Gene editing enables researchers to correct mutation in muscle stem cells in DMD model

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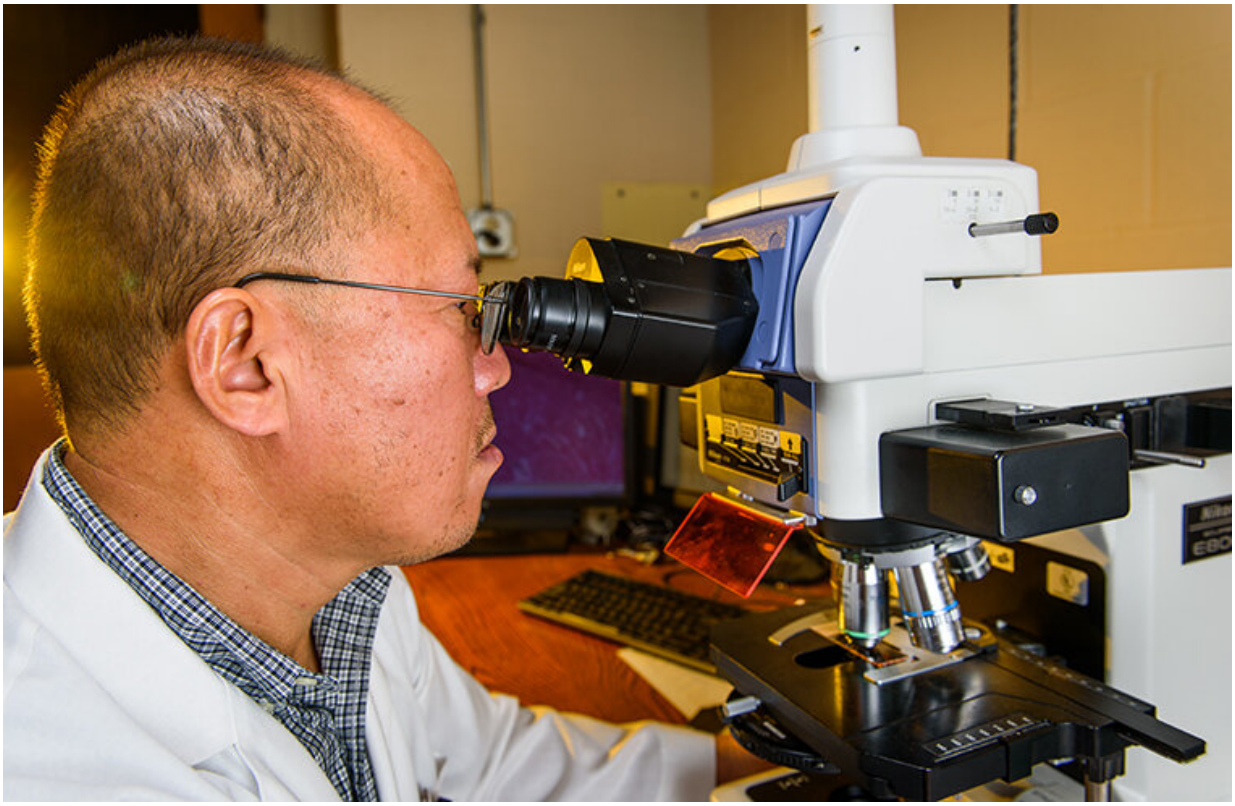

Credit: University of Missouri

Duchenne muscular dystrophy (DMD) is a rare but devastating genetic disorder that causes muscle loss and physical impairments. Researchers at the University of Missouri School of Medicine have shown in a mouse study that the powerful gene editing technique known as CRISPR may

provide the means for lifelong correction of the genetic mutation responsible for the disorder.

Children with DMD have a gene mutation that interrupts the production of a protein known as dystrophin. Without dystrophin, muscle cells become weaker and eventually die. Many children lose the ability to walk, and muscles essential for breathing and heart function ultimately stop working.

"Research has shown that CRISPR can be used to edit out the mutation that causes the early death of muscle cells in an animal model," said Dongsheng Duan, Ph.D., Margaret Proctor Mulligan Professor in Medical Research in the Department of Molecular Microbiology and Immunology at the MU School of Medicine and the senior author of the study. "However, there is a major concern of relapse because these gene-edited muscle cells wear out over time. If we can correct the mutation in muscle stem cells, then cells regenerated from the edited stem cells will no longer carry the mutation. A one-time treatment of the muscle stem cells with CRISPR could result in continuous dystrophin expression in regenerated muscle cells."

In collaboration with other MU colleagues and researchers from the National Center for Advancing Translational Sciences, Johns Hopkins School of Medicine and Duke University, Duan explored whether muscle stem cells from mice could be efficiently edited. The researchers first delivered the gene editing tools to normal mouse muscle through AAV9, a virus that was recently approved by the U.S. Food and Drug Administration to treat spinal muscular atrophy.

"We transplanted AAV9 treated muscle into an immune-deficient mouse," said Michael Nance, a MD-Ph.D. program student in Duan's lab and the lead author of the paper. "The transplanted muscle died first then regenerated from its stem cells. If the stem cells were successfully

edited, the regenerated muscle cells should also carry the edited gene."

The researchers' reasoning was correct, as they found abundant edited cells in the regenerated muscle. They then tested if muscle stem cells in a mouse model of DMD could be edited with CRISPR. Similar to what they found in normal muscle, the stem cells in the diseased muscle were also edited. Cells regenerated from these edited cells successfully produced dystrophin.

"This finding suggests that CRISPR gene editing may provide a method for lifelong correction of the genetic mutation in DMD and potentially other muscle diseases," Duan said. "Our research shows that CRISPR can be used to effectively edit the stem cells responsible for muscle regeneration. The ability to treat the stem cells that are responsible for maintaining muscle growth may pave the way for a one-time treatment that can provide a source of gene-edited cells throughout a patient's life."

With more study, the researchers hope this stem cell-targeted CRISPR approach may one day lead to long-lasting therapies for children with DMD.

More information: Michael E. Nance et al. AAV9 Edits Muscle Stem Cells in Normal and Dystrophic Adult Mice, *Molecular Therapy* (2019). DOI: 10.1016/j.ymthe.2019.06.012

Provided by University of Missouri

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