Molecular Pathways: Targeting IDO1 and Other Tryptophan Dioxygenases for Cancer Immunotherapy

Lijie Zhai\textsuperscript{1}, Stefani Spranger\textsuperscript{2}, David C. Binder\textsuperscript{2,3}, Galina Gritsina\textsuperscript{1}, Kristen L. Lauing\textsuperscript{1}, Francis J. Giles\textsuperscript{4,5,6}, Derek A. Wainwright\textsuperscript{1,7}

\textsuperscript{1}Department of Neurological Surgery, Northwestern University Feinberg School of Medicine, Chicago, IL 60611, USA.

\textsuperscript{2}Department of Pathology, \textsuperscript{3}Committee on Cancer Biology, The University of Chicago, Chicago, IL 60637, USA.

\textsuperscript{4}Northwestern Medicine Developmental Therapeutics Institute, \textsuperscript{5}Division of Hematology and Oncology, \textsuperscript{6}Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL 60611, USA.

\textsuperscript{7}Northwestern Brain Tumor Institute, Northwestern University Feinberg School of Medicine, Chicago, IL 60611, USA.

Running Title: Molecular Pathways of IDO in Tumor Immunotherapy

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Address correspondence to: Derek A. Wainwright, 300 E Superior Street-Tarry Bldg 2-703 Chicago, Illinois 60611, USA. Phone: 312.503.3161; Fax: 312.503.3552; E-mail: derekwainwright@northwestern.edu

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Abstract

Indoleamine 2, 3-dioxygenase 1 (IDO1), IDO2 and tryptophan 2, 3-dioxygenase (TDO) comprise a family of enzymes that catalyze the first- and rate-limiting step associated with the catabolic conversion of tryptophan (Trp) into kynurenine (Kyn). Through subsequent enzymatic and spontaneous reactions, Kyn is further converted into the energetic substrates, NAD$^+$ and ATP to fuel cellular metabolic functions. Coincidently, the depletion of Trp and accumulation of Kyn has been demonstrated to induce effector T cell apoptosis/dysfunction and immunosuppressive regulatory T cell induction, respectively. Similar to other immune checkpoints, IDO1 and TDO are suggested to be important targets for immunotherapeutic intervention. This is represented by the recent growth of efforts to inhibit the Trp to Kyn pathway as a means to control immunosuppression. Inhibitors currently in clinical trials, INCB024360, GDC-0919, Indoximod and an IDO1 peptide-based vaccine, are being evaluated for their efficacy against a wide range of cancers including melanoma, glioblastoma, non-small-cell lung-, pancreatic- and/or breast-cancer, as well as metastatic disease. Despite the rapid development of potent clinical-grade inhibitors, strategic questions remain. Here, we review the state of the literature with respect to current therapeutic inhibitors of tryptophan catabolism, evaluation of those efforts, preclinically and clinically, compensatory changes that occur with therapeutic targeting, as well as newly recognized signaling features that raise critical questions to the field. Given the rapidly evolving interest in determining how IDO1/TDO, and to an unknown extent, IDO2, can be targeted for increasing cancer immunotherapeutic efficacy, we present a brief but comprehensive analysis that addresses critical questions, while highlighting the mechanics that remain to be explored.
Background

Cancer immunology and immunotherapy

The immune system is composed of an immediate-acting innate arm comprised principally of granulocyte- and myeloid-lineage cells that quickly respond to cues of inflammation and/or injury, in addition to an adaptive arm, principally comprised of B and T cells that provide specificity and memory. Under normal circumstances, these immunological arms are mutually-dependent on one another for providing defense against infection, injury and/or malignancy. T cells, which primarily mature following immunological challenge(s), include CD4+ and CD8+ T lymphocytes that express a wide variety of cytokines based on the context of priming stimuli. Included in the CD4+ T cell compartment are highly immunosuppressive regulatory T cells (Treg; CD4+CD25+FoxP3+CTLA-4+) that mature naturally in the thymus (nTreg) or are post-thymically induced from naïve CD4+Foxp3- cells into Foxp3-expressing cells (iTreg) (1-3). With respect to solid cancer(s), immunosuppressive mechanisms utilized to evade anti-tumor immunity include Treg accumulation (4, 5) effector T cell expression of the PD-1 receptor (6), as well as high PD-L1 levels that localize to multiple types of cells in the tumor microenvironment (7, 8). Therefore, an active effort both clinically and preclinically are to develop strategies that re-active a productive antitumor effector T cell response, while simultaneously inhibiting immunosuppressive mechanisms.

