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A structural analysis of the regulatory domain from the cGMP-dependent protein kinase Iα

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Background

The cGMP-dependent protein kinase (PKG) has two tandem cyclic nucleotide binding (CNB) domains which act as the primary intracellular receptor for cGMP [1,2]. PKG exhibits a homodimeric rod-like structure which undergoes significant molecular rearrangements upon the binding of cGMP [3-5]. However, a detailed structural analysis of the core regulatory elements inherent to PKG is still required.

Results

We recently solved a crystal structure of the two cGMP binding sites from PKG Iα in order to highlight the atomic details of the regulatory domain. This PKG^{78-355} structure is free of cGMP and presents the protein in an elongated conformation. A surprising dimeric arrangement between PKG^{78-355} protomers is orchestrated via hydrophobic contacts between a novel helical element C-terminal to the second cGMP binding site (the switch helix) and the opposite CNB domain B (Figure 1). Small angle X-ray scattering (SAXS) of PKG^{78-355} suggests an overall molecular dimension of ~130 Å, consistent with the maximal linear dimension observed in our crystal structure. Upon incubation with cGMP, PKG^{78-355} contracted to ~95 Å. This molecular compaction was not observed in a construct lacking the switch helix (PKG^{78-326}), suggesting the additional importance of the switch helix in mediating cGMP-specific conformational changes inherent to the regulatory domain.

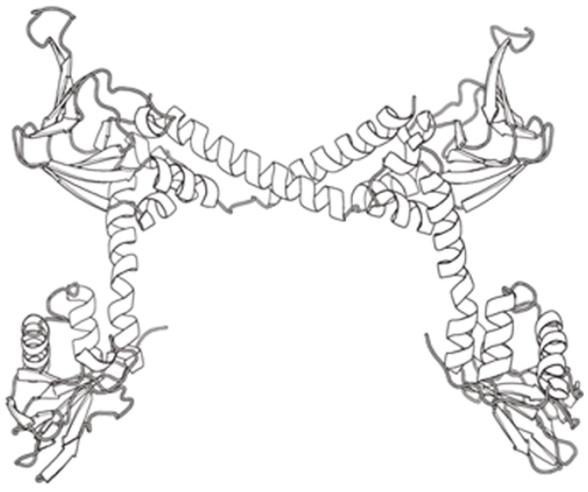

Figure 1 Overall fold of PKG^{78-355}. The crystal structure of the PKG regulatory domain identifies a novel allosteric interface between PKG^{78-355} protomers.

Conclusion

Overall, these studies provide the first atomic resolution model of tandem cGMP binding domains and expand our understanding of the allosteric mechanisms surrounding PKG activation.

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References

1. Pfeifer A, Ruth P, Dostmann W, Sausbier M, Klatt P, Hofmann F: **Structure and function of cGMP-dependent protein kinases.** *Rev Physiol Biochem Pharmacol* 1999, **135**:105-149.
2. Lincoln TM, Corbin JD: **Characterization and biological role of the cGMP-dependent protein kinase.** *Adv Cyclic Nucl Res* 1983, **15**:139-192.
3. Zhao J, Trewhella J, Corbin J, Francis S, Mitchell R, Brushia R, Walsh D: **Progressive cyclic nucleotide-induced conformational changes in the cGMP- dependent protein kinase studied by small angle X-ray scattering in solution.** *J Biol Chem* 1997, **272**:31929-31936.

4. Richie-Jannetta R, Busch JL, Higgins KA, Corbin JD, Francis SH: **Isolated regulatory domains of cGMP-dependent protein kinase Ialpha and Ibeta retain dimerization and native cGMP-binding properties and undergo isoform- specific conformational changes.** *J Biol Chem* 2006, **281**:6977-6984.
5. Alverdi V, Mazon H, Versluis C, Hemrika W, Esposito G, van den Heuvel R, Scholten A, Heck AJ: **cGMP-binding prepares PKG for substrate binding by disclosing the C-terminal domain.** *J Mol Biol* 2008, **375**:1380-1393.

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