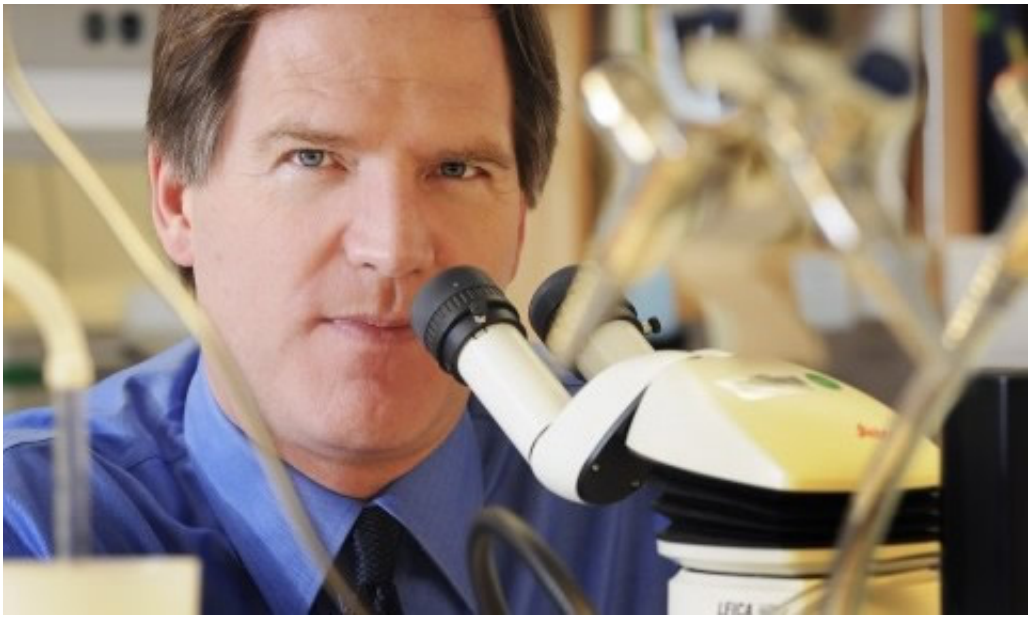
# New driver of breast cancer discovered

November 7 2013



This is Dr. Philip Shaul, Professor and Vice Chair for Research in Pediatrics and a member of the Harold C. Simmons Comprehensive Cancer Center Credit: UT Southwestern Medical Center

A team of researchers at UT Southwestern has found that as cholesterol is metabolized, a potent stimulant of breast cancer is created – one that fuels estrogen-receptor positive breast cancers, and that may also defeat a common treatment strategy for those cancers.

The multidisciplinary team discovered that a cholesterol metabolite called 27-hydroxycholesterol, or 27HC, promotes tumor growth in estrogen-receptor positive breast cancers, which are the most common

type of breast cancer. Estrogen-receptor positive breast cancer was previously believed to be stimulated primarily by the female sex hormone estrogen and it is commonly treated using endocrine-based medications that starve tumors of estrogen.

The discovery of 27HC as another driver of breast cancer may explain why endocrine-based therapy is often unsuccessful, providing a new target for therapy, the researchers say.

"This information can be used to develop new therapies that inhibit 27HC action or production, or increase its metabolism, in effect cutting the cancer off from a key growth stimulator," said senior author Dr. Philip Shaul, Professor and Vice Chair for Research in Pediatrics and a member of the Harold C. Simmons Comprehensive Cancer Center.

Implications of the research that appears in *Cell Reports* today are significant.

One million new cases of breast cancer are diagnosed each year, and about two-thirds of those are hormone receptor-positive, meaning they contain receptors for the hormones estrogen and/or progesterone, according to the American Cancer Society. Estrogen receptor-positive breast cancer is particularly prevalent following menopause.

Resistance to commonly used endocrine-based therapies occurs frequently, which led the researchers to recognize that important estrogen-independent processes must be driving the cancers' growth.

Dr. Shaul and his team first determined that 27HC stimulates the growth of breast cancer cells by hijacking growth-promoting mechanisms triggered by the estrogen receptor. The finding was first made in cultured cells, and then in mice. That prompted subsequent studies in postmenopausal women with estrogen receptor-positive breast cancer,

who were compared to cancer-free control subjects.

Using specialized techniques developed by Dr. Jeffrey McDonald, Associate Professor of Molecular Genetics, the research team quantified levels of 27HC in tissue samples from UT Southwestern's Center for Breast Care. They found that in the breast cancer patients, 27HC content in normal breast tissue was markedly increased compared to that in cancer-free controls, and that tumor 27HC content was further elevated.

To explain why 27HC is so abundant in tumors, the team then turned to prior research in cholesterol metabolism by Dr. David Russell, Vice Provost and Dean of Basic Research at UT Southwestern, who previously discovered an enzyme called CYP7B1, which metabolizes 27HC. Querying a large database of tumor genes, they found that CYP7B1 is diminished in breast tumors compared with normal breast tissue. Further analysis revealed that there is a more than 7-fold poorer overall survival in women whose tumors display low CYP7B1, compared with women with high tumor CYP7B1.

Prior studies have shown that estrogen upregulates the 27HC metabolizing enzyme CYP7B1. Therefore, the commonly-used therapies that block estrogen synthesis or action may actually increase the abundance of this newly discovered promoter of breast cancer, the researchers also concluded.

"Measurements of tumor CYP7B1 or 27HC content could provide a potentially critical new means to personalize endocrine-based therapy for women with breast cancer," said Dr. Shaul. "Ultimately, the translation of these new findings to the clinical setting may also involve determinations of tumor CYP7B1 or 27HC abundance to serve as prognostic indicators."

Provided by UT Southwestern Medical Center