In vitro study identifies potential combination therapy for breast cancer

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A study conducted at Boston University School of Medicine (BUSM) demonstrates an effective combination therapy for breast cancer cells in vitro. The findings, published in the July 2012 issue of *Anticancer Research*, raise the possibility of using this type of combination therapy for different forms of breast cancer, including those that develop resistance to chemotherapy and other treatments.

The study was led by researchers at the Boston University Cancer Center. Sibaji Sarkar, PhD, adjunct instructor of medicine at BUSM, is the study's corresponding author.

According to the Centers for Disease Control and Prevention, breast cancer is the most common cancer among women in the United States aside from non-melanoma skin cancer. Breast cancer also is one of the leading causes of cancer death among women of all races and Hispanic origin populations.

Triple negative breast cancer, which accounts for approximately 14 to 20 percent of all breast cancer cases, is a type of the disease that occurs when the cancer cells lack hormone receptors, including the receptor called HER-2, and typically will not respond to hormone and herceptin-based therapies. Triple negative breast cancer occurs more often in African-American women and is considered to be a more aggressive form of the disease with higher rates of recurrence and mortality than other forms of breast cancer.

"Cancer is like a car without brakes. Cell growth speeds up and it doesn't stop," said Sarkar. "When expressed, tumor suppressor genes, which work in a protective way to limit tumor growth, function as the brakes. They are not expressed in most cancers, causing the cancer to grow and potentially metastasize."

A major focus in the area of anti-cancer drug development is to find a way to re-express tumor suppressor genes so that they can help inhibit cancer cell growth. Some tumor suppressor genes are imprinted, meaning that from the two genes inherited from the mother and father, only one of the genes is functional. In cancer, both imprinted tumor suppressor genes may become non-functional and unable to stop tumor growth.

The researchers tested, in vitro, a combination therapy of an epigenetic drug with a protease inhibitor on breast cancer cell lines that are hormone responsive and breast cancer lines, like triple negative, that are not hormone responsive. They utilized histone deacetylases inhibitors (HDACi) and calpeptin, which inhibits calpain, a protein involved in the regulation of signaling proteins. Calpain inhibition is being studied as a potential treatment model for blood clots and other neurological diseases.

In this study, they found that the combination therapy both inhibited cell growth and increased cell death in both cancer cell lines by inducing cell cycle arrest and cell death. However, the mechanism of how the combination therapy stops the cells from growing was different. Cells in the hormone responsive line stopped the cell cycle in an earlier phase compared to the non-hormone responsive cells. In the triple negative breast cancer cell line, the inhibitors allowed an imprinted tumor suppressing gene, ARHI, to re-express, which helped stop the growth of the cancer cells and led to cancer cell death.

"The study data demonstrates that HDACi's bring back the brakes of the car, halting cell growth and promoting cell death," added Sarkar, who also is a faculty member at the Genome Science Institute at Boston University. "These results provide a model to investigate the re-expression of tumor suppressor genes, including imprinted genes, in many forms of breast cancer."

This study needs further investigation but raises the possibility of using this type of combination therapy for diverse types of breast cancers including those that are hormone refractory and develop drug resistance to conventional chemotherapy.

Provided by Boston University Medical Center