Medical Xpress

Cancer-promoting protein is vital to safe division of tumor cells

December 6 2013

Researchers have caught a protein they previously implicated in a variety of cancer-promoting roles performing a vital function in cell division, survival and development of brain tumors.

In a paper published in *Molecular Cell*, Zhimin Lu, Ph.D., professor of Neuro-Oncology at The University of Texas MD Anderson Cancer Center and colleagues report how a tumor-specific protein flips a crucial switch in an irregular mechanism for mitosis that allows cancer cells to safely divide.

"Our research shows that tumor cells rely heavily on a distinct mechanism for orderly cell division that's driven by oncogene-induced pyruvate kinase M2," Lu said.

After a cell begins division by replicating all of its chromosomes, mitosis separates them into two identical sets of chromosomes for both cells. After mitosis, cytokinesis completes cell divison.

"Without PKM2 regulating a checkpoint in mitosis, the tumor cell would not successfully divide," Lu said. "Depleting PKM2 led to an uneven distribution of DNA to the two new cells, triggering programmed cell death, or apoptosis, of those cells after division."

"This new, additional role for PKM2 in cancer development and survival may provide a molecular basis for diagnosing and treating tumors with upregulated PKM2," Lu said. He and his colleagues have now identified

four specific mechanisms by which PKM2 promotes cancer development.

PKM2 regulation of mitosis worsens tumors in mice; affects human glioblastoma

The key relationship between PKM2 activity and mitosis uncovered by the researchers led to rapid brain tumor growth when activated in mice, while blocking it reduced tumor volume by 83 percent and more than doubled survival from about 20 days to beyond 40 days.

Analysis of 50 human glioblastoma multiforme tumors and 50 lung cancer tumors confirmed the relationship in human cancer and indicated an effect on survival for patients with glioblastoma, the most common and lethal form of brain tumor.

PKM2 can act as a protein kinase, which gives orders to other proteins by attaching phosphate groups to them. While it plays a normal role in sugar metabolism, PKM2 also actively promotes cell growth during infancy when such growth is desired.

Usually, Lu said, it eventually turns off, but tumor cells reactivate PKM2, and it is famously overexpressed in solid tumors. This tumor-specific PKM2 is activated by the epidermal growth factor receptor (EGFR), which is overactive in a variety of cancers.

Deplete PKM2 in mitosis, tumor cells abnormally divide in multiple cancer types

A series of experiments in glioblastoma cell lines revealed that PKM2 phosphorylates a protein called Bub3, activating it to interact with others in a protein complex that assures orderly and equal chromosome

separation.

Depleting PKM2 blocked Bub3 activation, leading to an increase in cells with abnormal numbers of chromosomes and programmed cell death.

The team confirmed its findings in human breast, prostate, lung, pancreatic and colon cancer cell lines.

PKM2-induced Bub3 activation was essential for development of brain tumors in mice.

Experiments in the 50 glioblastoma and lung cancer tumors confirmed that phosphorylation of Bub3 correlates with phosphorylation of H3-S10, a marker of cell mitosis in tumor cells.

With low Bub3 phosphorylation, glioblastoma patients live longer

Among the 50 glioblastoma patients, the 15 with low levels of Bub3 phosphorylation had a median survival of 69.8 weeks, compared to 40.5 weeks for the 35 patients with high levels of Bub3 activation.

Previous research by Lu and colleagues showed PKM2, usually active outside the cell nucleus, slips into the nucleus where it promotes cancer formation, growth and survival by:

- Activating an important transcription co-factor that, in turn, activates other cancer-promoting genes.
- Phosphorylating the histone protein H3, loosening the packaging of DNA and leading to the activation of cell division genes.
- Inducing expression of glycolytic genes (including PKM2 itself) and triggering a glucose metabolism mechanism called the

Warburg effect that nourishes tumor cells.

Potential avenues for thwarting these effects identified in their experiments include two classes of drug that inhibit SRC and MEK activity.

"Our research further highlights the importance of PKM2 in human cancers and of developing ways to target its activity and use it as a biomarker to guide treatment," Lu said.

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

Citation: Cancer-promoting protein is vital to safe division of tumor cells (2013, December 6) retrieved 2 May 2024 from
https://medicalxpress.com/news/2013-12-cancer-promoting-protein-vital-safe-division.html