METASTASIS

Flying in the right direction

In spite of the fact that metastasis is the most dangerous aspect of tumour progression, it has been difficult to study in mammalian models because of variations in tumour and host genotypes. Raymond Pagliarini and Tian Xu addressed this issue by developing an elegant *Drosophila* model that simplifies the process of identifying genes that contribute to metastatic behaviour.

Drosophila develop tumours, and despite some key differences from mammals — such as lack of a vascular circulatory system — are becoming an important model system to study cancer. One of the key advantages to fruit flies is the ability to perform screens for genes that underlie specific phenotypes. Xu and colleagues have developed a new screen that allows them to look for genes that are involved in promoting metastasis. The assay begins with induction of non-invasive tumour formation in a defined location using cells that express an activated form of Ras and green fluorescent protein (GFP). The tumour cells are then mutagenized, through expression of the FLP recombinase, and flies are screened for mutants in which the GFP-labelled tumour cells have migrated to new tissues. Because *Drosophila* larvae are transparent, migration of fluorescent cells can be easily monitored.

The non-invasive tumours develop in the eye antennal disc/optic-lobe region (wild-type left panel, tumour right panel in photo) and do not spread beyond this region. Mutagenesis of these cells, however, results in the presence of GFP-labelled cells in ectopic sites. In one population of flies, the tumour cells migrated into the ventral nerve cord and eventually spread into the leg discs and tracheal vasculature. These tumour cells contained inactivating mutations in *scrib*, which encodes a protein that regulates cell polarity and size. Cells with mutations in *scrib* alone, however, grow poorly *in vivo* and do not invade other tissues, indicating that a combination of Scrib inactivation and Ras activation are needed to cause metastatic behaviour.

But how does inactivation of Scrib contribute to metastasis? Xu and colleagues observed that, similar to human malignant tumours, the basement membrane of the *Drosophila* tumours was degraded, and tumour cells downregulated E-cadherin expression — both these features promote cancer-cell migration. The authors found that disruption of other genes that regulate cell polarity and epithelial morphology, such as *dgl* and *cdc42*, also promoted metastasis in conjunction with activating Ras mutations.

So, what is the role of Ras in metastasis? Mutations in other genes that increase cell proliferation, growth or survival were not sufficient to cause the metastatic progression of $scrib^{-/-}$ cells, so further studies are needed to determine exactly how oncogenic Ras cooperates with cell-polarity genes to promote metastatic behaviour. The screen will probably yield other genes that are important for the induction of metastasis.

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References and links

ORIGINAL RESEARCH PAPER Pagliarini, R. A. & Xu, T. A genetic screen in *Drosophila* for metastatic behavior. *Science* 9 Oct 2003 (doi:10.1126/science.1088474)

FURTHER READING Steeg, P. S. Metastasis suppressors alter the signal transduction of cancer cells. *Nature Rev. Cancer* **3**, 55–63 (2003)

WEB SITE
Tian Xu's lab:
http://info.med.yale.edu/genetics/xu/