Structure watch

DECONSTRUCTING DYNAMIN

Dynamin-related proteins (DRPs) are multidomain GTPases that can regulate membrane remodelling events. Although DRPs are known to undergo oligomerization and GTP-dependent conformational changes, it is less clear how these properties drive membrane remodelling.

Ford *et al.* determined the crystal structure of a dynamin that is assembly deficient. They isolated a Gly397Asp mutation in rat dynamin 1 lacking its Pro-rich domain that strongly inhibits dynamin self-assembly. This allowed them to elucidate the crystal structure of dynamin 1 in a nucleotide-free state and revealed an extended structure, in which the GTPase domain and bundle signalling element (BSE) reside on top of a long helical stalk, with the pleckstrin homology (PH) domain positioned at the other end of the stalk. Faelber *et al.* similarly determined the crystal structure of human dynamin 1 in the nucleotide-free state by identifying mutations that disrupt oligomer formation. Further analysis by both groups characterized the role of the stalk region in mediating dimer and multimer formation.

Importantly, both groups examined where disease-related mutations in dynamin reside in these structures and how they may affect dynamin assembly. Modelling of these structures also provided important insights into how dynamin assembles into helical structures, and how its conformational changes may be coordinated with membrane remodelling.

ORIGINAL RESEARCH PAPERS Ford, M. G. J., Jenni, S. & Nunnari, J. The crystal structure of dynamin. *Nature* 18 Sept 2011 (doi:10.1038/nature10441) | Faelber, K. *et al.* Crystal structure of nucleotide-free dynamin1. *Nature* 18 Sept 2011(doi:10.1038/nature10369)

TUNING CaMKII

Ca^{2+}- and calmodulin-dependent kinase II (CaMKII) forms a dodecameric holoenzyme, in which each subunit is formed by a Ser/Thr-specific kinase domain, a regulatory segment that binds calmodulin and a flexible linker that connects to a hub domain. CaMKII responds to the amplitude and the frequency of Ca^{2+} spikes to regulate neuronal signalling, but how its activity is regulated is unclear.

Chao *et al.* provide insight into this by presenting the crystal structure of the full-length dodecameric human β7 isoform of CaMKII in an autoinhibited state. This reveals an unexpectedly compact arrangement, in which part of the regulatory segment is incorporated into the central hub domain β-sheet. This creates extensive autoinhibitory kinase–hub interactions, which block substrate-binding sites and make the calmodulin-recognition element inaccessible. Importantly, the authors also find that CaMKII isoforms with long linkers form conformations that are more open, have higher affinity for calmodulin and respond to lower Ca^{2+} spike frequencies. They propose that the response to the frequency of Ca^{2+} spikes can be tuned by altering the balance between compact and open conformations.

ORIGINAL RESEARCH PAPER Chao, L. H. *et al.* A mechanism for tunable autoinhibition in the structure of a human Ca^{2+}/calmodulin-dependent kinase II holoenzyme. *Cell* **146,** 732–745 (2011)