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Keynote 3: Order from Disorder: Towards molecular architecture of the muscle Z-disk assembly by integrative structural biology

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The sarcomere is the smallest contractile unit in 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 perform architectural, mechanical, and signalling functions. Sarcomere ultrastructure is highly organised and delimited by Z-disks, which play a critical role in mechanical stabilisation 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. To investigate the molecular structural architecture of the Z-disk, the assembly hierarchy, and structure-function relationships, we are employing an integrative structural biology strategy that combines molecular biophysics, structural, and biochemical approaches.
FATZ proteins interact with α-actinin and five other core Z-disk proteins, contributing to the assembly and maintenance of myofibrils as a hub for protein interactions. I will present our studies on the interaction of the major Z-disk protein α-actinin-2 with FATZ-1 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. Furthermore, our recent discover that FATZ-1 can phase-separate and form biomolecular condensates with α-actinin-2 and other three Z-disk proteins raises the intriguing question of whether FATZ proteins can create an interaction hub for Z-disk proteins during myofibrillogenesis via membrane-less compartmentalization.

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