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Structure, oligomerization and mechanism of dynamin superfamily proteins

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GTPases of the dynamin superfamily remodel cellular membranes in response to nucleotide binding and hydrolysis. The molecular details of membrane interaction and the role of nucleotide-dependent changes for the function of these proteins are just emerging. Here, I present structural data on the dynamin-related proteins EHD2 [1] and MxA [2] which shed light on the mechanism of oligomerisation and the mechano-chemical function of these proteins. EHD2 oligomerizes via two distinct interfaces in the GTPase domain resulting in ring-like oligomers. Using electron paramagnetic resonance studies, we show that not only the tips of the helical domains but also the amino-terminus contribute to lipid binding. Furthermore, the Eps15 homology domains of EHD2 might switch from the top of the GTPase domain, as found in the crystal structure, to the side of the GTPase domain and also participate in membrane binding. Another mode of oligomerisation is found in the antiviral MxA GTPases which oligomerises via the helical stalk region to form ring-like structures. Furthermore, the GTPase domains of MxA might contribute to oligomerisation by connecting neighbouring rings. This assembly mode suggests a mechanism for the mechano-chemical function which is consistent with previous models for dynamin function. Finally, I will show how structural information obtained for MxA can be employed to obtain insights into structure and function of the dynamin GTPase.

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Telomerase structure function

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Telomerase is a specialized DNA polymerase that extends the 3′ ends of eukaryotic linear chromosomes, a process required for genomic stability and cell viability. We have determined crystal structures of the active *Tribolium castaneum* telomerase catalytic subunit, TERT, alone [1] and in complex with an RNA-DNA hairpin designed to resemble the putative RNA-templating region and telomeric DNA [2]. The structures, together with existing biochemical data, provide novel insights into the basic mechanism of telomere replication and length homeostasis by telomerase. Moreover, this data further enriches our understanding of the mechanism of DNA replication by polymerases in general and it provides a framework to design small molecule modulators of telomerase activity that may be of therapeutic value for cancer and other diseases associated with cellular aging.

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Structural basis of the anaphase promoting complex

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The anaphase promoting complex or cyclosome (APC/C) is a multi-subunit cullin-RING E3 ubiquitin ligase that functions to regulate progression through the mitotic phase of the cell cycle and controls entry into S phase [1]. APC/C-mediated coordination of cell cycle progression is achieved through the temporal regulation of APC/C activity and substrate specificity. The APC/C is an unusually large E3 ubiquitin ligase assembled from 13 different proteins, mostly highly conserved and essential for function, generating a macromolecular machine exceeding 1.2 MDa in mass. Information on how its 13 constituent proteins are assembled, and how they interact with co-activators, substrates and regulatory proteins is limited.

We developed a recombinant expression system that allows the reconstitution of holo APC/C and its sub-complexes that, when combined with electron microscopy, mass spectrometry and docking of crystallographic and homology-derived coordinates, provides a precise definition of the organisation and structure of all essential APC/C subunits, resulting in a pseudo-atomic model for 70% of the APC/C. A lattice-like appearance of the APC/C is generated by multiple repeat motifs of most APC/C subunits. Three conserved tetratricopeptide repeat (TPR) subunits share related superhelical homo-dimeric architectures that assemble to generate a quasi-symmetrical structure. I will describe the structure of the APC/C and its complex with co-activator and a destruction box (D-box) substrate which indicates that the D-box binding site is formed from a co-receptor of Cdh1 and Apc10 [2-5].

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Complement convertase formation based on the structures of C3b in complex with factors B and D

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