# Breast tissue tumor suppressor PTEN: A potential Achilles heel for breast cancer cells

August 1 2018

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In an article published July 17, 2018 by *Nature Communications*, a highly collaborative team of researchers at the Medical University of South Carolina (MUSC) and Ohio State University report that normal breast cells can prevent successful radiation treatment of breast cancer due to dysregulation between tumor suppressors and oncogenes. Tumor suppressors act like brakes that stop cells from undergoing uncontrolled growth, while oncogenes are the gas pedal. The tumor suppressor gene of interest in this study is PTEN, which is often mutated in human cancer cells.

An initial surprising observation that the stroma, or supportive connective tissue, in some women without cancer had abnormally low PTEN fueled this study.

"The results suggest that PTEN loss in normal cells may be a biomarker for identifying breast cancer patients who would benefit from adding specific inhibitors in combination with the standard radiation therapy," says Michael C. Ostrowski, Ph.D., a professor in the Department of Biochemistry and Molecular Biology at MUSC, a member of the MUSC Hollings Cancer Center, and senior author on the article.

The cancer research field did not previously know that early PTEN-focused events in the breast stroma are capable of triggering malignant development in the breast.

In human breast cancer, expression of the tumor suppressor PTEN and the cell growth promoter active protein kinase B (AKT) are inversely correlated. In other words, when PTEN is reduced, AKT is significantly increased. However, researchers knew neither why this occurs nor how it could be useful clinically.

To address this specific question, the team developed a mouse model to look at what occurs when PTEN is not expressed specifically in the

breast stroma. This special model revealed that the absence of PTEN tumor suppressor in the breast stroma leads to larger mammary (breast) tumors.

Digging deeper, the MUSC researchers wanted to understand how stromal cells without PTEN could lead to such rapid growth of cancer cells. Surprisingly, connective stromal cells that do not have PTEN release more of soluble factors called EGF ligands. The EGF ligands promote abnormal growth in neighboring epithelial cells, which line the surfaces of internal organs including in breast tissue.

Radiation therapy is a mainstream treatment for breast cancers as radiation causes cell death in the targeted cells. When the PTEN level is low in the breast cancer connective tissue cells, the tumor cells have a high degree of genetic instability. Genetically unstable cells do not follow the normal growth checkpoints, meaning that the cells ignore cell death signals. The finding of the connection between low PTEN levels and reduced response to radiation therapy.

"This allows for a multi-pronged attack on the tumor, by predicting who will respond the best to radiation therapy in combination with chemotherapy and other targeted treatments" says Ostrowski.

The team of researchers was able to progress quickly from initial observation to preclinical findings because they could draw on the skill sets of oncologists, biostatisticians, pathologists, and researchers available via the MUSC Hollings Cancer Center Translational Core. Development of this core will enable vital cancer research, such as that reported in this work, to move from pre-clinical studies to clinical trial.

The research is moving quickly. Another publication looking at the PTEN mechanism even more in depth will soon be published. A small clinical trial to investigate the correlation between reduction in stromal

PTEN and radiation resistance would be game-changing to the field. One option is to use the PTEN data to divide the patients into groups, leading to more personalized medicine. Using this tool, physicians could decide which breast cancer patients would benefit the most from radiation and spare the patients who are not likely to respond from the costs and side effects of the treatment.

By discovering that normal connective tissue cells might be predisposing epithelial cells to cancerous changes, the research team may have pinpointed a vulnerability in cancer cells.

"We may have found an Achilles heel for cancer cells, because the stromal cells and PTEN pathways can be targeted," says Ostrowski.

**More information:** Gina M. Sizemore et al, Stromal PTEN determines mammary epithelial response to radiotherapy, *Nature Communications* (2018). DOI: 10.1038/s41467-018-05266-6

Provided by Medical University of South Carolina