

## HIGHLIGHT ADVISORS

### ANTON BERNIS

NETHERLANDS CANCER INSTITUTE, AMSTERDAM, THE NETHERLANDS

### PETER BOYLE

EUROPEAN INSTITUTE OF ONCOLOGY, MILAN, ITALY

### PETER CARMELIET

CATHOLIC UNIVERSITY LEUVEN, LEUVEN, BELGIUM

### RON DEPINHO

HARVARD MEDICAL SCHOOL, BOSTON, MA, USA

### STEPHEN W. FESIK

ABBOTT LABORATORIES, ABBOTT PARK, IL, USA

### ELI GILBOA

DUKE UNIVERSITY MEDICAL CENTER, DURHAM, NC, USA

### TOMAS LINDAHL

IMPERIAL CANCER RESEARCH FUND, HERTFORDSHIRE, UK

### LANCE LIOTTA

NATIONAL CANCER INSTITUTE, BETHESDA, MD, USA

### JANET D. ROWLEY

UNIVERSITY OF CHICAGO MEDICAL CENTER, CHICAGO, IL, USA

### DAVID SIDRANSKY

JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE, BALTIMORE, MD, USA

### JÜRIG TSCHOPP

UNIVERSITY OF LAUSANNE, EPALINGES, SWITZERLAND

### BERT VOGELSTEIN

JOHNS HOPKINS ONCOLOGY CENTER, BALTIMORE, MD, USA

### ROBERT A. WEINBERG

WHITEHEAD INSTITUTE FOR BIOMEDICAL RESEARCH, CAMBRIDGE, MA, USA

### SAVIO WOO

MOUNT SINAI SCHOOL OF MEDICINE, NEW YORK, NY, USA

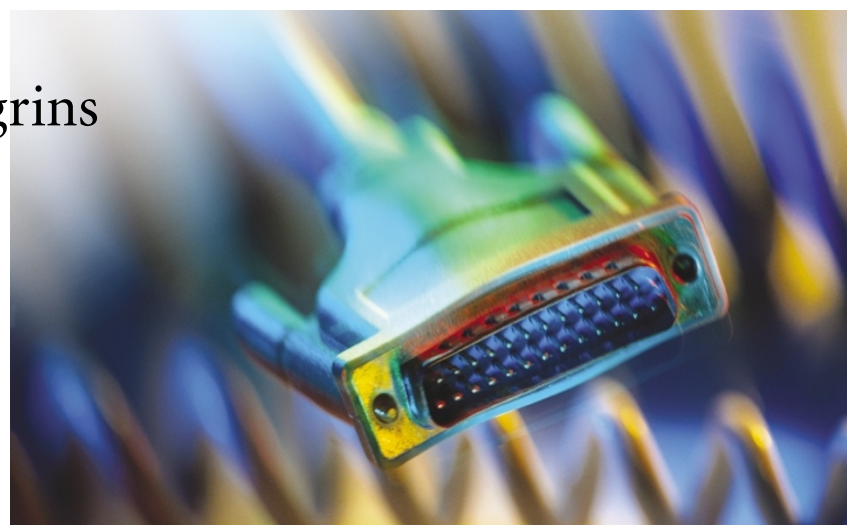
## METASTASIS

# Adaptable integrins

Adhesion is necessary for cell movement, so it comes as no surprise that many metastatic tumours overexpress integrins. But Livio Trusolino and colleagues now add a new dimension to our understanding of integrins in metastasis — one that doesn't involve adhesion at all.

A ligand-independent function for  $\alpha 6 \beta 4$  integrin in invasion was first suggested by Art Mercurio and colleagues in 1996, but what is its mechanism? Trusolino and colleagues wanted to know whether  $\alpha 6 \beta 4$  cooperates with another molecule that boosts invasive growth — Met, which is the receptor for hepatocyte growth factor (HGF; also known as scatter factor). Immunoprecipitations revealed that the two molecules physically interact, independently of HGF or cell attachment.

What effect does binding to  $\alpha 6 \beta 4$  have on Met's function? In response to HGF, cells expressing both molecules were much better at moving across matrigel than were cells expressing Met alone. The extracellular ligand for  $\alpha 6 \beta 4$  is laminin-5, but cells expressing Met and  $\alpha 6 \beta 4$  moved just as well over other substrates as they did over laminin-5, indicating that an interaction between  $\alpha 6 \beta 4$  and laminin-5 is not required for increased motility. Moreover, cells expressing a mutant form of the  $\beta 4$  subunit that lacks its laminin-5-binding domain were just as motile in response to HGF as cells expressing full-length  $\beta 4$ -integrin. And  $\alpha 6 \beta 4$  doesn't just help Met to



get cells moving — cell proliferation, survival and growth in soft agar were all improved by expression of  $\alpha 6 \beta 4$ . Furthermore, Met-expressing tumours grown in immunodeficient mice showed an increased ability to metastasize to lung when they also expressed  $\alpha 6 \beta 4$ .

If these responses don't involve adhesion, what else might  $\alpha 6 \beta 4$  be doing? Activation of Met increased phosphorylation of the  $\beta 4$  subunit on tyrosine. This phosphorylation seems to be direct because Met<sup>D</sup>, a mutant of Met that cannot bind any of its effectors, could still phosphorylate  $\beta 4$ . Might phosphorylated  $\beta 4$  recruit downstream signalling molecules? Agarose beads linked to the SH2 domain of the adaptor protein Shc, or an SH2 domain from phosphatidylinositol 3-kinase, could both pull down phosphorylated  $\beta 4$ -integrin. Signals downstream of these two proteins include mitogen-activated protein kinase and Akt (also known as protein kinase B) and, indeed, Met-induced activation of

both of these kinases was both longer and stronger in cells expressing  $\beta 4$ -integrin or the  $\beta 4$ -integrin mutant lacking its laminin-binding domain. Furthermore, cells expressing a  $\beta 4$  mutant lacking its Shc-binding tyrosine residues performed very poorly in invasion assays, and this mutant had a dominant-negative effect in cells expressing Met and  $\alpha 6 \beta 4$ .

So  $\beta 4$ -integrin is Met's accomplice in metastasis: only by working together can they recruit sufficient signalling molecules to yield powerful and sustained growth, survival and motility responses. Whether other integrins can help receptor tyrosine kinases out in this way is an intriguing question for the future.

*Cath Brooksbank*

## References and links

**ORIGINAL RESEARCH PAPER** Trusolino, L., Bertotti, A. & Comoglio, P. M. A signalling adapter function for  $\alpha 6 \beta 4$  integrin in the control of HGF-dependent invasive growth. *Cell* **107**, 643–654 (2001)

**FURTHER READING** Chao, C. *et al.* A function for the integrin  $\alpha 6 \beta 4$  in the invasive properties of colorectal carcinoma cells. *Cancer Res.* **56**, 4811–4819 (1996)