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IDO-Mediated Tryptophan Degradation in the Pathogenesis of Malignant Tumor Disease

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Abstract: Immune escape is a fundamental trait of cancer in which the Th1-type cytokine interferon- γ (IFN- γ) seems to play a key role. Among other tumoricidal biochemical pathways, IFN- γ induces the tryptophan-degrading enzyme indoleamine 2,3-dioxygenase (IDO) in a variety of cells including macrophages, dendritic cells (DCs) and tumor cells. IDO activity has been shown to reflect the extent and the course in a plethora of malignancies including prostate, colorectal, pancreatic, cervical, endometrial, gastric, lung, bladder, ovarian, esophageal and renal cell carcinomas, glioblastomas, mesotheliomas, and melanomas. Furthermore IDO activity during malignant tumor diseases seems to be part of the tumoricidal immune defense strategy, which in the long run is detrimental to the host, when tryptophan deprivation and production of pro-apoptotic tryptophan catabolites counteract T-cell responsiveness.

Keywords: IDO, Tryptophan, Malignant tumor disease

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Introduction

In vitro, Th1-type cytokine interferon- γ (IFN- γ) induces the tryptophan-degrading enzyme indoleamine 2,3-dioxygenase (IDO) in monocyte-derived macrophages, dendritic cells and in a variety of other cell types including tumor cells. *In vivo*, accelerated tryptophan degradation can be detected in body fluids by measurements of kynurenine and tryptophan concentrations. Calculating the kynurenine to tryptophan ratio (kyn/trp) serves as an estimate of IDO functional activity. A large proportion of patients with a variety of disorders like viral or bacterial infections, autoimmune syndromes or during allograft rejection presents with increased kyn/trp in serum/plasma or cerebrospinal fluid. Tryptophan degradation in these individuals reflects the extent, activity and the course of disease. In patients with malignant tumors, tryptophan degradation parallels disease progression, loss of immunocompetence and the development of cachexia and anemia. In addition, higher kyn/trp and lower tryptophan concentrations predict shorter overall survival.

The rate of tryptophan degradation in malignant cell lines is usually low but can be significantly enhanced by pro-inflammatory stimuli such as IFN- γ . Data suggest that tryptophan degradation in patients with cancer predominantly relates to enhanced IDO activity, which is stimulated during Th1-type immune response. This conclusion is further supported by the observation that kyn/trp in humans usually correlates closely with neopterin concentrations, which is released by human monocyte-derived macrophages and DCs particularly upon stimulation with IFN- γ , but not by stimulated tumor cells themselves. Degradation of essential amino acid tryptophan represents an effective anti-proliferative strategy, which is established during immune response. It is directed to stop malignant proliferation as is to halt growth of pathogens in infected cells.

In 1996 we demonstrated accelerated tryptophan degradation correlating to neopterin levels in normal human pregnancy, and 1998 Munn et al revealed IDO activity to be critical for the induction of maternal immunotolerance. Subsequent studies were able to substantiate the central role of IDO activation in the development of immunodeficiency and immunotolerance. Thereby IDO expression in DC is crucial in the control of regulatory T-cells.

Degradation of tryptophan in cancer patients suggests that IDO activity may be involved in several

typical symptoms of chronic inflammatory conditions. IDO is also related to impaired quality of life, and this correlation is obviously due to the close association between tryptophan and the biosynthesis of neurotransmitter serotonin. Therefore, tryptophan deficiency could represent an important aspect in the pathogenesis of cognitive impairment and depression in patients with immunopathologic clinical conditions.

Data on IDO thereby provide a basis to better understand the complex interplay between immune activation cascades and the development of immunodeficiency, or in other words, of the pro- and anti-inflammatory consequences of IFN- γ , among which IDO is a central component. IFN- γ -induced IDO activity during malignant tumor diseases is part of the physiologic tumoricidal immune defense strategy, which in the long run might be detrimental to the host, when tryptophan deprivation and production of pro-apoptotic tryptophan catabolites, counteracts T-cell responsiveness.

