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Crystal Structure of PDZ Domains, Protein Interaction Modules

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PDZ domains are molecular-recognition elements that mediate protein-protein interactions. The PDZ domain was discovered originally as a common motif present in three structurally related proteins: PSD-95 (postsynaptic density protein), Dlg (*discs-large* protein) and ZO-1 (zonula occludens-1). The PDZ domain is globular domain, containing about 80-100 amino acids, and a conserved motif with two alpha helices and six beta strands. Most of them bind selectively to the C-termini of the interacting proteins at the complexes of signaling molecules and membrane associated receptors. GRIP1 (glutamate receptor interacting protein 1) contains seven PDZ domains and has no catalytic domain. It was originally found to interact with postsynaptic AMPA-type glutamate receptors. In addition to the interaction with AMPA receptors, GRIP1 interacts with the C-termini of ephrin ligands and Eph receptors using the sixth PDZ domain. GRIP1 also binds by PDZ6 to the C-termini of liprins, which bind to the LAR family of receptor tyrosine phosphatases. These facts suggest that GRIP1 may play critical roles in early neuronal development as well as at both excitatory and inhibitory synapses and the GRIP1 PDZ6 may be involved more in the assembly of developmental signaling complex than the clustering of synaptic receptors. Here we present the structures of the PDZ6 domain of GRIP1 in complex with and in the absence of its synthetic peptide at 1.8 Å and 1.5 Å resolution, respectively. These structures reveal the recognition specificity of C-terminal binding and the homodimerization of PDZ domains at the molecular level.