An agrin minigene rescues dystrophic symptoms in a mouse model for congenital muscular dystrophy

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Congenital muscular dystrophy is a heterogeneous and severe, progressive muscle-wasting disease that frequently leads to death in early childhood. Most cases of congenital muscular dystrophy are caused by mutations in LAMA2, the gene encoding the alpha2 chain of the main laminin isoforms expressed by muscle fibres. Muscle fibre deterioration in this disease is thought to be caused by the failure to form the primary laminin scaffold, which is necessary for basement membrane structure, and the missing interaction between muscle basement membrane and the dystrophin-glycoprotein complex (DGC) or the integrins. With the aim to restore muscle function in a mouse model for this disease, we have designed a minigene of agrin, a protein known for its role in the formation of the neuromuscular junction. Here we show that this mini-agrin-which binds to basement membrane and to alpha-dystroglycan, a member of the DGC-amends muscle pathology by a mechanism that includes agrin-mediated stabilization of alpha-dystroglycan and the laminin alpha5 chain. Our data provides in vivo evidence that a non-homologous protein in combination with rational protein design can be used to devise therapeutic tools that may restore muscle function in human muscular dystrophies.
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