MS5 Structural information in drug design

Chairs: Michael Hennig, Vincent Mikol

MS5-P1 Probing calmodulin - peptide interactions of different species with the same target peptide

Zsolt Dürvanger[1], Tünde Juhász[2], Károly Liliom[2], Veronika Harmat[1,3]

1. Institute of Chemistry, Eötvös Loránd University, Budapest, Hungary
2. Institute of Enzymology, Research Centre for Natural Sciences, Hungarian Academy of Sciences, Budapest, Hungary
3. MTA-ELTE Protein Modelling Research Group, Budapest, Hungary

email: Drvanger@caesar.elte.hu

Calmodulin is a small calcium-binding protein that plays a key role in signal transduction pathways of all eukaryotic cells. The protein undergoes large conformational changes upon calcium binding, consequently its target binding hydrophobic residues become solvent accessible. These conformational changes create the possibility of calcium-dependent interactions with its target proteins. Some antimalarial drugs were reported to inhibit calmodulin action, suggesting that *Plasmodium falciparum* (a malaria causing parasite) calmodulin could be a target of antimalarial drug development. Though calmodulin is a highly conserved protein, structural differences between calmodulins from different organisms could provide a way of targeting calmodulin of disease causing organisms.

We solved the structure of mammalian calmodulin in complex with melittin, a well-known calmodulin binding model peptide, and refined the structure to 2.7Å resolution. Recently we determined the structure of *Plasmodium falciparum* calmodulin in complex with melittin, which provides the opportunity to compare the structures of calmodulin from two different organisms in complex with the same model peptide. Mammalian calmodulin shows 89% sequence identity with *P. falciparum* calmodulin, with the majority of the differing residues being on the surface, away from the protein – peptide interface. Despite the high sequence identity and the highly similar crystallization conditions, the structures of the two complexes differ significantly. While the orientation of the peptide is similar within the complexes, determined by a cluster of positively charged residues on the C-terminal part of the peptide, differences exist considering the backbone conformation and anchoring residues of the peptide. Moreover, the relative orientation of the two lobes of calmodulin shows a large difference, resulting in a more compact structure in the case of the mammalian calmodulin. Possible taxon-specific differences of the interactions are discussed.

This study was supported by BioStruct-X (No.283570) of European Community's 7th Framework Programme; the MedInProt program of the Hungarian Academy of Sciences; OTKA grants NK101072, K82092 and PD104344. We acknowledge SLS and EMBL-Hamburg for providing synchrotron radiation beamtime.

Keywords: calmodulin, protein/peptide complex, taxon-specific interactions, Plasmodium falciparum