We are only beginning to understand the complexity of pathophysiological cascades in the tumor microenvironment, where particular immune cells play important roles in terms of tumor development and progression. The Th1-type cytokine IFN- γ has been shown to be crucial in this process via serving as a stimulus for anti-proliferative biochemical pathways. These include the kynurenine pathway in which the immunomodulatory enzyme IDO and its recently discovered relative IDO2 initiate the first step in the degradation of the essential amino acid L-tryptophan to ultimately form a plethora of immunomodulatory metabolites. Encoded by the INDO gene at human chromosome 8p12, IDO is an isoenzyme of hepatic tryptophan 2,3-dioxygenase (tryptophan pyrrolase, TDO) which was first described and isolated in 1963.^{1,2} Over decades it has been reported that IDO plays an immunosuppressive role in a variety of chronic infections, including viral, parasitic and bacterial infections such as human immunodeficiency virus (HIV), malaria, hepatitis C, *Toxoplasma gondii* and Chlamydia.¹⁻³ IDO is widely expressed in human tissues and cell subsets and its immunoregulatory properties have been shown to play a dominant role in immune responses and regulation towards self and foreign antigens. A better understanding of these mechanisms will not only allow us to unveil the pathogenesis of many diseases but also discover new therapeutic approaches

in terms of prevailing tumor escape and inducing immune tolerance.⁴ Maternal tolerance towards the semi-allogeneic fetus is only one example in which IDO has been shown to mediate immune privilege by preventing T-cell driven rejection.⁵ This groundbreaking discovery paved the way for further research addressing the immunoregulatory potential of IDO including a series of studies focusing on the role of IDO-mediated tryptophan metabolites in the immune escape of tumors.⁶ This review highlights the experimental and clinical findings of IDO-induced tryptophan degradation in the pathogenesis of malignant tumor disease and discusses potential novel anti cancer-therapeutic strategies by targeting IDO.

IDO Mediated Tryptophan Metabolism

The two intracellular enzymes IDO and TDO initiate the rate limiting step in L-tryptophan degradation along the kynurenine pathway and ultimately form immunomodulatory metabolites like L-kynurenine, 3-hydroxykynurenine, 3-Hydroxyanthranilic acid

and picolinic acid. In case the immune system gets activated, high amounts of IFN- γ are released mainly by leukocytes. This results in sustained IDO activation most prominently in antigen presenting cells (APCs) like DCs, which leads to the afore-mentioned accumulation of downstream tryptophan products. Besides that, a small amount of tryptophan is used for melatonin synthesis in the pineal gland or metabolized to serotonin in the nervous system. Leucocytes are furthermore the cell source to produce redox active compounds like superoxide (OH^{*}), which generates Fe²⁺ from Fe³⁺ within the heme-prosthetic group of IDO allowing it to proceed tryptophan metabolism (Fig. 1). This mechanism suggests that IDO activity is restricted to sites of infection or inflammation.⁷⁻⁹ Furthermore the redox potential of the microenvironment seems to influence the function of tryptophan metabolites as well.⁹

Immunosuppressive Effects of IDO

The exact mechanism, how IDO acts immunosuppressive, is still under debate. Two main theories have

