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Single protein promotes resistance to widely used anti-estrogen drugs

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Researchers at Georgetown Lombardi Comprehensive Cancer Center have uncovered a single molecule they say is a major determinant of resistance to anti-estrogen therapy used to treat or prevent breast cancer in high-risk women.

In the July 1 issue of *Cancer Research*, the scientists say glucose-regulated protein 78 (GRP78), activated as breast cells undergo stress induced by the agents tamoxifen and fulvestrant, turns off apoptosis, a cell death response, and turns on autophagy. In autophagy, the cell "eats" and digests components within the cell body that have been harmed by the drugs, thus providing a blast of nutrients needed to maintain life.

The finding suggests that a novel agent that inhibits GRP78 might provide a solution for the tens of thousands of women who develop resistance to anti-estrogen drugs. While more than 70 percent of breast cancers express estrogen receptors that fuel growth of cancer, about one-third of these cases fail to be cured by therapies that target this receptor.

"Since GRP78 plays such an important role in drug resistance, it would be of great benefit to develop agents that target this protein," says the study's lead author, Katherine Cook, Ph.D., a postdoctoral investigator in the lab of Robert Clarke, Ph.D., D.Sc., professor of oncology and Dean for Research at Georgetown University Medical Center. Clarke is the study's senior author.

She adds that several GRP78 inhibitors have already been developed and

are already being tested, but not yet at the level of human clinical trials.

The study is not only the first to show that GRP78 is a regulator of resistance to tamoxifen and fulvestrant, it is also the first to reveal the mechanism by which GRP78 directly controls autophagy, says Clarke.

"Why estrogen-receptor positive breast tumors fail to respond, or respond initially and progress upon acquiring resistance to these agents, has been largely unknown, " he says. "The novel signaling that we have uncovered could have high translational impact and bring a new and important perspective to the molecular crosstalk between cell stress, apoptosis, and autophagy."

This research is a continuation of a string of studies on anti-estrogen resistance by Clarke, Cook, and their collaborators at Georgetown.

A paper published March 15 in Cancer Research, for example, described how a program known as the "unfolded protein response" or UPR, is activated in breast cells treated with the therapies once these cells sense stress. This response is activated when there is an accumulation of unfolded or misfolded proteins within the cell.

"Since cancers often grow rapidly, tumors may lack enough energy to properly fold proteins into the correct orientation. These misfolded proteins accumulate in the cell and trigger UPR," says Cook. "In normal cells, UPR is protective and if the stimuli lasts for an extended period of time UPR becomes pro-death. But we have found cancers use the UPR to promote survival."

In this study, the scientists zeroed in on GRP78 as the master regulator of UPR, thus promoting anti-estrogen resistance. It does this by preventing stressed cells to initiate programmed cell death, and by stimulating autophagy, which clears cells of the misfolded proteins while

providing beneficial nutrition to the cell.

When the scientists inhibited GRP78 in anti-estrogen resistant cells, they promoted cell death and inhibited autophagy, resulting in increased numbers of dead cells.

They also found that GRP78 does not play a role in breast cancers that never responded to anti-estrogen therapy, indicating that initial resistance and acquired resistance represent separate biological phenomenon. "This observation is consistent with the emerging concept that acquired resistance may be an adaptive response," Cook says.

She also notes that elevated GRP78 has been found in different cancer types, in addition to breast cancer, and in resistance to several different chemotherapy treatments.

"The basic principle we establish of using GRP78 to integrate the cellular functions of apoptosis and autophagy raises the provocative question that this signaling may be widely applicable and represent a major stress response," Cook says.

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