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Indoleamine 2,3 dioxygenase (IDO) in Intestinal Disease

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Abstract

Purpose of review—Several gastrointestinal diseases including the inflammatory bowel diseases (IBD) and malignancy are associated with elevated expression of indoleamine 2,3 dioxygenase-1 (IDO1). IDO1 initiates tryptophan catabolism along a pathway that generates several bioactive kynurenine-based metabolites. Promotion of T-cell mediated tolerance and antimicrobial effects are among the variety of functions attributed to IDO1 activity. Recent advances addressing the diverse implications of gut associated IDO1 expression are herein reviewed.

Recent Findings—In active IBD IDO1 is highly expressed both in cells of the lamina propria and epithelium. Experimental models demonstrate that IDO1 promotes gut immune homeostasis by limiting inflammatory responses and protecting the epithelium. In human colon cancer, high expression of IDO1 by the neoplastic epithelium correlates with poor prognosis. The serum kynurenine:tryptophan ratio is elevated in both active Crohn's disease and in colon cancer suggesting this measurement may prove useful as a disease biomarker. IDO1 inhibitors have moved to clinical trials providing new hope as immunotherapy for advanced malignancy.

Summary—IDO1 activity significantly shapes gastrointestinal disease pathophysiology and severity. Measures of IDO1 activity may be useful as a disease biomarker. Manipulation of IDO1 activity has great potential as treatment for both inflammatory and malignancy associated gastrointestinal disease.

Keywords

Tryptophan; colitis; cancer; biomarker; IDO; kyurenine

INTRODUCTION

Indoleamine 2,3 dioxygenase-1 (IDO1) is the first and rate limiting step in tryptophan catabolism along the kynurenine pathway (Figure 1). Several of the downstream metabolites are biologically active and ultimately provide substrate for de novo NAD+ synthesis. Though IDO1 is not the only enzyme able to metabolize tryptophan to kynurenine, it is the most-well characterized both in the gut and in general. Of the other two enzymes, the recently described IDO2 is most highly expressed in the kidney while tryptophan 2,3 dioxygenase is most highly expressed in the liver.[1–3] All three have been found in cancer.[4, 5] The essential amino acid tryptophan, substrate for IDO1, is also the precursor for synthesis of serotonin and melatonin if metabolized along an alternate pathway.

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The seminal observation that IDO1 promotes immune tolerance at the maternal-fetal interface launched myriad investigations to explore the role of this enzyme in other organ systems and disease processes.[6, 7] In this mechanistic paradigm, IDO1 activity by professional antigen presenting cells reduces local tryptophan concentrations and elevates toxic kynurenine metabolites to limit activated T-cell responses and promote regulatory T-cell activity. IDO1 is now recognized to also possess a non-enzymatic function that contributes to TGF-beta-driven tolerance in non-inflammatory contexts.[8]

In the gut, IDO1 is highly upregulated in response to inflammation and in malignancy. IDO1's ability to potently shape gastrointestinal (GI) disease pathophysiology and severity make an important target for drug discovery. IDO1 expression in the gut mucosa also changes systemic levels of tryptophan and kynurenine. This brings to light the potential to use IDO activity as a disease biomarker and also raises the question as to whether changes in tryptophan and kynurenine metabolites may contribute to extraintestinal manifestations of human inflammatory bowel disease (IBD) including disease-activity-associated mood-disturbance. This article provides historical context and reviews recent advances for the role of IDO1 in the gastrointestinal health and disease.

IDO1 IN COLITIS AND HUMAN INFLAMMATORY BOWEL DISEASE

In the homeostatic state gut expression of IDO1 is low and mostly occurs in cells of the lamina propria. IDO1 expression is stimulated by inflammatory cytokines including IFNγ, TNFα and IL1-B. Consistent with this, IDO1 is one of the most highly upregulated genes in human IBD and animal models of colitis.[9–13]

