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Abstract

Glutamine synthetase in cancer cell metabolism and oncogenesis

By

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Altered glutamine metabolism is a hallmark of cancer. It is widely appreciated that glutamine is catabolized to produce alpha-ketoglutarate as a substrate for the tricarboxylic acid (TCA) cycle. This is often due to upregulation of glutaminase (GLS) by a number of oncogenes. Our initial observation suggested that the proto-oncogene Myc was capable of regulating glutamine synthetase (GS) expression. GS is the sole enzyme responsible for *de novo* glutamine synthesis. Overexpression of Myc in the immortalized, but not transformed, mammary epithelial cells MCF10A led to an upregulation of GS. Subsequently, silencing of Myc in cancer cell lines led to a decrease of GS. This regulation of GS by Myc is controlled by an indirect epigenetic mechanism. The biological consequence for Myc induced upregulation of GS entailed increased glutamine synthesis, and GS expression played a cytoprotective role in response to glutamine limitation. Silencing of GS in Myc amplified mammary epithelial cells or cancer cell lines decreased the growth capacity *in vitro* and in xenograft studies. Genetic deletion of GS in pancreatic cancer further revealed the importance of glutamine synthesis in tumorigenesis. Previous studies have highlighted non-canonical glutamine metabolism in pancreatic ductal adenocarcinoma (PDAC). Deletion of GS hampered the capacity of PDAC cells to adapt to glutamine deprivation and utilize components of the glutamine synthetic pathway, namely aKG. Stable isotope tracing revealed that aKG was used to synthesize glutamine and contribute carbons to the TCA cycle. Newly synthesized glutamine was used to produce hexosamine sugars and nucleotides. As such, deprivation of glutamine led to induction of DNA damage, which could be partly prevented in GS proficient cells by supplying the precursors responsible for glutamine synthesis. In order to determine the contribution of GS for tumorigenic capacity, PDAC cells were implanted orthotopically into immunocompetent mice. Animals harboring GS KO cells had a significant increase in survival. It is tempting to speculate that this effect is due to depletion of glutamine in the local tissue and the generation of an inhospitable environment for cells unable to synthesize glutamine autonomously. These data suggest that GS may be a viable therapeutic target for cancer.

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