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Vinculin Tail Dimerization and Paxillin Binding

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Vinculin is a highly conserved cytoskeletal protein that is essential for regulation of cell morphology and migration, and is a critical component of both cell-cell and cell-matrix complexes. The tail domain of vinculin (Vt) was crystallized as a homodimer and is believed to bind F-actin as a dimer. We have characterized Vt dimerization by Nuclear Magnetic Resonance (NMR) Spectroscopy and identified the dimer interface in solution by chemical shift perturbation. The Vt dimer interface in solution is similar to the crystallographic dimer interface. Interestingly, the Vt dimer interface determined by NMR partially overlaps the paxillin binding region previously defined coarsely by deletion mutagenesis and gel-blot assays. To further characterize the paxillin binding site in Vt and probe relationship between paxillin binding and dimerization, we conducted chemical shift perturbations experiments using a paxillin derived peptide, LD2. Our NMR experiments have confirmed that the paxillin binding site and the Vt dimerization site partially overlap, and we have further characterized both of these two binding interfaces. Information derived from these studies was used to identify mutations in Vt that selectively perturb paxillin binding and Vt self-association. These mutants are currently being characterized for their utility in structural and biological analyses to elucidate the role of paxillin binding and Vt dimerization in vinculin function.