Structural Relays in Adhesion Signaling

Tina Izard, *Department of Hematology-Oncology, St. Jude Children's Research Hospital, Memphis, TN, USA*. E-mail: tina.izard@stjude.org

The formation of adherens junctions or focal adhesions relies on the interactions of the cytoskeletal proteins talin or α-actinin with vinculin, which binds to actin. Vinculin contains a head (Vh1) domain that interacts in an intramolecular fashion with its tail (Vt) domain, and this interaction clasps vinculin in its inactive state [1]. The signal(s) that disrupt the Vh1-Vt interaction to activate vinculin were unknown. Surprisingly, our crystal structures of full-length, inactive vinculin [1], and of the vinculin:talin [2,3] and vinculin:α-actinin [4] complexes, and our biochemical and biological studies, have revealed that talin and α-actinin trigger vinculin activation. Specifically, talin's and α-actinin's vinculin binding sites (VBSs) activate vinculin by displacing Vt from a distance, by provoking a totally new alteration in protein structure coined helical bundle conversion [2]. Strikingly, our structure of α-actinin's VBS (αVBS) in complex with vinculin established that this VBS must first unravel to bind and activate vinculin. αVBS then binds to vinculin's Vh1 domain in an inverted orientation compared to talin's VBSs, and provokes unique changes in the conformation of full-length vinculin, opening up far-distant regions in the molecule [4]. Collectively, these findings suggest that adhesion signaling involves a chain reaction of structural signals that is triggered by α-actinin and talin, which then activate vinculin.

[1] Borgon R.A., *et al.*, *Structure*, 2004, **12**, 1189. [2] Izard T., *et al.*, *Nature*, 2004, **427,** 171. [3] Izard T., Vonrhein C., *J. Biol. Chem.*, 2004, **279**, 27667. [4] Bois P.R.J., *et al.*, *Mol. Cell. Biol.*, *in press.*

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