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Inhibition of Fatty Acid Synthesis as a Therapeutic Strategy for Colorectal Cancer

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Colorectal cancer (CRC) is the second leading cause of cancer-related deaths in the United States. Activation of *de novo* lipogenesis and overexpression of lipogenic enzymes including fatty acid synthase (FASN) in cancer cells correlates with a poorer prognosis in CRC.

Our studies demonstrate that an increased expression of FASN is associated with increased CRC stage. We are the first to show the importance of FASN upregulation in the development of CRC metastasis and demonstrate that shRNA-mediated inhibition of FASN significantly reduces lung and hepatic metastases in nude mice and inhibits angiogenesis in an orthotopic CRC mouse model. Our recent studies, using primary CRC cells and patient-derived xenograft (PDX) models, show that FASN overexpression promotes CRC metastasis via an increase in sphingolipid metabolism. Moreover, overexpression of FASN promotes a metabolic switch that fuels bioenergetic pathways to enhance cancer cell survival and support metastasis, particularly under energy stress conditions. We show that even in the presence of exogenous fatty acids, CRC cells preferentially oxidize endogenous fatty acids synthesized by FASN, thus providing further evidence of the crucial role of *de novo* lipid synthesis in CRC progression.

Utilizing novel FASN inhibitors in PDX models, our ongoing studies of correlation between mutation and metabolic profiles of tumors and tumor response to FASN inhibition aim to identify a subset of CRC patients that are likely to respond to FASN-targeted therapy. Further understanding of genetic and metabolic characteristics of tumors susceptible to FASN inhibition may enable patient selection and personalized medicine approaches in CRC.

Biography:

Dr. Zaytseva completed a bachelor's degree at Rostov-on-Don State University in Russia with a major in biology and a minor in chemistry. In 2005 she was accepted to the Integrated Biomedical Science Graduate Program at the University of Kentucky. After obtaining her PhD in Biomedical Pharmacology in 2010 she joined Dr. Mark Evers' group as a post-doctoral scholar at the Markey Cancer Center. Dr. Zaytseva was awarded the NCI K22 career development grant and currently is an Assistant professor (tenure track) in the Department of Toxicology and Cancer Biology at the University of Kentucky.