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Meta-analysis and systematic review of the management of colorectal laterally spreading tumors

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Abstract (600 word limit)

Tumor metabolism is controlled by reversible post-translational modifications. We show here that mitochondrial Sirtuin5 (SIRT5), which regulates lysine desuccinylation, deglutarylation, and demalonylation, is involved in colorectal cancer (CRC) glutamine metabolic rewiring. Cancerous tumors have abnormal metabolic characteristics and have emerged as attractive therapeutic targets. Colorectal cancer (CRC), the fourth leading cause of cancer-related death worldwide, also exhibits deregulated metabolic profiles during tumorigenesis. It is unclear exactly how this happens. Based on metabolic profiling, deletion of SIRT5 leads to a marked reduction in 13C-glutamine incorporation into tricarboxylic acid (TCA) cycle intermediates and glutamine-derived non-essential amino acids. The present study reported that upregulation of SIRT5 is independently associated with poor outcomes for patients with CRC. A number of post-translational modifications (PTMs) have been demonstrated to modulate metabolic enzymes, including acetylation, succinylation, malonylation, glutarylation, methylation, propionylation, butyrylation, and crotonylation. In our in vitro and in vivo studies, GLUD1, an enzyme involved in glutaminolysis, was crucial for SIRT5-driven cancer progression. We tested whether SIRT5's catalytic activity is involved in the proliferation induced by the enzyme given that SIRT5 exhibits robust lysine desuccinylase, demalonylase, and deglutarylase activities. We have established stable cell lines expressing the vector control, SIRT5 wild type (SIRT5 WT), and SIRT5 H158Y, a catalytically inactive mutant lacking lysine deacylation activity. Deglutarylation of GLUD1 and activation of its function by SIRT5. According to our findings, SIRT5 might be an effective therapy for CRC. In both in vitro and in vivo, GLUD1 knockdown diminishes SIRT5-induced proliferation. Upon entering cells, glutamine is converted to glutamate by GLS. Through the action of GLUD1 or aminotransaminases, glutamate is converted into KG. We studied these glutamine-metabolizing enzymes in order to identify the mechanism by which SIRT5 promotes glutamine-derived carbon entry into the TCA cycle. Interestingly, knockdown or overexpression of SIRT5 did not result in significant differences in GLS, GLUD1, GOT1/2, GPT2, or PSAT1 protein levels. There is a significant correlation between overexpression of SIRT5 and poor prognosis in CRC. In malignant phenotypes of CRC, SIRT5 activates GLUD1 to facilitate glutamine entry into the TCA cycle through anaplerotic pathways.

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Biography (200 word limit)

Richard Smiley with a PhD in Gastroenterology. My experience includes managing projects, conducting research, and teaching. Gastroenterology has been a focus of my expertise. In addition, I have contributed to the development of various techniques to treat gastric related complications in both public and private companies. Currently, I am working at Washington University, Missouri. I am studying the role of the Meta-analysis and systematic review of the management of colorectal laterally spreading tumors.

About Research Topic (200 word limit)

Tumors with altered metabolic characteristics are regarded as hallmarks of cancer and are thus attractive targets for novel therapeutic approaches. Colorectal cancer (CRC) shows deregulated metabolic profiles during tumorigenesis as well as being the third most commonly diagnosed malignancy worldwide. The precise mechanism remains unknown. In the present study, we found that upregulation of SIRT5 independently correlated with poor outcomes in patients with CRC. As a result of the integration of high-throughput gas chromatography mass spectrometry (GC-MS) screening and 13C-based metabolic flux assay, we identified glutamine-dependent anaplerosis into the tricarboxylic acid (TCA) cycle as the major metabolic pathway regulated by SIRT5 in CRC cells. The PTM of lysine glutarylation is evolutionarily conserved and enriched in diverse metabolic enzymes. Unfortunately, how lysine deglutarylation affects cancer metabolism remains poorly understood. As a result of an interaction between SIRT5 and GLUD1, we detected deglutarylation of K545, which activated GLUD1 in CRC. ADP-ribosylation45 and acetylation44 have also been implicated in regulating GLUD1 function in cells. Due to its negatively charged nature and its large size, glutarylation may have a more profound impact on protein structure and function than other modifications.

About Institution (200 word limit)

Washington University in St. Louis (WashU, or WUSTL) is a private research university in Greater St. Louis with its main campus (Danforth) mostly in unincorporated St. Louis County, Missouri, and Clayton, Missouri. It also has a West Campus in Clayton, North Campus in the West End neighborhood of St. Louis, and Medical Campus in the Central West End neighborhood of St. Louis. Founded in 1853 and named after George Washington, the university has students and faculty from all 50 U.S. states and more than 120 countries. Washington University is composed of seven graduate and undergraduate schools that encompass a broad range of academic fields. To prevent confusion over its location, the Board of Trustees added the phrase "in St. Louis" in 1976. Washington University is a member of the Association of American Universities and is classified among "R1: Doctoral Universities – Very high research activity".

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