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LETTERS TO THE EDITOR

Expression of anti-metastatic gene *nm23*

Sir – We read with interest the guest editorial by Hart and Easty (*Br. J. Cancer*, 1991, **63**, 9–12), on the approaches to the identification and isolation of genes responsible for determining the metastatic phenotype, and wish to add further information regarding a specific gene highlighted in the review.

Expression of the anti-metastatic gene *nm23* has been shown to correlate with the known metastatic potential of cell lines in murine and rat tumour models. Cotransfection of rat embryo fibroblasts (REF) with the *ras* oncogene and the adenovirus 2 *E1a* gene was associated with higher levels of *nm23* expression compared to the REF cell lines which were transfected with the metastasis inducing *ras* oncogene alone (Steeg *et al.*, 1988). Two clones of the human *nm23* gene have been identified which are located on chromosome 16 and 17 (Steeg & Liotta, 1990), regions of the latter are commonly deleted in breast cancer and contain the p53 and HER2/*neu* gene loci.

The possible function of the *Nm23* protein in tumour metastasis is discussed in the review. However, more recent work has given further information, with the *Awd/Nm23* protein being identified by immunoblotting in cultured *Drosophila* cells, zebra fish embryos, cultured mouse cells, and demonstrated in *Drosophila* microtubule preparations (Biggs *et al.*, 1990). Loss of the *Nm23* protein may therefore cause defects in mitosis and/or protein synthesis due to disruption of spindle microtubule polymerisation. The exact mechanism by which the metastatic phenotype may be controlled by the *Nm23* protein remains unresolved.

In a limited series of 24 benign and malignant human breast tumours, *nm23* expression was assessed by mRNA hybridisation and *in situ* hybridisation, and high levels of *nm23* expression were associated with an absence of lymph node metastases (Bevilacqua *et al.*, 1989), leading the authors to suggest that the *nm23* gene may suppress the metastatic phenotype.

We have asssessed the level of *nm23* expression in human primary breast cancers, using the murine *pnm23*-1 plasmid and found there was differential expression of the *nm23* gene, with a variation of 120-fold (Hennessy *et al.*, 1991). *nm23* mRNA levels from 145 tumours have shown a significant inverse relationship with lymph node involvement: of 63 tumours from lymph node positive patients 39 (62%) demonstrated low levels of expression, whereas only 19 out of 46 tumours (41%), from lymph node negative patients, had similarly low levels ($P = 0.032$). Low levels of *nm23* expression were seen in poorly differentiated tumours ($P = 0.027$) and in oestrogen receptor negative tumours ($P = 0.054$). There were no significant correlations between *nm23* mRNA expression and tumour size, epidermal growth factor receptor status, or menopausal status. Also of interest is that there was no significant correlation between *nm23* and HER2/*neu* or p53 oncoprotein expression. In the 70 patients who have been followed-up for greater than 2 years, loss of *nm23* expression was associated with disease recurrence ($P = 0.003$) and poor patient survival ($P = 0.005$), and was second only to nodal status as a significant prognostic variable. We agree therefore that expression of the *nm23* gene may be an important marker for predicting tumour metastasis and outcome of disease; perhaps identifying a group of patients who might benefit from adjuvant therapy.

Yours etc.,

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