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A mutation-independent approach for muscular dystrophy via upregulation of a modifier gene.

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Abstract

Neuromuscular disorders are often caused by heterogeneous mutations in large, structurally complex genes. Targeting compensatory modifier genes could be beneficial to improve disease phenotypes. Here we report a mutation-independent strategy to upregulate the expression of a disease-modifying gene associated with congenital muscular dystrophy type 1A (MDC1A) using the CRISPR activation system in mice. MDC1A is caused by mutations in LAMA2 that lead to nonfunctional laminin-α2, which compromises the stability of muscle fibres and the myelination of peripheral nerves. Transgenic overexpression of Lama1, which encodes a structurally similar

protein called laminin-α1, ameliorates muscle wasting and paralysis in mouse models of MDC1A, demonstrating its importance as a compensatory modifier of the disease[1]. However, postnatal upregulation of Lama1 is hampered by its large size, which exceeds the packaging capacity of vehicles that are clinically relevant for gene therapy. We modulate expression of Lama1 in the dy^{2j}/dy^{2j} mouse model of MDC1A using an adeno-associated virus (AAV9) carrying a catalytically inactive Cas9 (dCas9), VP64 transactivators and single-guide RNAs that target the Lama1 promoter. When pre-symptomatic mice were treated, Lama1 was upregulated in skeletal muscles and peripheral nerves, which prevented muscle fibrosis and paralysis. However, for many disorders it is important to investigate the therapeutic window and reversibility of symptoms. In muscular dystrophies, it has been hypothesized that fibrotic changes in skeletal muscle are irreversible. However, we show that dystrophic features and disease progression were improved and reversed when the treatment was initiated in symptomatic dy^{2j}/dy^{2j} mice with apparent hindlimb paralysis and muscle fibrosis. Collectively, our data demonstrate the feasibility and therapeutic benefit of CRISPR-dCas9-mediated upregulation of Lama1, which may enable mutation-independent treatment for all patients with MDC1A. This approach has a broad applicability to a variety of disease-modifying genes and could serve as a therapeutic strategy for many inherited and acquired diseases.

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