Therapeutic targeting of inflammation and tryptophan metabolism in colon and gastrointestinal cancer

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Colorectal cancer (CRC) is the third most common cancer worldwide and the second leading cause of cancer death in the United States. Cytotoxic therapies cause significant adverse effects for most patients and do not offer cure in many advanced cases of CRC. Immunotherapy is a promising new approach to harness the body's own immune system and inflammatory response to attack and clear the cancer. Tryptophan metabolism along the kynurenine pathway (KP) is a particularly promising target for immunotherapy. Indoleamine 2,3-dioxygenase 1 (IDO1) is the most well studied of the enzymes that initiate this pathway and it is commonly overexpressed in CRC. Herein, we provide an in-depth review of how tryptophan metabolism and KP metabolites shape factors important to CRC pathogenesis including the host mucosal immune system, pivotal transcriptional pathways of neoplastic growth, and luminal microbiota. This pathway's role in other gastrointestinal (GI) malignancies such as gastric, pancreatic, esophageal, and GI stromal tumors is also discussed. Finally, we highlight how currently available small molecule inhibitors and emerging methods for therapeutic targeting of IDO1 might be applied to colon, rectal, and colitis–associated cancer. (Translational Research 2016;167:67–79)

Abbreviations: ACF = aberrant crypt foci; AHR = aryl hydrocarbon receptor; AOM = azoxymethane; APC = adenomatous polyposis coli; CAC = colitis-associated cancer; CD = cluster of differentiation; COX-2 = cyclooxygenase 2; CRC = colorectal cancer; DC = dendritic cell; DNA = deoxyribonucleic acid; GCN2 = general control nonderepressible 2; GSK-3β = glycogen synthase kinase 3 beta; IDO1 = indoleamine 2,3-dioxygenase 1; IDO2 = indoleamine 2,3-dioxygenase 2; IFN = interferon; IL = interleukin; iNOS = inducible nitric oxide synthase; KP = kynurenine pathway; KRAS = Kirsten rat sarcoma; 1 mT = 1-methyltryptophan; mTOR = mammalian target of rapamycin; NF-κB = nuclear factor kappa B; NO = nitric oxide; PDA = pancreatic ductal adenocarcinoma; QPRT = quinolinate phosphoribosyltransferase; STAT = signal transducers and activators of transcription; TDO2 = tryptophan dioxygenase; TGF-β = transforming growth factor β; TLR = toll-like receptor; TNF = tumor necrosis factor; Tregs = regulatory T cells

INTRODUCTION

Inflammation is a common feature of colorectal cancer (CRC).[1] Despite immune cell infiltration, CRCs evade immune surveillance and resist immune-mediated destruction. Metabolism of the essential amino acid tryptophan along the kynurenine pathway (KP) is one potential explanation for this phenomenon and is recognized as an important link between inflammation and neoplastic progression in many cancers.

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Indoleamine 2,3-dioxygenase 1 (IDO1) is the most well studied of the enzymes that initiate tryptophan's catabolism to kynurenine. High IDO1 expression is present in a subset of human CRC where it portends a worse prognosis.[2,3] IDO1 is also one of the most highly upregulated genes in human inflammatory bowel disease (IBD), a precancerous condition.[4,5] Local tryptophan depletion and the biologically active KP metabolites exert potent immunomodulatory effects to shape the tumor microenvironment and contribute to tumor immune escape.[6] In CRC, IDO1 also directly supports tumor growth independent of effect on adaptive immunity.[2] These features establish IDO1 and the KP as highly promising targets for immunotherapy of cancers including those of the gastrointestinal (GI) tract.

Herein, we provide an in-depth review of how tryptophan metabolism and KP metabolites shape factors important to CRC pathogenesis including the mucosal immune system, luminal microbiota, and pivotal transcriptional pathways for neoplastic growth. More limited coverage is provided on how this pathway affects other GI malignancies. Finally, we highlight how currently available agents and emerging methods for therapeutic targeting of the IDO1-KP might be applied to CRC.

BACKGROUND ON COLON CANCER AND INFLAMMATION

CRC is the third most common cancer worldwide,[7] and in the United States is the second leading cause of cancer-related death (almost 50,000 per year).[8] In most cases, the transition from normal colon epithelium to cancer is influenced by the acquisition of somatic mutations and environmental factors including diet and lifestyle.[9,10] The adenomatous polyposis coli (APC) gene is a key component to Wnt signaling and is mutated in most CRCs.[10]

Chronic inflammation is also a risk factor for CRC. Colitis-associated cancer (CAC) is a form of CRC that develops in patients with chronic IBD, including Crohn's disease and ulcerative colitis.[5] In IBD, dysregulated activation of the gut mucosal immune system driven by genetic susceptibility loci and environmental factors leads to chronic inflammation.[11] The risk of developing CAC correlates with the duration, extent, and severity of IBD activity.[5] Although estimates vary, ~2% of individuals diagnosed with ulcerative colitis will develop CAC by 10 years after symptoms emerge, and 18% by 30 years, vs a 5.2% lifetime risk of developing CRC for the US population.[12,13] Importantly, CAC often develops earlier in life and progresses more quickly than sporadic CRC, frequently affecting young persons in their prime productive years.

Several recent and excellent reviews highlight differences between CAC and sporadic CRC.[5,14,15] Notably the molecular steps and sequence of acquired genetic mutations vary between the 2. For example, the loss of APC gene function is considered a crucial early step in sporadic CRC, but occurs late in CAC tumors.[10] In CAC, reactive oxygen species and reactive nitrogen species produced by both immune cells and the inflamed epithelium are primary sources of DNA damage.[9] Ultimately, mutations in the Wnt-APC or inflammatory signaling pathways such as the phosphoinositide 3-kinase (PI3K)- Akt (PI3K-Akt) pathway support dysregulated β-catenin activity, which in turn leads to the transcription of genes such as cyclins, axin2, and c-Myc that promote proliferation and tumor growth.[16] Although CAC is a model disease to examine links between chronic inflammation and neoplasia, inflammation and immune cell infiltration also comprise a component of all CRC.[1] Once colon neoplasia begins to form, immune cells are invariably recruited to the tumor site. This immune cell infiltration can be somewhat paradoxical, as immune cells both contribute to tumorigenesis and participate in clearance of the tumor. Cytokines produced by the tumor-associated immune cells, including tumor necrosis factor α (TNF)-α, interferon gamma (IFN-γ), interleukin 1β (IL-1β), and IL-6, induce reactive oxygen species and reactive nitrogen species in the tumor, which potentiate genetic damage and tumor progression.[9] Conversely, the presence of natural killer and T lymphocytes in tumors correlates with better clinical outcome and longer survival in patients with CRC.[17-19] Despite the infiltration of natural killer and T cells, tumors are often able to evade cytolysis, indicating that mechanisms of immune suppression are present in the tumor milieu.[20] These findings highlight as an important focus in CRC research to target interruption of this process, known as immunoediting, with *immunotherapies*.

CURRENT THERAPEUTICS ILLUSTRATE A LINK BETWEEN INFLAMMATION AND COLON CANCER

In setting the stage for a detailed examination of tryptophan metabolism's role in inflammation and CRC, it is useful to have perspective on how current therapeutics fit into this paradigm. To date no *immunotherapy* is approved for CRC. However, observations from currently available therapeutics provide support for this concept and insight into the complex relationship between colon inflammation and cancer. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), reduce the risk of sporadic CRC in some individuals.[21] Aminosalycilates (mesalamine), integral maintenance anti-inflammatories for IBD, decrease the risk of CAC.[22] Nuclear factor kappa B modulation may