

Metabolic protein plays unexpected role in tumor cell formation and growth

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The embryonic enzyme pyruvate kinase M2 (PKM2) has a well-established role in metabolism and is highly expressed in human cancers. Now, a team led by researchers at the University of Texas MD Anderson Cancer Center reports in advance online publication of the journal *Nature* that PKM2 has important non-metabolic functions in cancer formation.

"Our research shows that although PKM2 plays an important role in cancer metabolism, this enzyme also has an unexpected pivotal function - it regulates cell proliferation directly," said senior author Zhimin Lu, M.D., Ph.D., associate professor in the Department of Neuro-Oncology at MD Anderson. "Basically, PKM2 contributes directly to gene transcription for cell growth - a finding that was very surprising."

The researchers demonstrated that PKM2 is essential for epidermal growth factor receptor (EGFR) - promoted beta-catenin activation, which leads to gene expression, cell growth and tumor formation.

They also discovered that levels of beta-catenin phosphorylation and PKM2 in the cell nucleus are correlated with brain tumor malignancy and prognosis and might serve as biomarkers for customized treatment with Src inhibitors.

In response to epidermal growth factor (EGF), the team found, PKM2 moves into the cell nucleus and binds to beta-catenin that has had a phosphate atom and three oxygen atoms attached at a specific spot called Y333 by the protein c-Src. This binding is essential for beta-catenin activation and expression of downstream gene cyclin D1. This newly discovered way to regulate beta-catenin is independent of the Wnt signaling pathway previously known to activate beta-catenin.

One enzyme controls both cancer cell metabolism and cell cycle progression

In metabolism, PKM2 enhances oxygen-driven processing of sugar known as aerobic glycolysis or the Warburg effect found in tumor [cells](#).

"Cancer cell [metabolism](#) and cancer cell cycle progression, which are essential for tumor formation, are conventionally thought to be regulated primarily by distinct signaling complexes," Lu said. The new findings integrate the two major mechanisms for regulating cancer [cell growth](#) by a key metabolic enzyme. "These two important regulatory processes are under the control of pyruvate kinase M2."

New insight into brain malignancies and cancer therapy

Beta-catenin activation that is independent of the Wnt signaling pathway have been observed in many types of cancer. This study reveals a critical mechanism underlying Wnt-independent beta-catenin activation and indicates that c-Src-phosphorylated beta-catenin and nuclear PKM2 are independent predictors of glioma malignancy.

The researchers analyzed brain tumors in 84 patients who had been treated with radiation and chemotherapy after surgery. Those who had low beta-catenin Y333 phosphorylation or low expression of PKM2 in the nucleus (28 cases each) had a median survival of 185 weeks and 130 weeks, respectively.

Median survival decreased for those who had high levels of beta-catenin phosphorylation or nuclear PKM2 expression (56 cases each) to 69.4 weeks and 82.5 weeks, respectively.

Findings include:

- PKM2-dependent beta-catenin activation is instrumental in EGFR-promoted tumor cell proliferation and brain tumor development.
- c-Src activity, beta-catenin Y333

phosphorylation, and PKM2 nuclear accumulation are positively correlated in human glioblastoma specimens.

- Levels of beta-catenin phosphorylation and nuclear PKM2 are correlated with grades of glioma malignancy and prognosis.

Personalized therapy with Src inhibitors

One potential implication of their research is the potential use of c-Src-dependent beta-catenin Y333 phosphorylation levels as a biomarker for selecting patients for treatment.

"This finding is very important because EGFR-based therapy is not very efficient due to drug resistance, and cancer patients need alternative treatment strategies," Lu said. "Thus, this discovery can potentially serve as a guideline for personalized [cancer](#) therapy in the treatment of glioma and other tumors with Src inhibitors."

Src inhibitors include dasatinib, which has been approved by the FDA for leukemia treatment, or bosutinib and saracatinib, which are in clinical trials.

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

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