Understanding cancer energetics

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(Medical Xpress) -- It's long been known that cancer cells eat a lot of sugar to stay alive. In fact, where normal, noncancerous cells generate energy from using some sugar and a lot of oxygen, cancerous cells use virtually no oxygen and a lot of sugar. Many genes have been implicated in this process and now, reporting in the May 27 issue of *Cell*, researchers at the Johns Hopkins University School of Medicine have discovered that this so-called Warburg effect is controlled.

"It turns out to be a feed-forward mechanism, where protein A turns on B, which in turn goes back and helps A do more," says Gregg Semenza, M.D., Ph.D., the C. Michael Armstrong Professor of Medicine, director of the vascular program in Hopkins' Institute for Cell Engineering and a member of the McKusick-Nathans Institute of Genetic Medicine. "PKM2 normally functions as an enzyme involved in the metabolism of glucose, but in this case we have demonstrated a novel role in the control of gene expression in cancer cells."

Nearly 20 years ago, Semenza's research team discovered that HIF-1 can turn on a number of genes that that help cells survive when oxygen levels fall too low. In addition to genes that contribute to building new blood vessels, HIF-1 also turns on genes involved in the metabolic process that turns glucose into energy. One of those genes, pyruvate kinase M2 or PKM2, catalyzes the first step of this metabolic process and is present only in cancer cells.

To figure out whether and if HIF-1 and PKM2 interact, the team first engineered cells to have or lack HIF-1. They kept them in high or low

oxygen for 24 hours and found that cells starved of oxygen, but containing HIF-1, had more PKM2 than cells without HIF-1, suggesting that HIF-1 controls the production of PKM2.

The team then asked if HIF-1 and PKM2 physically interact with each other by isolating one of the two proteins from cells; they found that pulling one out also resulted in the other coming along for the ride, showing that the two proteins do in fact bind to each other.

Knowing that the primary function of HIF-1 is to bind DNA and turn on specific genes, Semenza's team next asked whether PKM2 somehow helped HIF-1 do that. They examined genes known to be activated by HIF-1 in low oxygen after the removal of PKM2 and found that without PKM2, less HIF-1 was bound to DNA.

Now armed with evidence that PKM2 helps HIF-1 turn on genes, the team looked at the activity of genes directly involved in the metabolic pathway that burns so much sugar in cancer cells and compared genes known to be activated by HIF-1 with those not affected by HIF-1. Removing PKM2 from cells had no effect on genes not controlled by HIF-1 but reduced the activity of HIF-1-controlled genes.

"These results were really astounding," says Semenza. "In addition to solving the long-standing mystery of the Warburg effect, we also discovered that PKM2 may play a far broader role in promoting cancer progression than has been appreciated before."

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