PGK1 protein promotes brain tumor formation and cancer metabolism

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PGK1, a glycolytic enzyme, has been found to play a role in coordinating cellular processes crucial to cancer metabolism and brain tumor formation, according to results published in today's online issue of *Molecular Cell*. The findings may lay the groundwork for improved approaches to diagnosis and treatment of glioblastoma and other cancers.

The study, led by The University of Texas MD Anderson Cancer Center, showed that PGK1, which is associated with tumor metastasis and drug resistance, was instrumental in glycolysis and the citric acid cycle, both important for generating the energy that feeds cancer cells. The paper sheds further light on the Warburg effect, an enzymatic pathway that cancer cells employ to boost energy levels and produce cellular substances that lead to rapid cancer growth.

"The Warburg effect promotes tumor progression. Exactly how this is coordinated has remained elusive," said Zhimin Lu, M.D., Ph.D., professor of Neuro-Oncology. "Our study highlights that PGK1 acts as a protein kinase in coordinating glycolysis and the citric acid cycle in cancer metabolism and tumor formation."

Normal cells generate oxygen for survival via a relatively low rate of glycolysis, which converts glucose into the enzyme pyruvate. Pyruvate is used in the citric acid cycle (TCA), a series of chemical reactions that generate energy.

Cancer cells however produce energy by a high rate of glycolysis followed by lactic acid fermentation in the cell, a process that converts glucose into cellular energy and forms lactic acid. Normal healthy cells will bypass this fermentation process if oxygen is available. Malignant, rapidly growing tumors can experience glycolytic rates up to 200 times higher than those of healthy cells and will undergo lactic acid fermentation even in the presence of high oxygen levels.

"The Warburg effect is characterized by increased levels of glucose, lactate production and suppression of pyruvate metabolism in mitochondria," said Lu. "Exactly how this process is coordinated with cancer metabolism has been little understood."

Lu's team found that a cellular chain of events involving activation of cancer genes like EGFR, KRAS and B-Raf and the protein ERK, allowed PGK1 to "translocate" into the cell's mitochondria. Mitochondria are membrane-containing cell components crucial for producing energy. PGK1 acted as a protein kinase in mitochondria and activated a critical enzyme that inhibited the mitochondria's ability to use pyruvate, suppressed chemically reactive molecules containing oxygen and increased lactate levels.

"Our findings provided critical insight into the Warburg effect and demonstrates that PGK1 ultimately promotes cancer cell proliferation and tumor formation," said Lu. "It may help us to develop a molecular basis for improved diagnosis and treatment of cancer."

Provided by University of Texas M. D. Anderson Cancer Center