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Three-Dimensional Structure of Full Length Integrin embedded in Membrane

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Electron cryo-microscopy, three-dimensional image analysis and computational docking were used along with biochemical and biophysical approaches to provide the three-dimensional (3D) structure of full length $\alpha_{IIb}\beta_3$ integrin while in a membrane bilayer. Integrins are expressed on the cell surface in either an "on" or an "off" state with respect to ligand binding. Increased ligand binding affinity of integrins is central to cell migration, extracellular matrix assembly, immune response, and hemostasis. The transition between the on and off affinity states is referred to as activation, a topic that is under intense study, and which is often the subject of considerable debate.

Much of the current thought on the mechanism of integrin activation is inferred from crystal structures of the β3 integrin ectodomains. All of these structures show the receptor to adopt a "bent" conformation, where the headpiece containing the ligand binding site is pointed in the same direction as the tail. Attempts to reconcile these bent crystal structures with two-dimensional (2D) electron microscopy images that seem to indicate an upright conformation have led to the idea that the transition between conformations could equate to a biochemical transition in ligand binding affinity, or activation.

Our results provide direct structural evidence that both the "on" and "off" forms of integrin $\alpha_{IIb}\beta_3$ are distributed across multiple conformations, ranging from a compact nodule to a fully upright stance. The experimental system employed provides the means to examine the structure of full-length receptors in the presence or absence of their activators and thus does not rely on the "computational ligation" of independently determined structures of extracellular face and cytoplasmic domains. Here, in this study we identify the density associated with a cytoplasmic activator (talin) juxtaposed with the membrane where it associates with the C-terminal region of integrin while embedded in the membrane. Consequently, here we show that integrin extension does not equate to activation of ligand binding function and thus extension is not synonymous with activation, nor is the activation state of the integrin correlated with any particular global conformation. Together these observations suggest important revisions to the current models of integrin activation.

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