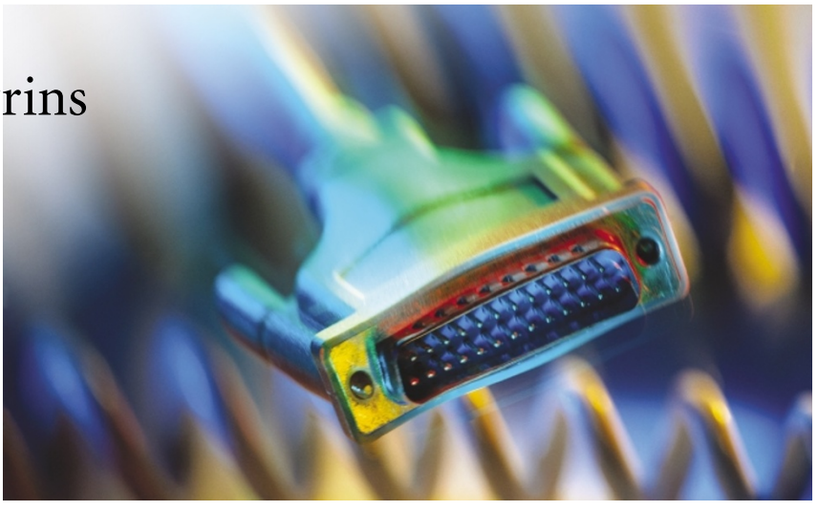
HIGHLIGHTS

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 a6b4 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 α6β4 cooperates with another molecule that boosts invasive growth — Met, which is the receptor for hepatocyte growth factor (HGF; also known as scatter factor). Immunopecipitations revealed that the two molecules physically interact, independently of HGF or cell attachment.

What effect does binding to α6β4 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 α6β4 is laminin-5, but cells expressing Met and α6β4 moved just as well over other substrates as they did over laminin-5, indicating that an interaction between α6β4 and laminin-5 is not required for increased motility. Moreover, cells expressing a mutant form of the β4 subunit that lacks its laminin-5-binding domain were just as motile in response to HGF as cells expressing full-length β4-integrin. And α6β4 doesn't just help Met to get cells moving — cell proliferation, survival and growth in soft agar were all improved by expression of α6β4. Furthermore, Met-expressing tumours grown in immunodeficient mice showed an increased ability to metastasize to lung when they also expressed α6β4.

If these responses don't involve adhesion, what else might α6β4 be doing? Activation of Met increased phosphorylation of the β4 subunit on tyrosine. This phosphorylation seems to be direct because Met^{D}, a mutant of Met that cannot bind any of its effectors, could still phosphorylate β4. Might phosphorylated β4 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 β4-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 β4-integrin or the β4-integrin mutant lacking its laminin-binding domain. Furthermore, cells expressing a β4 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 α6β4.

So β4-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.

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References and links

ORIGINAL RESEARCH PAPER Trusolino, L., Bertotti, A. & Comoglio, P. M. A signaling adapter function for α6β4 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 α6β4 in the invasive properties of colorectal carcinoma cells. *Cancer Res*. **56**, 4811–4819 (1996)