Order from disorder in sarcomeric Z-disks

K. Djinovic Carugo[1,2]

[1]European Molecular Biology Laboratory (EMBL) Grenoble, 71 Avenue des Martyrs, 38000 Grenoble, France;
[2]Department of Structural and Computational Biology, Max Perutz Labs, University of Vienna, Campus Vienna Biocenter 5, A-1030 Vienna, Austria **kristina.djinovic@embl.org**

The sarcomere is the minimal contractile unit in the cardiac and skeletal muscle, where actin and myosin filaments slide past each other to generate tension. This molecular machinery is supported by a subset of highly organised cytoskeletal proteins that fulfil architectural, mechanical and signalling functions. The ultra-structure of sarcomere is highly organized and delimited by Z-disks, which play a central role in the mechanical stabilization and force transmission.

In the Z-disks – the lateral boundaries of the sarcomere machinery – the protein α-actinin-2 cross-links antiparallel actin filaments from adjacent sarcomeres, and additionally serves as a binding platform for a number of other Z-disk proteins. In striated muscle cells, the Z-disk represents a highly organized three-dimensional assembly containing a large directory of proteins orchestrated in a multi-protein complex centred on its major component α-actinin, with still poorly understood hierarchy and three-dimensional interaction map. On the way to elucidate the molecular structural architecture of the Z-disk, the hierarchy of its assembly and structure-function relationships, we are studying binary and higher order sub-complexes of α-actinin using a combination of molecular biophysics, structural and biochemical approaches.

FATZ proteins interact with α-actinin and five other core Z-disk proteins, contributing to myofibril assembly and maintenance as a protein interaction hub. We determined the first structure and its cellular validation of α-actinin-2 in complex with a Z-disk partner, FATZ-1, which is best described as a conformational ensemble. We show that FATZ-1 forms a tight fuzzy complex with α-actinin-2 and propose a molecular interaction mechanism via main molecular recognition elements and secondary binding sites. The obtained integrative model reveals a polar architecture of the complex which, in combination with FATZ-1 multivalent scaffold function, might organise interaction partners and stabilise α-actinin-2 preferential orientation in the Z-disk. Finally, we uncover FATZ-1 ability to phase-separate and form biomolecular condensates with α-actinin-2, raising the intriguing question whether FATZ proteins can create an interaction hub for Z-disk proteins through membrane-less compartmentalization during myofibrillogenesis.

I will present our studies on the interaction of the major Z-disk protein α-actinin with FATZ and Z-portion of titin, forming dynamic fuzzy complexes, and discuss findings in view of asymmetric sorting of α-actinin and sarcomeric Z-disk architecture and assembly.