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CELL SIGNALLING

How to lead a double life

> "…kindlin-2 as a novel regulator of integrin activation…"

Integrins are bidirectional signalling molecules. Their affinity for ligands (integrin activation) is regulated by direct interactions of the β-subunit cytoplasmic tails with the cytoskeletal protein talin (inside-out signalling). Following ligand binding, integrins transduce signals into cells (outside-in signalling) by recruiting proteins to their cytoplasmic tails, which results in actin reorganization and modulation of signalling pathways. The current model proposes that talin binding is sufficient for integrin activation. Two studies now challenge this model and show that the focal adhesion protein kindlin-2 binds to the integrin tails and regulates integrin bidirectional signalling.

The groups of Reinhard Fassler and Edward Plow both show that kindlin-2 regulates integrin activation by binding to the integrin cytoplasmic domains at a distinct site from where talin binds. Expression of kindlin-2 with talin results in a synergistic effect on αIIbβ3 integrin activation, which suggests that kindlin-2 acts with talin to trigger activation of β3 integrins. In support of this finding, talin-induced αIIbβ3 activation was inhibited in kindlin-2-deficient cells.

Fassler and colleagues also showed that loss of kindlin-2 abrogates adhesion and spreading on extracellular matrix substrates and is associated with defects in filamentous actin polarization. These defects were attributed to the lack of interaction of kindlin-2 with the integrin-linked kinase (ILK) complex, which regulates cell spreading and actin-cytoskeleton organization. Kindlin-2 was found to interact with ILK and mediate ILK recruitment to focal adhesions. So, kindlin-2 might be the long-sought-after binding partner that brings ILK to these sites.

The role of kindlin-2 as a novel regulator of integrin activation was also confirmed *in vivo;* loss of kindlin-2 results in pre-implantation lethality caused by severe detachment of the endoderm and epiblast from the basement membrane owing to reduced integrin activation and integrin signalling.

These studies suggest that kindlin-2 is required for integrin inside-out and outside-in signalling.

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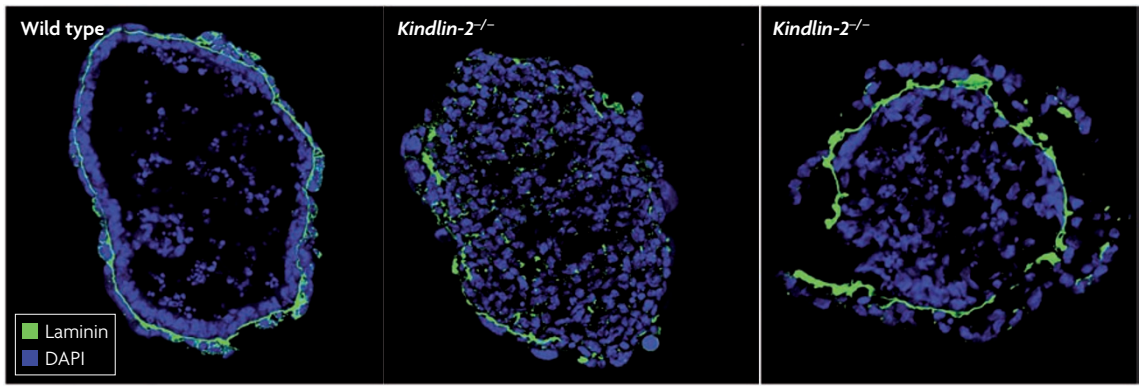

Abnormal basement membrane and cell adhesion in kindlin-2-deficient embryoid bodies. Image courtesy of M. Moser, Department of Molecular Medicine, Max Planck Institute of Biochemistry, Martinsried, Germany.