Researchers discover new way to 'rescue' treatment sensitivity of breast cancer cells

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A study by researchers from the Georgetown Lombardi Comprehensive Cancer Center at Georgetown University Medical Center (GUMC) identifies a potential new combination therapy to "rescue" treatment sensitivity to fulvestrant in estrogen receptor positive breast cancers. The findings were published on May 15, 2010 as the cover story of *Molecular Cancer Therapeutics*.

Fulvestrant is a common second-line therapy for women whose cancer progresses following anti-estrogen therapy. In this paper, Lombardi researchers identify a cytokine, a small protein called IFNγ, which appears to increase or even rescue sensitivity to fulvestrant.

Led by Robert Clarke, PhD, DSc, professor of oncology and physiology & biophysics at Lombardi, the research team identified a key downstream regulator of sensitivity to fulvestrant - the protein IRF1. When cells were treated with both fulvestrant and IFNγ, Clarke and colleagues saw an increase in expression of IRF1, which resulted in increased apoptosis - or programmed cell death - of the cancer cells.

The American Cancer Society estimates that in 2009, 192,000 women were diagnosed with invasive breast cancer, and approximately 70 percent of these cases were considered to be estrogen receptor-positive (ER+), meaning that estrogen and its receptor drive the disease. While a number of anti-estrogen therapies are able to successfully treat these cancers, resistance may develop, often leading to disease progression.

"This finding is significant because we and others in the field have been searching for a long time for clinically relevant ways to make anti-estrogen therapies more effective for women with ER+ breast cancer," says Rebecca Riggins, PhD, assistant professor of oncology at Lombardi and co-author of the paper.

Most of the genes and proteins regulated by the estrogen receptor are unknown, and the molecular effects of therapies such as anti-hormonal drugs are also largely unidentified, says Clarke, who also serves as interim director of GUMC's Biomedical Graduate Research Organization.

However, in this paper, the research team has identified that the induction of IRF1 expression involves regulation of well-known cell fate proteins including NF- κB and the BCL-2 family of proteins, leading to apoptotic pathways. Ultimately, Clarke and colleagues suggest that a combination of anti-estrogens and compounds that up-regulate IRF1 expression - like IFNγ - may be useful for the treatment of anti-estrogen resistant ER+ breast cancers.

Clarke was also recently awarded a major program grant by the National Cancer Institute to lead a Center for Cancer Systems Biology addressing estrogen receptor signaling in breast cancer resistance.

Provided by Georgetown University Medical Center