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Study reveals PGK1 enzyme as therapeutic target for deadliest brain cancer

February 23 2017

Discovery of a dual role played by the enzyme phosphoglycerate kinase 1 (PGK1) may indicate a new therapeutic target for glioblastoma, an often fatal form of brain cancer, according to researchers at The University of Texas MD Anderson Cancer Center.

Findings published in the Feb. 23 online issue of *Molecular Cell* determined PGK1 as instrumental in regulating both cell metabolism and autophagy, a cellular process crucial to tumor development and maintenance. In previous studies, PGK1 was shown to play a role in coordinating cellular activities tied to cancer metabolism and brain tumor formation, and is associated with tumor metastasis and drug resistance.

"Our finding that PGK1 acts as both a glycolytic enzyme and a protein kinase in cell metabolism, autophagy, and cell proliferation greatly enhances our understanding of protein enzymes controlling cellular function," said Zhimin Lu, M.D., Ph.D., professor of Neuro-Oncology. "Because it regulates both autophagy and cell metabolism, PGK1 proves its significance in maintaining cellular activities, thus offering a potential new approach for cancer treatment."

Lu's team found that PGK1 unexpectedly impacts the protein Beclin1 through phosphorylation, which modulates protein function. Beclin1 plays a central role in autophagy, a "recycling" process allowing cells to thrive even when starved of nutrients and/or oxygen. Autophagy has been increasingly linked to cancer since it permits tumors to access vital

energy sources and cellular building blocks necessary to grow and spread.

The researchers observed that lack of oxygen and the essential amino acid glutamine resulted in a complex protein-related chain of events where PGK1 phosphorylates Beclin1, which is required for autophagy and brain tumor development. The process is thought to be one reason why glioblastoma patients generally have poor prognoses.

"Upregulated tumor-protective autophagy is one of the reasons for cancer treatment resistance," said Lu. "These findings suggest that approaches inhibiting PGK1-regulated autophagy are likely to increase cancer treatment efficacy. Further investigations into this area of research are underway."

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