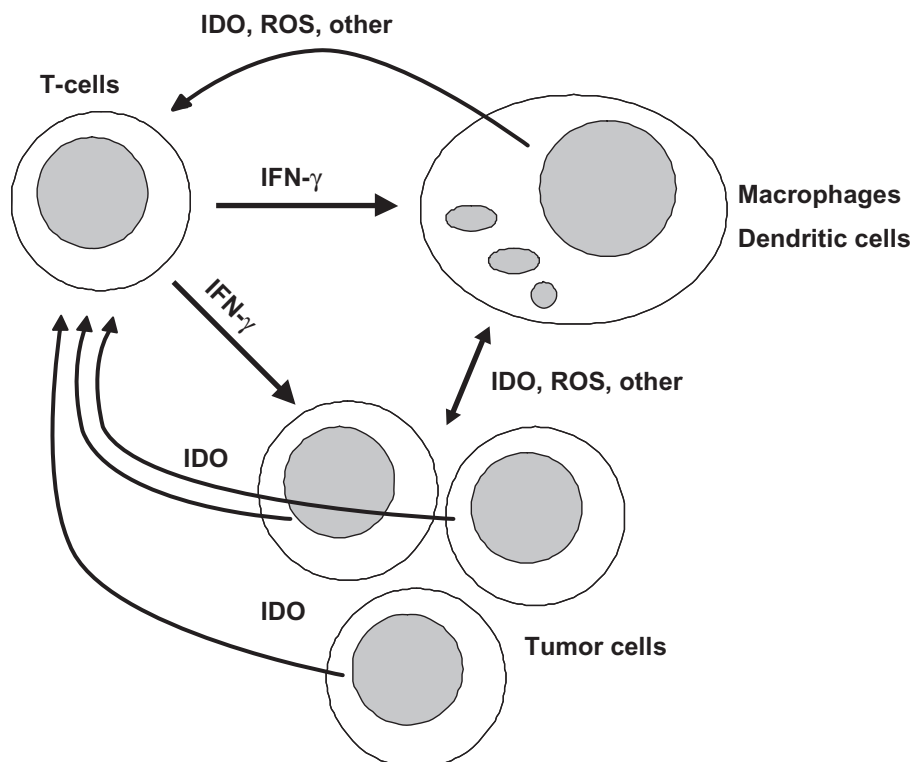


Figure 1. The developing malignant process is recognized by immunocompetent cells and a broad response of several immunocompartments is mounted against the foreign surface structures of tumor cells. Among the immunoregulatory cytokines released during innate and adaptive immune responses, Th1-type cytokine interferon- γ (IFN- γ) stimulates several antiproliferative and tumoricidal biochemical pathways such as the formation of reactive oxygen species (ROS) and the degradation of tryptophan by indoleamine 2,3-dioxygenase (IDO) in macrophages, dendritic cells and tumor cells. As one important consequence, tryptophan starvation and the formation of toxic effector molecules like kynurenine derivatives and anthranilate not only affect proliferation of target tumor cells but also of T-cells and their immunoresponsiveness.



been proposed either involving tryptophan metabolites or starving cells of tryptophan. After IDO activation has been described through the course of successful pregnancy,¹⁰ in 1998 Munn and Mellor discovered that IDO expression at the feto-maternal-interface was crucial to prevent fetal rejection in pregnant mice. Pharmacologic enzyme inhibition with 1-methyl-tryptophan (1-MT) resulted in T cell mediated rejection of allogeneic but non-syngeneic fetuses.⁵ This maternal tolerance concept was based on the theory that local tryptophan depletion would maintain pregnancies through suppression of T-cell driven fetal rejection. Tryptophan depletion induces cell cycle arrest in lymphocytes¹¹ ultimately driving these cells into apoptosis.¹² This is mainly regulated through the amino acid sensitive general control non-depressible 2 (GCN2) stress kinase pathway which becomes activated upon IDO-induced tryptophan degradation and production of uncharged tRNA in T cells.¹³ A tryptophan threshold in order to inhibit T cell proliferation could not be defined yet. Munn et al reported that tryptophan concentrations in vitro had to decrease below 0.5–1 μM to inhibit T-cell proliferation,¹¹ others report that even completely tryptophan free cell culture medium could not sufficiently inhibit T lymphocytes from growing.¹⁴ In humans, plasma tryptophan levels range between 50–100 μM . It is currently unclear to what extent tryptophan degradation and starvation accounts for IDO mediated immunosuppression since minimum tryptophan threshold limit values have not been defined and probably can not be defined in vivo. In case of inflammation and tumor growth necrotic cells release their intracellular stocks and thereby supply an additional source of tryptophan to the particular microenvironment. Furthermore, local decrease in tryptophan can easily be replaced through diffusion from surrounding tissues. Taken all of these afore mentioned results into consideration it is currently unclear to what extent tryptophan starvation accounts for IDO-mediated immunosuppression.

The tryptophan metabolite theory is nourished by the fact that downstream metabolites of tryptophan cause cell cycle arrest and apoptosis in lymphocytes.^{14–16} Furthermore, they foster via to date largely unknown mechanisms the differentiation of naïve CD4+ T cells into T regulatory cells (Treg).¹⁷ However one study suggests that 3-hydroxyanthralinic acid directly blocks

T cell antigen receptor-triggered nuclear factor- κB (NF- κB) activation through kinase 3-phosphoinositide-dependent protein kinase 1 (PDK1) signaling which ultimately leads to activated type 2 T helper cell death.¹⁸

In summary, both theories are not necessarily mutually exclusive but rather a concerted contribution of both mechanisms might contribute to IDO-mediated immune suppression in vivo.

