Resistance to anti-estrogen therapy in breast cancer due to natural cell response

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Most breast cancers are fueled by estrogen, and anti-estrogenic agents often work for a time to control the cancers. But many of these cancers become resistant to the drugs for reasons that are not understood, leaving patients with limited treatment options.

Now researchers at the Georgetown Lombardi Comprehensive Cancer Center, a part of Georgetown University Medical Center (GUMC), say that this resistance appears to be due to a natural stress response in cells, and that the biochemical molecules involved in this response might prove to be a new drug target. They reported their findings at the American Association for Cancer Research (AACR) 102nd Annual Meeting 2011.

They found that breast cancer cells protect themselves against two anti-estrogen drugs (Tamoxifen and Faslodex) by hijacking and switching on a biological process inside the cells that is normally used when proteins are produced that don't have the right shape.

It had not been known, before this study, that this program - the "unfolded protein response" or UPR - could be triggered when breast cancer cells are "attacked" by anti-estrogen drugs, says the study's lead investigator, Ayesha Shajahan, Ph.D., an oncology researcher instructor and researcher in the laboratory of Robert Clarke, Ph.D., D.Sc., Dean for Research at GUMC. Clarke will be presenting the results at AACR.

If a UPR is activated, a cell can do one of two things, Shajahan says: it

can turn on a pro-survival pathway or it can turn on a process that ultimately destroys the cell. The cells they studied all chose to "man the forts" to survive. They hunker down and wait out the attack, a tactic that allows the cell to resist anti-cancer treatment.

"We found that anti-estrogen resistant cancer cells are much more likely to turn on the pro-survival pathway than are cells that are sensitive to estrogen," says Shajahan.

They also found that anti-estrogen resistant breast cancer cells over-express the X-Box Binding Protein (XBP1), which turns on UPR signaling, and that specific resistance to Faslodex (Fulvestrant) occurs because of increased levels of over-expression of a XBP1 subtype, XBP1(s).

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