

Molecular Mechanisms of Cytoskeletal and Membrane-Associated Proteins: Annexins and Cyclase-Associated Protein

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Annexins are ubiquitous proteins found in all organisms. The proteins are important for the health of organisms and the term annexinopathies has been coined for annexin-related diseases. The best characterised example is the deficiency of annexin A5 in human placenta leading to recurrent pregnancy loss, and the associated conditions of anti-phospholipid antibody syndrome and *Lupus anticoagulants*. However, accumulating evidence implies equally important roles for parasite annexins in infectious diseases. While a wealth of molecular, structural and functional properties is known for mammalian annexins, the situation is different with non-vertebrate annexins such as the protein subfamilies of metazoans, plants and protists. Intriguingly, very little structural information is available for annexins in complex with other proteins and no three-dimensional structure of an annexin complex has been reported.

We have structurally characterised plant annexins from bell pepper and cotton and investigated their structure-function relationships that show distinct differences in solution structure and membrane binding mechanisms when compared to their mammalian relatives. Recently, we extended into the area of parasite annexins which will also take the project into drug discovery.

Various intra- and extra-cellular signals regulate the spatial and timely remodelling of the actin cytoskeleton through a network of actin-binding proteins. A central, highly conserved family of cytoskeletal regulators is the cyclase-associated proteins (CAPs). CAPs are part of the adenylyl cyclase -centered complex of proteins and bind to monomeric (G-) actin. So far, the molecular events surrounding CAP functions are unknown.

Structural information, some of which have been contributed by our group, is available for two domains of CAP, the N-terminal helix-barrel (N-CAP) and the C-terminal right-handed beta-helix (C-CAP).

The strong tendency of the protein to form oligomers is the major problem in crystallisation. Based on structural information from us and others, as well as a mutagenesis study, we developed a model of CAP oligomerisation behaviour. Current efforts concentrate on structural investigation of CAP interactions with its target proteins.