Tumor Immunity Through IDO Mediated Tryptophan Catabolism

Immune escape is a fundamental trait of cancer.¹⁹ A variety of tumor escape mechanisms have been elucidated over the past.^{6,20} Key players in this crucial escape mechanism are Tregs and regulatory DCs, which create tolerance to the antigen they are presenting. Furthermore, IDO also seems to play a detrimental role in tumor immunity by acting in a forward feedback loop to instruct naïve CD4+ T cells to become Tregs but also by mediating Tregs to drive naïve DCs into a regulatory status.^{21,22} By provoking a cycle of antigen tolerance IDO might switch the tumor microenvironment from hostile to supportive for tumor cells and also initiate a peripheral immune escape mechanism that facilitates progression to a more invasive tumor status.¹⁹ Supporting the fact that IDO has a fundamental role in immune control, recent evidence suggests that the immunosuppressive drug dexamethasone operates upon IDO induction in DCs by reverse signaling through the glucocorticoid induced B7 inhibitory T cell co-receptor.²³ IDO does not seem to be involved in tolerizing self-antigens but rather in creating a tolerant state for non-self antigens (e.g. fetal antigens) where immune non-responsiveness is important.²⁴ However in the eventuality of cancer, immune unresponsiveness to tumor antigens results in disease aggravation.

In addition, T cells also appear to be predominantly sensitive to IDO activation, since upon tryptophan starvation they cannot proliferate and become activated by means of antigen presentation and they rather translate into an anergic state. Tryptophan starvation furthermore triggers a Gcn2-dependent stress-signaling pathway that ultimately leads to cell growth arrest through phosphorylation and translational initiation at the ribosome.¹³ Furthermore T cells seem to be preferentially vulnerable to kynurenine derivatives and other catabolites generated by the IDO pathway²⁵



which along with tryptophan restriction appears to be important for induction of Tregs and immune suppression.^{22,26}

Clinical Significance of IDO Expression in Human Malignancies

IDO expression can be detected in most human cancers including prostate, colorectal, pancreatic, cervical, endometrial, gastric, lung, bladder, ovarian, esophageal and renal cell carcinomas, glioblastomas, mesotheliomas, and melanomas.²⁷⁻³³ Clinical studies stress that high IDO expression of tumor cells correlates with outcome (Table 1). In endometrial cancer, ovarian cancer and high-grade osteosarcomas, respectively, IDO expression correlates with poor overall survival.³⁴⁻³⁶ Furthermore, our own group was able to show that IDO had a significant prognostic value in terms of liver metastasis in patients with colorectal cancer. IDO expression goes along with reduced CD3⁺ lymphocyte infiltration suggesting a suppressive function on tumor reactive T-cells.³⁷ In patients with hepatocellular carcinoma similar findings were reported.³⁸ Furthermore a significant relationship was found between the amount of IDO positive tumor infiltrating cells and overall survival in non small cell lung cancer.³⁹ In addition the presence of metastatic infiltrating IDO positive cells into the lymph node at initial diagnosis correlated with a significantly worse clinical outcome in malignant lymphoma.⁴⁰ In contrast IDO expression in tumor endothelial cells in patients with renal cell carcinoma

correlates with long-term survival.⁴¹ Apart from IDO, pyrazinopyrimidine compound neopterin has been shown to be a reliable prognostic marker for human malignancies.⁴² Neopterin is released as an inflammatory marker in large amounts from human monocyte-derived macrophages and DCs preferentially following stimulation with the pro-inflammatory cytokine IFN- γ , thus reflecting the immune activation status. Increased neopterin levels in patients with melanomas, breast cancers, squamous cell carcinomas, gynecological tumors, and colorectal carcinomas have been shown to go along with poor prognostic outcomes.^{32,43-46}

Since IFN- γ is one of the strongest inducers of IDO expression⁴⁷ and due to its sustained effects on tumor cell proliferation the cross-linked interplay of IFN- γ and IDO seems to be of great importance. This hypothesis is additionally supported by *in vivo* studies in an ovarian carcinoma mouse model where IL-12, a cytokine with anti-tumor activity, induced complete regression of fibrosarcomas and ovarian carcinomas due to IFN- γ induced IDO activity.⁴⁸

Besides its anti-proliferative effects on transformed cells⁴⁹ IFN- γ seems to exert even stronger inhibitory effects on human cancer cell proliferation upon IDO expression. Almost two decades ago it has been shown *in vitro* that IFN- γ induced IDO expression leads to tryptophan degradation in cell culture medium resulting in cell proliferation arrest. However tryptophan supplementation of growth medium reversed the anti-proliferative effects of IFN- γ .⁵⁰

Table 1.

