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Hope builds for a drug that might shut down a variety of cancers

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The most frequently mutated gene across all types of cancers is a gene called p53. Unfortunately it has been difficult to directly target this gene with drugs. Now a multi-institutional research team, led by Dr. Lewis Cantley and investigators at Weill Cornell Medical College, has identified a family of enzymes they say is crucial for the growth of cancers that have genetic aberrations in p53. Targeting these enzymes with novel agents might prevent the growth of p53 mutant cancers, thereby benefiting a broad spectrum of cancer patients, including those with breast, ovarian, lung, colorectal and brain tumors.

In the Nov. 7 issue of *Cell*, investigators pinpoint two cellular enzymes—Type 2 phosphatidylinositol-5-phosphate 4-kinases α and β (Type 2 PIP kinases)—as essential for cancer growth when cells have lost p53, the powerful tumor-suppressor gene long dubbed the "guardian of the genome." More than half of all cancers lose this gene, allowing these cancers to grow at will.

The researchers discovered that the Type 2 PIP kinases are not critical for the growth of normal cells but become essential for cell growth when p53 is lost due to mutations or deletions. The scientists showed, in animal and lab studies of human cancer cells, that targeting these molecules effectively shuts down the growth of p53 mutant cancers.

Although the studies were conducted in human breast cancer cells, the researchers believe Type 2 PIP kinase inhibitors could block the growth of cancers with a mutated or missing p53 gene.

"The fact that one can delete the Type 2 PIP kinases in normal human cells or in mice with essentially no effect on cell survival suggests that inhibitors of these enzymes should have little toxicity," says Dr. Cantley, the study's senior author and director of the Cancer Center at Weill Cornell Medical College and NewYork-Presbyterian Hospital.

Dr. Cantley is already leading an effort to develop drugs to shut down these kinases. "Well-designed Type 2 PIP kinase inhibitors may turn the tide on p53 mutant cancer," he says.

A Crucial Link

Dr. Cantley is known for his discovery of the PI 3-kinase oncogene, and pioneering work in teasing apart how the gene contributes to cancer. PI 3-kinases (PI3K) have been linked to a wide variety of cellular functions, including cell growth and proliferation, and most cancers activate PI3K by one or more mechanisms. Dr. Cantley's discovery led to promising avenues for the development of personalized cancer therapies.

Activity of PI3K is in some cases linked to Type 2 PIP kinases, so in this study, Dr. Cantley sought to understand the function of these enzymes. Because the researchers knew that a subset of breast cancers over-express these molecules, investigators looked at their role in HER2-positive breast cancers, which typically are more aggressive tumors.

The researchers, including those from Harvard Medical School, Beth Israel Deaconess Medical Center and other institutions, discovered that the enzymes are silent in cells that have healthy p53. One critical role of p53 is to "rescue" cells that are producing excess reactive oxygen species (ROS), which are byproducts of cells that are growing too rapidly. The oxidative stress produced by ROS can damage cell structures, so p53

attempts to reduce ROS in affected cells. "If, however, ROS levels exceed the capacity of p53s to rescue it, then p53 takes on a second function, which is to kill the cell," Dr. Cantley says.

"That is why cancers often disable p53. If p53 is mutated or gone, then the cell keeps on growing at a very high rate," he says. "And then ROS begins to damage genes, making the cancer even more aggressive."

The Type 2 PIP kinases are the backup rescue system to p53. But they only reduce ROS enough to keep the cells from dying. (Too much ROS will also kill a cell.)

What this means is that cancer cells become "absolutely dependent on these kinases to be able to grow," Dr. Cantley says.

Taking Advantage of "Synthetic Lethality"

But there is a big and important hitch in this scenario, he adds. If the Type 2 PIP kinases are inhibited, and if p53 is deactivated, the cancer cell essentially "goes to sleep," he says. "It just stops dividing and growing. This is called synthetic lethality: You can get by without one gene or another, but if you lose both of them nothing can grow."

Shutting down these enzymes, as the researchers did in their experiments, puts cancer cells to sleep but has no effect on healthy cells. "A normal cell doesn't need Type 2 PIP kinases at all, so inhibitors of these enzymes should not be toxic to humans," Dr. Cantley says.

Because it is not possible to replace p53 proteins or the gene in cells that have lost it (many attempts have been made), deactivating Type 2 PIP kinases is the next-best thing, he adds. "This would likely be a very powerful advance in the treatment of many cancers."

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