Molecular assembly line brings muscles into shape

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Scientists at the Research Institute of Molecular Pathology (IMP) in Vienna, Austria and at the University of Cologne, Germany have discovered the molecular basis underlying the patterned folding and assembly of muscle proteins. They describe the strikingly new mechanism in the current issue of *Cell*.

Muscle development and function rely on the correct assembly of contractile units called the sarcomeres. Their main components, thin (actin) and thick (myosin) filaments are organized in a precisely ordered,

quasi-crystalline protein framework that mediates muscle contraction. Although the overall architecture of the sarcomere has been studied in detail, little is known about its complicated assembly process. In particular, the mechanism of myosin incorporation into thick filaments is poorly understood.

So far, it has been shown that the folding of myosin involves the assistance of certain molecular chaperones. Chaperones are specialised helper proteins that bring their client proteins into the correct fold and keep them in good shape. The myosin-specific chaperone UNC-45 has been known to play a central role in muscle formation, but its exact function has remained elusive so far.

To address the underlying principle of how myosin filaments are assembled in muscle cells, IMP-Senior Scientist Tim Clausen and PhD-students Linn Gazda and Doris Hellerschmied carried out a detailed biochemical and structural analysis of the UNC-45 protein from the nematode worm C. elegans. Strikingly, their data revealed that UNC-45 can polymerize into a linear protein chain. As a consequence, multiple binding sites for the myosin units as well as for the co-working chaperones are periodically arranged along the UNC-45 chain. Indeed, this multi-chaperone complex precisely mimics an industrial assembly line.

Thorsten Hoppe and Wojciech Pokrzywa from the University of Cologne were able to show that the observed UNC-45 chain also occurs in living cells and is critical for coupling myosin folding with myofilament formation. In C. elegans worms whose UNC-45 protein was defect, the arrangement of muscle filaments was severely disturbed. As a consequence, these worms were paralysed.

The newly discovered mechanism decisively alters the current view of how muscle filaments are formed and, later on, kept in shape. The

UNC-45 chaperone represents a novel type of filament assembly factor that provides a molecular scaffold for specific chaperones to work at regularly spaced positions on captured client proteins. "It will be interesting to see whether this "patterned folding" mechanism is critical for the assembly of other protein filaments and to what extent this mechanism is connected with protein folding diseases." says Tim Clausen.

Aberrant UNC-45 function is associated with severe muscle defects resulting in skeletal and cardiac myopathies. The new study which is published in the current issue of the journal *Cell* points to the importance of carefully controlling the level of UNC-45 in order to build-up functional myosin assembly complexes. The discovered mechanism may thus help to develop strategies against diseases connected with myosin assembly defects.

More information: Gazda et al., The Myosin Chaperone UNC-45 Is Organized in Tandem Modules to Support Myofilament Formation in C. elegans. *Cell*, Volume 152, Issue 1, 183-195, 17 January 2013.

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