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Natural Tumor Suppressor In Body Discovered By Medical Researchers

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A natural tumor suppressor that could potentially be turned on in certain cancer cells to prevent the formation of tumors has been discovered by researchers at the UCSD School of Medicine.

Located on chromosome 18 and called PH domain Leucine-rich repeat Protein Phosphatase (PHLPP, pronounced "flip"), the tumor suppressor is described in the April 1, 2005 issue of the journal *Molecular Cell*. The scientists demonstrated that PHLPP deletes a phosphate molecule, causing termination of cell-growth signaling by a protein called Akt that controls the balance between cell growth leading to cancer and cell death that prevents tumor formation.

"A drug that turns on PHLPP, so that it suppresses cell growth caused by Akt, could be a potential cancer therapy," said the study's senior author, Alexandra C. Newton, Ph.D., UCSD professor of pharmacology. "Currently there are no compounds identified to directly stop Akt from causing cancer growth, once Akt signaling has been initiated."

Scientists have known that Akt is critical in regulating cell growth and death, and that it is linked to some of the most common human cancers. Although one group of scientists discovered a molecule called PTEN *****, which prevents activation of Akt, no one to date had determined how to directly turn off Akt once it has been activated.

Since the Akt molecule is locked in the "on" position when it has phosphate on it, the UCSD team reasoned that there must be another molecule that will strip off the phosphate and lock Akt in the "off" position. The scientists conducted a database search of the human genome for a phosphatase, which is an enzyme that acts as a catalyst in regulating cellular processes by removing phosphate molecules. Based on the chemical components of Akt, they specifically looked for a phosphatase linked to the PH domain, a protein module found in a wide variety of chemical signaling proteins in organisms ranging from yeast to humans.

Once they found PHLPP, which they discovered was expressed throughout the body, the scientists used biochemical and cellular studies in human and other mammalian tissue to determine that PHLPP levels are markedly reduced in several colon cancer and gliobastoma human cell lines that had elevated Akt phosphorylation. Reintroduction of PHLPP into the cell lines caused a dramatic suppression of tumor growth. With additional laboratory tests, the team found that PHLPP stops tumor growth by deleting a specific phosphate molecule at a position called Ser473 on Akt.

The scientists noted that PHLPP's role as a tumor suppressor would apply to all cancers where Akt is elevated, "which is a large number of cancers," Newton said.

In addition to Newton, authors of the paper were first author Tianyan Gao, Ph.D., a research scientist in the UCSD Department of Pharmacology, and Frank Furnari, Ph.D., assistant professor, Ludwig Institute for Cancer Research, UCSD.

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***** *The first group to demonstrate the biological function of PTEN in 1998 at the University of Michigan was the lab of Jack Dixon, Ph.D., who is currently UCSD dean for scientific affairs and professor of pharmacology, cellular & molecular medicine, and chemistry & biochemistry. His team showed that PTEN deletes a phosphate molecule from a lipid called phosphatidylinositol 3,4,5-triphosphate (PIP3), which activates Akt.*

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