

INVITED LECTURE T9

PKA dynamics: Dynamics of activation by cAMP

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PKA, conserved in all mammalian cells, serves as a structural and biochemical prototype for the entire protein kinase superfamily and also reveals many of the unique features that are conserved within the AGC subfamily such as the C-terminal tail. In addition to understanding the molecular features of an active kinase, it is essential to know how each kinase is regulated. For PKA, activity is regulated by inhibitory regulatory (R) subunits that are also the major receptors for cAMP in mammalian cells. To understand the molecular basis for activation of PKA, we crystallized complexes of RI α and RII α with the C-subunit. The C-subunits serve as a stable docking platform in contrast to the highly malleable R-subunits which undergo major conformational changes as they release cAMP and wrap around the C-subunit. Mostly striking is the dramatic reorganization of the two cyclic nucleotide binding (CNB) domains. cAMP as a second messenger and the CNB domain have been conserved as a signaling mechanism from bacteria to man. These structures reveal for the first time the highly dynamic properties of this conserved cAMP binding motif.

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