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Marker may predict breast cancer response to tamoxifen

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The presence of lower-than-normal amounts of the protein TGFBR2 was associated with breast cancer resistance to treatment with the antiestrogen therapeutic tamoxifen, according to a study published in *Cancer Research*, a journal of the American Association for Cancer Research.

"Our studies established the role of the cell signaling protein TGFBR2 in hormone therapy resistance in breast cancer," said Susann Busch, PhD, a postdoctoral fellow at the Sahlgrenska Cancer Center in Gothenburg University, Sweden. "Our data indicate that TGFBR2, which detects TGF-beta and thereby activates subsequent cellular responses, could be used as a marker in the clinics to identify patient subgroups that may not benefit from hormone therapy alone and may require additional therapies."

Estrogen is an important hormone that induces breast cells to grow and divide, while the TGF-beta cell signaling pathway normally exerts growth-inhibitory effects, Busch explained. Previous studies have shown that both estrogen and TGF-beta signaling pathways can directly and indirectly interact with each other, and abnormal regulation of one signaling pathway can potentially interfere with activation of the other, she added.

Busch; Göran Landberg, MD, PhD, professor at Sahlgrenska Cancer Center; and colleagues analyzed tumor samples obtained from 564 premenopausal patients enrolled in a clinical trial between 1986 and

1991. The patients, after undergoing surgery and radiotherapy, were randomly assigned to either receive tamoxifen for two years (276 patients) or no systemic treatment (288 patients).

The researchers found that among women who received tamoxifen and whose tumors were estrogen receptor-positive, those whose tumors had low levels of TGFBR2 had a 73 percent lower recurrence-free survival rate, compared with those whose tumors had high levels of TGFBR2.

Further, low TGFBR2 was associated with worse recurrence-free survival when the researchers analyzed data from four independent, publicly available gene expression data sets of tamoxifen-treated breast cancer.

Busch and colleagues then conducted a series of laboratory experiments with breast cancer cell lines to understand how TGF-beta signaling influences antiestrogen treatment outcomes. They found that the absence of TGFBR2 changed cells so they would not respond to estrogen and tamoxifen treatment. In a drug-resistant cell line, they found low levels of TGFBR2 and abnormal pathway activation, confirming its importance in the development of drug resistance.

More information: "Loss of TGFβ Receptor Type 2 Expression Impairs Estrogen Response and Confers Tamoxifen Resistance" *Cancer Res* April 1, 2015 75:1457-1469; DOI: 10.1158/0008-5472.CAN-14-1583