

MS6 Molecular machines and big complexes

Chairs: Christoph Müller, Miquel Coll

MS6-O1 Fuzzy Sarcomeric Z-disk Complex: α -Actinin-FATZ

Kristina Djinovic-Carugo¹, Antonio Sponga¹, Ariadna Rodriguez Chamorro¹, Euripedes de Ribeiro¹, Georg Mlynek¹, Leo Geist¹, Joan Lopez Arolas¹, Robert Konrat¹

¹. Department of Structural and Computational Biology, Max F. Perutz Laboratories, University of Vienna

email: kristina.djinovic@univie.ac.at

The sarcomere is the minimal contractile unit in the cardiac and skeletal muscle, where actin and myosin filaments slide past each other to generate tension. This molecular machinery is supported by a subset of highly organised cytoskeletal proteins that fulfil architectural, mechanical and signalling functions, including the giant proteins titin, obscurin and nebulin as well as the cross-linking proteins α -actinin and myomesin (1).

The cross-linking of actin and myosin at the boundaries of their filamentous structures is essential for the muscle integrity and function. In the Z-disks – the lateral boundaries of the sarcomere machinery – the protein α -actinin-2 cross-links antiparallel actin filaments from adjacent sarcomeres, and additionally serves as a binding platform for a number of other Z-disk proteins. Among them is FATZ, also known as calsarcin and myozenin, which appears in the early stages of myofibrillogenesis together with α -actinin-2 [1]. α -Actinin is an antiparallel dimer, where each subunit is composed of an N-terminal actin binding domain, which is connected by a neck region to the four spectrin-like repeats (rod), and a C-terminal calmodulin-like domain. FATZ is composed of conserved N- and C-terminal regions connected by an intrinsically disordered segment. FATZ is believed to act as an adaptor protein linking α -actinin to other Z-disk proteins, but the structural information at molecular level on FATZ and complexes with any of its interaction partners still remains unknown.

We employed a combination of structural and biophysical approaches to elucidate the three-dimensional structure and dynamics of human α -actinin-FATZ complex. Circular dichroism, NMR and small angle X-ray scattering data of FATZ alone and in complex with α -actinin showed that FATZ is an IDP in solution, and that it does not fold upon binding. The non-bound portion displays pronounced structural plasticity and dynamics, characteristic of fuzzy complexes. Furthermore, the crystal structure shows that two stretches of FATZ interact in mostly extended conformation with the rod domain of α -actinin, and that FATZ binding might displace the N-terminal lobe of the calmodulin-like domain from the position found in the structure of full length α -actinin-2 [2], suggesting a specific role in the

hierarchy of Z-disk ultrastructure.

References

- [1] Stout et al. Cell Motil Cytoskeleton 2008; 65:353-67.
[2] Ribeiro Ede et al. Cell 2014; 159:1447-60

Keywords: Striated muscle Z-disk, actin based cytoskeleton, alpha-actinin:FATZ complex, intrinsically unstructured protein,

MS6-O2 Macromolecular machines in genome maintenance

Thomà H. Nicolas¹

1. Friedrich Miescher Institute for Biomedical Research
Maulbeerstrasse 66 4058 Basel Switzerland

email: Nicolas.Thoma@fmi.ch

UV-exposure of the skin result in the covalent cross-links of neighboring DNA nucleotides, introducing mutations in the genome if left unrepaired. Patients suffering from Xeroderma pigmentosum (XP) fail to effectively repair these DNA lesions, resulting in heightened propensity to develop skin cancers (melanomas, squamous cell, & basal cell carcinomas). My lab has solved the structures of these protein complexes and delineated their mode of action in respect to the ubiquitin proteasome system. We provided the mechanism by which this molecular sunscreen works, and how it is lost in XP cancer patients. In the presence of this DNA repair machine skin cancer rates are suppressed by more 1000-fold providing a major means of safeguarding the genome.

Keywords: DNA repair, ubiquitin, ligases