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Press release

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How the UNC-45 protein brings muscles into shape

Insight in the precise arrangement of muscle proteins provides new indications of muscular diseases and cardiac insufficiency

Cologne, January 17, 2013. Researchers of CECAD, the Cluster of Excellence at the University of Cologne, Germany, and the Research Institute of Molecular Pathology (IMP) in Vienna, Austria, provide mechanistic insight how muscle assembly is regulated in development and aging. Muscle formation and function rely on the correct assembly of myofilaments that are composed of actin and myosin molecules. In a novel study the researchers now discovered the molecular basis underlying the patterned folding and assembly of myosin filaments.

Muscle development and function rely on the correct assembly of contractile units called the sarcomeres. Its 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.
The Hoppe lab and others have shown before that the folding of myosin involves the assistance of three molecular chaperones including Hsp70, Hsp90 and a myosin-specific assembly protein called UNC-45. To address the underlying principle of how myosin filaments are formed in muscle cells, Prof Thorsten Hoppe and his postdoc Wojtek Pokrzywa teamed up with PD Dr. Tim Clausen and his group to perform a detailed structural and physiological analysis of the UNC-45 protein from the soil nematode *Caenorhabditis elegans*.
The striking findings of this collaboration, published in the scientific journal *Cell,* revealed that UNC-45 can polymerize into a linear protein chain. As a consequence, multiple binding sites for the myosin substrate as well as for the co-working chaperones Hsp70 and Hsp90 are periodically arranged along the UNC-45 chain. Indeed, this multi-chaperone complex that works on a series of myosin motor domains mimics an industrial assembly line (Fig.1). This mechanism decisively alters the current view of how muscle filaments are formed during development and kept in shape upon aging:
(1) The UNC-45 chaperone functions beyond simple nascent protein folding. It represents a novel type of filament assembly factor that provides the molecular scaffold for Hsp70 and Hsp90 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.

(2) The Hoppe lab showed before that aberrant UNC-45 function is associated with severe muscle defects resulting in skeletal and cardiac myopathies. Therefore, the discovered mechanism may help to develop strategies against diseases connected with myosin assembly defects.

Publication:
Gazda et al., The Myosin Chaperone UNC-45 Is Organized in Tandem Modules to Support Myofilament Formation in C. elegans, Cell (2013), http://dx.doi.org/10.1016/j.cell.2012.12.025

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Figure 1: The present work by Gazda et al demonstrates that UNC-45 establishes a multi-chaperone complex that allows the folding of myosin in a defined array along the thick filament. The cartoon illustrates the “patterned folding” principle, of how UNC-45 composes a protein assembly line that places the chaperone mechanics Hsp70 and Hsp90 (highlighted) at regularly spaced positions to work on the series of motor domains protruding from the myosin filament.