Recent studies have demonstrated great promise at targeting immunosuppression in cancer, including clinical trials aimed at inhibiting PD-1, PD-L1 and/or CTLA-4 in patients diagnosed with late-stage melanoma, non-small-cell lung cancer and/or renal-cell cancer (9-12). Follow-up studies have also shown that the benefit of combined PD-1/CTLA-4 inhibition is not restricted to
those patients previously treated with systemic therapy (13). Preclinical work using multiple tumor models in immunocompetent mice further confirm that these immune checkpoint-targeted therapies require effector T cells for antitumor activity, with several studies reporting a coincident neutralization of tumor-infiltrating Treg (14-16). These clinical studies, combined with extensive preclinical validation of combinatorial approaches confirm that, immunotherapy is a high-value strategy for treating patients with aggressive and immunosuppressive malignancies.

**IDO1, TDO, and the Trp→Kyn catabolic pathway**

L-tryptophan (L-Trp) is used in a variety of anabolic/catabolic processes and metabolized into serotonin, melatonin, protein and Kyn. IDO1 and TDO are the primary enzymes that catalyze the rate-limiting cleavage of the Trp indole ring 2,3-double bond and incorporation of molecular oxygen. The product of this reaction is N-formylkynurenine, which is rapidly and spontaneously converted into L-Kyn. The latter catabolite is further converted into downstream intermediates, including 3-hydroxy-L-kynurenine (3-HK), 3-hydroxyanthranilate (3-HAA) and quinolinic acid (Quin), which also impact immune responses (17).

Although IDO1 and TDO both catalyze Trp, their quaternary structures (18, 19), expression in normal versus transformed tissue (20, 21) and regulation (22, 23) are quite distinct. While monomeric IDO1 acts on a broad range of substrates and is capable of cleaving both D- and L-Trp, homotetrameric TDO is enantiomer-specific and only catabolizes L-Trp (24). IDO1 expression in adults is relatively limited to lymphoid tissues and placenta (20), whereas TDO is constitutively expressed in liver and brain (25, 26), likely reflecting their primarily immunomodulatory or energy regulating roles, respectively. Until 2007, IDO1 was the only
known indoleamine dioxygenase acting at the 2,3 double bond. Three independent groups then identified the novel paralog, IDO2 (27-29). While the IDO1 and IDO2 genes are 43% homologous and found directly adjacent to one another on chromosome 8, the $K_m$ of human IDO1 and IDO2 for $L$-Trp is $20.90 \pm 3.95 \mu M$ and $6809 \pm 917 \mu M$, respectively, indicating a substantial decrease in activity for the latter enzyme (30). This is particularly interesting given that the residues required for tryptophan catalytic activity are present in both gene products (27). Also notable is that mouse IDO2 has been shown to possess higher enzymatic activity than the human homolog, although the genetic depletion of mouse IDO2 has no impact on systemic Kyn levels (31); a dramatic contrast to the impact of IDO1-deficiency (32).

**IDO1 and the stress response**

Due to IDO1 expression induced in response to infection, it was originally thought that it serves as an innate immune effector to restrict the amount of Trp required for microbial growth (33). This initial hypothesis was revised by Munn and Mellor who demonstrated that the *in vivo* administration of an IDO1 inhibitor, 1-methyl tryptophan (1-MT), led to T cell-dependent fetal allograft rejection (34). Subsequent work demonstrated that IDO1-expressing-macrophages, -dendritic cells (DC) and -tumor cells mediate the inhibition of T cell proliferation (35-38). IDO1 responses were found to be mediated by downstream stress-response pathways including general control non-depressible 2 (GCN2) and mTOR; both important regulators that sense amino acid sufficiency (Figure 1). The GCN2 pathway is activated when amino acid deficiency increases overall uncharged tRNA levels, resulting in GCN2 kinase phosphorylation of the alpha subunit of translation initiation factor 2 alpha (eIF2α) and subsequent inhibition of translation. It was first discovered that GCN2-activated plasmacytoid DC could suppress T cell proliferation *in vivo*
by an IDO1-dependent mechanism (39). It was later discovered that the genetic deletion of IDO1, but not GCN2, prevented skin carcinogenesis in a mouse papilloma model, suggesting that additional critical pathways were downstream of IDO1 activity (40). In support of these findings, Metz et al. identified that IDO1-mediated Trp depletion suppressed mTOR, a critically important immunoregulatory kinase (40) that could be reactivated by treatment with D-1-MT, a Trp mimic, in vitro.

