Format: Abstract

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Amphiphysin 2 modulation rescues myotubular myopathy and prevents focal adhesion defects in mice.

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Abstract

Centronuclear myopathies (CNMs) are severe diseases characterized by muscle weakness and myofiber atrophy. Currently, there are no approved treatments for these disorders. Mutations in the phosphoinositide 3-phosphatase myotubularin (MTM1) are responsible for X-linked CNM (XLCNM), also called myotubular myopathy, whereas mutations in the membrane remodeling Bin/amphiphysin/Rvs protein amphiphysin 2 [bridging integrator 1 (BIN1)] are responsible for an autosomal form of the disease. Here, we investigated the functional relationship between MTM1 and BIN1 in healthy skeletal muscle and in the physiopathology of CNM. Genetic overexpression of human BIN1 efficiently rescued the muscle weakness and life span in a mouse model of XLCNM. Exogenous human BIN1 expression with adeno-associated virus after birth also prevented the progression of the disease, suggesting that human BIN1 overexpression can compensate for the lack of MTM1 expression in this mouse model. Our results showed that MTM1 controls cell adhesion and integrin localization in mammalian muscle. Alterations in this pathway in *Mtm1* $^{-/y}$ mice were associated with defects in myofiber shape and size. BIN1 expression rescued integrin and laminin alterations and restored myofiber integrity, supporting the idea that MTM1 and BIN1 are

functionally linked and necessary for focal adhesions in skeletal muscle. The results suggest that BIN1 modulation might be an effective strategy for treating XLCNM.

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