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Scientists identify key protein players in hard-to-treat breast cancers

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At the time of diagnosis, the majority of breast cancers are categorized as estrogen-receptor positive, or hormone sensitive, which means their cancerous cells may need estrogen to grow. Patients with this type of cancer often respond favorably to treatments called aromatase inhibitors, like tamoxifen, which cause cell death by preventing estrogen from reaching the cancerous cells. Over time, however, the disease often becomes resistant to estrogen deprivation from the drugs—making treatment options more limited.

New findings that will be presented at the AACR Annual Meeting 2012 on Sunday, April 1, by researchers from Fox Chase Cancer Center in Philadelphia, identify a pair of proteins that could play a crucial role in restoring treatment sensitivity to these resistant cancerous cells —possibly leading to more treatment options in the future.

In experiments on cancer cell lines, Joan Lewis-Wambi, Ph.D., a tumor biologist at Fox Chase and lead author on the study, found that the two proteins, called STAT-1 and PLSCR-1, were 10 and 20 times more abundant respectively in breast cancer cells that are resistant to estrogen deprivation than in cancerous cells that died without estrogen. The researchers also showed that the treatment-resistant cancerous cells underwent apoptosis, or cell death, in the presence of estrogen—which suggests the hormone has a complicated relationship with breast cancer.

"Breast cancer cells that are hormone dependent need estrogen to grow," says Lewis-Wambi. "But these resistant cells have the opposite response

to estrogen—instead of stimulating growth, estrogen actually induces death."

Lewis-Wambi says she and her colleagues are trying to understand the complex relationship between estrogen and the behavior of these cancerous cells. In further experiments, they found increased levels of the two proteins when estrogen caused apoptosis in the cancerous cells. Previous experiments have shown that the proteins are also associated with inteferon-alpha, a protein that promotes cell death and is often used to treat solid tumors.

The new findings suggest that a therapy that uses estrogen, along with interferon-alpha, may offer a treatment option for patients whose disease is resistant to estrogen-depriving drugs. Such a treatment may use the two proteins to successfully induce the cancerous cells to undergo cell death.

"The models we've developed in the lab are reflective of what happens in the clinic when you have patients with hormone-dependent disease," says Lewis-Wambi. "Initially they respond to treatment, but over time the disease becomes resistant to the drug, and the drug no longer works."

Previous studies have suggested that the STAT-1 and PLSCR-1 proteins help induce cell death, but their exact functions have remained a mystery. Lewis-Wambi and her colleagues, including researchers from the University of Rochester, suspected that the proteins might help explain how interferon-alpha works in a cell. The researchers studied the proteins using cancer cells that were originally estrogen-receptor positive but, over time, developed resistance to drugs that starved them of estrogen.

Lewis-Wambi says that they're now following up their promising in vitro results with in vivo experiments to see if the proteins behave similarly in

animal models. Once they can demonstrate the results in animals, the scientists can think about how their work might influence treatment.

In addition to suggesting an interferon- and estrogen-based treatment, the proteins may help identify patients most likely to respond to a particular kind of therapy. This kind of personalized cancer treatment, based on the molecular biology of a person's disease rather than the site or size of the tumor, has the potential to be more effective and have fewer side effects than conventional chemotherapies.

"We know that no two patients are the same," Lewis-Wambi says. "One drug may work perfectly well in one patient but have no effect in another. That comes back to the fact that a tumor's molecular profile looks different from one individual to another. Our goal is to identify the genes that make patients more or less likely to respond to a drug. Then you're treating the individual, as opposed to the group."

Provided by Fox Chase Cancer Center