Signaling in the Catalytic Subunit of Protein Kinase A via Hydrophobic Motifs

Eukaryotic protein kinases (EPKs) constitute a class of allosteric switches that mediate several signaling events. Protein kinase A is a prototypical kinase of paramount biological importance as it is involved in a myriad of cellular processes. Using side-chain methyl group NMR relaxation measurements, we traced the allosteric signaling through the hydrophobic spines of the enzyme in the apo, binary (nucleotide bound) complex and ternary (nucleotide and pseudo-substrate bound) forms. In the apo form, the C-spine is disassembled, with the two lobes of the enzyme dynamically uncommitted. Nucleotide binding locks the architecture of the catalytic spine, synchronizing the motions (committed dynamics) in the hydrophobic core. While pseudo-substrate binding further rigidifies of the spines, the conformational dynamics of the core are retained with natural substrates. Since the C-subunit is highly conserved within the kinase family, the present study offers novel mechanistic insights into intramolecular signaling of protein kinases that can serve for the design of novel activators or inhibitors of kinases.