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Physiological impact and disease reversion for the severe form of centronuclear myopathy linked to Dynamin

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Abstract

Classical dynamins are large GTPases regulating membrane and cytoskeleton dynamics and are linked to different pathological conditions ranging from neuromuscular diseases to encephalopathy and cancer. Dominant DNM2 (dynamin 2) mutations lead to either mild adult onset or severe neonatal centronuclear myopathy (ADCNM). Our objectives were to better understand the pathomechanism of severe ADCNM and test a potential therapy. Here, we created the Dnm2SL/+ mouse line harboring the common S619L mutation found in patients with severe ADCNM and impairing the conformational switch regulating dynamin self-assembly and membrane remodeling. The Dnm2SL/+ mouse faithfully reproduces severe ADCNM hallmarks with early impaired muscle function and force together with myofibers hypotrophy. It revealed swollen mitochondria lacking cristae as the main ultrastructural defect and potential cause of the disease. Patient analysis confirmed this structural hallmark. In addition, DNM2 reduction with antisense oligonucleotides after disease onset efficiently reverted locomotor and force defects after only 3 weeks of treatment. Most histological defects including mitochondria alteration were partially or fully rescued. Overall, this study highlights an efficient approach to revert the severe form of dynamin-related centronuclear myopathy. These data also reveal that the dynamin conformational switch is key for muscle function and should be targeted for future therapeutic developments.

Keywords: Genetic diseases; Muscle; Muscle Biology; Neuromuscular disease; Therapeutics.