Scientists identify protein involved in restoring effectiveness of common treatment for breast cancer

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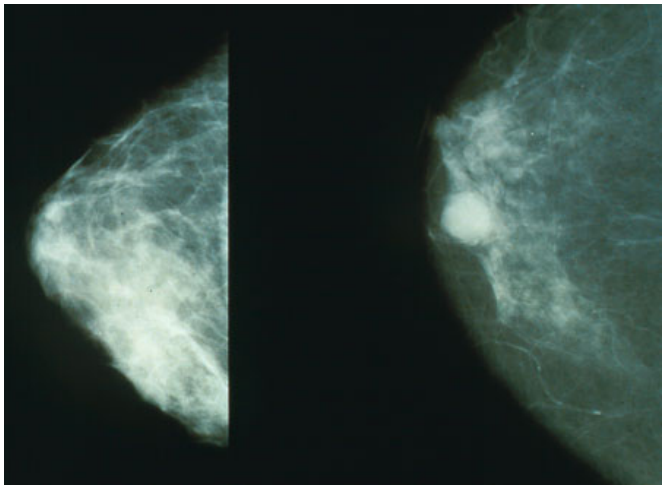

Mammograms showing a normal breast (left) and a breast with cancer (right). Credit: Public Domain

Breast cancer is the most frequently diagnosed cancer among women, with estrogen-receptor-positive (ER+) being the most common type. Drugs used to treat this cancer, such as tamoxifen and Faslodex, block the hormone estrogen receptor that ER+ cancer cells need to grow. One problem with these treatments is that many tumors initially responsive to the drugs develop resistance, making the medicines less effective.

However, scientists at Wake Forest Baptist Medical Center have succeeded in enhancing and restoring sensitivity to an estrogen-blocking drug in ER+ tumors in an animal model. The research findings are published in the Oct. 1 issue of the journal *Cancer Research*.

Previous research showed that glucose-regulated protein 78 (GRP78) is elevated in breast cancer tumors and that targeting it could enhance and restore sensitivity in estrogen targeted therapy-resistant cells in vitro. In this study, the researchers sought to determine if they could target GRP78 in breast cancer tumors in an animal model.

They first tested a GRP78-targeting molecule called a morpholino, which can modify gene expression. The morpholino successfully inhibited GRP78 and restored sensitivity to tamoxifen in the resistant tumors.

"Morpholinos are candidate drugs already being used to target other proteins in clinical trials to treat prostate cancer, but this is the first time inhibiting the gene expression of GRP78 with these agents may have potential to overcome resistance to chemotherapy," said Katherine Cook, Ph.D., assistant professor at Wake Forest School of Medicine, a part of Wake Forest Baptist,Scid and the study's lead author.

In addition, metabolic analysis of breast cancer cells showed that suppressing GRP78 increased the intracellular concentrations of essential polyunsaturated fats, including linoleic acid. These data suggest a novel role of GRP78 in mediating cellular lipid metabolism.

To validate the effect of GRP78-regulated metabolic changes, the scientists treated the same tumor-bearing mice with different doses of linoleic acid and found that this approach had the same effect as targeting GRP78 in restoring tamoxifen sensitivity to the tumors.

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