

 MILESTONE 12

First (focal) contact



Benny Geiger and Keith Burridge launched the molecular era of focal adhesion research.

Rick Horwitz



The attachment of cells to the extracellular matrix (ECM) underpins activities from embryogenesis to tumorigenesis. In the late 1970s and early 1980s, advances in microscopy allowed researchers to visualize the focal adhesions that link cellular actin microfilaments to the ECM (see [Milestone 2](#)). The initial identification of focal contact proteins, and early insights into cell–substratum attachment, laid the groundwork for continuing studies into cell adhesion and migration.

In 1978, Heath and Dunn provided the first evidence that actin microfilament bundles terminated at a focal contact with the ECM. The identification of focal adhesion proteins proceeded concurrently, as Lazarides and Burridge reported in 1975 that the cytoskeletal protein α -actinin localized at actin filament termini. A few years later, Geiger *et al.* found that the cytoskeletal protein vinculin co-localized with α -actinin at focal adhesions, indicating the importance of these two proteins in attaching actin filaments to the ECM.

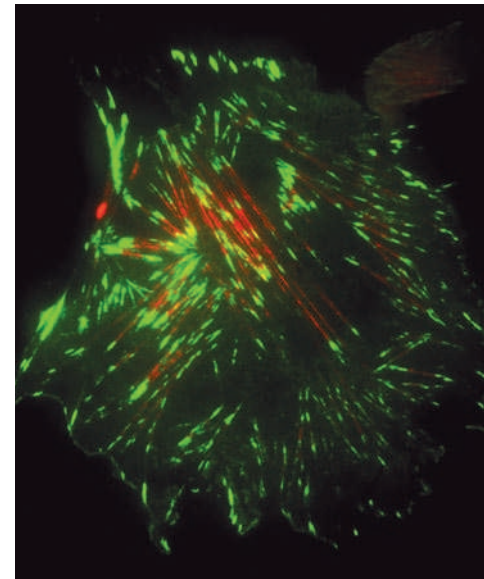
A link between intercellular proteins and the ECM was identified that same year, when Hynes and Destree detected the ECM protein fibronectin at actin microfilament termini. This was later confirmed by electron microscopy (see [Further reading](#)). However, it was the work of Horwitz *et al.* in 1986 that elucidated how cytoplasmic actin fibres made

contact with extracellular fibronectin. They found that cell-surface receptors known as integrins, which had previously been shown to bind to fibronectin, also interacted with the cytoskeletal protein talin, which in turn bound vinculin. These observations provided the first model of the focal adhesion as a multiprotein complex in which integrins link actin-associated cytoplasmic proteins to the ECM.

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ORIGINAL RESEARCH PAPERS Lazarides, E. & Burridge, K. Alpha-actinin: immunofluorescent localization of a muscle structural protein in nonmuscle cells. *Cell* **6**, 289–298 (1975) | Heath, J. P. & Dunn, G. A. Cell to substratum contacts of chick fibroblasts and their relation to the microfilament system. A correlated interference-reflexion and high-voltage electron-microscope study. *J. Cell Sci.* **29**, 197–212 (1978) | Hynes, R. O. & Destree, A. T. Relationships between fibronectin (LETS protein) and actin. *Cell* **15**, 875–886 (1978) | Geiger, B. *et al.* Vinculin, an intracellular protein localized at specialized sites where microfilament bundles terminate at cell membranes. *Proc. Natl Acad. Sci. USA* **77**, 4127–4131 (1980) | Horwitz, A. *et al.* Interaction of plasma membrane fibronectin receptor with talin—a transmembrane linkage. *Nature* **320**, 531–533 (1986)

FURTHER READING Geiger, B. A 130K protein from chicken gizzard: its localization at the termini of microfilament bundles in cultured chicken cells. *Cell* **18**, 193–205 (1979) | Singer, I. I. The fibronexus: a transmembrane association of fibronectin-containing fibers and bundles of 5 nm microfilaments in hamster and human fibroblasts. *Cell* **16**, 675–685 (1979) | Burridge, K. & Connell, L. Talin: a cytoskeletal component concentrated in adhesion plaques and other sites of actin–membrane interaction. *Cell Motil.* **3**, 405–417 (1983)



Paxillin (green), a marker of adhesions, and the myosin regulatory light chain (red) in a Chinese hamster ovary cell; note the actomyosin filaments that link adhesions. Image courtesy of M. Vicente-Manzanares and A. F. Horwitz, University of Virginia, USA.