Targeting breast cancer stem cells in mice

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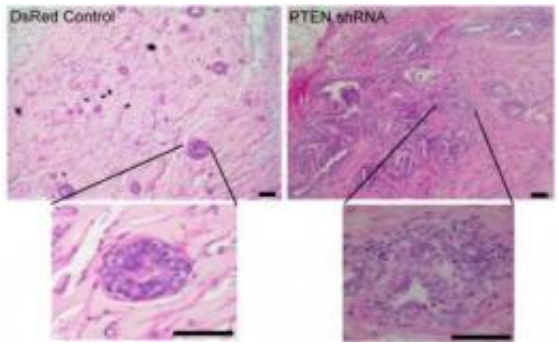

These are tumors generated from normal breast cells and from breast cells in which PTEN has been deleted. Credit: University of Michigan Health System

Cancer develops when cells known as cancer stem cells begin to divide in an uncontrolled manner. Researchers from the University of Michigan Comprehensive Cancer Center have identified roles for the gene PTEN, which is already well known for its ability to suppress tumor growth, and for several pathways linked to PTEN in the growth of cells that give rise to breast cancer. The work, published in this week's issue of the open-access journal *PLoS Biology*, also reports that a drug that interferes with the activity of one of these pathways leads to a 90 percent decrease in the number of cells able to form tumors in mice.

PTEN is the most frequently inactivated tumor suppressor gene in several cancers, including breast cancer, where it is inactivated in about 40 percent of patients. PTEN inactivation is associated with poor patient outcomes, aggressive tumor growth, and resistance to chemotherapy and

current targeted therapies.

Researchers first deleted PTEN from tumor cells grown in cell culture and from tumors in mice, and found an increase in the number cells able to form new tumors, which suggests that PTEN influences the cancer stem cell population. They also looked at pathways associated with PTEN and reported that the activity of the PI3-K/Akt pathway also regulates the size of the tumor-forming cell population by activating the Wnt pathway, another pathway previously implicated in multiple cancer types.

"Although there has been considerable progress in identifying cancer stem cells in a variety of tumor types, the pathways that drive the transformation of these cells are not well understood," says lead study author Hasan Korkaya, D.V.M., Ph.D., a research investigator in internal medicine at the University of Michigan Medical School.

Stem cells in breast cancer represent fewer than 5 percent of the cells in a tumor but are believed to be responsible for fueling a tumor's growth and spread. Researchers believe that the ultimate cure of cancer will require killing these cancer stem cells.

In the current study, researchers looked at a drug called perifosine, which inhibits the Akt pathway. Tumors in mice were treated with perifosine or docetaxel, a standard chemotherapy drug. The docetaxel alone treatment showed no effect on the number of tumor-forming cells, but the addition of perifosine reduced the tumor-forming cell population by up to 90 percent. Additionally, cells treated with perifosine - either with or without docetaxel - were less likely to form tumors when reintroduced into mice when compared to cells treated with docetaxel alone. These results suggest that perifosine specifically targets the breast cancer stem cell population.

"This is most exciting since perifosine and other drugs that target this pathway are currently in clinical development. If cancer stem cells do contribute to tumor relapse, then adding drugs that target these cells may help to make our current therapies more effective," says study senior author Max S. Wicha, M.D., Distinguished Professor of Oncology and director of the University of Michigan Comprehensive Cancer Center.

More information: Korkaya H, Paulson A, Charafe-Jauffret E, Ginestier C, Brown M, et al. (2009) Regulation of Mammary Stem/Progenitor Cells by PTEN/Akt/b-Catenin Signaling. PLoS Biol 7(6): e1000121. doi:10.1371/journal.pbio.1000121; biology.plosjournals.org/perls … journal.pbio.1000121

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