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Investigational drug tested for preventing muscle fiber death in muscular dystrophy

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An investigational antiviral drug currently undergoing human trials in Europe for treating Hepatitis C infections may have potential to reduce muscle cell damage in Duchenne and other forms of muscular dystrophy (MD). A research team led by Cincinnati Children's Hospital Medical Center reported their results using three different mouse models of MD in a letter posted online March 16 by the journal *Nature Medicine*.

The investigational drug, Debio-025, is a known inhibitor of the protein cyclophilin D, which regulates the swelling of mitochondria in response to cellular injury. Researches decided to test the drug in mice engineered to carry MD after earlier laboratory tests showed deleting a gene that encodes cycolphilin D reduced swelling and reversed or prevented the disease's muscle-damaging characteristics. The mice were engineered as models of Duchenne muscular dystrophy and forms caused by a deficiency of two structural proteins, delta-sarcoglycan and laminin alpha2.

"Similar to deleting the gene encoding cyclophilin D, we found that treatment with Debio-025 reduced mitochondrial swelling and necrotic manifestations in mice with muscular dystrophy. This is why we believe inhibiting cyclophilin D could be a new treatment strategy," said Jeff Molkentin, Ph.D., corresponding author of the study and a researcher in the Division of Molecular Cardiovascular Biology at Cincinnati Children's. "Debio-025 has already passed Phase II clinical trials in Europe and is considered safe in people, so we want to explore the possibility of conducting clinical trials in patients with Duchenne MD."

During the onset of muscular dystrophy, the loss of certain proteins critical to muscle function – such as dystrophin – can lead to contraction-related micro-tears in muscle fibers and an influx of calcium around muscle tissue. When this happens, cyclophilin D is instructed to make the membranes of mitochondria more permeable. This causes mitochondria to be flooded by calcium and reorganize, swell and eventually rupture. This triggers cell death in muscle fibers and leads to the progressive muscle weakness, wasting and often early death associated with muscular dystrophy.

Mice lacking the protein delta-sarcoglycan exhibited severe dystrophy and swelling in both skeletal and heart muscle. When Dr. Molkentin and his colleagues deleted the gene encoding cyclophilin D in these mice, the muscle cells returned to near normal and did not show appreciable signs of swelling and cell death. The investigators repeated the experiment with mice lacking a gene encoding laminin alpha2, which causes a more severe dystrophy, swollen skeletal muscle cells and premature death before the mice reach two months of age. In contrast, mice lacking both laminin alpha2 and cyclophilin D showed much healthier muscle cells, increased body weight and walked more. Also, 75 percent of the mice lacking laminin alpha2 and cyclophilin D lived more than three times longer than mice lacking only laminin alpha2.

These findings led the research team to look for pharmacological treatments that also could inhibit cyclophilin D. The drug cyclosporine is a well-documented inhibitor of the protein, but its use is problematic because it also inhibits a protein, calcineurin, crucial to skeletal muscle cell repair after injury and to the development of skeletal muscle cells. The advantage of Debio-025 is that while it inhibits cyclophilin D and blocks cell death in a number of situations, the drug does not suppress the immune system or block calcineurin. The drug is manufactured by DebioPharm S.A. of Lausanne, Switzerland, which provided Debio-025 for use in the study.

The researchers also found their study may have implications beyond skeletal muscle disease as cyclophilin D deletion reduced cardiac dysfunction caused by calcium-overload induced necrosis. This led the team to suggest that mitochondrial-dependent necrosis may also function as a common disease mechanism underlying a number of long-term degenerative disorders, something they plan to study in future research projects.

Muscular dystrophies are inherited disorders that mostly affect striated muscle tissue and more commonly occur in boys. This disease results in progressive muscle weakness, wasting and in many instances death. There is no known cure for muscular dystrophy, although Cincinnati Children's is a recognized leader in disease-related research and a multi-disciplinary approach to patient treatment focused on maximizing ambulatory function and quality of life.

Source: Cincinnati Children's Hospital Medical Center