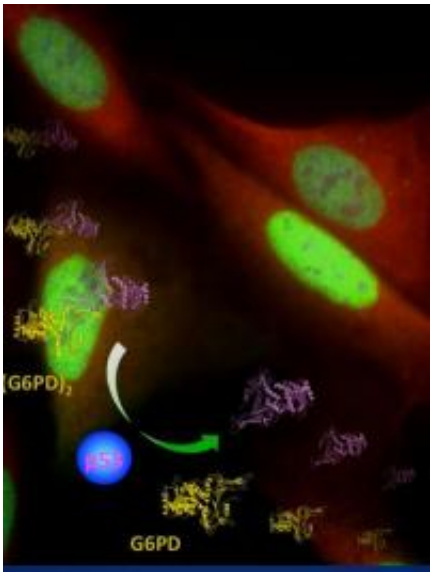
Researchers find new role for cancer protein p53

March 2 2011



The tumor suppressor p53 inhibits glucose-6-phosphate dehydrogenase (G6PD) by catalytically converting the active dimer to an inactive monomer. Through the inhibition of G6PD, p53 suppresses glucose consumption and biosynthesis. However, tumor-associated p53 mutants lose this function, which contributes to the Warburg effect and enhanced biosynthesis in tumor cells. The background shows images of p53 and G6PD localization in the cell. Credit: Lili Guo, PhD, Peng Jiang, PhD, and Wenjing Du, PhD

The gene for the protein p53 is the most frequently mutated in human cancer. It encodes a tumor suppressor, and traditionally researchers have assumed that it acts primarily as a regulator of how genes are made into proteins. Now, researchers at the University of Pennsylvania School of

Medicine show that the protein has at least one other biochemical activity: controlling the metabolism of the sugar glucose, one of body's main sources of fuel. These new insights on a well-studied protein may be used to develop new cancer therapies.

Xiaolu Yang, PhD, associate professor of Cancer Biology at the Abramson Family Cancer Research Institute, along with Mian Wu, PhD, at the University of Science and Technology of China and Nanjing University, report in the current issue of Nature Cell Biology that p53 controls a molecular crossroads in the cell's glucose metabolic pathway.

They found that p53 physically binds to and inhibits an enzyme -- glucose-6-phosphate dehydrogenase (G6PD), which catalyzes the first step of the pathway. If p53 can't do its intended job, cells grow out of control.

Blocking this pathway shunts glucose away from energy storage and towards making genetic building blocks and lipids that contribute to cells' proliferation. p53 normally serves to dampen synthesis of molecules and cell reproduction by forcing the cell to take up less glucose.

In tumors, more than half of which carry mutations in the p53 gene, this routing function is abolished, enabling cells to build biomass and divide with abandon.

The findings provide a biochemical explanation for the Warburg effect, which explains how cancer cells, regardless of type, seem inevitably to boost their glucose consumption, but not in an energy efficient way.

"We found a connection between the most frequently mutated gene in cancer cells and how that mutation contributes to tumor growth," says Yang.

Making a Choice

When it takes up glucose, a cell has three choices: It can store the sugar, turn it into energy, or use it to make nucleic acids and lipids. As Yang explains, researchers have recognized for years that tumor cells consume glucose far faster than non-cancerous cells, but also that they don't seem to use the most energy efficient pathway to burn the fuel. What, then, were they doing with it?

Yang and his team found in both human colon cancer cells and fibroblast cells from mouse embryos that loss of p53 leads to increased glucose consumption though the energy inefficient pathway. This increase was associated with greater lipid synthesis and increased activity of G6PD, the enzyme that p53 is supposed to latch onto to shunt glucose into storage, not wild synthesis.

The team found that p53 binds directly to G6PD to inhibit its activity, apparently by interfering with the ability of G6PD to form a molecular complex. In contrast, p53 mutants lack this binding activity. In effect, demonstrating the binding role of p53 is distinct from its function as a regulator of protein transcription.

Intriguingly, Yang and his team estimate that the level of p53 is only about 3 percent that of G6PD. So in the cell, the p53/G6PD ratio is very low. But p53 has a dramatic effect on the overall activity of G6PD. This suggests that one p53 molecule can inactivate many G6PD molecules. This qualifies p53 as a catalyst. It appears to act almost as an enzyme to convert its much more abundant binding partner into an inactive form via transient rather than stable interactions.

Normally, when one protein binds to and inhibits another, that inhibition lasts only as long as the two proteins are bound together; dissolution of the complex almost invariably activates the released proteins. But in the

case of p53 and G6PD, transient interaction with p53 is sufficient to convert G6PD into an inactive form - a property that is most often associated with enzymes. Says Yang, this enables p53, which at most is present at 10 percent the abundance of G6PD, to regulate its binding partner.

"By converting G6PD from active to inactive form, p53 also has an enzymatic function," says Yang. That kind of mechanism, he says, is "totally new" for p53, and a new paradigm for signal transduction in general.

"This non-stoichiometric effect of p53 on G6PDH is intriguing as it proposes a catalytic role for p53, something that even in the p53 world, which is accustomed to occasional twists, is surprising," wrote Eyal Gottlieb of Cancer Research UK in an accompanying editorial.

Now, says Yang, the question is whether this new role for p53 can be exploited to yield novel anticancer therapies. "Previously," he says, "people were hesitant to target the inefficient pathway because they thought it was stimulatory. Our data suggests the pathway is a good target."

Provided by University of Pennsylvania School of Medicine