BIN1 gene replacement reverts BIN1-related centronuclear myopathy

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Résumé

Centronuclear myopathies (CNM) are severe genetic disorders characterized by generalized muscle weakness associated with organelle mispositioning in myofibers. Most CNM cases are caused by mutations in proteins involved in membrane remodeling, including amphiphysin 2 (BIN1). There is no treatment and the pathological mechanisms are not understood. Here, we aimed to cure the *Bin1*-CNM mouse model (*Bin1*mck-/-) via an adeno-associated virus (AAV)-based gene replacement strategy. Early systemic exogenous BIN1 expression efficiently prevented disease progression. Moreover, BIN1 expression after disease onset reverted all disease signs four weeks after treatment, including motor defects, muscle weakness, muscle and myofibers hypotrophy, kyphosis, nuclei and mitochondria misposition, and altered T-tubules network. We then validated the most efficient construct combining a myotropic AAV serotype with the muscle BIN1 isoform. The rescue correlated with normalization of autophagy and excitation-contraction coupling markers. Cellular and in vivo investigations revealed that different BIN1 natural isoforms shared similar beneficial effects. Artificial constructs coding for separated protein domains rescued different CNM hallmarks. Only the muscle-specific BIN1 isoform combined the different cellular functions of BIN1 on membrane tubulation and dynamin (DNM2) regulation necessary for a full rescue. Overall, this study validates BIN1 gene replacement as a promising strategy to cure BIN1-related centronuclear myopathy.

Mots-Clés: congenital myopathy, myotubular myopathy, amphiphysin, BIN1, BAR domain, endocytosis, membrane remodeling, gene therapy, adeno, associated virus

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