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Metabolic protein launches sugar feast that nurtures brain tumors

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Researchers at The University of Texas MD Anderson Cancer Center have tracked down a cancer-promoting protein's pathway into the cell nucleus and discovered how, once there, it fires up a glucose metabolism pathway on which brain tumors thrive.

They also found a vital spot along the protein's journey that can be attacked with a type of drug not yet deployed against glioblastoma multiforme, the most common and lethal form of brain cancer. Published online by Nature Cell Biology, the paper further illuminates the importance of pyruvate kinase M2 (PKM2) in cancer development and progression.

"PKM2 is very active during infancy, when you want rapid cell growth, and eventually it turns off. Tumor cells turn PKM2 back on - it's overexpressed in many types of cancer," said Zhimin Lu, M.D., Ph.D., the paper's senior author and an associate professor in MD Anderson's Department of Neuro-Oncology.

Lu and colleagues showed earlier this year that PKM2 in the nucleus also activates a variety of genes involved in cell division. The latest paper shows how it triggers aerobic glycolysis, processing glucose into energy, also known as the Warburg effect, upon which many types of solid tumors rely to survive and grow.

"PKM2 must get to the nucleus to activate genes involved in cell proliferation and the Warburg effect," Lu said. "If we can keep it out of

the nucleus, we can block both of those cancer-promoting pathways. PKM2 could be an Achilles' heel for cancer."

By pinpointing the complicated steps necessary for PKM2 to penetrate the nucleus, Lu and colleagues found a potentially druggable target that could keep the protein locked in the cell's cytoplasm.

MEK, ERK emerge as targets

The process begins when the epidermal growth factor connects to its receptor on the cell surface. This leads to:

- Activation of the MEK protein, which in turn activates ERK.
- ERK sticking a phosphate group to a specific spot on PKM2.
- Phosphorylation priming PKM2 for a series of steps that culminate in its binding to the protein importin, which lives up to its name by taking PKM2 through the nuclear membrane.

Once in the nucleus, the team showed that PKM2 activates two genes crucial to aerobic glycolysis and another that splices PKM RNA to make even more PKM2.

An experiment applying several kinase-inhibiting drugs to human glioblastoma cell lines showed that only a MEK/ERK inhibitor prevented EGF-induced smuggling of PKM2 into the nucleus. ERK activation then is mandatory for PKM2 to get into the nucleus.

"MEK/ERK inhibitors have not been tried yet in glioblastoma multiforme," Lu said. Phosporylated PKM2 is a potential biomarker to identify patients who are candidates for MEK/ERK inhibitors once those drugs are developed.

MEK inhibitor blocks tumor growth

The researchers also found that the two glycolysis genes activated by PKM2, called GLUT1 and LDHA, are required for glucose consumption and conversion of pyruvate to lactate, crucial factors in the Warburg Effect. Depleting PKM2 in tumor cell lines reduced glucose consumption and lactate production.

In mice, depleting PKM2 blocked the growth of brain tumors. Re-expressing the wild type protein caused tumors to grow. However, re-expression of a PKM2 mutant protein that lost its ability to get into the nucleus failed to promote tumor formation. Experiments in human glioblastoma cell lines showed the same effect.

Injecting the MEK inhibitor selumetinib into tumors inhibited tumor growth, reduced ERK phosphorylation, PKM2 expression and lactate production in mice. In 48 human tumor samples, the team found that activity of EGFR, ERK1/2 and PKM2 were strongly correlated.

Cause of PKM2 overexpression

Lu and colleagues also published a paper in *Molecular Cell* that revealed a mechanism for overexpression of PKM2 in glioblastoma. They found that EGF receptor activation turns on NF-?B, which leads to a series of events culminating in PKM2 gene activation.

PKM2 levels were measured in tumor samples from 55 glioblastoma patients treated with standard of care surgery, radiation and chemotherapy. The 20 with low PKM2 expression had a median survival of 34.5 months, compared to 13.6 months for the 35 patients with high levels of PKM2.

Level of PKM2 expression in 27 low-grade astrocytomas was about half of the expression found in higher grade glioblastomas.

"In these two papers, we show how PKM2 is overexpressed in tumors, how it gets into the nucleus, that nuclear entry is essential to tumor development, and identified potential drugs and a biomarker that could usefully treat people," Lu said.

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