsurge of T regulatory cells and a decline in effector T cell activity. That is why it is known to be an important enzyme in the immune system, in cancer development, and viral and bacterial infection. Various studies have documented high levels of IDO expression in diverse types of cancers, bacterial infections, and viral infections. Nevertheless, the increased synthesis of IDO induces a tolerogenic effect, aiding the affected cells in evading immune responses. Consequently, IDO possesses the potential as an exceptional therapeutic agent for combating cancer and eliminating virus-infected cells.

Key Words: Indolamine, Dioxygenase, Tryptophan, Immune system

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INTRODUCTION

Indolamine-2,3-dioxygenase (IDO), an intracellular enzyme containing a heme group, is directly involved in the synthesis of kynurenine as a result of tryptophan breakdown.[1,2] The primary site for the kynurenine pathway is the liver, which holds all the essential enzymes for the transformation of tryptophan into NAD+.

In normal circumstances, approximately 90% of tryptophan degradation in the liver or hepatic cells is attributed to the kynurenine pathway.[3]

The initial steps of the kynurenine pathway in the liver are regulated by Tryptophan 2,3-dioxygenase (TDO) and exhibit a higher degree of substrate specificity compared to IDO.[4]

Normally, IDO accounts for approximately 5-10% of tryptophan degradation[5], but its significance increases during immune activation.[6,7] IDO serves as an essential enzyme to promote tolerance and suppress adaptive immunity as it converts tryptophan into L-kynurenine.[8] There are two isoforms of IDO: IDO1 and IDO2. IDO1, which plays an important role in the immune, has become a focal point of the research system as it exhibits higher expression levels than IDO2.[9] In this article, the term "IDO" specifically refers to IDO1.

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Normally, IDO1 has a limited role in tryptophan metabolism.[10] However, during inflammation, bacterial and viral infections, the release of interferons and other cytokines leads to increased activation of IDO, resulting in its up-regulation.[11] By controlling the level of tryptophan in the body, IDO synchronizes the immune function. Tryptophan is one of the vital amino acid beings is required for cellular growth as well as for immune function. Overexpression of IDO suppress the immune system of the body by reducing the metabolic fuel, tryptophan, required for immune activity. The high expression of IDO contributes to the up-regulation of T regulatory cells and the low expression of effector T cell activity, resulting in immune system suppression.[12,13] In essence, the high expression of IDO leads to immunosuppression. It assumes a pivotal role in various malignancies, infections, and autoimmune diseases.[14] Numerous studies demonstrate that the levels of IDO and tryptophan in the blood are involved in the diagnosis and treatment of various diseases.

Role of IDO as an immunosuppressive enzyme associated with the development of cancer:

Overexpression of IDO helps cancerous cells to outflow from the immune system. Being an immunosuppressive molecule it helps in the prognosis of tumors. Different studies show that IDO expression is increased in different cancer which helps the cancerous cell to escape from the anti-tumor immune response.[15] IDO up-regulates the growth and spread of tumors, by serving as an important link between inflammation, vascularization, and immune evasion.[16] Excessive production of IDO has been observed in the lymphatic drainage regions of multiple deadly cancers, including stomach carcinomas[7], colorectal cancer[17], ovarian cancer[18,] and various others.[19]

IDO and ovarian cancer:

Elevated expression of IDO results in an increase in pro-inflammatory cytokine levels whereas through tryptophan depletion it is responsible for the reduction of effector T cells within the tumor cells. Further research has indicated that in ovarian cancer, IDO-derived tumor cells are not only involved in the suppression of the ability of tumor-infiltrating effector T cells to fight it but alongside enhance the production of immunosuppressive cytokines in ascites. This creates an environment wherein the cancer cells can spread without any resistance.[20,21]

To create clones of cells overexpressing IDO, they transfected the cDNA of IDO into a murine ovarian carcinoma cell line called OV2944-HM-1, which was then referred to as HM-1-IDO. Control cells were also transfected with a control vector, known as HM-1-mock. Subsequently, both HM-1-mock and HM-1-IDO cells were transplanted into immune-deficient mice of the same strain. The mice that received HM-1-IDO grafts exhibited significantly lower survival rates, increased volume of ascites, and elevated tumor weight in the peritoneal dissemination area compared to the control mice.[21]

The tumor-promoting effect is interrelated with a decline in CD8+ T cells along with natural killer cells within the tumor cells. On the other hand, it results in an upsurge in the levels of transforming growth factor-β along with interleukin-10 in the ascites.[21]

IDO and gastric cancer:

In a study led by Nishi et al., 2018, the levels and mechanism of IDO in stage III gastric cancer were investigated. The study revealed a significantly lower survival rate among patients who tested positive for IDO compared to the IDO-negative group. IDO was found to contribute to immune tolerance and poor prognosis by suppressing Treg activation in gastric cancer. Alongside this, this study established a positive link between IDO and TGF-β expressions. Whereas the TGF-β expression was found to be related to the activity of Foxp3, a known factor involved in the development and function of Treg cells, in patients with stage III gastric

cancer. Li et al., 2019, conducted a study to further verify that the levels of IDO Foxp3 can be used to foretell prognosis in gastric cancer.[22]

IDO and breast cancer:

The overexpression of IDO plays a crucial role in breast cancer. In addition to increased expression, the activity of IDO is remarkably high in paclitaxel-resistant breast cancer cells, leading to poor prognosis and reduced response to chemotherapy. However, IDO also serves as an important biomarker for assessing chemotherapy efficiency, as tryptophan catabolism is associated with tumor response.[23] Asghar et al., 2019 conducted a study to examine the expression of IDO in patients with triple-negative breast cancer (TNBC) at the tissue level.[24] The findings of this study demonstrated that IDO is overexpressed in TNBC patients compared to normal individuals. Furthermore, patients with a high IDO score exhibited lower survival rates than those with a low IDO score. In addition to suppressing the immune response against tumor cells, IDO also promotes angiogenesis in breast cancer.[25]

IDO and Prostate Cancer

IDO activity is also over-expressed in prostate cancer. The progression and prognosis of prostate cancer are influenced by inflammation, as evidenced by histological studies of prostatectomy samples revealing significant inflammation during the early stages of malignancy.

