Deciphering the molecular structure of muscle Z-disk assembly: an integrative structural biology approach

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Sarcomeres are the smallest contractile units found in cardiac and skeletal muscle, where actin and myosin filaments move 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. The ultrastructure of a sarcomere is highly ordered and bordered by Z-disks, which play an essential role in mechanical stability and force transmission.

The protein α-actinin-2 acts as a binding platform for other proteins and cross-links antiparallel actin filaments in Z-disks, the lateral borders of the sarcomere machinery. The Z-disk is a highly-organized three-dimensional assembly a highly organized three-dimensional assembly centred on α-actinin, with still a poorly three-dimensional interaction map. We are employing an integrative structural biology approach that melds molecular biophysics, structural, and biochemical methods to explore the Z-disk's structural framework, its assembly order, and the interplay between its structure and function.

FATZ proteins, which interact with α-actinin and other key Z-disk proteins, play a central role in the formation and stability of myofibrils by serving as a nexus for protein interactions. In my presentation, I'll discuss our research on the interactions between the prominent Z-disk protein α-actinin-2, FATZ-1, and the Z-portion of titin. These interactions result in dynamic, fuzzy complexes, which have implications for the asymmetrical distribution of α-actinin, as well as the structure and formation of the sarcomeric Z-disk.

Additionally, our latest discovery that FATZ-1 undergoes phase separation to create biomolecular condensates with α-actinin-2 and other Z-disk proteins introduces the fascinating concept that FATZ proteins might function as a central hub for Z-disk proteins during the development of myofibrils through a process of membrane-less compartmentalization.