HIGHLIGHTS

METASTASIS

From breast to bone…

Breast cancer frequently metastasizes to bone, but is this because of an innate property of the breast cancer cells or do they acquire the necessary changes as they evolve? Joan Massagué and colleagues, reporting in *Cancer Cell*, show that even in the primary tumour a few cells express the genes needed to metastasize to bone.

The authors injected human breast cancer MDA-MB-231 cells into immunodeficient mice, and ~30% of these developed bone cancer within 12 weeks. These metastases were isolated, grown in culture and reinjected into mice. Interestingly, these cell populations had differing abilities to form bone metastases, and gene- expression profiling allowed the reason for this to be elucidated.

A gene-expression signature that correlated with metastasis and poor survival of breast cancer patients had previously been determined, and both the parental and highly metastatic cells shared a similar gene-expression profile, indicating that a different subset of genes must determine the metastatic ability. By comparing the profiles of weakly and highly metastasizing cell populations, the authors identified 102 genes that had significant differences in expression and examined four — *IL-11*, *MMP1*, *CXCR4* and *CTGF* — that were highly overexpressed in the metastatic population and that have diverse functions.

When expressed alone in the parental cells, only the bone-homing chemokine receptor *CXCR4* and the the protease *MMP1* were able to enhance metastasis. As *IL-11* induces osteoclast formation, the authors thought that it might promote metastasis when expressed with osteopontin (*OPN*), which stimulates osteoclast adhesion to the bone matrix and is also overexpressed in highly metastatic cells. Indeed, the two genes were found to collaborate to induce metastasis and, when combined with either *CXCR4* or the growth factor *CTGF*, generated cells that were almost as aggressive as the highly metastatic selected populations.

So, are these highly metastatic cells present in the original tumour, or are they selected for following further mutations? To investigate this, the authors isolated single cells from the parental population and grew them in culture. When injected into mice, several cell populations resulted in aggressive bone metastases, and these also expressed four or five of the genes — *IL-11, MMP1, CXCR4, CTGF* and *OPN* — that are involved in this process. Populations that did not express any of these genes did not form metastases. Interestingly, comparative genomic hybridization analysis did not reveal a significant increase in chromosome aberrations in the metastatic cells, compared with the parental cells, so the metastatic cells must be present in the primary tumour.

Only a few cells in the primary tumour therefore have the ability to metastasize, and a distinct set of genes facilitates this. Their identification unleashes new opportunities for therapeutic intervention.

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References and links

ORIGINAL RESEARCH PAPER Kang, Y. *et al.* A multigenic program mediating breast cancer metastasis to bone. *Cancer Cell* **3**, 537–549 (2003)

WEB SITES

Joan Massagué's lab:
http://www.mskcc.org/mskcc/html/10614.cfm