

...and secreted tumour suppressors

Sir — Recently, Jensen *et al.* suggested that BRCA1 and possibly BRCA2, two proteins encoded by the currently known inherited breast cancer genes, belong to the granin protein family¹. They show that BRCA1 is secreted and others have reported that BRCA1 is upregulated during pregnancy^{2,3}, its expression is induced by estrogens²⁻⁴ and it is present in breast milk. Jensen *et al.* speculated that BRCA1, like other granins⁵ may undergo proteolytic cleavage leading to release of biologically active peptides. They further hypothesized that the protective role of pregnancy and lactation in breast cancer may be mediated by BRCA1 and possibly BRCA2. BRCA1 is a growth inhibitor in breast and ovarian cell lines⁶.

Prostate specific antigen (PSA) is a serine protease of the kallikrein gene family that has recently been found in the female breast⁷⁻⁹. PSA is secreted by breast epithelial cells¹⁰, its production is increased during pregnancy and it is also present in amniotic fluid¹¹. PSA is found in milk of lactating women¹², and its presence in breast discharge fluid is associated with low risk for breast cancer. In women with a family history of breast cancer or with sporadic breast cancer, PSA levels in breast discharge fluid are dramatically reduced (Sauter, E.R. *et al.*, submitted manuscripts). Women with PSA in their tumours live longer and relapse less frequently¹³. Like BRCA1, PSA is regulated by steroid hormones¹⁴. Together, these data

suggest that PSA and BRCA1 are two secreted protective factors in breast cancer. Their possible interactions and relationship have not been examined. Since PSA is a proteolytic enzyme and BRCA1 may be a precursor of bioactive peptides, it is tempting to speculate that they might interact as an enzyme-substrate pair for the release of peptides protective from breast cancer. The widespread availability of purified BRCA1 protein should allow such hypotheses to be tested.

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