

Protein that functions in normal breast may also contribute to breast cancer metastasis

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The trefoil factor 3 (TFF3) protein protects and maintains the integrity of the epithelial surface in the normal breast. New research has found that while TFF3 protein expression is higher in well-differentiated low grade tumors and therefore associated with features of a good prognosis, it has a more sinister role in breast cancer invasion and metastasis. The report is published in the March issue of the *American Journal of Pathology*.

"Our findings suggest that TFF3 is regulated by estrogen and has beneficial properties in breast epithelia," says lead investigator Felicity E.B. May, PhD, of the Northern Institute for Cancer Research and the Department of Pathology at Newcastle University, UK. "We propose that early during breast tumorigenesis, TFF3 retains its association with normal functionality of breast epithelial cells. Subsequently, with the loss of tumor [cell differentiation](#), its function is subverted to promote the development of tumors and infiltration and [lymph node metastasis](#)."

To determine the role of TFF3 in breast cancer, researchers measured its level in tissue samples from normal breasts, benign breast lesions, in situ carcinomas, invasive carcinomas, and involved lymph nodes. TFF3 was expressed in the majority of benign and malignant breast lesions studied. Well-differentiated tumor types expressed higher levels of TFF3. There was a positive association between TFF3 [protein expression](#) and microvessel density, suggesting that it stimulates angiogenesis in [breast tumors](#).

A striking finding of the study is the strength and consistency of the association between TFF3 expression and a more metastatic phenotype in [invasive breast cancer](#). TFF3 was expressed at higher levels in primary tumors with associated metastasis, and its expression was higher in malignant cells that have metastasized away from those within the primary tumor. There appears to be a switch in the normal polarized secretion of TFF3 in [invasive cancer](#), which allows it to exert invasion-promoting effects.

The study suggests that TFF3 may be one of the genes that mediate the various effects of estrogens in breast cancer. "The paradox remains, however, for both the estrogen receptor and TFF3, that they contribute to the normal physiology of the breast epithelium yet are involved in the progression of cancer," notes Dr. May.

Importantly, the investigators also evaluated the potential of TFF3 as a biomarker of lymphovascular invasion and lymph node metastasis. They found that TFF3 had greater predictive power than other markers analyzed, including tumor grade, age, tumor size and type, and estrogen and progesterone receptor status. "Our study reinforces the view that TFF3 expression merits evaluation as a prognostic biomarker and as a predictive marker of response to therapy," concludes Dr. May. "It is probable that its malign effects will be mitigated by adjuvant endocrine therapy in women with hormone-responsive cancers. However, the usefulness of TFF3 as a marker of hormone responsiveness needs to be evaluated."

More information: The article is "TFF3 Is a Normal Breast Epithelial Protein and Is Associated with Differentiated Phenotype in Early Breast Cancer but Predisposes to Invasion and Metastasis in Advanced Disease," by A.R.H. Ahmed, A.B. Griffiths, M.T. Tilby, B.R. Westley, and F.E.B. May ([doi: 10.1016/j.ajpath.2011.11.022](https://doi.org/10.1016/j.ajpath.2011.11.022)). It will appear in *The American Journal of Pathology*, Volume 180, Issue 3 (March 2012)

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