Penn researchers find diabetes drug kills some cancer cells

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Researchers at the University of Pennsylvania School of Medicine have found that a commonly prescribed diabetes drug kills tumor cells that lack a key regulatory gene called p53. Results from current studies in mice may result in new therapies for a subset of human cancers that tend to be aggressive and resistant to existing treatments. Additionally, the findings open up a new avenue for targeting cancers whose hallmark is the absence of this regulatory gene.

The Penn team reported their findings last month in *Cancer Research*.

“This is the first time you can show that tumor growth is impaired by a diabetes drug,” says senior author Craig B. Thompson, MD, Director of the Abramson Cancer Center and Chairman and Professor of Cancer Biology and Medicine. “It is specific for tumors that lack p53, which is the most common mutation in human cancer.”

More than half of all human cancers have lost the p53 gene. Yet even in an era of molecularly targeted therapies scientists have had trouble figuring out how to compensate for the absence of a gene. Unlike a genetic mutation that changes the function or activity of a gene, which can be inhibited by a well-tailored drug, loss of a gene leaves nothing for the drug to target.

Thompson and his team, however, have been accumulating evidence over the last several years that p53, best known as a regulator of cell division, controls several metabolic pathways in cells. For potential

cancer therapies, that means a drug that affects pathways controlled by p53 could help control p53-deficient tumors.

Significantly, the regulation of metabolic pathways by p53 is also influenced by metformin, the most widely used diabetes drug. Metformin activates the metabolic enzyme AMPK (AMP activated protein kinase), which exerts changes on cellular metabolism by affecting p53 function. Two observational studies already show that diabetic patients who take metformin have a lower rate of cancer diagnosis and mortality than other diabetics.

Thompson's group hypothesized that metformin may specifically slow the growth of cancers that lack p53. To find out, they injected human colon cancer cells that have normal p53 function into one side of mice and colon cancer cells that lack p53 into the other side. Four days later they started treating the animals with a daily injection of either a saline control solution or with metformin, using a dose comparable to diabetic treatment in humans.

Four weeks later, the p53-deficient tumors in mice treated with metformin were half the size of the p53 deficient tumors in control mice. There was no difference in the size of the p53 normal tumors between the animals treated with metformin or saline. They concluded that metformin slowed the growth of the colon cancer cells that lack a normal p53 function.

The researchers found that metformin instructs cells to switch metabolic pathways. Instead of using the most energy efficient pathway – called oxidative phosphorylation – the cells are forced to use stress-related ones, which are typically used when the cell is short on oxygen, glucose or other nutrient sources. But in the absence of p53, the cells can't make the switch. "Without p53, if we force cells to live on alternative substrates, they can't do it," explains Thompson.

Thompson's team is now working with collaborators to decide how best to translate these novel observations into clinical practice. If preclinical tests continue to look promising, development of metformin as a cancer therapy may move quickly as the drug is already approved by U.S. Food and Drug Administration for use in humans, the researchers surmise.

Source: University of Pennsylvania School of Medicine