Natural IDO1 expression modifies colitis severity

Our group was among the first to evaluate the functional significance of IDO1 expression in the gut.[14] Gurtner demonstrated that IDO1 expression and functionality was increased over baseline in acute TNBS (trinitrobenzene sulfonic acid) colitis. Disease severity was worsened in mice receiving the IDO inhibitor 1-DL-methyl tryptophan (1mT), suggesting IDO1 down-regulates Th1 inflammatory responses within the intestinal tract. Matteoli further observed that CD103+ gut dendritic cells expressing IDO1 support regulatory T-cell conversion while suppressing Th1/Th17 differentiation to promote oral tolerance and limit gut inflammation.[15] CD103+ DCs have recently been shown to accept luminal antigen from small intestinal goblet cells[16] which also appear capable of expressing IDO1.[17, 18]

IDO1 was also evaluated in two other colitis models with some relevance to IBD. Jasperson demonstrated a role for IDO1 in a model of graft versus host disease. He found IDO1 upregulation particularly apparent in the colonic epithelium of WT mice with disease and showed that IDO1$^{-/-}$ mice exhibited greater colitis severity, T-cell infiltration and mortality.[19] Subsequently, the authors demonstrated that induction of IDO1 primarily in professional antigen presenting cells (APC) by a TLR-7/8 agonist reduced colon injury and ameliorated lethality.[20] In an infectious colitis model using *Citrobacter rodentium,* IDO1$^{-/-}$ mice demonstrated resistance to colonization and developed an attenuated colitis compared to WT mice.[21] The authors then identified that IDO1$^{-/-}$ mice exhibit elevated non-specific IgA antibodies in the serum and stool at baseline. Thus, it was proposed that IDO1 mediated inhibition of B-cell responses to commensal microflora may explain these intriguing findings while still maintaining consistency with the recognized role of IDO1 as an inhibitor of lymphocyte responses in the gastrointestinal tract.[22]

Induction of IDO1 prevents colitis

We extended our initial observations by looking at IDO1 induction as a method to prevent colitis severity.[18] We demonstrated that a synthetic toll like receptor-9 (TLR9) agonist

with anti-colitis effects[23] potently induced IDO1 in the colon and small intestine. In both the acute and chronic TNBS colitis models as well as the dextran sodium sulfate (DSS) model, IDO1 induction was critical to the anti-colitic effects of this agent. This study highlighted the potential of IDO1 induction as a therapeutic strategy for human IBD. Similar to our findings with the TLR9 agonist, CTLA-4 based molecules with IDO1-inducing capacity have more potent anti-colitic effects in experimental models than those which do not induce IDO1 (reference[24] and our unpublished observations). This finding may help explain why Abatacept (a CTLA4 molecule lacking IDO1 inducing capacities[25]) failed to meet endpoints in clinical trials evaluating its efficacy as an IBD therapy.[26]

Cellular source of IDO1

APCs are known to possess potent IDO1-dependent suppressive effects on T-cell proliferation[27–29] and surely mediate tolerance in the gut.[15] However, it should be appreciated that epithelial cells are represent a major source of gut IDO1 activity during inflammatory states.[9, 10, 30] IDO1 expression is particularly apparent in epithelial cells near sites of ulceration.[10] Though the function of epithelial IDO1 is not fully elucidated, antimicrobial properties may be particularly important considering the epithelial barrier dysfunction associated with IBD.[31, 32] Supporting this, IL-27 (a cytokine with Th17 cell inhibitory properties) was recently shown to block growth of intestinal bacteria and mediate epithelial barrier protection via induction of IDO1 in human and mouse intestinal epithelial cells.[33] Our work also demonstrated the epithelium to be a major source of IDO1 in response to the anti-colitis TLR9 agonist, which was associated with enhanced epithelial proliferation.[18]

Taken together the data suggest that in colitis IDO1 expressing cell types function as a negative feedback mechanism to limit the development of chronic inflammation. It is possible that IDO1 expression by APCs is critical to suppressing inflammatory T-cell responses while epithelial IDO1 activity functions predominantly to limit microbial invasion and perhaps promote epithelial repair. This supposition could be confirmed by a model enabling tissue specific deletion of IDO1 expression. The physiologic balance between IDO1-mediated tryptophan depletion and role that this essential amino acid appears to play in maintaining mucosal homeostasis[34] remains to be answered.

