

Order from disorder in the sarcomere: FATZ forms a fuzzy complex and phase-separated condensates with α -actinin

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In sarcomeres, α -actinin crosslinks actin filaments and anchors them to the Z-disk. FATZ proteins interact with α -actinin and five other core Z-disk proteins, contributing to myofibril assembly and maintenance as a protein interaction hub.

Here we report 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.

Keywords: striated muscle Z-disk; α -actinin; FATZ; protein-protein interaction hub; intrinsic disorder; tight fuzzy complex; liquid-liquid phase separation; integrative structural biology;