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Iron-regulating protein is strong predictor of breast cancer prognosis, study shows

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A new study by researchers at Wake Forest University Baptist Medical Center (WFUBMC) may soon help to spare some women with breast cancer from having to undergo invasive and toxic treatments for their disease.

Investigators found that low levels of ferroportin, the only known protein to eliminate iron from cells, are associated with the most aggressive and recurring cancers. The finding suggests that testing for ferroportin levels in women with breast cancer may one day help doctors to more accurately predict whether their patients' cancer will return. It may also help some women with high levels of the protein to avoid invasive or toxic treatments such as chemotherapy.

The study, funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), of the National Institutes of Health (NIH), appears today in the online version of the journal Science Translational Medicine.

"Ferroportin expression may help predict whether women who have had breast cancer will relapse or not," said Frank M. Torti, M.D., M.P.H., director of the Comprehensive Cancer Center at WFUBMC, senior author on the paper and co-lead investigator for the study. The findings also suggest that levels of ferroportin may eventually help guide therapy for breast cancer patients.

"There is a group of high-risk women with breast cancer who have high

ferroportin levels and do quite well," Torti said. "We may eventually be able to adjust our treatments so that these patients can avoid chemotherapy and all the side effects that go along with it. The ability to predict which women will be okay without such intense treatment would be a tremendous help."

The findings are the result of a series of experiments by Torti and colleagues at WFUBMC.

Drawing on the hypothesis that iron may be altered in breast cancer and that the alteration might be important in the behavior of the cancer, the researchers first looked at isolated human breast cancer cells and found that there was a significant reduction of ferroportin in the cancerous cells compared to that of normal breast cells.

There are changes in many of the genes and proteins in cancer cells, Torti explained, so the researchers next explored whether the reduction in ferroportin in cancer cells directly contributed to the growth of the cancer or whether it was simply a consequence of the disease. To do this, the researchers artificially increased ferroportin to near normal levels in an aggressive breast cancer cell line in which ferroportin levels were initially very low. Using a mouse model, the researchers watched the growth of tumors formed by these cells, and found that the ones in which the levels of ferroportin had been restored to normal grew more slowly than the tumors formed by cells with depleted levels of the protein.

"The reason for that is simple," explained Suzy V. Torti, Ph.D., an associate professor of biochemistry at Wake Forest Baptist and co-lead investigator on the paper. "In the case of cancer, the ability to remove iron from cells is reduced by the depleted ferroportin levels, and as a result, iron accumulates in cancer cells. Cancer cells require iron, which allows the tumor to grow faster and perhaps become more aggressive.

Because ferroportin can remove iron from the cell, when we put the protein back into the cell, the ferroportin removed the cancer's growth stimulus. Our findings suggest that ferroportin is a substantial influence on the behavior of the cancer."

She noted that though the iron at issue acts as a growth stimulus for cancer, the study focused on cellular and not dietary iron or iron supplements. When regulated appropriately, iron is vital to all cell development - including that of healthy cells - and patients should not change the amount of iron in their diets.

Next, the researchers looked at ferroportin levels in human breast cancer tissue. As predicted, they found that ferroportin levels were lowest in the most aggressive areas of cancer, confirming that the relationship does not only occur in cell culture and isolated breast cancer cells, but also in the actual tissue of women with cancer.

So, the Tortis and their team, including Lance D. Miller, Ph.D., a bioinformatics expert, proceeded to explore four large study databases of breast cancer patients to see if ferroportin levels in human breast cancer were associated with long-term outcomes. The data included gene expression information at the time of diagnosis and multi-year clinical follow-up for more than 800 breast cancer patients from around the world.

"Uniformly, we found that ferroportin levels were a strong predictor of the propensity for a woman's breast cancer to recur," Frank Torti said. "It's a striking prediction. This marker separates women into good and poor prognostic groups independently from any other factors such as tumor size, grade, lymph node status, or other conditions."

The researchers' next step, he added, will be to extend their results to larger populations that include women of various ethnicities and

demographics.

"We are excited that we, and our Cancer Center, have made a discovery that not only increases our understanding of the basic biology of breast cancer, but may eventually be directly useful in treating patients," Frank Torti said.

Provided by Wake Forest University Baptist Medical Center

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