Analysis of Breast-Cancer Gene Role Offers Promising Target for Drugs to Stop Or Slow Progression

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Researchers at UT Southwestern Medical Center have for the first time described how multiple copies of a gene are responsible for metastases in early-stage breast cancer and poor prognosis for patients.

In a study published in this week's issue of the *Proceedings of the National Academy of Sciences*, the gene, called uPAR, offers a promising target for therapeutic drugs to stop or slow the progression of the disease and could serve as a screening tool for assessing which types of drugs a patient will respond to.

The gene launches a biochemical process in which a molecule called plasmin perforates the membranes of tissues, causing the membranes to break down and allowing the cancer cells to escape into the bloodstream and to adjacent tissues. The result is metastasizing breast cancer. About 20 percent to 25 percent of breast-cancer patients were shown to have uPAR gene amplification, which means they carry too many copies of the gene.

"The uPAR system probably plays a role in metastases in many of the common solid tumors," said Dr. Jonathan Uhr, professor in the Cancer Immunobiology Center and of microbiology and the study's senior author.

While analyzing slides of individual tumor cells – either from the

primary tumor or circulating tumor cells – of 72 patients with advanced recurrent breast carcinoma, the UT Southwestern research team discovered how uPAR may work in concert with another known breast cancer gene, HER-2.

The researchers suggest that uPAR may amplify the cancer-causing effects of HER-2.

“This gene, uPAR, is an important oncogene, and that is why we determined whether or not it is amplified,” said Dr. Uhr. “Unexpectedly, it is usually amplified in the same tumor cell with HER-2 gene amplification. This has significant implications for treatment with targeting agents. Moreover, we stress the value of individual tumor cell analysis for providing information that cannot be obtained by conventional pathological examination."

Dr. Debu Tripathy, professor of internal medicine, director of the Komen/UT Southwestern Breast Cancer Research Program and a coauthor of the study, said the biochemical process triggered by uPAR, called the urokinase plasminogen activator system, is one of the breast-cancer prognostic factors that has the greatest level of evidence.

“All the work has been on the protein and enzymatic activity and not amplification of the gene, which is a very reliable and easy-to-use diagnostic test called FISH,” said Dr. Tripathy. “The other important finding is that HER-2 and uPAR gene amplification tend to co-exist, and this has implications in new strategies to address HER-2-positive breast cancer with drugs that block both HER-2 and urokinase given together.”

The study opens a promising avenue to increase the effectiveness of the drug trastuzumab (Herceptin) by adding a second drug seeking to neutralize the uPAR gene.

“One major avenue of investigation would be to develop an antibody that prevents uPAR from binding to a molecule called uPA that can activate uPAR,” Dr. Uhr said.

Source: UT Southwestern Medical Center