IFN-γ, a pro-inflammatory cytokine, up-regulates the production of IDO. This enhanced production of IDO helps prostate tumor cells circumvention of the immune response.[26] However, the expression of the IDO gene in the urine of men acts as a potential marker for the development of prostate cancer and may reduce the need for prostate biopsies.[27] Banzola et al., 2018 researched the effect of inflammatory triggers on the creation of prostate cancer-related soluble factors, like IDO and interleukin 6 (IL-6). They used IFN-γ and TNF-α to induce IDO and IL-6 genes respectively.[28] Research has shown that IDO expression can be used to accurately predict recurrence-free survival in individuals who are diagnosed with prostate cancer. On the other hand, IL-6 gene expression did not seem to have a significant role in predicting recurrence-free survival among prostate cancer patients.

IDO and Hepatitis:

Hepatitis, also known as viral hepatitis, is characterized by inflammation of the liver and is primarily caused by viral infections. According to epidemiological reports, Hepatitis B Virus (HBV) affects about 350 million people around the world, with more than 780,000 deaths per year due to liver ailments.[29] Patients with HBV infection exhibit higher kynurenine to tryptophan ratios compared to non-infected individuals due to increased activity of IDO.[30] HBV infection impairs the response of virus-specific T-cells by promoting the expansion of myeloid-derived suppressor cells (MDSCs). HBeAg-induced MDSC expansion impairs the function of T-cells through the IDO pathway, facilitating the establishment of persistent HBV infection. Yang et al., 2019 investigated the frequency of circulating myeloid-derived suppressor cells in patients with chronic hepatitis B and healthy individuals.[31] In comparison to healthy individuals, the percentage of myeloid-derived suppressor cells came out to be higher in HBV-infected individuals. Additionally, exposure of peripheral blood mononuclear cells (PBMCs) from healthy donors to HBeAg resulted in significant upregulation of IDO, IL-1β, IL-6, and expansion of MDSCs.[30]

Hepatitis C Virus (HCV) affected almost 170 million people around the world and the infected ones are more vulnerable to developing chronic liver diseases. In comparison to healthy individuals, the HCV-infected patients portray higher IDO levels.[14] IDO expression is enhanced by the synergistic effect of Lipopolysaccharide (LPS), interleukin-1 (IL-1) and tumor necrosis factor (TNF) with interferon-γ (IFN-

γ).[32,14] Upon stimulation with IFN-γ and co-culture with activated T-cells, Huh 7 cells, which support HCV replication, exhibit higher levels of IDO mRNA expression compared to healthy individuals.[33,34] HCV infection induces the production of MDSC-like monocytes through the TLR2/PI3K/AKT/STAT3 pathway. These monocytes suppress the activation of CD4+ T-cells and promote the development of CD25+, Foxp3+, and CD4+ regulatory T-cells (Tregs) in the presence of IDO, leading to the accumulation of kynurenine.[35]

Therapeutics of IDO

It is obvious from the above explanation that IDO helps in the escape of tumor cells and virus-infected cells from the immune response. So, IDO can act as a marvelous therapeutic agent for the cure of cancer and viral infections.[36] According to recent studies, IDO can be used as a biomarker to monitor immune status. Zhu et al. (2020) investigated the relationship between IDO activity and clinical diagnosis in patients with early-stage non-small cell lung cancer in patients who underwent stereotactic body radiotherapy (SBRT).[6] They quantitatively analyze the immune activity of IDO in serum before and after SBRT and explore the changes in immune ne activity of IDO mediated by SBRT and its relationship with patient survival. SBRT could alter IDO-mediated antitumor immune activity. The post/pre kynurenine ratio was found to have a direct correlation with higher progression-free survival. The expression of T-regs produced by IDO secreted by dendritic cells decreased in the presence of 1-methyl tryptophan (1-MT)fingolimodimod (inhibitor of IDO). So, 1-MT can be served as one of the best strategies to boost the immune responses in HCV infection.[14] The inhibitors of IDO show anti-cancer behavior in different types of cancer.[37] There are different inhibitors of IDO but three strong inhibitors, indoximod, INCB024360, and NLG-919 are in clinical trials.[38]

CONCLUSION

Millions of people die due to both cancer and infectious disease (whether bacterial or viral) every year in the world. There is no proper treatment to cure these diseases. So, there is a dire need for the development of treatment for these mortal diseases. There is ample evidence of increased production of IDO in cancer, bacterial and viral diseases which help infect cells to escape from the immune response. That is why IDO can act as both an important diagnostic as well as a therapeutic agent to diagnose and cure different cancerous and infectious diseases. Inhibition of IDO will help to drive anti-tumor immune effects and lead to the removal of cancerous and infected cells from the body. Many drugs, which act as inhibitors of IDO, are in clinical trials. To achieve exceptional therapeutic effects in humans, extensive study of the immunological function of IDO is required.

AUTHOR'S CONTRIBUTION

FA: Conception and data collection
MSQ: Conception and proofreading
ZA: Data collection and drafting
AK: Data collection and drafting
ZK: Drafting and proofreading
IG: Final drafting and proofreading
MSA: Final drafting and proof reading

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