IDO1 EXPRESSION AS A BIOMARKER OF GI DISEASE

There is a clinical need for new biomarkers which specifically reflect gastrointestinal disease pathophysiology. Biomarkers support clinical decision making by providing supplemental information for disease diagnosis, determination of disease activity, prognosis/risk stratification and prediction of response to therapy. Many biomarkers currently in use are not disease specific, but reflect generalized inflammation. Promise is held for new, more specific biomarkers that detect differences in genomics (genotype and gene expression), proteomics and metabolomics.[35] Biomarkers should ideally be readily obtained, inexpensive to perform, consistently quantifiable across labs, and unaffected by co-morbid factors.[36] Recent studies support targeting the IDO1-mediated tryptophan catabolism pathway as a biomarker of gastrointestinal inflammatory diseases and malignancy.[35]

Biomarker in IBD

Serum changes reflective of IDO1 activation in the gut correlate with Crohn’s disease (CD) activity.[30] Kynurenine is an initial metabolite in IDO1 mediated tryptophan catabolism. The kynurenine/tryptophan (K/T) ratio is a surrogate marker for IDO1 activity in the setting of an activated immune system. Using this ratio (vs either alone) limits potential bias related to differences in dietary intake of tryptophan.[37] Examining serum from a well-

characterized cohort of CD patients and controls we found that serum tryptophan was depressed while the K/T ratio was elevated in active CD. Both measurements correlated with CD activity assessments and the acute phase reactants ESR and CRP. Activity for all Montreal Classifications of CD location could be identified by the K/T ratio. Finally, serial measurements from a subgroup of CD patients revealed that as CD activity improved, tryptophan and kynurenine levels normalized as did the K/T ratio.

Other human and animal studies also point to IDO1 activity as a biomarker worth pursuing for diseases of intestinal inflammation including IBD and potentially also celiac disease.[38] A historical report identified low serum tryptophan in CD patients.[39] As kynurenine was not measured, the finding was attributed to compromised absorption. Similarly a recent detailed serum aminogram investigation identified low tryptophan in both active CD and UC patients compared to controls.[40] Serum levels of tryptophan are also reduced by nearly 80% in mice with dextran sodium sulfate induced colitis.[41] Kynurenine and kynurenic acid were found to be elevated in small cohort studies of CD and UC patients compared to controls.[42, 43] In the IL-$10^{-/-}$ model of experimental colitis, metabolomic profiling identified elevation of urinary xanthurenic acid, a kynurenine metabolite.[44, 45] Subsequent investigations revealed elevated plasma levels of kynurenine and 3-hydroxykynurenine in colitic mice and showed that urinary xanthurenic acid levels correlated with colitis severity.[46]

Reflecting Mucosal Inflammation

New blood or stool based biomarkers for IBD ideally will be able to assess mucosal healing in order to provide the best predictive value for treatment success and clinical prognosis.[47–49] Measurement of serum tryptophan and kynurenine pathway metabolites has great potential as an objective surrogate marker of gut mucosal immune activation and biomarker for CD activity and perhaps ulcerative colitis as well. Increased IDO1 expression in the gut reflects immune activation and inflammation. Inflammatory cytokines IFNγ and TNFα induce IDO1. IDO1 expression and the K/T ratio normalize with effective IBD therapy.[12, 30, 50] Though mucosal healing was not directly assessed in our study, we found that changes in K/T ratio with active CD were greater than in any illness outside of sepsis resulting in death.[30] These profound differences are likely attributable to the large surface area and multiple cell types expressing IDO1 within the gut mucosa during active disease. Given recent metabolomics data, confirmative studies may utilize a panel of kynurenine metabolites as well as tryptophan.

