

Bivalent peptides as models for multimeric targets of PDZ domains.

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Streszczenie

PDZ domains are among the most common modules in eukaryotic, including human, genomes. They are found exclusively in large, multidomain cytosolic proteins—often with other domains that belong to a variety of families—and are involved in a plethora of physiological and pathophysiological events. PDZ domains mediate protein–protein interactions by binding to solvent-exposed and extended C-terminal short fragments of membrane-associated proteins, such as receptors and ion channels. Most of what is known about the mechanisms of target binding by PDZ domains is inferred from studies that involve isolated recombinant PDZ domains and short synthetic peptides that represent the targets. These binary systems constitute an obvious oversimplification and disregard factors such as noncanonical modes of binding and enhanced affinity due to multimeric interactions mediated by clusters and oligomers of PDZ-domain-containing proteins. We have tested whether the interaction between a dimeric form of PDZ domain that mimics a functional dimeric guanine nucleotide exchange factor, PDZ-RhoGEF (PDZ-containing RhoA-specific guanine nucleotide exchange factor) or LARG (leukemia-associated RhoA specific guanine nucleotide exchange factor), and a bivalent peptide that mimics the dimer of the plexin B receptor, could enhance the interaction between the two moieties. Peptide dimerization was achieved by cross-linking the N-terminal ends of peptides attached to Wang resin with poly(ethylene glycol) spacers (30–45 Å in length). The interaction of dimeric PDZ domains with dimeric peptides resulted in an up to 20-fold increase in affinity compared to the simple binary system. This is consistent with the notion that multimerization of both receptors and PDZ-containing proteins might constitute an important regulatory mechanism.

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