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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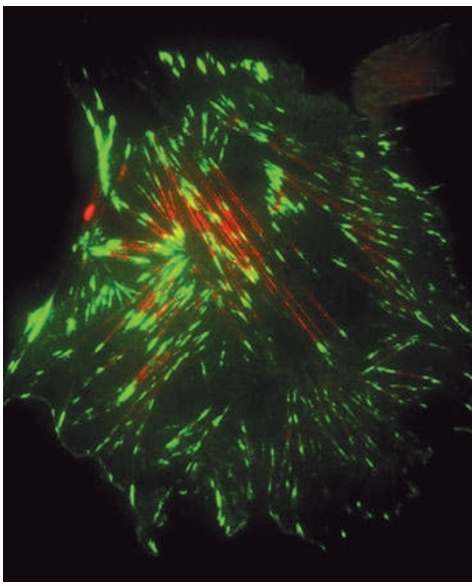

Paxillin (green), a marker of adhesions, and the myosin regulatory light chain (red) in a chinese hamster ovary cell; note the actomyosin filaments that link adhesions. Image courtesy of M. Vicente-Manzanares and A. F. Horwitz, University of Virginia, USA.