

P001 The high-affinity AKAP18 δ -PKA interaction yields novel PKA anchoring disruptor peptides

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A kinase-anchoring proteins (AKAPs) tether protein kinase A (PKA) to subcellular compartments by direct interaction with its regulatory subunits (RI or RII). AKAPs preferentially bind RII subunits *via* their RII-binding domains. RII-binding domains form structurally conserved amphipathic helices with unrelated sequences. Their binding affinities for RII subunits greatly differ within the AKAP family. Amongst the AKAPs binding RII α subunits with high affinity is AKAP18 δ (K_D of 31 nM). Here we show that 25 amino acid residues long peptides derived from the RII-binding domain of AKAP18 δ bind RII α subunits with higher affinity ($K_D = 0.4 \pm 0.3$ nM) than peptides derived from other RII binding domains. The AKAP18 δ -derived peptides and stearate-coupled, membrane-permeable versions thereof effectively disrupt AKAP-RII subunit interactions *in vitro* and in cell-based assays. Thus they are valuable novel tools for studying anchored PKA signalling. Molecular modelling indicated that the high affinity binding of AKAP18 δ with RII subunits involves both the hydrophobic and the hydrophilic faces of the amphipathic helix forming the RII-binding domain. Alanine scanning of the RII binding domain revealed that hydrophobic amino acid residues form the backbone of the interaction and that hydrogen bond- and salt bridge-forming amino acid residues increase the affinity of the interaction.