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GENE THERAPY

Going from strength to strength

Effective muscle contraction depends on efficient neurotransmission at neuromuscular junctions (NMJs). In humans, inherited mutations affecting NMJ function cause chronic muscle weakness (myasthenia), and there is no effective treatment for many of these patients. In this study, Arimura *et al.* show that, in mouse models of myasthenia, use of a gene therapy approach to upregulate a key protein involved in NMJ maintenance, administered after disease onset, leads to increases in NMJ size and efficiency, as well as a marked increase in muscle strength.

Various myasthenias are caused by defects in NMJ structure. The maintenance of NMJ structure is dependent on skeletal muscle receptor tyrosine-protein kinase (MUSK), which is activated by DOK7. In both mice and humans, defective DOK7 causes muscle weakness and NMJs that are smaller than normal.

In a previous study, the authors showed that overexpression of DOK7 in wild-type mice promotes MUSK activation and enlarges NMJs. As the size of an NMJ is important in determining its efficiency of transmission, the authors reasoned that forcibly increasing NMJ size might enhance neurotransmission and thereby reduce muscle weakness in mice with myasthenia-like symptoms.

To test this hypothesis, they generated mice that harboured a copy of a mutated variant of *Dok7* that caused a reduction in DOK7 function and myasthenia-like symptoms. After symptom onset, they treated the mice with a recombinant adeno-associated virus vector carrying human *DOK7* (AAV-D7) to increase DOK7 expression in muscle cells.

A single dose of AAV-D7 was sufficient to markedly increase MUSK phosphorylation and NMJ size 5 days after treatment. The injected mice also showed improvements in muscle strength. Indeed, by postnatal day 56, these animals had similar levels of motor function and body weight to those of controls, and they survived for at least a year with no apparent abnormalities.

Given that *DOK7* therapy enhances NMJ size in wild-type and *Dok7*-mutant mice, the authors hypothesized that this therapy might have positive effects in other mouse models involving defects in NMJ structure. Emery–Dreifuss muscular dystrophy (AD-EDMD) is caused by a mutation in the gene encoding lamin A/C. A single dose of AAV-D7 given to mice with this mutation, after onset of symptoms, was sufficient to increase NMJ size, increase MUSK phosphorylation, and enhance motor function and survival time.

Overall, these findings suggest that a variety of myasthenic syndromes might be helped by a gene therapy approach that upregulates *DOK7* expression, or any equivalent method that stably and safely enlarges the NMJ.

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ORIGINAL RESEARCH PAPER Arimura, S. *et al.* *DOK7* gene therapy benefits mouse models of diseases characterized by defects in the neuromuscular junction. *Science* **345**, 1505–1508 (2014)

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