Combined targeting of PDK1 and EGFR triggers regression of glioblastoma by reversing the Warburg effect.

Velpula KK, Bhasin A, Asuthkar S, Tsung AJ.
Cancer Biology and Pharmacology, University of Illinois College of Medicine.

Abstract
Glioblastoma multiforme (GBM) is the most aggressive primary brain tumor in adults. Overexpression of the EGF receptor (EGFR) is recognized as a widespread oncogenic signature in GBM, but the complexity of its contributions are not fully understood, nor the most effective ways to leverage anti-EGFR therapy in this setting. Hypoxia is known to drive the aggressive character of GBM by promoting aerobic glycolysis rather than pyruvate oxidation carried out in mitochondria (OXPHOS), a phenomenon termed the Warburg effect which is a general feature of oncogenesis. In this study, we report that hypoxia drives expression of the pyruvate dehydrogenase kinase PDK1 and EGFR along with the hypoxia-inducing factor HIF-1α in human GBM cells. PDK1 is a HIF-1-regulated gene and our findings indicated that hypoxia-induced PDK1 expression may promote EGFR activation, initiating a feed-forward loop that can sustain malignant progression. RNAi-mediated attenuation of PDK1 and EGFR lowered PDK1-EGFR activation and decreased HIF-1α expression, shifting the Warburg phenotype to OXPHOS and inhibiting GBM growth and proliferation. In clinical specimens of GBM, we found that immunohistochemical expression of PDK1, EGFR, and HIF-1α were elevated in GBM specimens when compared to normal brain tissues. Collectively, our studies establish PDK1 as a key driver and candidate therapeutic target in GBM.

PMID: 24148623 [PubMed - as supplied by publisher]