enzymes. The latter includes the HECT domains, the RING finger domains, and the recently identified U-box domain¹². Hakai belongs to the second group, as it has a RING finger domain highly related to that of the Cbl proto-oncoprotein. The relationship with Cbl may go beyond this domain and its function, as Hakai also exhibits a phosphotyrosine-binding domain and an extended proline-rich region that are highly related to those of Cbl. Although initial work indicated that the primary function of Cbl is to promote the downregulation of EGF receptors, a more complex picture has emerged from the realization that the internalization mechanism of a receptor can determine the repertoire of downstream signalling molecules it can activate¹³. In addition, Cbl itself is a substrate for tyrosine kinases and can function as an adaptor molecule, providing docking sites for the adapter protein CrkL and the p85 subunit of phosphatidylinositol-3-OH kinase¹⁴. Thus, Cbl

may function as an adaptor molecule, as well as a regulator of receptor trafficking and signalling, by functioning as an E3 ubiquitin ligase.

Many lines of research have demonstrated that cadherins can function as signal-transducing molecules, in addition to their better-understood function in cell adhesion¹⁵. These observations raise the possibility that Hakai may also regulate the signalling properties of E-cadherin, together with its likely function in regulating the dynamic remodelling of E-cadherin-based adherens junctions, under both physiological and pathological conditions. The many therapeutic implications of understanding, and thus controlling, cadherin recycling and its regulation will certainly fuel the interest of basic and translational scientists alike in the race to evaluate these exciting possibilities, and to elucidate fully their underlying molecular mechanisms. □

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1. Kemler, R. *Semin. Cell Biol.* 3, 149–155 (1992).
2. Takeichi, M. *Curr. Opin. Cell Biol.* 7, 619–627 (1995).
3. Gumbiner, B. M. *J. Cell Biol.* 148, 399–404 (2000).
4. Fujita *et al.* *Nature Cell Biol.* 4, 222–231 (2002).
5. Bonifacino, J. S. & Weissman, A. M. *Annu. Rev. Cell Dev. Biol.* 14, 19–57 (1998).
6. Hicke, L. & Riezman, H. *Cell* 84, 277–287 (1996).
7. Kamei, T. *et al.* *Oncogene* 18, 6776–6784 (1999).
8. Birchmeier, W. & Behrens, J. *Biochim. Biophys. Acta* 1198, 11–26 (1994).
9. Battle, E. *et al.* *Nature Cell Biol.* 2, 84–89 (2000).
10. Calautti, E. *et al.* *J. Cell Biol.* 156, 137–148 (2002).
11. Angst, B. D., Marozzi, C. & Magee, A. I. *J. Cell Sci.* 114, 625–626 (2001).
12. Patterson, C. *Sci. STKE* (cited 22 Jan 2002), http://stke.sciencemag.org/cgi/content/full/OC_sigtrans;2002/116/pe4 (2002).
13. Di Fiore, P. P. & De Camilli, P. *Cell* 106, 1–4 (2001).
14. Thien, C. B. & Langdon, W. Y. *Nature Rev. Mol. Cell Biol.* 2, 294–307 (2001).
15. Pece, S. & Gutkind, J. S. *J. Biol. Chem.* 275, 41227–41233 (2000).

Ready and Abl

The actin cytoskeleton is a dynamic network that is affected by signals generated from either growth factors or extracellular matrix proteins. The reverse is also true, as rearrangements in the actin cytoskeleton can influence signal transduction. c-Abl, a non-receptor tyrosine kinase, is at the interface of this crosstalk between growth-factor signalling, the extracellular matrix and cytoskeletal dynamics. c-Abl phosphorylates proteins involved in regulating actin dynamics; it also has an F-actin-binding domain (FABD). Because F-actin can inhibit c-Abl *in vitro*, it is highly likely that c-Abl and F-actin act together to regulate the actin cytoskeleton. Woodring *et al.* show in the latest edition of *The Journal of Cell Biology* (*J. Cell Biol.* 156, 879–892; 2002) that F-actin and c-Abl do indeed interact with one another to regulate the dynamics of cell morphology and motility.

Woodring *et al.* previously showed that purified c-Abl is inhibited by F-actin, an inhibition that can be relieved if the FABD in c-Abl is mutated. In suspended cells c-Abl colocalizes with F-actin, which correlates with a reduction in c-Abl kinase activity, but in adhered cells c-Abl dissociates from F-actin and remains dissociated at a steady state. This correlates with an increase in c-Abl kinase activity. Treating cells with latrunculin, which disrupts the structure of the actin cytoskeleton, prevents c-Abl and F-actin from associating, and increases the activity of c-Abl.

The authors also demonstrate that the formation of actin microspikes in fibroblasts that are spreading on fibronectin requires c-Abl, but not Src or the Rho family of GTPases (see figure; c-Abl is shown in red and actin is shown in green). Although this activation of actin microspikes does not require the FABD, it does require c-Abl's kinase activity. This raises an interesting reciprocal interaction between c-Abl and F-actin. c-Abl can clearly activate actin microspike formation independently of the FABD, while at the same time F-actin can act to inhibit c-Abl

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activity via the FABD.

Clearly crosstalk between the actin cytoskeleton and c-Abl is more complicated than previously thought. Interactions between both c-Abl and F-actin might provide a feedback mechanism that allows cells to regulate actin cytoskeleton dynamics.

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