MedicalXpress

Sunday driver gene headed the wrong way in inherited muscle diseases

March 26 2014

Skeletal muscle cells with unevenly spaced nuclei, or nuclei in the wrong location, are telltale signs of such inherited muscle diseases as Emery-Dreifuss muscular dystrophy, which occurs in one out of every 100,000 births, and centronuclear myopathy, which affects one out of every 50,000 infants.

What goes wrong during myogenesis, the formation and maintenance of muscle tissue, to produce these inherited muscle diseases?

Research using the fruit fly *Drosophila melanogaster* has implicated the gene known as Sunday Driver (Syd) as a novel regulator of myogenesis. The fruit fly studies showed that Syd encodes a protein, the transport adapter Syd, which interacts with cortical factors that enable the motor protein Dynein to pull muscle nuclei into place.

The scientists, who are based at Weill Cornell Graduate School of Medical Sciences and the Sloan Kettering Institute of Memorial Sloan-Kettering Cancer Center, both in New York City, mutated the Syd gene in embryonic and larval muscles of the fruit fly. As a result, the nuclei in the fly's muscle cells were unevenly spaced and clustered.

The scientists also determined that JNK (c-Jun N-terminal kinase) signaling was essential for correct intracellular organization. In the absence of JNK signaling, Syd and Dynein proteins were restricted to the space surrounding the cell nucleus. While overactive JNK signaling allowed the correct transport of Syd and Dynein to the cell cortex at the

muscle ends, it prevented their downstream functions that work to pull muscle nuclei into proper position. These defects could be rescued by expression of JIP3 (JNK Interacting Protein 3), the mammalian homolog of *Drosophila* Syd, suggesting that these cellular activities are conserved from flies to humans and highlighting the utility of *Drosophila* as a model organism to elucidate key features of human disease.

Most important, during locomotion assays, the larvae with defective Syd protein and abnormally positioned nuclei were weak crawlers, mimicking disease states in humans. While muscle-specific depletion of Syd reduced muscle output, locomotion was rescued by expression of mammalian JIP3, suggesting that muscle cell nuclear position and muscle force generation are functionally linked in muscle disease.

More information: Abstract: "Sunday Driver (Syd/JIP3) and JNK Signaling are Required for Myogenesis and Muscle Function." Victoria K. Schulman1,2, Eric S. Folker2, Mary K. Baylies1,2. 1) Weill Cornell Graduate School of Medical Sciences, New York, NY; 2) Sloan-Kettering Institute, New York, NY. abstracts.genetics-gsa.org/cgi …il.pl?absno=14531108

Provided by Genetics Society of America