'New' estrogen receptor found to be key player in tamoxifen resistance

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Researchers at Georgetown University Medical Center have discovered a novel way in which breast cancer cells become resistant to tamoxifen, the world's largest-selling breast cancer prevention and treatment drug. They say the findings could provide a way to identify tamoxifen users who are no longer benefiting from the drug, allowing doctors to try another therapy option sooner.

In the November 1 issue of the journal *Cancer Research*, the researchers show that breast cancer cells that are resistant to tamoxifen display few of the "alpha" estrogen receptors that the drug is designed to bind on to and inhibit, but many more "gamma" estrogen-related receptors, which tamoxifen seems to activate. These two receptors are not closely related – they are more like distant cousins than siblings, researchers say, adding that understanding how these gamma estrogen-related receptors work may— eventually— help in designing new, more effective drugs targeting these receptors.

In fact, they track how, as resistance develops over time, breast cancer cells gradually lose the alpha receptors while gaining the estrogen-related receptor gamma subtype.

The study offers two new insights, according to lead author Rebecca Riggins, Ph.D., a research assistant professor of oncology at GUMC's Lombardi Comprehensive Cancer Center.

One is a clearer understanding of the importance of the gamma estrogen-

related receptor in breast cancer. "Until now, this receptor has not been viewed to be of much importance in any type of breast cancer," Riggins says. "All that was known is that there were more of these receptors in breast cancer than in normal breast tissue, we hadn't gone much further than that."

A second important insight is that the discovery could help explain why invasive lobular carcinoma – the sub-type of breast cancer in which these findings were made – may not respond as well to tamoxifen as perhaps other subtypes do, she says.

"It is unclear whether tamoxifen is very effective in this cancer, and has been a point of debate among clinicians," Riggins says. "This study is a good first step toward clarifying the role that tamoxifen resistance apparently plays in treatment of invasive lobular cancer."

Invasive lobular carcinoma, which accounts for 15 percent of newly diagnosed invasive breast cancers diagnosed each year, appear under the microscope as long, very thin tumors – actually a single stream of cancer cells that line up in a row. That makes them much harder to diagnose than the more common cancer type, invasive ductal carcinoma, in which tumors form more discrete lumps.

But what the researchers found in invasive lobular carcinomas – the specific cancer they studied - may also be true of tamoxifen resistance in other cancer types," she said "No one has looked for gamma estrogen-related receptors in tamoxifen resistance in invasive ductal carcinoma."

In addition to its use as a cancer preventive, tamoxifen is approved to treat both early and advanced breast cancer that is estrogen-receptor positive. (Estrogen-receptor positive cancer means that estrogen is the primary fuel that promotes cancer development and growth.) Tamoxifen binds to the estrogen receptors (alpha) that stud tumors and other breast

tissue, not allowing estrogen to latch on and turn on a program of growth inside the cells. But it is estimated that 30 to 50 percent of breast cancer patients eventually become resistant to tamoxifen.

"The magnitude of this health issue is huge. More than 178,000 women will be diagnosed this year with invasive breast cancer, and 70 percent of them will have estrogen receptor-positive tumors," Riggins says. "It is clear that we need to understand why this resistance occurs."

"This is a very nice story of tamoxifen resistance in a somewhat under-investigated group of breast cancers," says the study's senior investigator, Robert Clarke, Ph.D., professor of oncology, physiology and biophysics and director of GUMC's Biomedical Graduate Research Organization. "It identifies a new player and shows some of its downstream signaling and how this affects responsiveness to tamoxifen in these breast cancers."

The findings came about after the research team developed the first cell culture model of tamoxifen-resistant, invasive lobular carcinoma. To do this, they took cells of this subtype and exposed them to low amounts of tamoxifen and allowed the cells to adapt to the agent. The researchers slowly increased the tamoxifen to match the dosage that a woman taking the drug would be exposed, and during this 10-month process, watched the cells develop resistance to the drug.

"Initially the cells were sensitive to tamoxifen, but as the dose increased, the sensitive cells died off, and the tumor repopulated itself with resistant cells," Riggins says.

During the experiment, the investigators measured gene expression, and were able to track higher and higher expression of the gamma estrogen-related receptor subtype.

"Clearly, the gamma estrogen-related receptors, which have a role in cell metabolism, are stimulating cancer growth, and it is possible that tamoxifen is activating this receptor, " Riggins says.

If alpha estrogen receptors can be used as a drug target, then perhaps the gamma estrogen-related receptor subtype can as well, she adds.

Source: Georgetown University