Molecular basis of telethonin-mediated linkage of the N-terminus of titin within the sarcomeric Z-disc

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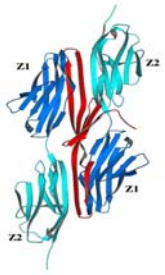
Severe heart and muscle diseases, like dilated cardiomyopathy, result from mutations in components of multi-protein complexes, such as the N-terminus of titin, α-actinin and telethonin. These are localised at the Z-disk of skeletal and cardiac striated muscle sarcomeres and are essential for myofibril assembly and maintenance. To unravel the molecular basis of the titin/telethonin interactions in the Z-disk, we have determined the crystal structures of the titin N-terminus in the absence and presence of telethonin. The complex structure reveals a titin-telethonin-titin antiparallel arrangement, suggesting an unexpected telethonin-mediated linkage of the N-termini of two titin filaments.



The complex is formed by four independent binding sites, involving two α-hairpin wing motifs of telethonin, where each wing binds two IG-like domains from two different titin molecules in opposite orientations. The titin/telethonin complex is formed exclusively by intermolecular β-sheet interactions and is insensitive to single residue mutations, as shown by in-vitro binding data and colocalisation data of several titin/telethonin in neonatal rat cardiomyocytes. The titin/telethonin complex may serve as a hub to bind several other protein ligands inside and outside the Z-disk. For one of these components, MLP, a structural model is provided suggesting a telethonin-mediated functional linkage of MLP and titin. The availability of a second titin-filament cross-linking system by telethonin, in addition to that formed by α-actinin, allows to approach a structural model of the Z-disk providing rationales for anchoring and precise alignment of major sarcomeric filaments such as actin and titin.