MS03-P03 | MOLECULAR INVESTIGATION OF MUSCLE Z-DISC ASSEMBLY CENTERED ON THE COMPLEX HUMAN A-ACTININ ISOFORM-2 AND ZASP

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In skeletal and cardiac muscle, proteins are organized into sarcomeric units, which lateral borders are delineate by the Z-discs. ZASP is a Z-disc protein involved in the early stage of myofibrillogenesis. It belongs to the Enigma family, which is one of the prevailing protein families involved in dilated cardiomyopathies [1]. ZASP acts as a mediator between cytoskeletal elements and signaling cascades and its presence in the Z-disc is essential for integrity of the sarcomere during contraction [1]. In the Z-disc protein network, ZASP interacts with various binding partners [2;3], in particular with α-actinin 2 (ACTN2), which is one of the most abundant proteins in the Z-disc, designed to cross-link actin filaments from adjacent sarcomeres [4].By integrative structural approaches, we aim to explore the function and dynamics of ACTN2-ZASP complex in presence of its binding partners FATZ, titin and F-actin. We show that ZASP binds ACTN2 with nanomolar affinity, which makes the complex amenable for crystallization and subsequent X-ray diffraction experiments. Moreover, preliminary XL-MS analysis delineated the binding sites of ZASP on ACTN2, providing constrains for modeling of solution structure ZASP-ACTN2 complex using the data obtained by small-angle X-ray scattering. We also show that ZASP and ACTN2 can form a ternary complex with the Z-disc protein FATZ-1. Further studies will provide insights into formation and function of the ZASP-ACTN2-FATZ-1 complex as well its organization at molecular level, which might help to reveal essential implication of ZASP in the formation of the Z-disc.

[1] Lin, 2014
[2] Au, 2004
[3] Ming Zheng, 2009
[4] Ribeiro, 2014