Cholesterol appears to promote tamoxifen resistance in some breast cancer cells

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Breast cancer cells in the laboratory that don't respond to tamoxifen may be producing high amounts of cholesterol in order to provide a kind of shield against the drug, say researchers at Georgetown University Medical Center (GUMC).

They say their study, presented at the Annual Meeting of the American Association for Cancer Research (AACR), suggests that currently available statin drugs that reduce cholesterol might be useful in patients with tamoxifen-resistant breast cancer. Alternatively, investigators say, new agents could potentially be designed that specifically inhibit the molecules they found to be responsible for this excess production of cholesterol.

"We have shown that if you inhibit the activity of either of two molecules that we identified in these resistant breast cancer cells, cholesterol production is reduced," says the study's lead investigator, Rebecca Riggins, PhD, a research assistant professor of oncology at GUMC's Lombardi Comprehensive Cancer Center in Washington.

"We are now looking at whether these cells become re-sensitized once more to tamoxifen when cholesterol production is blocked, and our bet is that they do," she says.

The researchers are trying to understand why some women with estrogen receptor-positive (ER+) invasive lobular breast cancer do not benefit as much from hormonal therapy such as tamoxifen when compared to

women with other forms of ER+ breast cancer. Each year in the U.S., approximately 127,000 women develop ER+ breast cancer, and an increasing percentage of these are specifically diagnosed with invasive lobular breast cancer.

They have concluded that cholesterol production inside these cancer cells is one culprit.

Cholesterol causes a number of important actions within a cell, Riggins says, and there are two potential explanations as to why high levels of cholesterol might be related to tamoxifen resistance, Riggins says.

"One is that cholesterol is an essential part of the plasma membrane that surrounds all eukaryotic cells. A high level of cholesterol can make this membrane more rigid, impairing the ability of drugs to enter cells and thus altering how sensitive a cancer cell is to this type of drug treatment," she says.

"A second possibility is that our tamoxifen-resistant breast cancer cells have increased amounts of cholesterol specifically in the mitochondria. Mitochondria supply a cell with energy, but they also are responsible for determining how a cell responds to a death signal," Riggins says. "High levels of mitochondrial cholesterol can delay or block cell death. This is important because many cancer drugs, including tamoxifen, have been shown to induce breast cancer cell death through the mitochondria."

This study continues a string of discoveries the researchers have made regarding tamoxifen resistance. They had earlier found that invasive lobular breast cancer has many more so-called "gamma" estrogen-related receptors than the typical "alpha" estrogen receptors that tamoxifen was designed to inhibit.

In this study, they looked at HMGCS2, an enzyme in the mitochondria

known to be regulated by gamma estrogen-related receptors and AP1, a transcription factor that binds on to the receptor and activates it. HMGCS2 generates chemicals that are necessary for the production of cholesterol. They found that breast cancer cells that are resistant to tamoxifen exhibits very high levels of the gamma estrogen-related receptors, AP1, and HMGCS2, and contains significantly greater amounts of cholesterol, than do breast cancer cells that are sensitive to tamoxifen.

The investigators then found that by inhibiting AP1 with an experimental drug, the production of cholesterol was reduced, as was the expression of HMGCS2.

Much remains unclear about the connection between cholesterol and tamoxifen resistant breast cancer cells, Riggins says. Studies that have looked at the connection between statin use and breast cancer risk have had inconsistent results, and while women taking tamoxifen do have lower levels of cholesterol in their blood, that does not take into account the amount of cholesterol that may be in the cancer cells themselves.

"This study gives us a new direction to go in, and a potential treatment strategy to investigate," she says.

Source: Georgetown University Medical Center (news : web)