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The first crystal structure of cyclic GMP-dependent protein kinase Iβ dimerization/docking domain reveals molecular details of isoform-specific anchoring

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Background

Cyclic GMP-dependent protein kinase (PKG) is the main mediator of the NO/cGMP signaling pathway and plays a central role in regulating cardiovascular and neuronal functions. Subcellular targeting of PKG provides a mechanism for achieving substrate specificity and is mediated by the most N-terminal ~50 amino acids, which are required for homo-dimerization of the kinase and association with isoform-specific G-kinase anchoring proteins (GKAPs). To understand the molecular details of PKG dimerization and targeting to GKAPs, we solved a crystal structure of the PKG Iβ dimerization/docking domain.

Results

The structure reveals two helices wrapping around each other into a left-handed helix and forming a parallel coiled-coil. Two unusual interhelical salt bridges stabilize the coiled-coil, as confirmed by the destabilizing effects of single alanine substitutions. The two interhelical ion pairs flank a patch of acidic residues that are crucial for GKAP binding. This is the first crystal structure available for PKG; it demonstrates not only the molecular details of PKG Iβ dimerization, but also reveal the docking surface for GKAPs.

It is increasingly evident that the fidelity of signal transduction is dependent on the ability of proteins to assemble into pathway specific multiprotein complexes. We also showed that the surrogate domain of the closely related cAMP-dependent protein kinase (PKA) forms an

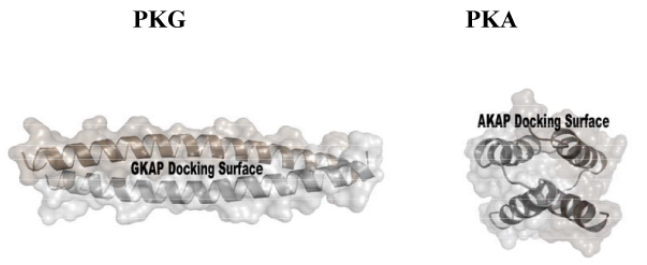

Figure 1
Structures of the Dimerization/Docking domains.

X-type helical bundle (Figure 1), providing a completely different docking surface for binding PKA specific anchoring proteins [1]. The coiled-coil is also a highly important model system for studying fundamental principles in protein folding, stability and specificity.

References

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