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Triggering regeneration and tackling apoptosis: a combinatorial approach to treating congenital muscular dystrophy type 1 A.

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Abstract

Merosin-deficient congenital muscular **dystrophy type 1A** (MDC1A) is an autosomal recessive disorder caused by mutations in the laminin- α 2 gene (OMIM: 607855). Currently, no treatment other than palliative care exists for this disease. In our previous work, genetic interventions in the Lama2(Dy-w) mouse model for MDC1A demonstrated that limited **regeneration** and uncontrolled **apoptosis** are important drivers of this disease. However, targeting one of these disease drivers without addressing the other results in only partial rescue of the phenotype. The present study was designed to determine whether utilizing a **combinatorial treatment approach** can lead to a more profound amelioration of the disease pathology. To accomplish this task, we generated Bax-null Lama2(Dy-w)mice that overexpressed muscle-specific IGF-1 (Lama2(Dy-w)Bax(-/-)+IGF-1tg). Further to test the translational potential of IGF-1 administration in combination with Bax inhibition, we treated Lama2(Dy-w)Bax(-/-) mice postnatally with systemic recombinant human IGF-1 (IPLEXTM). These two **combinatorial** treatments lead to similar, promising outcomes. In addition to increased body and muscle weights, both transgenic overexpression and systemic administration of IGF-1 combined with Bax-inhibition resulted in improved muscle phenotype and locomotory function that were nearly indistinguishable from wild-**type** mice. These results provide a fundamental proof of concept that justifies the use of a combination therapy as an effective treatment for MDC1A and highlights a compelling argument toward shifting the paradigm in **treating** multifaceted

neuromuscular diseases.

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