MX-32: "Crystal structure of the N-terminal capping domains Z1Z2 from the gigantic muscle protein titin"

Status: structure elucidation completed
PDB codes: 1RJ0

Manuscripts related to this work:

1. Marino M, Zou P, Svergun D, Garcia P, Edlich C, Simon B, Wilmanns M, Muhle-Goll C, Mayans O. (2006). "The Ig doublet Z1Z2: a model system for the hybrid analysis of conformational dynamics in Ig tandems from titin." Structure. 14(9):1437-47.

This manuscript reports the crystal structure elucidated in this ESRF visit.
Abstract: Titin is a gigantic elastic filament that determines sarcomere ultrastructure and stretch response in vertebrate muscle. It folds into numerous Ig and FnIII domains connected in tandem. Data on interdomain arrangements and dynamics are essential for understanding the function of this filament. Here, we report a mechanistic analysis of the conformational dynamics of two Ig domains from the N terminus of titin, Z1Z2, by using X-ray crystallography, SAXS, NMR relaxation data, and residual dipolar couplings in combination. Z1Z2 preferentially adopts semiextended conformations in solution, with close-hinge arrangements representing low-probability states. Although interdomain contacts are not observed, the linker appears to acquire moderate rigidity via small, local hydrophobic interactions. Thus, Z1Z2 constitutes an adaptable modular system with restricted dynamics. We speculate that its preexistent conformation contributes to the selective recruitment of the binding partner telethonin onto the repetitive surface of the filament. The structural interconversion of four Z1Z2 conformers is analyzed.

2. Marino M, Svergun D, Kreplak L, Konarev P, Maco B, Labeit D, Mayans O (2005) "Poly-Ig tandems from I-band titin share extended domain arrangements irrespective of the distinct features of their modular constituents". J. Muscle Res Cell Mot. 26(6-8):355-65

Abstract: The cellular function of the giant protein titin in striated muscle is a major focus of scientific attention. Particularly, its role in passive mechanics has been extensively investigated. In strong contrast, the structural details of this filament are very poorly understood. To date, only a handful of atomic models from single domain components have become available and data on poly-constructs are limited to scarce SAXS analyses. In this study, we examine the molecular parameters of poly-Ig tandems from I-band titin relevant to muscle elasticity. We revisit conservation patterns in domain and linker sequences of I-band modules and interpret these in the light of available atomic structures of Ig domains from muscle proteins. The emphasis is placed on features expected to affect inter-domain arrangements. We examine the overall conformation of a 6Ig fragment, I65-I70, from the skeletal I-band of soleus titin using SAXS and electron microscopy approaches. The possible effect of highly conserved glutamate groups at the

linkers as well as the ionic strength of the medium on the overall molecular parameters of this sample is investigated. Our findings indicate that poly-Ig tandems from I-band titin tend to adopt extended arrangements with low or moderate intrinsic flexibility, independently of the specific features of linkers or component Ig domains across constitutively- and differentially-expressed tandems. Linkers do not appear to operate as free hinges so that lateral association of Ig domains must occur infrequently in samples in solution, even that inter-domain sequences of 4-5 residues length would well accommodate such geometry. It can be expected that this principle is generally applicable to all Ig-tandems from I-band titin.

3. Lee EH, Hsin J, Mayans O, Schulten K. (2007) "Secondary and tertiary structure elasticity of titin Z1Z2 and a titin chain model." Biophys J. 93(5):1719-35.

Abstract: The giant protein titin, which is responsible for passive elasticity in muscle fibers, is built from approximately 300 regular immunoglobulin-like (Ig) domains and FN-III repeats. While the soft elasticity derived from its entropic regions, as well as the stiff mechanical resistance derived from the unfolding of the secondary structure elements of Ig- and FN-III domains have been studied extensively, less is known about the mechanical elasticity stemming from the orientation of neighboring domains relative to each other. Here we address the dynamics and energetics of interdomain arrangement of two adjacent Ig-domains of titin, Z1, and Z2, using molecular dynamics (MD) simulations. The simulations reveal conformational flexibility, due to the domain-domain geometry, that lends an intermediate force elasticity to titin. We employ adaptive biasing force MD simulations to calculate the energy required to bend the Z1Z2 tandem open to identify energetically feasible interdomain arrangements of the Z1 and Z2 domains. The finding is cast into a stochastic model for Z1Z2 interdomain elasticity that is generalized to a multiple domain chain replicating many Z1Z2-like units and representing a long titin segment. The elastic properties of this chain suggest that titin derives so-called tertiary structure elasticity from bending and twisting of its domains. Finally, we employ steered molecular dynamics simulations to stretch individual Z1 and Z2 domains and characterize the so-called secondary structure elasticity of the two domains. Our study suggests that titin's overall elastic response at weak force stems from a soft entropic spring behavior (not described here), from tertiary structure elasticity with an elastic spring constant of approximately 0.001-1 pN/A and, at strong forces, from secondary structure elasticity.