

Poster Presentation

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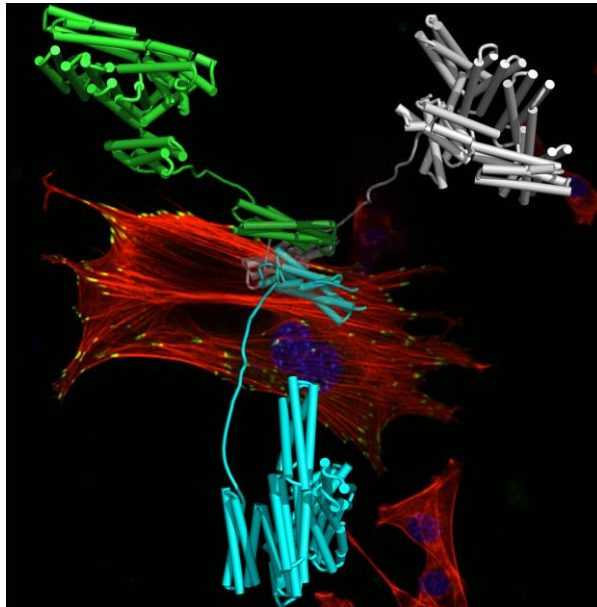
Lipid-directed cytoskeletal protein oligomerization at sites of cell adhesion

K. Chinthalapudi¹, E. Rangarajan¹, D. Patil¹, T. Izard¹

¹The Scripps Research Institute, Jupiter, USA

Vertebrate cell growth, division, migration, morphogenesis, and development, rely on the dynamic interactions of cells with components the extracellular matrix (ECM) via cell surface complexes. These focal adhesions (FAs) are comprised of integrin receptors, associated signaling molecules, and talin, which is required for “inside-out” signaling that stabilizes contacts of integrin receptors with the ECM by linking FAs to the actin cytoskeleton by binding to vinculin. The highly dynamic interactions with the actin cytoskeleton are also essential for the formation of membrane protrusions (lamellopodia and filopodia). Second messengers are found at the plasma cell membrane and include signaling lipids such as phosphoinositides, which play essential roles in signal transduction pathways and in directing the oligomerization of cytoskeletal proteins that function as essential links of FAs to the actin cytoskeleton. Notably, the most abundant phosphoinositide, phosphatidyl (4,5) bisphosphate (PIP2), directly binds to key cytoskeletal proteins, where it triggers homotypic and heterotypic interactions that amplify binding to the actin network. Binding of the inositol head group and the hydrophobic acyl chain pose difficulties in generating protein/PIP2 complex crystals and here we present the only second non-membrane protein structure of such a complex. Our crystal structure and biochemical approaches define the roles of PIP2 in controlling the oligomerization of cytoskeletal proteins and their binding to adhesion receptors and to the actin cytoskeleton. Importantly, we also determined the contribution of PIP2-directed oligomerization of cytoskeletal proteins to the formation and stabilization of adhesion complexes. These studies provide important new insights into how dynamic interactions of cytoskeletal proteins with the lipid membrane, adhesion complexes, and the actin network direct the mechanical behaviors of cells.

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