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#### METASTASIS

# Bad company

The company we keep can have a dramatic effect on our behaviour, and this holds true at the molecular level, too. Take transforming growth factor- $\beta$ (TGF- $\beta$ ), for instance: in the presence of active Ras, TGF- $\beta$  turns from a tumour suppressor, capable of inducing growth arrest and apoptosis, into a disruptor of cellular peace that causes metastasis. How does Ras coerce TGF- $\beta$ into such bad behaviour? Elzbieta Janda and colleagues give some explanations in the 21 January issue of *The Journal of Cell Biology*.

Several rather loosely defined terms have been used to describe migratory phenotypes in epithelial cells that might be related to metastasis. One of these, epithelial-mesenchymal transition (EMT), is used to mean the transformation of polar epithelial cells into spindle-shaped, motile cells that can pass through the basement membrane. By contrast, the term scattering was initially defined as induction of epithelial-cell motility in culture. Using a mouse breast epithelial cell line (EpH4) transformed by Ras (EpRas), the authors have distinguished between these two processes in the same cell type by measuring the expression of epithelial (E-cadherin and ZO-1) and mesenchymal (vimentin) markers. In response to hepatocyte growth factor or fibroblast growth factor, EpRas cells took on a fibroblast-like appearance and lost the polarized distribution of epithelial markers, but expression of these markers was maintained. TGF- $\beta$ , by contrast,



EpH4 cells overexpressing a MAPK-selective signalling mutant of Ha-Ras, in the absence (left) and presence (right) of TGF- $\beta$ , showing relocalization of  $\beta$ -catenin (green) and expression of vimentin (red) in response to TGF- $\beta$ . Courtesy of Stefan Grunert, Institute of Molecular Pathology, Vienna, Austria.

caused the loss of epithelial markers and the upregulation of mesenchymal markers. Inhibition of Ras with a farnesyltransferase inhibitor caused reversion to the epithelial phenotype.

Ras activates several effector pathways, including the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) pathways. Which of these mediates Ras's collaboration with TGF-β? The use of small-molecule inhibitors or selectively signalling Ras mutants showed that TGF- $\beta$  combined with hyperactive MAPK signalling was sufficient to induce EMT, whereas TGF-β plus elevated PI3K signalling induced scattering only: epithelial markers were retained (see picture). However, cells without elevated PI3K signalling were more sensitive to TGF-β-induced apoptosis.

Do these results hold true *in vivo*? EpH4 cells expressing constitutively active Ras or its MAPK- or PI3Kselective variants all formed tumours when injected into nude mice, whereas untransfected EpH4 cells, or cells that were protected from apoptosis by overexpressing Bcl-2, did not. But a metastasis assay revealed that only cells derived from tumours in which the MAPK pathway was hyperactive formed metastases.

Whether the PI3K pathway is required for TGF- $\beta$ -mediated metastasis has been a long-standing controversy. By differentiating scattering from EMT, Janda and colleagues might have drawn this discussion to a close: PI3K signalling protects cells from the lethal effects of TGF- $\beta$ , whereas the MAPK pathway cooperates with TGF- $\beta$  to drive metastasis.

Cath Brooksbank

# **W** References and links

**ORIGINAL RESEARCH PAPER** Janda, E. *et al.* Ras and TGF-β cooperatively regulate epithelial cell plasticity and metastasis: dissection of Ras signaling pathways. *J. Cell Biol.* **156**, 299–313 (2002)

#### WEB SITE Hartmut Beug's lab:

http://www.imp.univie.ac.at/groups/res.html