Nuclei in wrong place may be cause, not result, of inherited muscle diseases

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Incorrectly positioned nuclei are not merely a sign but a possible cause of human congenital myopathies, a string of inherited muscle diseases, Victoria Schulman, graduate student at Weill Cornell Graduate School of Medical Sciences, and Mary Baylies, Ph.D., developmental biologist at the Sloan Kettering Institute of Memorial Sloan-Kettering Cancer Center (MSKCC) in New York City, will report on Monday, Dec. 16, at the American Society for Cell Biology annual meeting in New Orleans

The researchers found that the whimsically named fruitfly gene, Sunday Driver, a.k.a. syd, and its mammalian analog, JIP3, seem to be in the driver's seat when it comes to parking the multiple nuclei of a skeletal muscle cell in their correct places.

When the researchers mutated the syd gene in a fruitfly, Drosophila melanogaster, model system, the nuclei of both the embryonic and larval muscle tissue cells were unevenly spaced and clustered. The hatched larvae with defective Syd protein were hobbled, crawling much more slowly than their healthy counterparts. Adding mammalian JIP3 protein to the syd gene mutant flies resulted in normal nuclear spacing and locomotive ability.

Looking at flies to investigate the cell biology of human muscle diseases may seem like the long way around, but Schulman and Dr. Baylies said that they could get clearer answers to basic questions in the flexible fly model than in traditional human muscle cell cultures.

Congenital myopathies account for one-tenth of all neuromuscular disorders, causing deterioration of skeletal muscle and eventually death. Despite advances in research and medicine, there are currently no cures, and treatment is largely palliative.

Studying congenital myopathies such as EDMD poses special challenges for cell biologists. Unlike typical cells, which have a single nucleus located in the center of each cell, muscles are composed of long multi-nucleated cells with the nuclei strung out like seeds in a bean pod because muscle cells arise from the fusion of numerous myoblasts, the building blocks of muscles.

Post-fusion, the many nuclei within the new cell spread out to maximize inter-nuclear distance and usually move to the cell periphery to avoid interfering with muscle contraction. Skeletal muscle cells with unevenly spaced nuclei, or nuclei parked in the wrong spot, are telltale in tissue biopsies of patients with suspected inherited muscle disease such as EDMD (1/100,000 births) and centronuclear myopathy (1/50,000 births). And yet no one was certain whether out-of-position nuclei are a cause or consequence of muscle disease.

Using the fruit fly model system, Schulman and Dr. Baylies identified three types of proteins required for correct myonuclear positioning: cytoskeletal filaments known as microtubules, which serve as "tracks" or cellular "roadways"; the motor proteins kinesin and dynein, which travel along these tracks; and motor protein regulators such as Ensconsin and Sunday Driver (Syd). Mechanistically, Syd works as a control switch to activate one motor at a time to coordinate their collective efforts to pull and move muscle cell nuclei into correct positions.

"Collectively, we implicate syd as a necessary regulator of nuclear positioning in muscle tissue, and show that mispositioned nuclei are a possible cause, not a consequence, of muscle disease," the researchers

wrote. They also point to the utility of model organisms in understanding a human disease as complex and dangerous as congenital myopathy.

More information: The authors will present, "Sunday Driver (Syd) regulates myonuclear positioning and muscle function," on Monday, Dec. 16, during the 1:30 to 5:30 p.m. poster session, "Tissue Development and Morphogenesis II."

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