BREAST CANCER

A DEAR 1

Young women diagnosed with breast cancer tend to have a more aggressive disease than women diagnosed later in life. Discovering genes that lead to breast cancer in younger women is imperative if treatment is to improve. Ann McNeill Killary and colleagues have identified a potential candidate — ductal epithelium-associated RING chromosome 1 (DEAR1).

DEAR1 is a member of the tripartite motif subfamily of RING finger proteins, some of which have been implicated in the development of tumours in other tissues. Killary and colleagues identified the link between early onset breast cancer and *DEAR1* through screening of a subtractive hybridization library. *DEAR1* maps to chromosome 1p35.1, a region that is subject to loss of heterozygosity in patients with breast cancer and is associated with a poor prognosis. Northern blots and immunohistochemistry showed that *DEAR1* is expressed in normal ductal and glandular epithelium and that expression of DEAR1 is reduced or lost on transition to ductal carcinoma *in situ*. Sequencing and denaturing high performance liquid chromatography on 12 breast cancer cell lines and 55 primary breast tumour samples indicated that *DEAR1* can be subject to missense mutation and homozygous deletion.

How does DEAR1 function? Expressing wild-type DEAR1 in breast cancer cells isolated from a 36-year-old woman with invasive

breast cancer who had a missense mutation in *DEAR1* restored normal acinar morphogenesis (apicobasal polarization and lumen formation) when these cells were grown in three-dimensional basement membrane culture. Conversely, suppression of *DEAR1* expression in immortalized human mammary epithelial cells using short hairpin RNAs resulted in the loss of normal acinar morphogenesis (both cell polarity and lumen formation).

Analysis of a tissue array containing breast tumour samples from 158 premenopausal women aged 25–49 for which there are 20 years of follow-up data indicated that 56% of these tumours had no expression of DEAR1. Further analyses on 123 of the samples indicated that loss of DEAR1 expression correlated with a familial predisposition to breast cancer, was not associated with

loss of either *BRCA1* or *BRCA2* and was associated with triple-negative cancers (no expression of the oestrogen receptor, progesterone receptor or ERBB2). Moreover, expression of DEAR1 was significantly associated with local recurrence-free survival in patients with early onset breast cancer.

Further analyses are needed to verify whether loss of DEAR1 expression is a biomarker for early onset breast cancer as these data indicate, and whether loss of DEAR1 expression could be used to identify patients with a high risk of disease recurrence who might benefit from increased monitoring and adjuvant therapy.

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ORIGINAL RESEARCH PAPER Lott, S. T. et al. *DEAR1* is a dominant regulator of acinar morphogenesis and an independent predictor of local recurrence-free survival in early-onset breast cancer. *PLoS Med.* 6, e1000068 (2009)

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