Possible therapy for tamoxifen resistant breast cancer identified

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(Medical Xpress)—A study by researchers at the Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James) has discovered how tamoxifen-resistant breast-cancer cells grow and proliferate. It also suggests that an experimental agent might offer a novel targeted therapy for tamoxifen-resistant breast cancer.

Like a second door that opens after the first door closes, a signaling pathway called hedgehog (Hhg) can promote the growth of breast-cancer cells after tamoxifen shuts down the pathway activated by the hormone estrogen. A second signaling pathway, called PI3K/AKT, is also involved.

Activation of the Hhg pathway renders tamoxifen treatment ineffective and enables the tumor to resume its growth and progression. As part of the study, the researchers analyzed over 300 human tumors and found that the tumors with an activated Hhg pathway had a worse prognosis.

Finally, the researchers showed that an experimental drug called vismodegib, which blocks the Hhg pathway, inhibits the growth of tamoxifen-resistant human breast tumors in an animal model. The drug is in clinical trials testing for other types of cancer.

Currently, chemotherapy is used to treat hormone-resistant breast cancers, but this is associated with significant side effects. This study has identified targeted therapies that could be an alternative to chemotherapy

for these resistant tumors.

The study is published in the journal *Cancer Research*.

"Our findings suggest that we can target this pathway in patients with estrogen-receptor breast cancers who have failed tamoxifen therapy," says first author Dr. Bhuvaneswari Ramaswamy, a medical oncologist specializing in breast cancer at the OSUCCC – James.

"We describe a link between the hedgehog signaling pathway, which promotes tamoxifen resistance and the PI3K/AKT pathway," says principal investigator Sarmila Majumder, research assistant professor in molecular and cellular biochemistry at the OSUCCC – James. "Targeting the hedgehog pathway alone or in combination with the PI3K/AKT pathway could be a novel therapeutic option for treating tamoxifen-resistant breast cancer."

Ramaswamy, an assistant professor of internal medicine at Ohio State, emphasizes that novel options are needed for these patients.

"A combined targeted therapy using both hedgehog and PI3K inhibitors could lead to a novel treatment for endocrine-resistant tumors in the future without use of chemotherapy," says Ramaswamy. "And these agents we have identified are all in clinical development for other kinds of cancer."

Approximately 230,000 new cases of breast cancer are expected in the United States in 2012, and almost 40,000 Americans will die from the disease. More than two-thirds of breast cancer cases show high levels of the estrogen receptor (ER). Doctors use the drug tamoxifen to treat these ER-positive tumors, and Ramaswamy notes that the drug has improved the disease-free survival of people with ER-positive breast cancer by 50 percent.

"But 30 to 40 percent of patients taking tamoxifen become resistant to it after about five years," she says. Currently, there are very limited options for these patients and most end up receiving chemotherapy.

Key findings for this study include:

- Tamoxifen-resistant breast cancer depends on the Hhg pathway for cell growth;
- The PI3K/AKT pathway protects key Hhg signaling proteins from degradation, which promotes activation of the Hhg pathway.
- Analysis of 315 invasive breast cancers showed that high levels of the protein GLI1, an important Hhg marker, was correlated with poorer disease-free survival and overall survival.

"Our next step is to organize a clinical trial to evaluate vismodegib in patients with tamoxifen-resistant breast cancer," Ramaswamy says.

More information: cancerres.aacrjournals.org/con … CAN-12-1248.abstract

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