Researchers say flower power may reduce resistance to breast cancer drug tamoxifen

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Combining tamoxifen, the world's most prescribed breast cancer agent, with a compound found in the flowering plant feverfew may prevent initial or future resistance to the drug, say researchers at Georgetown Lombardi Comprehensive Cancer Center.

The finding, reported online in *FASEB* Feb. 12, provides new insight into the biological roots of that resistance, and also tests a novel way to get around it.

"A solution to tamoxifen resistance is sorely needed, and if a strategy like this can work, it would make a difference in our clinical care of breast cancer," says the study's lead investigator, Robert Clarke, PhD, DSc, a professor of oncology and physiology & biophysics at Lombardi, a part of Georgetown University Medical Center (GUMC). Clarke is also the interim director of GUMC's Biomedical Graduate Research Organization.

Clarke added that the purified research chemical they tested, parthenolide, a derivative of feverfew, is being tested by other scientists as treatment for a variety of cancers, as well as other health conditions. Feverfew has long been a staple of natural medicine, and is particularly known for its effects on headaches and arthritis. Latin for "fever reducer," feverfew is a common garden bush with small daisy-like flowers.

"The chemical clearly has potential, and we ought to be able to figure out

fairly quickly if it can help solve tamoxifen's resistance problem," Clarke says.

Tamoxifen is a treatment of choice for breast cancer that is estrogen receptor positive (ER+), meaning that the hormone estrogen drives cancer growth. Most newly diagnosed breast cancers - about 70 percent - fall into that category. But about half of these cancers do not initially respond to tamoxifen, which is designed to block the hormone from binding to the cell's protein receptor, and many patients that do respond are at risk for developing resistance and cancer relapse.

In this study, Clarke and a team of researchers set out to study if, as previous research had suggested, tamoxifen resistance is regulated by the protein complex NF- κB (nuclear factor kappa B), which is often found to be over-expressed in ER+ breast cancer. NF- κB is known to help cells survive when damaged.

The researchers had earlier discovered that NF- κB is over-expressed in cells that are resistant to tamoxifen, and they had found that resistance to another tamoxifen-like drug, fulvestrant, was controlled by a protein (Bcl2) that is, itself, regulated by NF- κB.

"Our scientific quest was to see if blocking NF- κB affects tamoxifen resistance, and if it does, why?" says Clarke.

They conducted a variety of tests using parthenolide, which has been shown to act on NF- κB. They found that in resistant breast cancer cells, the chemical blocked the activity of NF- κB, making the cells sensitive once again to tamoxifen. They then silenced NF- ?B in tamoxifen resistant cells, and found that this had the same effect as using parthenolide.

They further found that increased activation of NF- κB can alter

sensitivity of tamoxifen by modulating the protein CASP8, which is involved in programmed cell death. That then affects Bcl2, which also helps push a damaged cell to die.

"When you give tamoxifen to a breast cancer cell, that is essentially a pro-death signal, because you are blocking the cell's access to estrogen, and the cell recognizes this is a mortal blow," Clarke says. "Such a damaged cell uses CASP8 and Bcl2 to trigger the cell machinery needed for dying.

"But the cell has ways to counteract the pro-death signal, and one important one is to activate NF- κB, which can control expression of genes necessary for survival," he says. "Now the cell thinks it should be living, not dying."

Because NF- κB controls CASP8 and Bcl2, it can turn those proteins essentially off, Clarke says. "The pro-survival signals override the pro-death signals."

Still, as much as this study advances the understanding of tamoxifen resistance, there is much that is not understood, he adds. "We don't know when NF- κB becomes over-expressed in the transformation of tamoxifen-sensitive to a tamoxifen-resistant breast cancer cells, and we don't know of other adaptations the cell may have made," he says. "It is probably fair to say this is a hideously complex process."

To that end, Clarke cannot predict how many women who try a combination of tamoxifen and parthenolide will benefit. He says the science is much too early to make any recommendations and strongly warns women against adding feverfew supplements to their cancer treatment.

Still, he is hopeful. "Every breast tumor slightly different, but we know

many do use NF- κB because excess amounts of the protein are found in these cancers," he says. "That suggests they may be sensitive to targeted approaches that shut down this pro-survival signal."

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