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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

IDO in Colorectal Tumorigenesis: Involvement of Immune Tolerance and Significance in Prevention and Therapy

Colorectal cancer (CRC) ranks third in incidence and second in mortality worldwide,[1] and the incidence rates have been increasing in less developed regions and in younger individuals in many developed countries.[2] Despite the significant improvements in primary prevention, screening, and to a lesser extent, treatment,[2] the prognosis of patients with metastatic colorectal cancer (mCRC) remains poor.[3] Recently, immune checkpoint inhibitors (ICIs) demonstrated exciting efficacy in CRC characterized by mismatch repair (MMR)–deficient or high levels of microsatellite instability (MSI) in multiple clinical trials, and pembrolizumab, nivolumab, and the combination of nivolumab and ipilimumab have been approved by the U.S. Food and Drug Administration for treatment of MMR-deficient/high MSI CRCs.[3] However, the majority of CRC (85%) and mCRC (95%) cases are MMR-proficient or MSI low and are essentially nonresponsive to ICIs.[3] Other potential immunotherapies and combinations, including ICIs other than inhibitors of PD-1/PD-L1 or CTLA-4, are under active pursuing.

IDO is one of the well-recognized immune suppressive molecules. Both IDO and TDO catalyze the rate-limiting cleavage of essential amino acid tryptophan (Trp) into kynurenine (Kyn) pathway, resulting in depletion of Trp and production of immunoregulatory molecules including Kyn. While TDO exists mainly in liver and brain, IDO, specifically IDO1, is expressed in certain endothelial and epithelial cells in response to certain pathological conditions such as inflammation and cancer.[4] High IDO expression in CRC is associated with immune tolerance, metastasis, and poor prognosis, and increased serum Kyn-to-Trp ratio could serve as a screening marker of CRC.[4] Kyn is an agonist of aromatic hydrocarbon receptor (AhR), which induces differentiation of regulatory T (Treg) cells and the expression of PD-1 in $CD8^+$ T cells,[4] and intestinal epithelial loss of AhR enhanced cecum and colon tumorigenesis.[5] Mechanistically, IDO and its Kyn pathway metabolites have been reported to activate β-catenin and PI3K-Akt signaling pathways to promote cancer cell proliferation and inhibit apoptosis and thus facilitate colon tumorigenesis.[6,7] However, the involvement of IDO in immune tolerance, which has been well characterized in other cancers and is more relevant to immunotherapy efficacy, has not been determined in CRC, and the exact mechanisms by which IDO regulates the fate of immune cells in colorectal tumor microenvironment remain unknown.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Zhang et al[8] carefully examined the impact of activated IDO in colon cancer cells on T cells and mice spleen lymphocytes using conditioned medium from IDO-activated colon cancer cells, then validated their findings using azoxymethane (AOM)/dextran sodium sulfate (DSS)–induced colitis-associated cancer (CAC) model in $IDO^{-/-}$, $Rag1^{-/-}$, and wild-type mice.[8] The conditioned medium inhibited proliferation of activated T cells (Jurkat cells) by cell cycle arrest, and promoted transdifferentiation of mice spleen lymphocytes into $FoxP3^+$ Treg cells instead of $CD8^+$ T cells, in a Trp-independent, AhR-dependent, and Kyn-like manner. These results not only confirmed the immune-suppressive effects of IDO activation in CRC, but also provided new mechanistic interpretation of the previously documented IDO-mediated increase of Treg cells in CRC mice models.[9]

Previous studies reported that both genetic knockout and pharmacological inhibition of IDO attenuated AOM/DSS-induced mice colon tumorigenesis, while the involvement of adaptive immune response was excluded.[6,7] Zhang et al[8] demonstrated similar phenotypic results in the present article and their previous publication.[10] Interestingly, decreased Treg cells and increased $CD8^+$ T cells were detected in tumors of $IDO^{-/-}$ CAC mice, while Kyn treatment significantly counteracted the effects of IDO deficiency, suggesting an important role of IDO-Kyn-AhR-FoxP3–mediated immune-suppressive environment in colon tumorigenesis. It is noteworthy that the role of AhR in colon tumorigenesis has been controversial, and it has also been recognized as a tumor suppressor.[5,11] Such controversary might result from the complexity and plasticity of AhR signaling,[12] and thus AhR may not be a good target candidate of immunotherapies. On the other hand, $Rag1^{-/-}$ mice without mature T and B cells were more susceptible to AOM/DSS-induced CAC, which further supports the importance of T cells in colon carcinogenesis. Surprisingly, IDO deficiency in a $Rag1^{-/-}$ background ($IDO^{-/-}$::$Rag^{-/-}$ mice) also inhibited AOM/DSS-induced CAC,[7] suggesting that further investigations are guaranteed.

Among the known immune checkpoint molecules, IDO is the only one that can be targeted by small molecules. Therefore, IDO inhibitors are of special interest to medicinal chemists and pharmaceutical industry. IDO inhibitors or in combination with anti-PD-1/PD-L1 therapies have been extensively investigated in various cancers, and very promising results have been obtained in preclinical and early phase clinical investigations. Unfortunately, the enthusiasm has been greatly dampened by lack of efficacy in recent clinical trials.[13] However, as suggested by Zhang et al[8,10] and others,[14] IDO inhibitors may find a better avenue in prevention of CRC. Indeed, the inducible expression of

IDO by inflammatory stimuli is especially interesting for colorectal carcinogenesis, as inflammatory bowel diseases are well recognized as a risk factor of CRC.[2] Chemoprevention of CRC by anti-inflammatory drugs such as celecoxib and aspirin has been successful. Although inhibition of IDO may augment colitis,[15] Thaker et al[7] proved that such an effect was dependent on the severity of colitis. IDO inhibitors, at the crossroad of chemoprevention and immunoprevention, definitely deserve further investigation as a preventive agent of CRC or therapy of precancerous colorectal lesions.

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