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Amino acid transporter SLC6A14: a novel drug target for colorectal cancer

ABSTRACT

Colorectal cancer (CRC) is the third most cause of cancer morbidity and mortality in the USA. Current treatment strategies for CRC are less efficacious compared to other cancers because of its complex etiology. Therefore, new drug targets and new therapeutic approaches are desperately needed for CRC. Tumor cells have an increased demand for amino acids to sustain their rapid growth and proliferation and to feed their unique re-programmed metabolic pathways. Tumor cells meet this increased demand by upregulating selective amino acid transporters. We discovered one such amino acid transporter that is upregulated the most in CRC. This transporter, SLC6A14, is broad-selective and highly concentrative because of the multiple driving forces that energize its transport function. Now the question is: Does this transporter drive CRC and, if so, would deletion of SLC6A14 or pharmacologic blockade of its function suppress CRC growth? I addressed these questions in my project. We identified α-methyl tryptophan (α-MT) as a selective blocker of SLC6A14. Treatment of colon cancer cells with α-MT in vitro caused significant amino acid starvation, decreased mTOR activity, increased autophagy and apoptotic cell death, and decreased proliferation and invasion. In studies with xenografts in immunocompromised mice and syngeneic transplants in immunocompetent mice, silencing of SLC6A14 by shRNA or blocking its function by α-MT suppressed tumor growth. Slc6a14-null mice showed significant protection from CRC in both Apcmin/+ and AOM/DSS experimental models. Our findings suggest that SLC6A14 is potentially a novel drug target and that α- MT might be an effective drug for CRC. We also uncovered that activation of canonical Wnt signaling is responsible for SLC 6A14 upregulation in CRC. Moreover, this study have shown that α-MT is also a potent inhibitor of the immunosuppressive enzyme IDO1, indicating that this compound could suppress CRC not only as a chemotherapy agent but also as an immunotherapy agent.