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METASTASIS

Regressing to self-renewal

The epithelial–mesenchymal transition (EMT) is a developmental process that appears to be adopted by tumour cells to confer malignant traits such as invasiveness, survival and motility. However, how malignant cells that have undergone an EMT are able to propagate tumour growth at distant sites has remained unclear. Sendurai Mani, Robert Weinberg and colleagues now provide evidence that the EMT also confers stem cell-like properties.

Using immortalized human mammary epithelial cells (HMECs) Mani and colleagues induced an EMT through ectopic expression of the development-associated transcription factors TWIST or SNAIL, or through exposure to transforming growth factor β1 (TGFβ1). The cells were fractionated by flow cytometry based on the expression of the cell surface markers CD44 and CD24. They found that cells that had undergone an EMT exhibited $CD44^{high}/CD24^{low}$ expression, the fraction usually associated with mammary epithelial stem cells. Consistently, they found that HMECs that had undergone an EMT formed 30–40-fold more mammospheres in suspension culture, which indicates the acquisition of mammary epithelial stem cell properties. Next, they showed that these cells also acquired self-renewal properties and that they were multipotent — capable of producing both luminal and basal cell lineages. Matrigel culture also revealed that HMECs that had undergone an EMT were capable of forming complex secondary structures comparable to normal mammary ducts. Collectively, these data indicate that the EMT confers stem-like properties to non-transformed HMECs.

So, do stem cells exhibit EMT markers? The authors assessed the RNA expression profiles of monolayer cultures of fractionated HMECs (that had not undergone experimentally induced EMT) and found that $CD44^{high}/CD24^{low}$-expressing cells exhibited an EMT-associated gene expression profile. Moreover, they showed that mouse mammary stem cells (isolated using the homologous $CD49f^{high}/CD24^{med}$ antigen phenotype) exhibited self-renewal properties and expressed markers associated with passage through the EMT.

Is this relevant to breast cancer? Using serial analysis of gene expression on three reduction mammoplasty and five breast carcinoma samples, the authors found that $CD44^{high}/CD24^{low}$ cells expressed high levels of mRNAs encoding mesenchymal markers. This indicates that mammary epithelial stem cells can be generated from more differentiated cell populations that undergo an EMT and that the EMT could produce the so-called 'cancer stem cells' from more differentiated tumour cells. Indeed, *ERBB2*-transformed HMECs that have undergone an EMT formed at least 10-fold more tumour spheres and colonies in soft agar than those that had not undergone an EMT and the expression of SNAIL or TWIST in HRAS-V12-transformed HMECs increased the number of tumour-initiating cells by about twofold, as determined by xenograft experiments.

Mani, Weinberg and colleagues suggest that the EMT might be a pathway that confers both metastatic and self-renewal properties to breast tumour cells, enabling disseminated tumour cells to produce macroscopic growths at sites of metastasis.

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ORIGINAL RESEARCH PAPER Mani, S. A. *et al.* The epithelial-mesenchymal transition generates cells with properties of stem cells. *Cell* **133**, 704–715 (2008)
FURTHER READING Thiery, J. P. Epithelial–mesenchymal transitions in tumour progression. *Nature Rev. Cancer* **2**, 442–454 (2002)