by introduction of the β_4 subunit. Importantly, a mutant version of β_4 lacking the entire ectodomain was as efficient as full-length β_4, indicating that $\alpha_6\beta_4$ integrin promotes invasion in a substrate-independent manner. Knock-down of β_4 production in A431 cells by antisense technology reduced the ability of A431 cells to respond to HGF in the invasion assays. In addition, HGF-induced anchorage-independent growth, a characteristic of tumour cells, was enhanced by production of $\alpha_6\beta_4$ integrin, supporting the notion that $\alpha_6\beta_4$ integrin was required for several Met-mediated functions.

Because the β_4 ectodomain was dispensable for the observed co-operation with Met, Comoglio and colleagues[3] speculated that Met would regulate $\alpha_6\beta_4$ signalling. They found that activation of Met did indeed lead to phosphorylation of $\alpha_6\beta_4$ integrin on tyrosine residues. Remarkably, a mutant version of Met carrying two phenylalanine-to-tyrosine substitutions, which ablate most of Met's signalling functions during development, could still mediate tyrosine phosphorylation of $\alpha_6\beta_4$, suggesting that $\alpha_6\beta_4$ is a direct substrate of Met. Tyrosine-phosphorylated $\alpha_6\beta_4$ recruited Shc and PI-3-kinase, and HGF triggered the phosphorylation of the downstream targets mitogen-activated protein kinase (MAPK) and protein kinase B (PKB)/Akt. Because Met signalling also activates these pathways via recruitment of Grb2 and Gab1, these findings suggested that β_4 acts as an important amplifier of Met signalling, independent of its role as a matrix receptor. Further proof for this concept was provided by experiments in which the Shc binding site on β_4 was mutated. Such a β_4 mutant had dominant-negative effects on the invasive behaviour of cells endogenously expressing Met and $\alpha_6\beta_4$. These findings therefore suggested that β_4 acted as an adaptor protein providing additional Shc binding sites to the Met–$\alpha_6\beta_4$ receptor complex, thereby amplifying Met signalling above a critical threshold for invasive behaviour (Fig. 1).

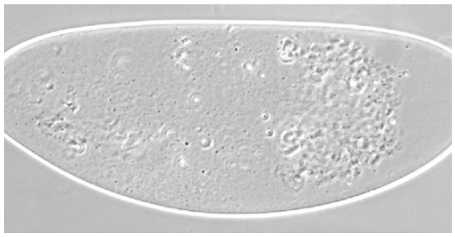
In summary, Comoglio and colleagues[3] present a new concept for integrin function. In untransformed cells, $\alpha_6\beta_4$ integrin serves mainly as an adhesive device, providing a link between the extracellular matrix and the cytoskeleton. However, in transformed cells, $\alpha_6\beta_4$ integrin functions as an intracellular adaptor for a receptor tyrosine kinase and its downstream oncogenic signalling pathways, independent of β_4's adhesive function. Conversion of adhesive receptors into signalling effectors might also provide an explanation of why oncogenic cells can grow in an anchorage-independent fashion.

This work also contributes to the much-debated issue of the specificity of signal transduction[12,13]. How can receptor tyrosine kinases mediate distinct biological effects? Do they provide a generic 'go' signal that is interpreted differently by individual cells or do they activate specific pathways by recruiting different effector proteins in different cells? Previous data from my lab had suggested that Met uses generic signalling mediators such as the multisite adaptor Gab1 and superimposes qualitatively different signals to achieve specific biological outcomes during development[14]. The exclusive association between Met and $\alpha_6\beta_4$ integrin in cancer cells supports the notion of receptor signalling specificity by association with unique partners to trigger precise cellular responses. □

Rüdiger Klein is in the Max-Planck Institute of Neurobiology, Department of Molecular Neurobiology, Am Klopferspitz 18A, D-82152 Martinsried, Germany.
e-mail: rklein@neuro.mpg.de

