Structural basis of Shank PDZ interaction with the C-terminal peptide of GKAP protein and the mode of PDZ domain dimerization

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Abstract: *We have crystallized and determined the structures of the Shank PDZ domain, alone and in complex with the synthetic C-terminal hexapeptide of GKAP protein at resolutions of 1.8 Å and 2.5 Å, respectively. The structure revealed the structural basis of the ligand recognition by Class I PDZ-ligand interaction. Moreover, dimeric structure of Shank PDZ domain suggests that the βA strand is a common surface for dimerization of PDZ domains.*

Introduction: The Shank/ProSAP family of multidomain proteins is known to play an important role in organization of synaptic multiprotein complexes via the protein-protein interaction modules. Shank proteins with marked heterogeneity share a common domain organization, consisting of N-terminal seven ankyrin repeats, followed by an SH3 domain, a PDZ domain, a long proline-rich segments, and a SAM domain. PDZ domains containing about 80-100 amino acids are molecular-recognition elements that mediate protein-protein interactions. Here, to elucidate the structural mechanism of protein-protein interaction of Shank1 PDZ with GKAP protein, we determined the crystal structures of Shank PDZ domain in peptide-free form and in complex with its specific peptide ligand by multiwavelength anomalous dispersion and molecular replacements.

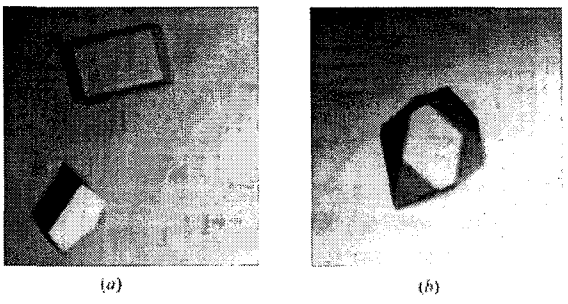

Figure 1: (a) Crystal of the Shank1 PDZ domain. (b) Crystal of Shank1 PDZ complexed with the GKAP C-terminal octapeptide.

Molecular basis of peptide recognition:

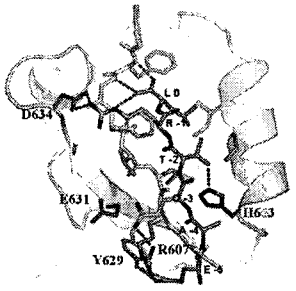

Figure 2: Ball and stick model of the peptide binding pocket and its specific ligand (EAQTRL).

The peptide ligand inserts into the peptide biding pocket antiparallel to the βB strand making extensive network of hydrogen bonds and hydrophobic interaction (Figure 2). The structure shows that the C-terminal sequence preferred by Shank's PDZ domain is –X-T/S-R/K-L.

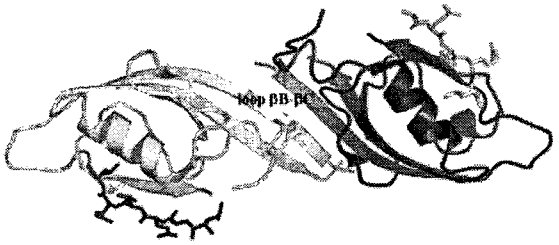

Figure 3: Dimeric structure of Shank PDZ domain.

Dimerization of PDZ6 domain: The structure revealed that Shank PDZ forms an antiparallel dimer through an interface located at a site distal to the peptide-binding groove (Figure 3). The structure suggests that N-terminal βA strand of the PDZ domains may provide the protein-protein interaction surfaces through the formation of antiparallel β-sheet interaction.

Summary: The crystal structures of Shank PDZ-peptide complex shows that it belongs to the Class I PDZ-peptide interaction, and the additional interactions at -1, -3 and -5 positions contribute to the specific recognition of GKAP C-terminal peptide. The dimeric structure of Shank PDZ domain showed the possibilities of PDZ domain-mediated multimerization in Shank proteins facilitating the clustering of related proteins.