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Researchers: tamoxifen's power comes from endoxifen

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Mayo Clinic researchers have discovered that a chemical known as endoxifen appears to be the primary metabolite responsible for the effectiveness of tamoxifen in treating breast cancer, and that it works against cancer in an entirely unexpected way.

Their study, being presented at the Cancer Therapy & Research Center-American Association for Cancer Research (CTRC-AACR) 31st annual San Antonio Breast Cancer Symposium, finds that, in contrast to the other tamoxifen metabolites, endoxifen degrades the estrogen receptor, and inhibits the growth of breast cancer cells even when tamoxifen is present. These new findings are believed to be the most definite laboratory analysis yet on how tamoxifen and its two main metabolites - endoxifen and 4HT (4-hydroxytamoxifen) -act against breast cancer.

"Tens of thousands of women in this country are prescribed tamoxifen for either treatment or prevention of breast cancer, and while it has shown remarkable success, it does not work for a substantial number of patients," says the study's lead investigator, John Hawse, Ph.D. "These findings increase our understanding of tamoxifen and, we hope, could pave the way for improved therapies."

Tamoxifen is designed to treat estrogen-receptor positive breast cancer (70-80 percent of all breast cancer) because this receptor fuels the cancer's growth. But tamoxifen is a "pro-drug," which means that it is relatively inactive until converted into active "metabolites" - the 4HT and endoxifen chemicals that actually perform the work of the drug.

Researchers at Mayo Clinic earlier discovered that tamoxifen is less effective in women who had a deficiency in the enzyme CYP2D6, which is responsible for converting tamoxifen to endoxifen. The CYP2D6 gene is present in different forms in different people. A team of Mayo Clinic investigators, including Matthew Goetz, M.D., Matthew Ames, Ph.D., and James Ingle, M.D., have shown that women with certain variations in the CYP2D6 gene - so-called "poor metabolizers" - have a significantly higher risk of relapse when they take tamoxifen.

But it has been unclear which of tamoxifen's metabolites is most crucial to tamoxifen's effectiveness. Previous research suggested that both metabolites were similar.
To find the answer, Dr. Hawse, who works in the laboratory of molecular biologist Thomas Spelsberg, Ph.D., designed an in vitro model system for treating cancer cells with tamoxifen, 4HT, and endoxifen in amounts that mirrored doses found in women who were prescribed tamoxifen therapy.

The researchers were surprised to find that endoxifen actually degraded estrogen receptors in these cancer cells, thus slowing their growth.

"We all thought tamoxifen works by blocking the estrogen receptor so it can't bind to estrogen, but now we find that endoxifen actually degrades the estrogen receptor," Dr. Hawse says. "This goes a long way toward explaining why tamoxifen can be so effective in women who can effectively convert tamoxifen to endoxifen."

Dr. Hawse found that tamoxifen had little effect on the growth of the cancer cells. They also discovered that when they introduced into the cells a combination of estrogen and tamoxifen, the cells grew just as much as if they were given estrogen alone.

With endoxifen, the results were different. At low concentrations, such

as would be seen in the blood of women who were poor metabolizers because of their CYP2D6 gene variant, there was little inhibition of cell growth. But at higher concentrations, similar to what good metabolizers produce, cancer growth drastically slowed and the estrogen receptor was degraded.

Adding the low concentrations of 4HT found in human blood to the cancer cells also had little effect, and cell growth also increased when estrogen was added. "This is not to say that 4HT is ineffective, but that the liver makes so little of it from tamoxifen that it can't work as well as it might if there was more of it," Dr. Hawse says.

"That was the evidence we needed," says Dr. Spelsberg. "It showed that tamoxifen is activated via the CYP2D6 enzyme into a completely different molecule that has a completely different mechanism of action from tamoxifen and even 4HT."

Based on these findings, the researchers say an agent that mimics endoxifen might be a better, more responsive drug than tamoxifen.

"These findings open the door to exploring the use of endoxifen as a drug that might be able to replace tamoxifen," says Dr. Goetz. "We believe it is the most potent metabolite, and we would not be restricted by CYP2D6's inability to metabolize it, or by limits on how much endoxifen the liver could make. It will take years before we know whether this is the case, but we are excited about the possibility."

Source: Mayo Clinic