Cell study finds receptor can fight tamoxifen-resistant breast cancer cells

April 27 2010

A receptor that is present in the nucleus of cells can, when activated, slow the growth of tamoxifen-resistant breast cancer cells, a new study found. The study built on the recent discovery that farnesoid X receptor (FXR) — a nuclear receptor found mainly in the liver — is found in breast cancer tissue. Although previous research showed that FXR can slow proliferation of breast cancer cells, it was not known whether it could do the same with tamoxifen-resistant cells.

The research is part of an effort to overcome tamoxifen resistance in breast cancer patients who are good candidates for tamoxifen treatment, but who either do not respond to the drug or who develop resistance over time. These findings suggest that FXR, when activated by chenodeoxycholic acid (a bile acid) or GW4064 (a synthetic), can slow the proliferation of breast cancer cells that are tamoxifen resistant, said one of the study's authors, Cinzia Giordano.

Giordano, Donatella Vizza, Salvatore Panza, Ines Barone, Daniela Bonofiglio, Suzanne A. Fuqua, Stefania Catalano and Sebastiano Andǒ carried out the study, "Activated farnesoid X receptor inhibits growth of tamoxifen resistant breast cancer cells." The researchers are from the University of Calabria in Italy, except Dr Fuqua, who is with Baylor College of Medicine in Houston.

The study will be presented at the Experimental Biology 2010 conference on Saturday, April 24 and again on Tuesday, April 27. The American Society for Investigative Pathology is sponsoring the sessions.

The conference takes place in Anaheim April 24-28.

Maintaining tamoxifen sensitivity is key

Tamoxifen is an effective breast cancer treatment for patients who are estrogen receptor positive - the majority of breast cancer patients. Breast cancer cells, which need estrogen to grow, have estrogen receptors to allow them to take in estrogen. Tamoxifen interferes with the cancer cells' ability to get estrogen and in the process inhibits the ability of the cancer cells to proliferate.

Tamoxifen generally works well on breast cancer cells that are estrogen receptor positive, but some cells that are receptor positive either do not respond to the drug, or they become resistant. When tamoxifen is unable to inhibit breast cancer cell growth in estrogen-positive patients, it is called hormonal resistance.

Recent studies had already shown that FXR, commonly found in the liver, induces death in breast cancer cells. The researchers wanted to find out if FXR, when activated in breast cancer tissue, would control the growth of tamoxifen-resistant cells. They used two types of receptor-positive breast cancer cells:

1. MCF-7, which is sensitive to tamoxifen; that is, tamoxifen keeps these cancer cells in check

2. MCF-7TR, which is resistant to tamoxifen; that is, the drug does not keep the cancer in check.

The research team activated FXR with either a bile acid, chenodeoxycholic acid, or a synthetic, GW4064. Once FXR was activated, the researchers found that it reduced the survivability of both

the tamoxifen-sensitive and tamoxifen-resistant cells. In fact, FXR inhibited the tamoxifen-resistant cancer cells (MCF-7TR) more than the tamoxifen sensitive cells.

How does it work?

The researchers found that FXR inhibited expression of a growth factor signaling mediator -- human epidermal growth factor receptor 2 (HER2). HER2 is present in 20% of breast cancers and is associated with enhanced malignancy and poorer prognosis. The over-expression of HER2 on the breast cancer cell surface is believed to disrupt the cell's ability to control growth, Giordano said, allowing the cells to rapidly proliferate. FXR seems to inhibit that process.

Why would FXR work better against MCF-7TR, the tamoxifen-resistant cells? Part of the explanation may be that MCF-7TR relies more on HER2, and FXR targets HER2, Giordano said. That would make the tamoxifen-resistant cancer cells more vulnerable to activated FXR, she said.

"This is an 'in vitro' preclinical study, but of course the next step will be to test this in vivo using mice implanted with tamoxifen-resistant breast cancer cells," said Giordano.

Provided by Federation of American Societies for Experimental Biology