

POSTER PRESENTATION

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

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From 5th International Conference on cGMP: Generators, Effectors and Therapeutic Implications
Halle, Germany. 24-26 June 2011

Background

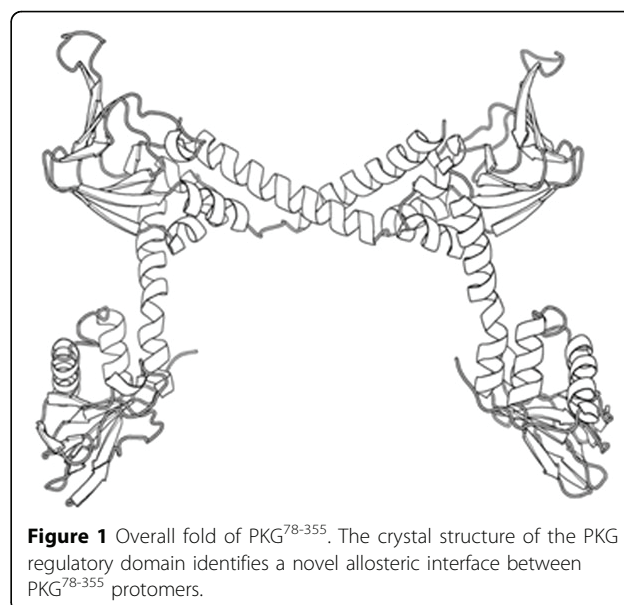
The cGMP-dependent protein kinase (PKG) has two tandem cyclic nucleotide binding (CNB) domains which act as the primary intracellular receptor for cGMP [1,2]. PKG exhibits a homodimeric rod-like structure which undergoes significant molecular rearrangements upon the binding of cGMP [3-5]. However, a 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 α in order to highlight the atomic details of the regulatory domain. This PKG⁷⁸⁻³⁵⁵ structure is free of cGMP and presents the protein in an elongated conformation. A surprising dimeric arrangement between PKG⁷⁸⁻³⁵⁵ 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 PKG⁷⁸⁻³⁵⁵ suggests an overall molecular dimension of ~130 Å, consistent with the maximal linear dimension observed in our crystal structure. Upon incubation with cGMP, PKG⁷⁸⁻³⁵⁵ contracted to ~95 Å. This molecular compaction was not observed in a construct lacking the switch helix (PKG⁷⁸⁻³²⁶), suggesting the additional importance of the switch helix in mediating cGMP-specific conformational changes inherent to the regulatory domain.

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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Published: 1 August 2011

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doi:10.1186/1471-2210-11-S1-P53

Cite this article as: Osborne *et al.*: A structural analysis of the regulatory domain from the cGMP-dependent protein kinase α . *BMC Pharmacology* 2011 **11**(Suppl 1):P53.

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