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EDITORIAL

Role of Membrane Transporters in Intestinal Cancers

In recent years, considerable evidence has emerged indicating a potential role of intestinal epithelial luminal membrane transporters (eg, cystic fibrosis transmembrane conductance regulator [CFTR], Sodium hydrogen (Na^+/H^+) exchanger 8 [NHE8], sodium (Na^+) coupled monocarboxylate transporter 1 [SMCT1], glucose transporter 1 [GLUT1], Monocarboxylate transporter 1 [MCT1], and sodium hydrogen (Na^+/H^+) exchanger 3 [NHE3]) in intestinal cancers. However, the molecular mechanisms underlying the role of these transporters in this phenomenon are not well understood.

Recently, it was shown that CFTR (ABCC7) was down-regulated in small and colorectal cancers.[1] Furthermore, epidemiologic and clinical studies have indicated that cystic fibrosis patients were at high risk for developing tumors in the small intestine and colon.[2] Interestingly, CFTR deficiency in mice resulted in impaired mucosal barrier function,[3] compromised resistance to bacterial colonization, abnormal innate and adaptive immune responses, and increased inflammation.[3] It was suggested that all these factors together played a role in tumorigenesis.[3] More importantly, when the effects of CFTR knockdown on gastrointestinal cancer was examined in adenomatous polyposis coli; multiple intestinal neoplasia [Apc^{Min}] mice carrying an intestine-specific deletion of Cftr, it was observed that these mice developed significantly more tumors in the small intestine and colon compared with Apc^{Min} Cftr wild-type mice, suggesting that CFTR is a tumor-suppressor gene in the intestinal tract.[4] These tumors were shown to express increased levels of wingless/integrated/β-catenin target genes, indicating that Cftr-deficient tumors likely arose from activation of β-catenin.

In recent years, it has been shown that although NHE8 is one of the apically expressed Na^+/H^+ exchanger (NHE) isoforms in the intestine, it has other functions besides playing a potential role in Na^+ absorption. NHE8 deficiency in mice was shown to be associated with spontaneous colitis (similar to human ulcerative colitis), dysbiosis, increased epithelial cell proliferation, and high susceptibility to dextran sodium sulfate (DSS)-induced colitis.[5] In this issue, Xu et al[6] showed that loss of NHE8 function resulted in increased tumor burden in mice similar to what was observed in the CFTR study described earlier. In this study, NHE8 expression was found to be intact in healthy colorectal tissues, whereas it was undetectable in colorectal cancer tissues. The susceptibility of NHE8 knockout (KO) mice to colon cancer was investigated further using an inflammation-associated azoxymethane (AOM)/DSS colon cancer model. NHE8 KO mice developed a higher number and larger-sized tumors in the colon in response to AOM/DSS compared with wild-type mice. Xu et al[6] attributed this phenomenon to increased Lgr5 expression in the colon of mice. Lgr5, a leucine-rich, repeat-containing, G-protein–coupled receptor 5 is a member of the Wnt/β-catenin signaling pathway and is shown to be overexpressed in intestinal adenomas and colorectal cancer tissues.[7] Furthermore, the expression of β-catenin and c-Myelocytomatosis (c-Myc) also was increased significantly in colonic tissues of AOM/DSS-treated NHE8 KO mice. These studies suggested that loss of NHE8 expression significantly up-regulated β-catenin/Lgr5/c-Myc expression, resulting in hyperproliferation and high tumor incidence in AOM/DSS-treated NHE8 KO mice. These findings provide novel evidence for the role of the Lgr5-mediated mechanism by which loss of NHE8 function contributes to the pathogenesis of colitis-associated colon cancer.

There is some evidence that the Na^+-coupled monocarboxylate transporter (SMCT1, SLC5A8) also may be protective against tumorigenesis.[8] The tumor-suppressive function of SLC5A8 relates to the ability of its substrates, butyrate, propionate, and pyruvate, in inhibiting histone deacetylases.[9] However, deletion of Slc5a8 in mice did not increase the incidence or progression of colon cancer in inflammation-associated colon cancer (AOM/DSS) and genetically driven colon cancer (ApcMin/+) models.[10]

It should be noted that not all intestinal epithelial transporters act as tumor suppressors. In fact, there are a number of transporters that serve as tumor promoters because tumor cells have an increased demand for nutrients to support their rapid growth. The facilitative glucose transporter SLC2A1 (GLUT1) is up-regulated in almost all cancers[8] to provide glucose as the energy source for the tumor cells to survive. The monocarboxylate transporter SLC16A1 (MCT1) and the Na^+/H^+ exchanger SLC9A3 (NHE3) also have been shown to be up-regulated in tumor cells to prevent cellular acidification caused by a higher metabolic rate of cancer cells.[8] Thus, these transporters appear to play a role in promoting tumorigenesis and hence represent potential drug targets for cancer therapy.

Since carcinogenesis is a multifactorial phenomenon, it seems that dysregulation or deletion of certain intestinal transporters represents one of the risk factors in tumorigenesis or in tumor progression. Further studies are needed to better understand the precise mechanism underlying the role of the gut transporters in intestinal cancers.

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Conflicts of interest

The authors disclose no conflicts.

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