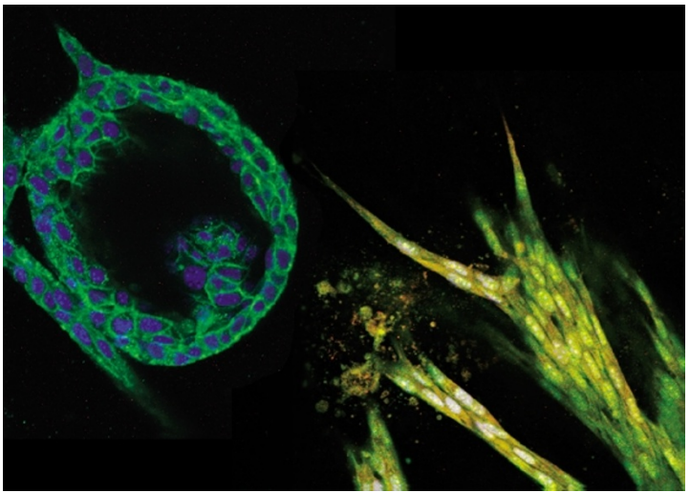
# HIGHLIGHTS



METASTASIS

## Bad company



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

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-β (TGF-β), for instance: in the presence of active Ras, TGF-β 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-β 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-β, by contrast, 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-β 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 PI3K-selective 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-β-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-β, whereas the MAPK pathway cooperates with TGF-β to drive metastasis.

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### 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