Biomarker in CRC

The IDO1-kynurenine pathway might also be exploited as a biomarker for colon cancer. Though the stage of cancer was not reported, Liu identified a near doubling of the K/T ratio in patients with CRC verses controls.[51] Reduced serum tryptophan correlated with quality of life deterioration in patients with metastatic CRC in another study.[52] Finally, a study evaluating colonic secretions found a tripling of kynurenic acid levels in patients with colon cancer and doubling in patients with tubulovillous adenomas as compared to healthy controls.[53]

IDO1 AND COLON CANCER

IDO1 is expressed by several human cancers and its presence has been linked to poor prognosis.[54] The IDO1 like enzymes TDO and IDO2 have also been identified in several cancers. As such, significant attention has been given to targeting inhibition of tryptophan-kynurenine pathways for cancer therapy. In cancers of the GI tract, IDO1 seems to be the most upregulated of these enzymes, though TDO expression has also been reported.[4, 5]

Human observational studies

IDO1 may play a role in colorectal cancer (CRC) pathophysiology. Ferdinande reported that IDO1 expression was particularly high in the neoplastic epithelium at the tumor's invasion front. Moreover, high level IDO1 expression in the neoplastic epithelium correlated with metachronous metastases and reduced survival in this study.[55] Brandacher also found high IDO1 expression in ~40% of CRCs where it significantly associated with increased liver metastases, but not reduced mortality.[56] Another study found a correlation between high density of $IDO1^+$ cells in tumor draining lymph nodes and reduced 5-year survival rates in colon cancer patients.[57] Even in isolation, several colon cancer cell lines constitutively express IDO1.[58]

Several questions remain with regard to the function of IDO1 expression in colon cancer and in particular IDO1 expression by the neoplastic epithelium. Available retrospective studies on human resection specimens are limited in their ability to inform us how IDO1 activity might shape colon cancer progression. It has been suggested by these studies that the function of IDO1 in colon cancer is akin to what has been reported in other cancers. In this paradigm IDO1 activity contributes to pathogenesis by reducing tumor-reactive T-cell activity and inducing regulatory T-cells to foster tumoral-immune tolerance. However, the observed relationship between IDO1 expression and T-cell infiltration has not been consistent.[55, 56]

Experimental models

In extrapolating data from other cancers, it would be assumed that breaking tolerance in CRC by inhibiting IDO1 would be a beneficial. However, a recent report evaluating potential cardiac and gastrointestinal liabilities in an IDO1 knockout mouse had findings which may contradict this supposition. Using a model of colon tumorigenesis induced by genotoxin administration followed by single episode of colonic injury with dextran sodium sulfate, IDO1 null mice developed greater colitis severity and increased tumor formation. [59] This phenotype was lost in a subsequent experiment when different doses of the genotoxin and colitic agent were used and the findings were not confirmed by use of and IDO1 inhibitor. Regardless, one would have predicted enhanced tumor immune surveillance and thus small tumors in the IDO1 null mice. These results require clarification as CRC is a major cause of death and these findings may temper enthusiasm for testing promising IDO1 inhibitors in trials for colon cancer.

IDO POTPOURRI

Other recent and interesting, yet preliminary observations relevant to IDO1, tryptophan catabolism and gastrointestinal disease deserve mention.

IDO1 and novel probiotics

Existent and novel probiotics may exert immunomodulatory effects via induction of IDO1 expression. Peptidoglycan purified from a Lactobacillus salivarius species was able to reduce experimental colitis in an IL-10-dependent manner. The protection was also correlated with an upregulation of IDO1 and favored the development of tolerogenic (CD103+) dendritic cells and regulatory T cells.[60] Early colonization of mice with a defined mixture of commensal intestinal bacteria species (Clostridium clusters IV and XIVa) was found to promote a colonic environment rich with TGF-B and regulatory T-cells while offering protection from colitis.[61] Intestinal epithelial cells from the mice colonized with the Clostridium mixture expressed high levels of IDO1.

IDO1 inhibitors

Several inhibitors of the IDO pathway have been described and some are now in phase I clinical trials in cancer including D-1mT[62, 63] and INCB023843.[51] The latter appears to potently inhibit IDO1 in a specific manner[51], efficiently reduces tryptophan metabolism in CT26 colon cancer cells in vitro[64] and was well tolerated in a phase I clinical trial which included >50% patients with CRC.[65] The proposed effect of inhibiting IDO is to break immune tolerance against tumor-associated antigens. As such these agents may be used as concomitant therapy with chemotherapy or vaccines.[66]

IDO1 and the Gut-Brain axis

Current evidence supports the role of cell mediated immune activation as an important biologic contributor to the onset of sickness and depressive behavior.[67] In animal models of chronic inflammation, associated depressive behavior is eliminated by IDO1 inhibition or genetic ablation.[68] Furthermore, brain IDO1 activity contributes to depression associated with chronic pain.[69] In human IBD anxiety and depression are common, and in both CD and UC depression and anxiety state (but not trait) are worse during periods of active disease.[70] These findings suggest a potential role for IDO1 in mediating gut-brain interactions and mood disturbance in IBD.

