MedicalXpress

How protein networks stabilize muscle fibers: Same mechanism as for DNA

January 23 2012

The same mechanism that stabilises the DNA in the cell nucleus is also important for the structure and function of vertebrate muscle cells. This has been established by RUB-researchers led by Prof. Dr. Wolfgang Linke (Institute of Physiology) in cooperation with American and German colleagues. An enzyme attaches a methyl group to the protein Hsp90, which then forms a complex with the muscle protein titin. When the researchers disrupted this protein network through genetic manipulation in zebrafish the muscle structure partly disintegrated. The scientists have thus shown that methylation also plays a significant role outside the nucleus. They published their results in *Genes and Development*.

Enzymes, called methyltransferases, transfer methyl (CH3) groups to specific sections of the DNA in the nucleus. In this way, they mark active and inactive regions of the genes. However, not only DNA but also nuclear proteins incur methylation, mostly at the amino acid lysine. Methylated lysines on nuclear proteins promote the formation of protein complexes that control, for example, DNA repair and replication. However, methyltransferases are not only found in the nucleus, but also in the cellular fluid (cytoplasm). Yet, it is not well established which proteins they methylate in the cytoplasm and how this methylation may affect function.

The researchers first identified an enzyme which is mainly present in the cytoplasm and which methylates the amino acid lysine (Smyd2). Then they searched for interaction partners of the enzyme Smyd2 and found

the heat shock protein Hsp90. The scientists went on to show that Smyd2 and methylated Hsp90 form a complex with the muscle protein titin. "Titin is the largest protein in the human body and known primarily for its role as an elastic spring in muscle cells" explains Linke. "Precisely this elastic region of titin is protected by the association with methylated Hsp90."

In skeletal muscle cells of the zebrafish, Linke's team explored what happens when the protection by the methylated heat shock protein is repressed. By genetic manipulation they altered the organism in such a way that it no longer produced the enzyme Smyd2, which blocked the methylation of Hsp90. Without methylated Hsp90, the elastic titin region was unstable and muscle function strongly impaired; the regular muscle structure was partially disrupted.

More information: L.T. Donlin, C. Andresen, S. Just, E. Rudensky, C.T. Pappas, M. Kruger, E.Y. Jacobs, A. Unger, A. Zieseniss, M.-W. Dobenecker, T. Voelkel, B.T. Chait, C.C. Gregorio, W. Rottbauer, A. Tarakhovsky, W.A. Linke (2012): Smyd2 controls cytoplasmic lysine methylation of Hsp90 and myofilament organization, Genes and Development, doi: 10.1101/gad.177758.111

Provided by Ruhr-University Bochum