METASTASIS

That time of the month

As much as we women like to deny it, there is always a certain 'time of the month' when we are more emotionally sensitive. According to a study in *Cancer Research* by Ann F. Chambers and colleagues, emotions aren't the only thing affected by the menstrual cycle — it also affects the metastatic ability of cancers cells.

They injected hormone-independent B16F10 melanoma cells into the tail vein of mice, predicting that most cells would lodge in the lungs and the rest would escape and disseminate. Mice were injected at two different phases of oestrous — during proestrus, when oestrogen levels are high, or during metestrus, when progesterone levels are high. After 24 days, as expected, metastatic burden was observed in both groups of mice with no significant difference between the number and size of lung metastases. But, when they examined extrapulmonary metastases they found astonishing differences. After 7 days, 16.7% of mice injected during metestrus had ovarian micrometastases and this rose to 31.6% with prominent ovarian metastases after 24 days. However, metastases were absent in mice injected during proestrus. The incidence of non-ovarian extrapulmonary metastases was not statistically significant between the two groups. So, it seems that the fluctuating hormonal environment at different stages of oestrous can have different effects on circulating tumour cells.

As B16F10 cells are hormone-independent, these effects seem to be caused by hormone sensitivity of the host. But why is the timing of tumour cell entry into the bloodstream crucial to the formation of metastases? Blood flow to the ovaries increases during metestrus and decreases during proestrus, indicating differential delivery of the cancer cells to the ovaries. Alternatively, differential support of growth in the ovaries at different stages of oestrous might occur because of hormone-induced gene expression. So, both theories require thorough investigation.

It is clear that this work might have serious implications for patients with breast cancer, as timing of surgery could have a marked effect on metastasis and, ultimately, survival. Previous clinical study results have been mixed and controversial. This model system should help to determine whether changes in clinical practice are necessary.

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References and links

ORIGINAL RESEARCH PAPER Vantyghem, S. A. *et al.* Estrous cycle influences organ-specific metastasis of B16F10 melanoma cells. *Cancer Res.* **63**, 4763–4765 (2003)

WEB SITE

Ann Chambers' lab:
http://www.lrcc.on.ca/research/staff/achambers/index.xml

BREAST CANCER

Recurrence

Some types of tumour are more likely than others to recur after surgical removal, and there is evidence indicating that processes triggered by surgery itself stimulate recurrence. However, the reasons why certain tumours recur more often than others are unclear. Human epidermal receptor 2 (HER2, also known as ERBB2) is expressed in 20–25% of breast carcinomas, and these tumours show a high frequency of recurrence. In the August issue of *The Lancet*, Sylvie Ménard and colleagues investigate the effects of surgery on proliferation of HER2-expressing breast carcinomas, and conclude that the release of specific growth factors triggered by surgery causes the high level of recurrence of these tumours.

The authors showed that overexpression of HER2 correlates with an increased number of proliferative cells in residual tumour tissue that remains after surgery. They also showed a similar effect *in vitro* by incubating breast-carcinoma cell lines with wound-drainage fluid obtained from patients with breast cancer after surgery. In these experiments, cells that overexpress HER2 showed higher levels of proliferation than other breast-carcinoma lines. Importantly, serum samples taken after surgery stimulated higher levels of proliferation in HER2-expressing cells than samples from the same patients taken before surgery, indicating that processes triggered during surgery cause the HER2-dependent increase in proliferation.

Growth factors are prime candidates for substances released after surgery that might trigger cell proliferation, and Ménard and colleagues found increased levels of epidermal growth factor (EGF)-like growth factors in serum samples taken after removal of breast carcinomas. Antibodies targeted against two of these molecules, transforming growth factor-α and heparin-binding EGF, which are released during wound healing, decreased the proliferative effect of drainage fluid on HER2-expressing cells by up to 50%. This indicates that cellular damage incurred during surgery might trigger growth-factor release and therefore induce proliferation through HER2. In support of this, the authors showed a correlation between the amount of tissue damage after surgery and both the levels of EGF-like factors present in serum and the level of drainage-fluid-induced proliferation.

Trastuzumab, an antibody against HER2, is already used to treat patients with HER2-expressing breast carcinomas. Ménard and colleagues investigated the potential to use this drug to inhibit the proliferation of HER2-expressing cells after surgery, and saw a decrease in proliferation when trastuzumab was added to cells one day before the addition of drainage fluid. This indicates that treatment of patients with HER2-expressing breast carcinomas with trastuzumab before surgery might be an effective way of minimizing the recurrence of this type of tumour.

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References and links

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Sylvie Ménard's lab:
http://www.istitutotumori.mi.it/int/oncologia/bersagli_molecolari.asp?Li