Investigational agent reduces tumor resistance to breast cancer therapy

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Researchers at Georgetown Lombardi Comprehensive Cancer Center have found a way to cleverly override signals that tell breast cancer cells to keep surviving in the face of anticancer treatment. The investigational agent they used renews the sensitivity of these breast cancer cells to treatment by fulvestrant (Faslodex®) which had stopped working.

They add that this method will likely work equally well with tamoxifen, the world's most commonly used breast cancer drug. Both fulvestrant and tamoxifen are used in women with estrogen-receptor-positive metastatic breast cancer and both exhibit substantial issues with eventual tumor resistance. Fulvestrant is typically used when women stop responding to tamoxifen.

In the January 6, 2010 issue of PLoS ONE, the Lombardi researchers report that the agent (YC137) they tested, a broadly active drug that inhibits multiple members of the Bcl2 family of proteins, restored the ability of breast cancer cells to self destruct in a number of different ways.

This is a new finding, given that it was believed that the Bcl2 protein family is involved in just apoptosis, one method of cell death that programs self destruction, says the study's lead investigator, Robert Clarke, PhD, DSc, a professor of oncology and physiology & biophysics at Lombardi, a part of Georgetown University Medical Center (GUMC). Clarke is also the interim director of GUMC's Biomedical Graduate Research Organization.

"There are other ways that a cell dies, and our research shows that Bcl2 is involved in these processes as well. That means it is possible to hit a number of these Bcl2 pathways that breast cancer cells use to evade the killing effects of a drug," Clarke says. "We need to block all of the alternative routes cancer uses to survive."

The routes include pushing a cell into autophagy, in which a damaged cell is destroyed and digested, and necrosis, in which the cell falls apart when apoptosis and autophagy fail. Until now, it had not been known that the protein family was involved in regulating autophagy and necrosis in response to anticancer drugs like fulvestrant, Clarke says.

In this study, laboratory experiments using the investigational agent restored the ability of fulvestrant to bind to and destroy estrogen receptors in several different lines of tumor cells. Normally this destruction would signal the cell to die but Bcl2 proteins, which are highly expressed in many different kinds of cancer, can save the cell.

The findings explain why treatments that target just one member of the Bcl2 family have not done as well as anticipated in clinical trials, and it suggests that using an agent that can hit multiple Bcl2 proteins will be more effective, says Clarke.

That could mean a Bcl2 blocking drug could be administered along with other traditional cancer therapies to keep the tumor cells from becoming resistant due to activation of a Bcl2 survival mechanism.

Several Bcl2 blocking drugs are now in clinical trials, Clarke adds. In addition, other strategies to overcoming tumor resistance are being explored at Lombardi including using agents (sorafenib) that destroy mechanisms the cell creates to survive the onslaught of drugs. Also, researchers are looking at the use of estrogen to kill breast tumor cells, which represents a paradigm shift in the way we think estrogen receptor-

positive breast cancer behaves. If successful, these agents could possibly be tested in patients who haven taken fulvestrant or tamoxifen and don't respond as they should, or who have become resistant to either or both drugs, he says.

But while this study has added to knowledge of how cells can be forced to self-destruct, Clarke says there may be other proteins that cancer uses to protect against cell death. "We are using a systems biology approach that looks at all genes and proteins involved in breast cancer to identify what else is playing a role in keeping these cells alive," he says. "We want to know what all the targets are that we need to hit to make sure these cells are destroyed, and these might provide other exciting opportunities for drug discovery."

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