IDO1-mediated suppression of T cell activity is hypothesized to rely on the depletion of free Trp. This premise requires cell-specific transport mechanisms that includes both the transporter System L, which shuttles Trp and other large hydrophobic amino acids through a low affinity ($K_m = 20-30 \mu M$) (41) interaction, as well as through an independent high affinity ($K_m = 200-300 nM$) interaction. Interestingly, the high affinity transporter is upregulated in differentiated myeloid-derived macrophages (MDM) but not in T cells. In support of the requirement for transport, both Trp and the competitive inhibitor, L-1-MT, inhibit Trp uptake into cells, collectively suggesting that competitive IDO1 inhibitors target the transporter and enzyme, simultaneously.

**Regulation of IDO1/IDO2/TDO**

The literature is replete with redundant pathways that lead to IDO1 expression and activity. Pro-inflammatory signals including IFN-$\gamma$, CpG DNA and LPS are potent inducers of IDO1 expression (33, 42-44). Cytokines, including TNF-$\alpha$, IL-6 and IL-1$\beta$, synergize with each other to dramatically increase IDO1 expression. Other IDO1 modulators include soluble GITR, prostaglandin E2, the oncogene, c-KIT, as well as the tumor suppressor, Bin1 (45). Interesting new data suggests that Wnt5$\alpha$ also mediates IDO1 activity through $\beta$-catenin signaling in DC
(46), while maintaining continuous expression through an AhR-IL-6-STAT3 signaling loop in some cancer cells lines (47). Thus, based on the large number of pathways that modulate and/or sustain IDO1 expression/activity, the direct targeting of IDO1, rather than pathways that are up- or down-stream, will likely be the most effective modality for controlling the overall impact mediated by this Trp dioxygenase.

Similar to IDO1, TDO mRNA expression has also been found in human tumors (21). Dominant factors that affect TDO expression and/or activity include sex steroid hormones (48) and glucocorticoids (22). New preclinical data also suggest that tumor-infiltrating T cells may regulate TDO expression based on findings from intracranially-injected syngeneic murine brain tumors grown in Rag1−/− mice (15). Notably, intraperitoneally-injected mastocytoma cells overexpressing TDO induces potent immunosuppression that can be reversed with a pharmacological inhibitor of enzymatic activity, leading to immune-mediated tumor rejection ($P<0.001$) (21).

In contrast, the newest member of the tryptophan catabolic family, IDO2, has yet to be confirmed as a critical contributor to Kyn accumulation and tumor immunity. Notably, while mouse IDO2 possesses some capacity for Trp→Kyn conversion, the human ortholog is devoid of the same enzymatic capacity at physiological Trp levels (30). Furthermore, transcriptome analysis of 129 human tumor samples and 25 human tumor cell lines has demonstrated limited IDO2 expression (49). As IDO2 was originally cloned from liver (27), it is still unknown whether there are IDO2 splice variants specific to subtypes of differentiated- and/or transformed-tissues.

**IDO1 and inflammation in tumors**
It is notable to highlight the interaction between inflammation, IDO1 and cancer (50, 51), raising critical questions regarding how and when to optimally target tryptophan catabolism for therapeutic purposes. Furthermore, despite the presence of antigen-specific T cells within the microenvironment, tumors often escape, immunologically, without loss of antigen expression or presentation (MHC molecule) capacity. This effect is mediated, in-part, through the induction, upregulation and/or enhanced participation of immunosuppressive T cell-impairing ligands, CTLA-4 and PD-L1 (52). Similar to PD-L1, IDO1 expression also increases through a response to IFN-γ released in the tumor microenvironment (53) as a potent compensatory mechanism contributing to the resistance of productive antitumor immunity (54). Interestingly, only a subset of patients have a T cell infiltrating presence within the tumor microenvironment, an observation reported for head and neck- and bladder-cancer, as well as melanoma, lung adenoma and glioblastoma (55). A notable observation from those patients treated with the immune checkpoint inhibitor, PD-1, correlate a high degree of clinical response to the pre-existence of tumor-infiltrating T cells (56). This observation, paired with the association of IDO1 induction by T cell-derived, IFN-γ, leads to the hypothesis that IDO1 inhibitors will be most effective against T cell-inflamed tumors; either de novo or caused by immunotherapeutic intervention. Preclinical studies support this hypothesis, providing evidence that, combinatorial immune checkpoint blockade and IDO1-pathway inhibition provide potent reactivation of tumor-infiltrating T cells and/or decreased tumor-resident immunosuppressive regulatory T cells ($P<0.01$) (15, 57).

