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Structure of muscle α-actinin: Insights into its regulation and Z-disk assembly

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α-Actinin is the major component of the Z-disk, where it cross-links actin filaments from adjacent sarcomeres. It is an antiparallel dimer of 200 kDa, containing in each subunit an N-terminal actin binding domain (ABD), a central rod domain assembled from spectrin-like repeats that mediate the antiparallel assembly, and a C-terminal calmodulin-like (CaM-like) domain with 4 EF-hand motifs. Additionally to actin filaments, α-actinin binds multiple other cytoskeletal and signalling proteins. In striated muscle, the tightly defined numbers of α-actinin crosslinks between the antiparallel actin filaments at the Z-disk are organised by specific binding sites on the giant molecular blueprint of the sarcomere, titin. These titin Z-repeats contain a short, hydrophobic, α-actinin binding motif. To achieve ordered cytoskeletal assemblies, the binding properties of α-actinin must be tightly spatiotemporally regulated, in muscle α-actinin its actin and titin binding properties are regulated by phosphoinositide. Biochemical analyses led to propose previously that the α-actinin - titin interaction is regulated by an intramolecular mechanism, where the short sequence between the ABD and the rod interacts with the CaM-like domain in a pseudoligand complex, acting effectively as an intramolecular autoinhibitor. Here, we present the first complete crystallographic structure of sarcomeric human α-actinin complemented by small angle X-ray scattering data, electron-electron paramagnetic resonance, biochemical and in vivo cell biophysics studies of structure-informed mutants, which give insight into its molecular assembly and Z-disk architecture as well as into the mechanism of α-actinin function and regulation.

Keywords: muscle Z-disk, α-actinin regulation, PIP2, titin Z-repeat 7