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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PDZ domains bind to short segments within target proteins in a sequence-specific fashion. GRIP/ABP family proteins contain six to seven PDZ domains and interact via its sixth PDZ domain (class II) with the C-termini of various proteins, including liprin-α. In addition the PDZ456 domain mediates the formation of homo- and heteromultimers of GRIP proteins. To better understand the structural basis of peptide recognition by a class II PDZ domain and DZ-mediated multimerization, 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 shows a slight reorientation of helix αB, indicating that the second hydrophobic pocket undergoes a conformational adaptation to accommodate the bulkiness of the Tyr's side chain, and 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.