**Clinical-Translational Advances**

No IDO1 inhibitor is currently approved by the US Food and Drug Administration. However, results of recent Phase I-II studies suggest that indoximod ($\text{D-1-MT}$), INCB024360 and/or IDO1-
targeting vaccines are well tolerated by cancer patients, with clinical anticancer effects in a subset of patients (58, 59). Notably, the number of clinical trials focused on IDO1 has recently grown in size, with many coupling multiple modalities to test the combinatorial benefit (Table 1). These recent reports, in addition to preclinical data suggest that, combining tryptophan enzyme targeting with chemotherapy, radiotherapy and/or immunotherapy, may be an effective tool against a wide range of malignancies.

The seminal observation associating IDO1, immunosuppression and cancer utilized a polyclonal antibody to identify the immunohistochemical frequency of expression among different human malignancies (60). Unexpectedly, recent analyses utilizing a novel monoclonal anti-human IDO1 antibody has demonstrated distinct differences compared to those original observations (20). While it was initially reported that, 90-100% of human prostate and pancreatic tumors, as well as glioblastoma, were IDO1 positive, the latter study found only 42%, 38% and 8% of those malignancies positive, respectively. Since the antibodies were well-vetted in both investigations, these conclusions present a cautionary tale that likely reflect more than simple differences in antibody specificity, but more broadly, the potential for alternative splice variants and/or post-translational modifications resulting in antigenic variation. Thus, immunohistochemical studies associating IDO1 expression and survival should be interpreted carefully (61). Furthermore, these conflicting findings complicate strategies that would ideally use IDO1 IHC as a prognostic tool for selecting patients that would benefit most from IDO1 inhibition.

Recent work studying the Kyn/Trp ratio in patients with glioblastoma has suggested that analyzing a time point well after surgical tumor resection, 10+ weeks post-operative, may be prognostically valuable to clinicians planning to enroll patients in immunotherapy (62). While
this finding requires further validation in a larger patient cohort, it suggests the possibility that IDO1 activity increases well after GBM patients are operated on, as well as highlights the potential relevance of utilizing a clinical inhibitor against IDO1, systemically. Similarly, the Kyn/Trp ratio was recently validated as a prognostic tool in cervical cancer patients whereby, low Trp levels indicated a tumor size greater than 4cm and metastatic spread to the lymph node (63). Accordingly, high Kyn/Trp ratios in patient sera were associated with lymph node metastasis, FIGO stage, tumor size, parametrial invasion and poor disease-specific survival, further suggesting the relevance of IDO1 targeting based on a tryptophan catabolic signature. Similar work was recently shown in a clinical study that identified higher Kyn/Trp ratios in T-cell lymphotropic virus type-1 asymptomatic carriers when compared to healthy controls (64). Importantly, the serum Kyn/Trp ratio was a significantly independent detrimental prognostic factor in patients with adult T-cell leukemia/lymphoma. These collective analyses have begun to elucidate the relevance of determining an IDO1 enzymatic ‘signature’ in patient sera, which preliminarily, appears to be both prognostically valuable and clinical-informative.

Given that the majority of clinical studies aimed at IDO1 inhibition that are currently ongoing, have yet to report results, we can gain insight into preclinical analyses that have shown great potential targeting this immunosuppressive mediator. However, these models possess limited usefulness when considering the potential effects that standard of care treatment have on IDO1 activity and/or expression, as well as the potential change of expression between primary and recurrent tumors. Given that inflammation is a primary driver of IDO1 expression, it may be relevant to prognostically stratify tumors that possess a wide range of T cell infiltrating-heterogeneity, when compared to the primary versus relapsed malignancy (65, 66).
Concluding Remarks

