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Crystal Structure of GRIP1 PDZ6-peptide complex reveals the structural basis for class II PDZ target recognition and PDZ domain-mediated multimerization

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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, these globular domains each contain two α helices and six β strands [1]. They usually bind selectively to the C-terminus or a short internal segment of interacting proteins. Members of the GRIP family proteins contain six to seven PDZ domains. GRIP PDZ6 interacts with the C-terminus of ephrin-B1 ligand and EphB2/EphA7 receptor as well as with the C-terminus of the liprin-α protein [2]. PDZ456 region mediates homo- and heteromultimerization of GRIPs. This study describes the first crystal structure of a class II PDZ domain non-covalently complexed with its specific peptide ligand, showing an additional role of PDZ domains in the multimerization of PDZ containing proteins.

Results and Discussion

Molecular basis of peptide recognition

PDZ domains bind to short segments within target proteins in a sequence-specific fashion. GRIP1 PDZ6 recognizes the hydrophobic residues of the ligand at 0 and -2 position. Remarkably, unlike other class II PDZ domains, Ile736 at αB5 rather than conserved Leu732 at αB1 makes a direct hydrophobic contact with the side chain of the Tyr at the −2 position of the ligand (Figure 1).

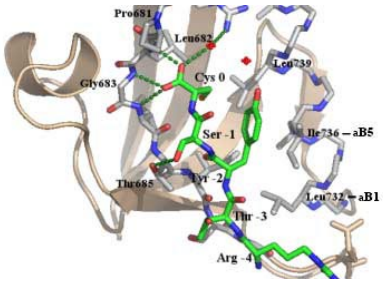

Figure 1: Molecular surface of GRIP PDZ6 showing the hydrophobic binding pocket and the bound peptide

Dimerization of PDZ6 domain

The structure revealed that GRIP1 PDZ6 forms an antiparallel dimer through an interface located at a site distal to the peptide-binding groove (Figure 2) resulting in independent target binding by the PDZ multimers.

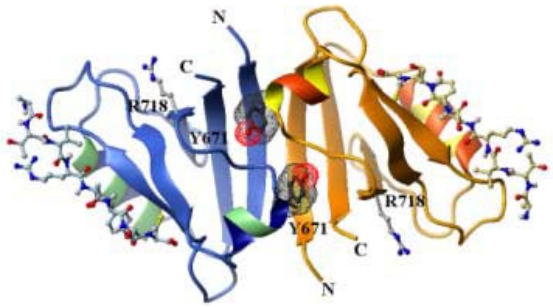

Figure 2: Dimeric structure of PDZ6 domain.

Conclusion

We determined the crystal structures of the GRIP1 PDZ6 domain, alone and in complex with a synthetic C-terminal octapeptide of human liprin-α, at resolutions of 1.5 Å and 1.8 Å, respectively. Remarkably, unlike other class II PDZ domains, Ile736 at αB5 rather than conserved Leu732 at αB1 makes a direct hydrophobic contact with the side chain of the Tyr at the −2 position of the ligand. Moreover, the peptide-bound structure of PDZ6 forms an antiparallel dimer through an interface located at a site distal to the peptide-binding groove. This configuration may enable formation of GRIP multimers and efficient clustering of GRIP-binding proteins.

References

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