CONCLUSION

The IDO1 mediated trytophan catabolism pathway has important roles in the gut both in health and disease. Baseline expression of IDO1 in APCs contributes to immune tolerance. Upregulation of IDO1 occurs during inflammatory states including human IBD and colon cancer. Serum levels of tryptophan and kynurenine pathway metabolites change with IDO1 activity and may serve as a useful biomarker for mucosal immune activation. IDO1 activity may also influence a diverse set of extraintestinal manifestations including mood disturbance. Pharmacologic agents which inhibit or potentiate IDO1 expression and activity have the potential to impact a diversity of intestinal disorders.

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KEY POINTS

- IDO1 expression and activity is an important mediator of intestinal homeostasis both in health and disease.
- Experimental models suggest that IDO1 upregulation observed in Crohn's disease and ulcerative colitis acts to limit the inflammatory response and may be exploitable for disease therapeutics.
- IDO1 activity in the gut mucosa during active inflammatory bowel disease changes serum levels of tryptophan and kynurenine based metabolites positioning the pathway as a potential disease biomarker.
- Most colon cancers express IDO1; while its presence has been linked to poor prognosis, how IDO1 contributes to colon tumorigenesis requires further exploration.

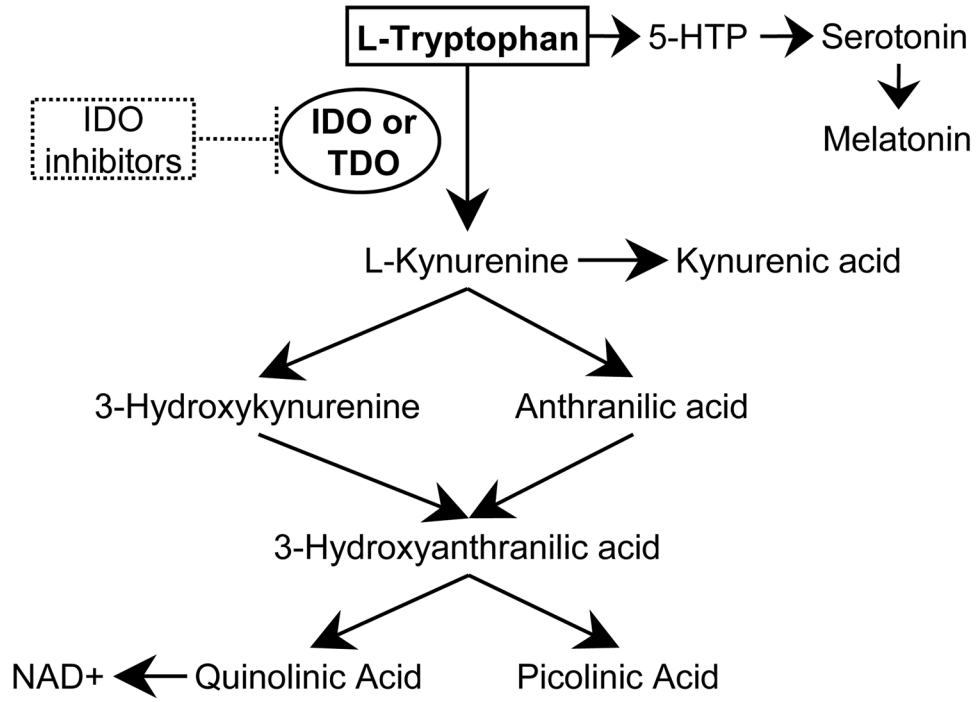

Figure 1.
Tryptophan catabolism pathways and the IDO1 kyurenine metabolite pathway