MedicalXpress

Study helps explain fundamental process of tumor growth

March 12 2008

Nearly 80 years ago, scientist Otto Warburg observed that cancer cells perform energy metabolism in a way that is different from normal adult cells. Many decades later, this observation was exploited by clinicians to better visualize tumors using PET (positron emission technology) imaging. But it has not been known exactly how tumor cells perform this alternate metabolic feat, nor was it known if this process was essential for tumor growth.

Now, two papers appearing in the March 13 issue of the journal *Nature* help answer these questions. Led by researchers at Beth Israel Deaconess Medical Center (BIDMC) and Harvard Medical School, the papers find that the metabolic process that has come to be known as the Warburg effect is essential for tumors' rapid growth, and identifies the M2 form of pyruvate kinase (PKM2), an enzyme involved in sugar metabolism, as an important mechanism behind this process. This discovery could provide a target for the development of future cancer therapies.

"With this study we have answered a fundamental question regarding the ability of tumor cells to rapidly grow and proliferate," explains senior author Lewis Cantley, PhD, Director of the Cancer Center at BIDMC and Professor of Systems Biology at Harvard Medical School.

Metabolic regulation in rapidly growing tissues, such as fetal tissue or tumors, is different from that of normal adult tissue, Cantley explains. "Through aerobic glycolysis, or the Warburg effect, cancer cells produce energy by taking up glucose at much higher rates than other cells while,

at the same time, using a smaller fraction of the glucose for energy production. This allows cancer cells to function more like fetal cells, promoting extremely rapid growth." This unique metabolic property of cancer cells has led to the success of PET imaging as a means of cancer detection; because radioactive glucose injected into patients prior to the imaging exam is preferentially taken up by glucose-hungry tumor cells, the areas of high glucose uptake are displayed dramatically on the PET scan.

Using a novel proteomic screen to identify new phosphotyrosine binding proteins, Cantley and his colleagues first determined that PKM2 can bind to phosphotyrosine-containing peptides. "We observed that in contrast to the forms of pyruvate kinase found in most normal adult tissues, only PKM2, which is found in fetal cells, interacted with phosphotyrosine," explains Cantley. "This finding was particularly interesting because previous reports had shown that this M2 form was the pyruvate kinase form used by all cancer cells."

In order to understand the implications of this discovery, Cantley and his coauthors next embarked upon experiments to evaluate the importance of PKM2 to cancer cells. Reasoning that tumor tissue switches pyruvate kinase expression from an adult M1 isoform to the embryonic M2 isoform, they performed immunoblotting and immunohistochemistry analysis of numerous cancer cell lines, breast cancer models and human colon cancer, confirming that PKM2 was the only form of pyruvate kinase found in cancerous tissue.

The authors then knocked down PKM2 expression in human cancer cell lines and expressed the adult M1 form instead. This switch from the fetal M2 form to the adult M1 isoform led to reduced lactate production and increased oxygen consumption – a reversal of the Warburg effect.

"We were able to show that only cells which express the M2 form of

pyruvate kinase – and metabolize glucose in the way described by Otto Warburg 80 years ago – had the ability to form tumors in mice," notes Cantley. In addition, the investigators demonstrated that it is the ability of PKM2 to interact with phosphotyrosine that enables this form of pyruvate kinase to promote the unique glucose metabolism seen in cancer cells, thereby allowing these cells to make tumors in vivo.

The findings are consistent with the idea that tumor cells preferentially use glucose for purposes other than making adenosine triphosphate (ATP), the energy currency used by normal cells. "We suspect that this mechanism evolved to ensure that fetal tissues only use glucose for growth when they are activated by appropriate growth factor receptor protein-tyrosine kinases," adds Cantley. "By re-expressing PKM2, cancer cells acquire the ability to use glucose for anabolic processes.

"Because PKM2 is found in all of the cancer cells that we have examined, because it is not found in most normal adult tissues, and because it is critical for tumor formation, this form of pyruvate kinase is a possible target for cancer therapy," he adds.

Source: Beth Israel Deaconess Medical Center