Tumor entity	Overall survival of patients with increased IDO expression	Progression-free survival of patients with increased IDO expression	References
Malignant melanoma	Reduced	Reduced	31,32
Acute myeloid leukemia	Reduced	Reduced	33
Ovarian serous carcinoma	Reduced	Not evaluated	34
Ovarian clear cell carcinoma	No correlation	Not evaluated	34
Endometrial carcinoma	Reduced	Reduced	35
Osteosarcoma	Reduced	Reduced	36
Colorectal carcinoma	No correlation	Not evaluated	37
Hepatocellular carcinoma	Not evaluated	Prolonged	38
Renal cell carcinoma	Prolonged	Not evaluated	41
Esophageal squamous cell carcinoma	Not evaluated	Not evaluated	29
Lung cancer	Not evaluated	Not evaluated	30



In conclusion, IDO induction seems to be one mechanism by which IFN- γ inhibits malignant cell outgrowth thereby being a decisive mechanism of tumor attack.

IDO Inhibition, a Potential Mechanism of Cancer Therapy in the Future?

Since IDO plays a major role in the escape of malignant cells from immunological attack it is obvious that blocking its activity should increase the anti-tumoral response and halt tumor progression. In vitro studies showed that 1-MT treatment delayed outgrowth of mouse melanoma cells that have been engrafted into syngeneic hosts.⁵¹ Furthermore over-expression of IDO promotes tumor growth, which again could be partially reversed by pharmacologic inhibition.²⁸ However, in a murine breast cancer model it has been shown recently that 1-MT, although present in sufficient concentrations, only slightly retarded autochthonous breast cancer. Because 1-MT only seems to be able to slow down and not to prevent tumor growth it was combined with several chemotherapeutic drugs or radiotherapy resulting in even more pronounced anti-tumoral effects.^{52,53} The molecular mechanism by which IDO inhibition contributes to the beneficial partnership with chemotherapy still remains to be elucidated. 1-MT exists in two isoforms, L-1-MT and D-1-MT which both inhibit IDO and its relative IDO2, respectively. In subsequent murine tumor models it turned out that only D-1-MT significantly prolonged survival when combined with conventional chemotherapeutics.⁵³ However, IDO has a tenfold higher affinity for the L-isomer than the D-isomer, indicating that D-1-MT is less efficient in blocking IDO enzymatic activity. Interestingly D-1-MT did not block IFN- γ treated tumor cell lines or IDO transfected cell lines.⁵³ However, in some other experiments it was able to block tryptophan degradation of IDO expressing DCs that were used as stimulator cells in allogeneic mixed lymphocyte culture and accordingly increased T-cell proliferation in the co culture system. The question why D-1-MT inhibits IDO activity in only some cells and does not inhibit the activity of the purified IDO enzyme was answered when another IDO isoform was discovered. The gene IDO2 encodes an IDO-like protein and has recently been detected on the human chromosome 8. IDO2 is inhibited by D-1-MT but unaffected by L-1-MT⁵⁴

and is constitutively expressed in several tissues.⁵⁵ When compared to IDO, IDO2 has only 3%–5% of enzymatic activity, however this activity can be increased through modified assay conditions.^{4,55} Although D-1-MT has recently entered clinical trials (NCT00567931; New link genetics corporation; Patent Storm) therapeutic effects in humans still have to be figured out. Current data have revealed that only the Levo-isoform of 1-MT has IDO blocking capacities in human malignancies where only IDO but not IDO2 is expressed.⁵⁶ Furthermore, even if IDO2 would be active, only a subset of patients would benefit from therapy with D-1-MT as 50% of Caucasians lack functional IDO2 alleles.^{4,54}

Conclusion

Summarizing the experimental and clinical data above, there is clear evidence that IDO interferes with immune regulation. IDO has evolved from a simple tryptophan catabolizing enzyme into an important immune regulator and an important player in tumor immunosurveillance. There is a great body of evidence that IDO is expressed by tumor cells, tumor infiltrating immune cells and in tumor draining lymph nodes and that the expression of IDO contributes to the ability of tumors to evade the immune system. Taken together these facts offer a rationale for the clinical investigation of the capacity of IDO inhibitors to increase the efficacy of anticancer immunotherapy, in addition to conventional tumor radiation and chemotherapeutic agents. In particular, combining chemotherapy with pharmacologic IDO inhibition seems to be key to success in preventing IDO mediated immunologic tolerance when chemotherapy has already destroyed tumor cells and released tumor antigens.

Studying IFN- γ -induced IDO activity in tumors may also lead to a better general understanding of immunoregulation in cancer and foster novel therapeutic strategies for modern cancer warfare.

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Disclosures

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