

### **Integrins, Focal Adhesions and all That**

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The integrin family of cell adhesion molecules provide a mechanical link between the extracellular matrix (ECM) and the cytoskeleton, and form the nuclei of structural and signaling complexes that regulate cell migration, proliferation and survival, typically in concert with receptors for soluble ligands. Integrins are initially activated by intracellular (“inside-out”) signals; following ligation to the ECM, “outside-in” signals lead to reorganization of the cytoskeleton and activation of intracellular signal transduction pathways. Recent studies have demonstrated a critical role for the cytoskeletal protein talin, which binds to the integrin  $\beta$  subunit cytoplasmic tail, disrupting  $\alpha\beta$  tail association and promoting a conformational change in the extracellular domains that leads to enhanced affinity for ECM proteins, and the subsequent clustering of integrins on the cell surface. So what activates talin? Recent evidence points to a prominent role for the enzyme, phosphatidylinositol phosphate kinase type 1- $\gamma$  (PIP1 $\gamma$ ), which forms complexes with both Src and talin at focal adhesions. PIP1 $\gamma$  synthesizes the lipid phosphatidylinositol 4,5 bisphosphate (PtdIns(4,5)P<sub>2</sub>), a key activator of proteins involved in focal adhesion assembly, including talin and vinculin. Our latest structural studies on integrin, PIP1 $\gamma$ , talin and vinculin and their complexes, will be discussed in this context.

**Keywords:** cell adhesion, integrins, intracellular signals