METASTASIS

One step closer

The mystery of why breast cancer cells that express ERBB2 (HER2), a member of the epidermal growth factor receptor family, have a higher incidence of metastasis to specific organs is now one step closer to being solved. Hung and colleagues show that ERBB2 signalling increases the expression of a chemokine receptor whose ligand is highly expressed in lung, liver and bone marrow where metastases of breast cancer commonly develop.

Chemokines are a superfamily of small cytokine-like peptides involved in cell adhesion and migration. The expression of the CXC chemokine receptor 4 (CXCR4) and its natural ligand CXC chemokine ligand 12 (CXCL12) are known to be involved in breast cancer metastasis. As ERBB2 and CXCR4 can both be expressed in breast cancer cells, Hung and co-workers investigated whether there was a link between the two.

In human breast cancer cell lines, they showed that transgenic expression of *ERBB2* leads to increased CXCR4 expression, most likely through an increased rate of translation of *CXCR4* mRNA. Further *in vitro* studies demonstrated that blocking the activity of ERBB2 with the inhibitor trastuzumab (Herceptin), suppresses CXCR4 expression and blocks invasion mediated by CXCL12. Furthermore, inhibition of CXCR4 by a neutralizing antibody inhibits the migration and adhesion of ERBB2-expressing cells mediated by CXCL12. The authors also have evidence that degradation of CXCR4, once it has bound CXCL12, is reduced in ERBB2-expressing cells. This might be because ERBB2, by an unknown mechanism, reduces the ubiquitylation of CXCR4. In addition, studies in immunocompromised mice show that ERBB2-expressing breast cancer cells that no longer express significant levels of CXCR4, due to RNA interference, have a markedly reduced capacity to form lung metastases.

The human breast cancer biopsy samples that Hung and colleagues examined show that CXCR4 expression correlates with both increased ERBB2 expression and a poor prognosis. These findings indicate that targeting both the CXCR4–CXCL12 pathway and ERBB2 might improve the survival of breast cancer patients with ERBB2-positive tumours.

Nicola McCarthy

References and links

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FURTHER READING Epstein, R. The CXCL12–CXCR4 chemotactic pathway as a target of adjuvant breast cancer therapies. *Nature Rev. Cancer* **4**, 901–909 (2004)

CARCINOGENESIS

Unexpected origins

Helicobactor pylori infection and the associated chronic gastric inflammation often progresses to adenocarcinoma. Bone-marrow-derived cells (BMDCs) are recruited to sites of inflammation and JeanMarie Houghton *et al.* now report that these cells actually contribute to *Helicobactor*-induced gastric tumours — challenging the widely held view of the epithelial origin of gastric cancer.

The authors investigated the role of BMDCs in gastric carcinogenesis using a mouse model in which gastric cancer is induced by *Helicobactor felis* infection. Female mice were lethally irradiated and then transplanted with male bone marrow tagged with β-galactosidase (β-gal) or green fluorescent protein (GFP). Three weeks of *H. felis* infection led to intense bone-marrow-derived inflammation. After 20 weeks of infection, apoptosis levels increased in the gastric mucosa and β-gal- or GFP-positive glands appeared. By 52 weeks, 90% of the proximal mucosa had been replaced with BMDCs that were β-gal or GFP positive and also positive for trefoil factor 2, which is expressed in metaplastic mucosal cells and is often overexpressed in cancer. At this stage the tissues showed histological signs of metaplasia and dysplasia, and 1 year after infection intramucosal carcinoma or high-grade gastrointestinal intraepithelial neoplasia (GIN) was evident. The GIN lesions comprised of BMDCs, which were not only β-gal or GFP positive but also contained the Y-chromosome, were actively proliferating and stained positive for standard epithelial markers such as cytokeratins but negative for the haematopoietic cell marker CD45. The authors concluded that the BMDCs had differentiated into a gastric epithelial phenotype.

Helicobactor infection seems to be necessary for this phenotype because uninfected mice did not show any BMDC engraftment, and other types of tissue injury such as acute gastric ulceration or depletion of one of the main types of gastric epithelial cells did not induce BMDC recruitment either. Importantly, fusion between BMDCs and gastric epithelial cells was ruled out as a possible origin of the cancer cells.

So, what population of bone-marrow cells is responsible for *Helicobactor*-induced gastric cancer? Houghton *et al.* cultured haematopoietic stem cells or mesenchymal stem cells with soluble factors from primary gastric epithelial cell cultures. Only the mesenchymal stem cells showed upregulation of gastric mucosal cell gene expression pattern, including trefoil factor 2.

These data offer a new model for development of epithelial cancer from chronic inflammation, which has implications for our general understanding of cancer initiation and progression.

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References and links

ORIGINAL RESEARCH PAPER Houghton, J. *et al.* Gastric cancer originating from bone marrow-derived cells. *Science* **306**, 1568–1571 (2004)