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Leukemia drug reverses tamoxifen-resistance in breast cancer cells

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Taking a leukemia chemotherapy drug may help breast cancer patients who don't respond to tamoxifen overcome resistance to the widely-used drug, new research from the Kimmel Cancer Center at Jefferson suggests.

Interestingly, researchers found that taxoxifen combined with dasatinib, a protein-tyrosine kinase inhibitor, reverses the chemo-resistance caused by cancer-associated fibroblasts in the surrounding tissue by normalizing glucose intake and reducing mitochondrial oxidative stress, the process that fuels the cancer cells.

Previous animal studies have confirmed that combining tyrosine kinase inhibitors with anti-estrogen therapies, like tamoxifen, can prevent drug resistance, but none have suggested that the target of the inhibitors is the cancer-associated fibroblasts.

The researchers report their findings in the August 1 issue of *Cell Cycle*.

About 70 percent of women diagnosed with breast cancer will have estrogen receptor positive (ER(+)) disease, which indicates that the tumor may respond to tamoxifen. However, a large percentage of these tumors—up to 35 percent—have little to no response to the drug or eventually develop resistance to it.

In this study, researchers sought to better understand drug resistance by looking at the metabolic basis in an ER (+) cell line and cancer-

associated fibroblasts. The researchers have previously established a relationship between the two, where cancer cells induce aerobic glycolysis by secreting hydrogen peroxide in adjacent fibroblasts via oxidative stress. In turn, these fibroblasts provide nutrients to the cancer cells to proliferate, a process that ultimately makes tumors grow.

Here, they investigated and then demonstrated that this interaction was also the basis of tamoxifen resistance.

In a sense, the drug combination had an "antioxidant effect" in these types of cancer cells, according to Michael P. Lisanti, M.D., Ph.D., Professor and Chair of Stem Cell Biology and Regenerative Medicine at Jefferson Medical College of Thomas Jefferson University and a member of the Kimmel Cancer Center.

"The fibroblasts are what make ER (+) cancer cells resistant to the tamoxifen," said Dr. Lisanti. "But the tamoxifen plus dasatinib maintained both fibroblasts and cancer cells in a 'glycolytic state,' with minimal oxidative stress and more cell death, most likely because of an absence of metabolic coupling. The supply between the two was cut."

"This suggests resistance to chemotherapeutic agents is a metabolic and stromal phenomenal," he added.

Researchers showed that ER (+) cancer cells alone responded to tamoxifen but when co-cultured with human fibroblasts had little to no effect. Similarly, dasatinib, a chemotherapy drug used to treat leukemia patients who can no longer benefit from other medications, had no effect on fibroblasts alone or cancer cells. Together, however, the drugs prevented the cancer cells co-cultured with the fibroblasts from using high-energy nutrients from the fibroblasts.

This combination resulted in nearly 80 percent cell death, the team

reported—a two to three fold increase when compared with tamoxifen alone.

"The drugs have no effect when they are used alone—it's in unison when they effectively kill the cancer cells in the presence of fibroblasts," said Dr. Lisanti. "This opens up the door for possible new treatment strategies. This 'synthetic lethality' may help patients overcome resistance in the clinic."

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