Our substantial knowledge of the role and expression of IDO1 in cancer has continued to expand over the past 2 decades, yet critical questions regarding alternative functions regulated by posttranslational modifications, the role that IDO2/TDO plays in the absence or inhibition of IDO1, as well as the impact of tissue-specific alternative splicing, still remain. Most inhibitory strategies against IDO1 focus on disabling enzymatic activity. However, preclinical mouse tumor models suggest that this tactic, alone, will not lead to effective antitumor immunity; further suggesting that IDO1 inhibition is best suited for combinatorial therapeutic strategies. However, these findings also raise the intriguing, yet unproven possibility that, IDO1 subsumes a new/alternative immunosuppressive role when Trp catabolism is abrogated, in vivo. In support of this hypothesis, it’s notable that indoximod (D-1-MT), currently cast as an IDO1 pathway inhibitor, does not inhibit Trp to Kyn catabolism (67, 68) (Supplementary Table S1). This combination of reported observations and untested hypotheses paint a blurry picture of a highly immunosuppressive player in tumor immunity. Unmistakably, IDO1 is a critical mediator that, given the normal limited expression throughout the body, makes it an ideal target for cancer immunotherapy. The central question going forward, thus becomes, how can we best inhibit the activity of this pleiotropic target?

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References


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Table 1. Ongoing and historical clinical trials that target tryptophan catabolism in cancer.

Clinical trials were identified on the website clinicaltrials.gov as of 07/15/2015.
Figure 1. Signaling pathways associated with tryptophan (Trp) dioxygenases and cancer.

The high expression of active IDO1 leads to a commensurately high rate of tryptophan conversion and depletion. This induces cell cycle arrest and/or anergy in the effector cytotoxic lymphocyte (CTL) compartment via the eIF2α kinase-dependent GCN2 pathway. Simultaneously, this mechanism also contributes to the activation/maturation of Treg in association with CTLA4-mediated CD80/CD86 co-inhibition. Kynurenine (Kyn) directly induces the apoptosis of CTL by an uncharacterized mechanism, while interacting with the aryl hydrocarbon receptor (AhR) in naïve CD4^+ T cells, resulting in the induction of FoxP3^+ iTreg. AhR interacts with the aryl hydrocarbon receptor nuclear translocator (ARNT) to mediate the specific transcriptional programming. Coincidently, IDO1 non-enzymatically enforces immunosuppression through two intrinsic immunoreceptor tyrosine-based inhibitory motifs (ITIM) in antigen presenting cells (APC). TGF-β signaling results in the phosphorylation of the IDO1 ITIM, triggering non-canonical NF-κB activation and phosphorylation of IKKα, followed by nuclear translocation of the NF-κB subunits, p52 and RelB and autocrine reinforcement of IDO1 and TGF-β expression. The high affinity Trp transporter is expressed by APC and tumor cells, with the majority of agonists leading to IDO1 activity demonstrated in APC. Similarly, the oncogene, c-KIT, and tumor-suppressor gene, Bin1, as well as the IL-6/AhR/STAT-3 signaling loop, have also been shown to impact the regulation of IDO1 in tumor cells. (39, 69-76).

Notably, in the presence of IDO1/IDO2/TDO, Kyn accumulation simultaneously contributes to Treg activation, promoting the disabling and/or apoptosis of CTL, thereby supporting tumor outgrowth by virtue of an unproductive antitumor response. TGF-βR: transforming growth factor-beta receptor; IL-6R: interleukin-6 receptor; IRF1: interferon response factor 1; GITRL: glucocorticoid-induced TNFR-related protein ligand; IFN-αR: interferon alpha receptor; TLR4:
toll-like receptor 4; LPS: lipopolysaccharide; MHC I/II: major histocompatibility complex I/II; EP2: prostaglandin receptor E2; PGE2: prostaglandin E2; TNF-αR: tumor necrosis factor alpha; SHP: SH2 domain containing protein tyrosine phosphatase; SOCS3: suppressor of cytokine signaling 3; mTOR: mammalian target of rapamycin; Etv4: ETS translocation variant 4; STAT: signal transducer and activator of transcription; PKCθ: protein kinase C theta; Bin1: Myc box-dependent-interacting protein 1; GCN2: general control nonderepressible 2; PKA: protein kinase A.
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Figure 1:

[Diagram showing various pathways and molecules related to tumor cell growth and immune response.]

Key elements include:
- TGFβ
- SOCS3
- Proteasome degradation
- IL6
- IL6R
- Trp depletion
- Kynurenine accumulation
- APC
- Treg
- p52-RelB
- IRF1
- STAT1
- STAT3
- Etv4
- KIT
- IL6
- ARNT
- p38 MAPK
- TLR4
- NF-κB
- Idox
- TDO
- mTOR
- Autophagy
- PKC
- AhR
- Kyn
- TNFα
- IFNα
- IFNγ
- CTLA4
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