Gene variant may provide novel therapy for several cancer types

June 7 2013

(Medical Xpress)—A novel gene variant found in human and animal tissue may be a promising treatment for cancer, including breast and brain cancer, according to scientists from the Icahn School of Medicine at Mount Sinai. The variant, called PTEN-long, may contribute to a cell's healthy function and also suppress tumor cell development. This landmark study is published in the June 6, 2013 issue of the journal *Science*.

Ramon Parsons, MD, PhD, Professor and Chair of Oncological Sciences led the team that discovered a mutation in the tumor suppressor gene PTEN, which has subsequently been recognized as the second most common mutation in cancer, especially in breast, prostate, and brain cancers. PTEN encodes a 403 amino acid lipid phosphatase protein that is critical to cellular growth, proliferation, and survival. Genetic inactivation of PTEN causes tumor development.

In the current study, Dr. Parsons and his team analyzed human cells and discovered a PTEN variant that has an additional protein sequence and is 43 percent longer than normal PTEN. They called this new variant PTEN-Long. Like PTEN, the long form has the same enzymatic activity, but unlike PTEN, it is secreted by the cell and can enter other cells, indicating that the added protein sequence acts as a delivery system for the tumor suppressor gene.

"This study culminates more than a decade of research that began soon after we learned the therapeutic potential of PTEN and the PI3K

pathway," said Dr. Parsons. "We are excited about the potential of PTEN-Long as a therapy for multiple cancer types."

Using human breast and brain tumor cells that lacked PTEN and PTEN-Long, the research team introduced and overexpressed PTEN-Long and PTEN into the cells. They found that, similar to PTEN, PTEN-Long decreased the signaling activity on the PI3K pathway, thus reducing cellular proliferation. They also found that PTEN-Long was reduced in breast tumor tissue compared to healthy breast tissue.

To test the therapeutic potential of PTEN-Long, Dr. Parsons and his team injected mice with tumor cells, then administered PTEN-Long or a control preparation to the mice. For one of their tumor models, after five days of treatment, the tumors disappeared completely. The authors conclude that PTEN-Long alters signaling on the PI3K pathway to inhibit tumor growth and that its ability to enter other cells is critical to this process. As insulin operates on the PI3K pathway as well, the research team also noticed a brief increase in glucose concentration in the PTEN-Long treated mice.

"These findings indicate that PTEN-Long may contribute to cell homeostasis and suppression of cancer," said Dr. Parsons. "This gene variant has significant potential as a protein-based therapy to treat cancer, and may have implications in diseases such as diabetes."

Next, Dr. Parsons plans to study the normal functions of PTEN-Long, how tumors become resistant to it, what happens when it is missing, and how it can be used as a tool for therapy.

More information: "A Secreted PTEN Phosphatase that Enters Cells to Alter Signaling and Survival" www.sciencemag.org/content/ear … 6/05/science.1234907

Provided by The Mount Sinai Hospital