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Crystal Structures of GRIP1 PDZ6-Peptide (liprin C-termius) complex and Shank PDZ-Peptide (GKAP C-terminus) complex

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Introduction

Synaptic localization and clustering of ion channels and receptors is often mediated by scaffolding molecules containing the protein-protein interaction motifs called PDZ domains.

Glutamate receptor interacting protein (GRIP) contains seven PDZ domains and interact via the sixth PDZ domain with the C-terminus of liprin-α. In addition the PDZ456 domain mediates the formation of homo- and heteromultimers of GRIP proteins.

The Shank PDZ domain binds to the C-terminus of guanylate kinase-associated protein, which in turn interacts with the guanylate kinase domain of postsynaptic density-95 scaffolding protein.

Results and Discussion

Overall Structure of the GRIP PDZ6 domain

GRIP PDZ6 is a compact, globular domain containing six β-strands that form an antiparallel β-barrel and two α-helices. GRIP PDZ6 binds to the liprin-α C-terminal TYSC sequence via a class II hydrophobic PDZ interaction (Figure 1).

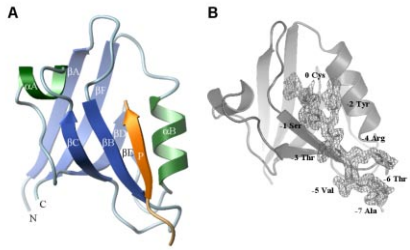

Figure 1. Structure of the GRIP1 PDZ6 domain

Dimerization of GRIP PDZ6 domains

To confirm the configuration of PDZ6 dimerin solution, we did mutational analysis on the residues at the dimeric interface and measured the molecular weights of the mutants and wild type PDZ domains in solution using size exclusion chromatography (Figure 2). The Y671D mutant, which was expected to disrupt the hydrophobic interaction in the dimeric interface, was eluted as a monomer, while the wild type PDZ6 was a dimer in solution. The disruption of salt-bridge by the mutation R718D on the residue participating in self-association of the domains in the crystalline state did not affect the oligomeric state of the PDZ domains

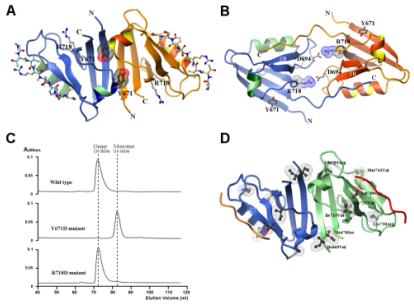

Figure 2. Dimerization of GRIP PDZ6

Structure of Shank PDZ-GKAP C-terminus peptide complex

The crystal structures of Shank PDZ in its peptide free form and in complex with the C-terminal hexapeptide (EAQTRL) of guanylate kinase associated protein (GKAP) determined at 1.8 and 2.25 Å resolutions, respectively (Figure 3A and B).

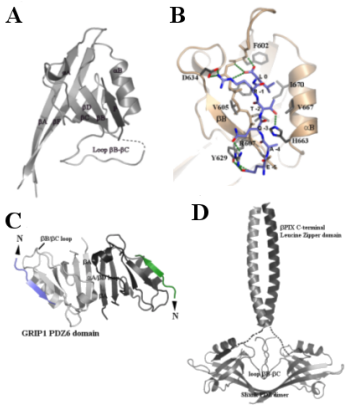

Figure 3. Overall structure of Shank PDZ domain

Shank PDZ dimer

Shank PDZ domains form dimmers with a conserved βB/βC loop and N-terminal βA strands, suggesting a novel mode of PDZ-PDZ homodimerization. This configuration may provide a means of facilitating dimeric organization of PDZ target assemblies (Figure 3C and D).

References

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