Lipogênese no câncer. No glioblastoma multiforme a ATP citrato liase está super ativada e o hidroxicitrato diminui a invasividade, a clonogenicidade e a migração das células cancerosas

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A ativação da enzima ATP citrato liase mantém o fenótipo glicolítico no glioblastoma multiforme e a adição de hidroxicitrato diminui a invasividade e a migração tumoral aumentando a sobrevida.

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Identification of ATP citrate lyase as a positive regulator of glycolytic function in glioblastomas.
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Abstract
Glioblastomas, the most malignant type of glioma, are more glycolytic than normal brain tissue. Robust migration of glioblastoma cells has been previously demonstrated under glycolytic conditions and their pseudopodia contain increased glycolytic and decreased mitochondrial enzymes. Glycolysis is suppressed by metabolic acids, including citric acid which is excluded from mitochondria during hypoxia. We postulated that glioma cells maintain glycolysis by regulating metabolic acids, especially in their pseudopodia. The enzyme that breaks down cytosolic citric acid is ATP citrate lyase (ACLY). Our identification of increased ACLY in pseudopodia of U87 glioblastoma cells on 1D gels and immunoblots prompted investigation of ACLY gene expression in gliomas for survival data and correlation with expression of ENO1, that encodes enolase 1. Queries of the NIH's REMBRANDT brain tumor database based on Affymetrix data indicated that decreased survival correlated with increased gene expression of ACLY in gliomas. Queries of gliomas and glioblastomas found an association of upregulated ACLY and ENO1 expression by chi square for all probe sets (reporters) combined and correlation for numbers of probe sets indicating shared upregulation of these genes. Real-time quantitative PCR confirmed correlation between ACLY and ENO1 in 21 glioblastomas (p < 0.001).

Inhibition of ACLY with hydroxycitrate suppressed (p < 0.05) in vitro glioblastoma cell migration, clonogenicity and brain invasion under glycolytic conditions and enhanced the suppressive effects of a Met inhibitor on cell migration. In summary, gene expression data, proteomics and functional assays support ACLY as a positive regulator of glycolysis in glioblastomas.
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