PROGNOSIS

A healing process

Tumours have often been referred to as 'wounds that never heal'. A report published by Marc van de Vijver and colleagues used gene-expression-profiling analysis to make a direct comparison between wounds and tumours, and found that a wound-response gene-expression pattern can indeed predict metastasis and survival likelihoods in patients with breast cancer.

Processes involved in wound healing, such as activation of matrix remodelling, cell motility and angiogenesis, are also common features of tumour progression. By analysing the gene-expression patterns of cells that mediate the wound-healing response, researchers previously identified a 'core serum response' signature that excluded cell-cycle genes and was representative of this process. Previous studies showed that in common epithelial tumours such as breast, lung and gastric cancers, expression of this wound-response signature predicted poor overall survival and increased risk of metastasis.

Van de Vijver and colleagues set out to validate these observations in a large independent data set. Using a database of 295 patients with breast cancer, they tested the reproducibility of the association between the wound-response signature and breast cancer progression by comparing the expression of 280 of the 459 core serum-response genes. They found that tumours with the activated wound-response signature were more likely to metastasize. Furthermore, patients with these tumours had decreased survival times.

In patients diagnosed with early breast cancer, there is a 30% risk of developing distant metastases. This risk can be decreased by giving adjuvant systemic chemotherapy and/or hormonal therapy after surgical removal of the primary tumour. Using the wound-response signature, the authors were able to more accurately identify the patients who later developed metastases — after 10 years, 49% of patients with an activated wound signature developed distant metastases. Adding this signature to other prognostic tests could therefore help to determine which patients could forgo adjuvant chemotherapy, and which ones should be recommended for more intensive forms of treatment.

The authors also conclude that identifying the molecular mechanisms that activate, sustain and eventually shut down the wound response in epithelial tumours might lead to targeted therapeutics.

Kristine Novak

References and links

ORIGINAL RESEARCH PAPER Chang, H. Y. *et al.* Robustness, scalability and integration of a wound-response gene expression signature in predicting breast cancer survival. *Proc. Natl Acad. Sci. USA* 8 Feb 2005 (doi:10.1073/pnas.0409462102)

BREAST CANCER

Of MYC and MET

Despite the increasing evidence that some breast tumours might arise from a tumour stem cell, current transgenic mouse models of this cancer generally use gene promoters that are active primarily in differentiated cells. An innovative model of breast cancer developed by Alana Welm and colleagues redresses this and provides evidence that MET and MYC, when overexpressed in progenitor cells, cooperate in breast tumorigenesis.

The authors used a retroviral vector called pMIG, which was developed from mouse stem-cell virus, with the aim that it would be expressed in progenitor or stem cells. This was confirmed by using the vector to express green-fluorescent protein (GFP) in mouse primary mammary epithelial cells, and transplanting the cells into mouse fat pads, which forced the cells to expand. Moreover, the cells developed into GFP-expressing mammary glands.

Overexpression of the proto-oncogene *MET* is evident in a subset of breast cancers and is strongly associated with poor prognosis, but little is known about its involvement in tumorigenesis. Also, MET expression increases fivefold during the differentiation of human breast progenitor cells. So Welm and colleagues isolated mammary epithelial cells from a transgenic mouse that expresses *MET* under the control of a tetracycline-response element. These cells were infected with pMIG expressing a tetracycline-repressible transactivator protein. Once the cells were transplanted, the recipient mice were either treated with the tetracycline derivative doxycycline, to repress *MET* expression, or left untreated, for overexpression driven by the transactivator.

Overexpression of MET led to the development of neoplastic clusters of epithelial cells in the reconstituted mammary glands, unlike the doxycycline-treated glands. Immunohistochemistry confirmed that the MET protein was actively signalling in the abnormal cells. Importantly, the overexpression of MET correlated with presence of the CK6 protein, a candidate marker for breast progenitor cells. However, the mice did not develop malignant tumours, indicating the involvement of other factors. The authors theorized that one of these might be MYC, which is also overexpressed in some breast cancers, although whether MET and MYC are usually co-expressed in human tumours is not known. Using the pMIG vector to overexpress MYC and MET in the mammary cells produced focal palpable tumours in the reconstituted glands; no tumours occurred in glands expressing MYC alone. Although the MYC/MET tumour cells were highly proliferative, no metastases were found.

The authors suggest that their approach will be useful in examining how other genes affect mammary tumorigenesis when expressed in progenitor cells. In addition, the use of this model might help to determine the characteristics of breast cancers that arise from less differentiated mammary epithelial cells.

Helen Dell

References and links

ORIGINAL RESEARCH PAPER Welm, A. L., Kim, S., Welm, B. E. & Bishop, J. M. MET and MYC cooperate in mammary tumorigenesis. *Proc. Natl Acad. Sci.* 28 Feb 2005 (doi:10.1073/pnas.0500470102)

FURTHER READING Smalley, M. & Ashworth, A. Stem cells and breast cancer: a field in transit. *Nature Rev. Cancer* **3**, 832–844 (2003)