

**cAMP-DEPENDENT PROTEIN KINASE: DYNAMICS OF CATALYSIS  
AND DOCKING**

SUSAN S. TAYLOR, PEARL AKAMINE, JERRY YANG, JIAN WU,  
GANESH IYER, GANESH ANAND, MARAT VALIEV, JOHN H. WEARE  
and DONNA D. JOHNSON

Department of Chemistry and Biochemistry, Howard Hughes Medical Institute,  
University of California, San Diego, La Jolla, CA 92093, USA

cAMP-dependent protein kinase (PKA) is one of the simplest members of the protein kinase superfamily, one of the largest families encoded for by higher eukaryotic genomes. It is a highly dynamic protein that is poised to rapidly transfer the  $\gamma$ -phosphate of ATP to a protein substrate. The crystal structure of the C subunit in the presence of various substrates and inhibitors reveals not only the intramolecular network of interactions that extend throughout the molecule but also the intrinsic flexibility of the motions that allow for opening and closing of the active site cleft. The structure of the apoenzyme, in particular, highlights the different dynamic properties of the small and large lobes. Crystal structures of the C subunit bound to various analogs of balanol, a natural product inhibitor of PKC, PKA, and PKG, show how specificity can be achieved for PKA vs PKC. Hydrogen/deuterium exchange coupled with mass spectrometry has allowed us to map the dynamic features of the C subunit and also to map the binding surface for RI $\alpha$ . In addition, point mutations in the C subunit such as Tyr204Ala and Glu230Gln, show selective changes in this dynamic behavior and highlight the extended networks. Quantum mechanical calculations of residues at the active site cleft predict a very rapid phosphoryl transfer process and highlight the critical role of Lys168 in mediating this process.

Funded in part by NIH Grant GM 19301 to ST.