Researchers find animal model for understudied type of muscular dystrophy

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Researchers at the University of Minnesota have developed an animal research model for facioscapulohumeral muscular dystrophy (FSHD) to be used for muscle regeneration research as well as studies of the effectiveness of potential therapies for FSHD.

The research is published in the current edition of the journal *Cell Reports*.

There is no treatment for FSHD, which is thought by many to be the most common type of muscular dystrophy. FSHD is an unusual genetic disorder because, unlike most genetic diseases, it is not caused by the loss of a functional gene, but rather by the modification of an existing gene, through a genetic mutation. This mutation makes the gene more active so patients with FSHD express a protein, named DUX4, which interferes in an unknown way with muscle maintenance.

"We felt that an animal model would advance progress towards a cure for FSHD for two reasons," said Michael Kyba, Ph.D., lead researcher and associate professor in the Medical School at the University of Minnesota. "First, it would allow us to understand what DUX4 does in muscle to cause muscle loss, and second, it would provide a system in which efficacy of potential therapies could be evaluated before they are tested in humans."

The mouse model designed by Kyba and his team allows the disease-associated DUX4 protein to be produced when mice are treated with doxycycline. The amount of DUX4 can be controlled by varying the dose of doxycycline. Researchers expected the mice to be normal until they were treated with doxycycline, however even when DUX4 was in the "off" state, mice showed profound disease effects, some related to FSHD as well as additional effects not seen in FSHD patients.

"Nothing is black and white in biology," says Kyba. "No gene is truly off, and the off state in this case resulted in enough leaky DUX4 expression to kill the mice."

The team solved this problem by moving the gene to the X chromosome. Because females have two X chromosomes, only one of which is actively used in each cell, the female mice were healthy enough to enable the DUX4 mice to reproduce even though all of their male progeny with the DUX4 gene died. The fact that multiple levels of turning off the DUX4 gene were necessary to allow mice to survive showed that DUX4 is more toxic than researchers expected.

"We learned a lot with this animal model, but perhaps the most important finding was what we observed when we transplanted skeletal muscle stem cells," said Kyba.

The team could isolate muscle stem cells from the male mice before they died and when they transplanted them into muscle-damaged recipient mice, they found that the stem cells were able to regenerate new muscle. But when even low doses of doxycycline were given to the recipients to turn on DUX4 in the skeletal muscle stem cells, muscle regeneration was severely impaired. This suggested that a defect in skeletal muscle regeneration may contribute to muscle loss in FSHD. The finding also provides a very sensitive quantitative readout of DUX4 activity.

"This assay, in which we count new muscle fibers produced by transplanted DUX4-expressing muscle stem cells, will be very useful in testing therapeutics," says Kyba. "Drugs that target DUX4 should allow these transplanted DUX4-expressing muscle stem cells to make more new muscle fibers."

As researchers develop drugs that target the DUX4 protein, the hope is that these mice will be used to determine whether such drugs can reach skeletal

muscle and allow muscle damage to be repaired, even in the presence of DUX4.

More information: www.cell.com/cell-reports/abst … 2211-1247(14)00658-5

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