

Researchers find possible clues to tamoxifen resistance in breast cancer patients

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Breast cancer patients who become resistant to tamoxifen may have low levels of a protein called Rho GDI-alpha, according to a study published online March 30 in the *Journal of the National Cancer Institute*.

Women whose tumors have estrogen receptors (ERs) often take tamoxifen after surgery to prevent recurrence of the cancer and keep it from metastasizing to other parts of the body. Some patients, however, become resistant to the drug even though their tumors remain ERpositive.

To explore the mechanisms of this resistance, Suzanne Fuqua, Ph.D., professor of medicine in the Lester and Sue Smith Breast Center at Baylor College of Medicine in Houston and colleagues compared two groups of ER-positive tumors: four primary tumors from women who took tamoxifen and did not have a recurrence and five metastatic tumors from women taking tamoxifen whose tumors spread while they were on the drug. The authors found that Rho GDI-alpha was under-expressed—its levels were low—in the women with tamoxifen-resistant metastatic disease. They validated the association of low Rho GDI-alpha with tamoxifen resistance in laboratory cells, in human tumors implanted in mice, and in genetic data from 250 women whose ER-positive breast tumors were treated with tamoxifen.

They also found that levels another <u>protein</u>—MTA2--rose markedly when Rho GD1-alpha dropped and that levels of MTA2 and Rho GDIalpha combined predicted recurrence.



"These are the first data suggesting a tight, clinically important connection between the two pathways, Rho GDI-alpha and MTA2," the authors write. "Our data also suggest a possible mechanism, in which the loss of Rho GDI-alpha function promotes distant progression of breast tumors by triggering downstream molecules, such as MTA2, with metastasis-promoting activities."

In an accompanying editorial, Matthew J. Ellis, Ph.D. and Brian A. Van Tine, M.D. of Washington University in St. Louis note that other studies have found the proteins to be associated in various ways with <u>breast</u> <u>cancer</u>. But not all these previous findings are consistent with the findings of this study. "Thus, the status of Rho GDI-alpha as a marker of <u>tamoxifen</u> resistance is unclear," they write.

The editorialists also comment on the increasing number of genetic alterations emerging in breast cancer. "In the next several years," they write, "many entire breast cancer genomes will be published, revealing for the first time the enormous scale of the disruption of the human genome associated with the development of this disease." After that, they say, efforts to understand the functions of disrupted genes "will be essential for the next surge of progress."

Provided by Journal of the National Cancer Institute

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