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LD motif interacting networks in cell-matrix adhesion

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Statement of the Problem: Cell-matrix adhesion requires assembly of large multi-protein complexes linked to the cyto-domains on the integrin adhesion receptors. These complexes dynamically change in response to the adhesion forces and environmental signals. Mechano-sensitive adaptor protein talin couples the force and adhesion signaling by acting as a hub for numerous, often competitive, interactions. The molecular mechanism that controls the co-ordination of the interactions in time and space is currently not understood. The aim of this study is to define the interactions between talin and Rho-GAP Deleted in Liver Cancer 1 (DLC1) that regulates adhesion forces.

Methodology: Structure of the talin/DLC1 complex was solved by X-ray crystallography and the interactions between the proteins analyzed by NMR spectroscopy. Fluorescent imaging was used to define the interactions within the adhesion complexes and cancer cell lines were employed to characterize the effect of the interaction on the biological activity.

Findings: We defined the atomic details of the talin/DLC1 interactions and used this information to identify signaling protein paxillin as a talin ligand. Based on the structural information we designed a range of talin mutants that modulate the interactions and demonstrated that the mutations reduce DLC1 signaling in adhesion.

Conclusion & Significance: Talin recognizes LD motifs in DLC1 and paxillin through a set of well-defined charge interactions. These interactions are like other LD motif interactions previously identified in signaling pathways. These interactions are also like the interactions between talin, RIAM and vinculin that were previously not assigned to the LD motif family. Together, the relatively weak LD motif interactions within the adhesion complex create a protein network that could dynamically respond to the adhesion signals.

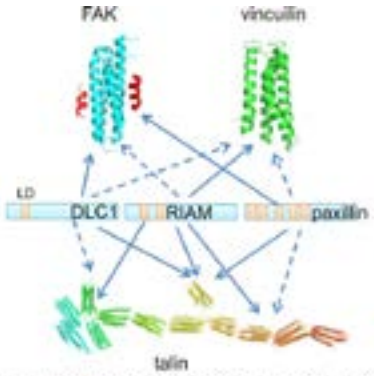

Figure 1. LD motif interactions inter-connecting adhesion proteins

Biography

Igor L Barsukov has expertise in Structural Biology, primarily using NMR spectroscopy and X-ray crystallography. The focus of his research has been on the structure and function of integrin-mediated cell-matrix adhesions, where he directed full structural analysis of the key adhesion proteins talin, leading to the currently widely used model of stretch-dependent talin activation. He is currently extending the model of talin functionality to include competitive, talin based, interaction networks. Recently he identified interactions between neuronal scaffold proteins Shank3 and Ras-family GTPase that regulate integrin activity and have implications for control of synaptic plasticity.

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