1. Ruoslahti, E. *Adv. Cancer Res.* **76,** 1–20 (1999).
2. Boudreau, N. & Bissell, M. J. *Curr. Opin. Cell Biol.* **10,** 640–646 (1998).
3. Trusolino, L., Bertotti, A. & Comoglio, P. M. *Cell* **107,** 643–654 (2001).
4. Mercurio, A. M., Rabinovitz, I. & Shaw, L. M. *Curr. Opin. Cell Biol.* **13,** 541–545 (2001).
5. De Arcangelis, A. & Georges-Labouesse, E. *Trends Genet.* **16,** 389–395 (2000).
6. Rabinovitz, I., Toker, A. & Mercurio, A. M. *J. Cell Biol.* **146,** 1147–1160 (1999).
7. Shaw, L. M., Rabinovitz, I., Wang, H. H., Toker, A. & Mercurio, A. M. *Cell* **91,** 949–960 (1997).
8. Dans, M. *et al. J. Biol. Chem.* **276,** 1494–1502 (2001).
9. Shaw, L. M. *Mol. Cell. Biol.* **21,** 5082–5093 (2001).
10. O'Connor, K. L., Shaw, L. M. & Mercurio, A. M. *J. Cell Biol.* **143,** 1749–1760 (1998).
11. Comoglio, P. M. & Boccaccio, C. *Semin. Cancer Biol.* **11,** 153–165 (2001).
12. Pawson, T. & Nash, P. *Genes Dev.* **14,** 1027–1047 (2000).
13. Schlessinger, J. *Cell* **103,** 211–225 (2000).
14. Maina, F. *et al. Mol. Cell* **7,** 1293–1306 (2001).

Reach for the stars



The landmark *Drosophila melanogaster* genetic screen carried out by Christiane Nüsslein-Volhard and Eric Wieschaus in 1980 (*Nature* **287**: 795-801) identified many mutants with defects in the embryonic cuticle (a secretion product of the epidermis). Twenty-five years later we are still trying to clone some of these genes and determine their functions. New work in *Nature* by Elisabeth Knust and colleagues (*Nature*, **414**: 638–642 2001), and Yuh-Nung Jan and colleagues (*Nature*, **414**: 634–637 2001), solves the mystery of one of these genes, *stardust*.

stardust mutants have severe embryonic defects similar to both *crumbs* and *shotgun* mutants (Crumbs encodes a transmembrane protein essential for establishing epithelial polarity, and Shotgun encodes DE-Cadherin, which is a component of the apical adherens junction). The mutant embryos in all three cases are literally blown to pieces (see picture). Until recently, however, the molecular nature of *stardust* was unknown. In the December 6th issue of *Nature* two groups show that the *stardust* gene encodes a MAGUK (membrane associated guanylate kinase) protein. MAGUK proteins contain one or several PDZ domains, one SH3 (Src homology) domain and one guanylate kinase domain. Jan and colleagues identified two MAGUK *sdt* isoforms, whereas Knust and colleagues identified one of these and an additional *sdt* isoform that only contains the guanylate kinase domain.

As *crumbs* (*crb*) mutants look similar to *stardust* (*sdt*) mutants, both groups went on to see whether the two proteins interact. Sdt does indeed bind to the carboxyl terminus of Crb. In addition, loss of either *sdt* or *crb* prevents formation of the SAC (subapical complex), a process essential for the formation of apical adherens junctions (a process that also includes the recruitment of E-Cadherin) and leads to a loss of epithelial polarity.

Interestingly, neuroblast polarity is unaffected. Neuroblasts form by delaminating from the epithelial layer; once they have separated from this layer, however, neither *sdt* or *crb* are needed to ensure their polarity.

One by one the pieces that will allow us to understand how epithelial polarity is generated are falling into place. It seems that Crb recruits Sdt into a complex (or vice versa), which is essential for epithelial cells to establish their initial polarity. As the molecular function of Sdt and its partners becomes clearer, we will be able to determine how this complex affects the recruitment of E-Cadherin and hence cell adhesion.

SARAH GREAVES