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LES SÉMINAIRES DE L'INMG

Myostatin – A novel biomarker for *Dnm2* therapy in Myotubular Myopathy mice

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Jeudi 11 Octobre 2018
11 heures

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Abstract :

Centronuclear myopathies (CNM) are non-dystrophic muscle diseases for which no effective therapy is currently available. The most severe form, myotubular myopathy (X-linked CNM), is caused by myotubularin 1 (*MTM1*) loss-of-function mutations, while the main autosomal dominant form is due to dynamin2 (*DNM2*) mutations. We have shown that antisense oligonucleotide (ASO) mediated DNM2 knockdown can efficiently correct muscle defects due to loss of MTM1 in mice, providing an attractive therapeutic strategy for this disease. We are now investigating blood-based biomarkers that can be used to monitor disease state and rescue in myotubular myopathy mice. Myostatin is a protein produced and released by myocytes, which acts in an autocrine function to inhibit muscle growth and differentiation. Our results suggest myostatin pathway is 'turned down' at the mRNA level in muscle biopsies, leading to low levels of circulating and endogenous muscle myostatin in plasma. We have generated preliminary data suggesting ASO-mediated DNM2 reduction results in an increase in circulating myostatin. With clinical trials for myotubular myopathy currently in progress, identification of novel blood-based biomarkers such as myostatin may allow for monitoring of treatment efficacy in patients.

Selected Publications:

1. Tasfaout H, Lionello VM, Kretz C, Koebel P, Messaddeq N, Bitz D, Laporte J, Cowling BS. Single Intramuscular Injection of AAV-shRNA Reduces DNM2 and Prevents Myotubular Myopathy in Mice. Molecular Therapy. 2018 Apr 4;26(4):1082-1092. doi: 10.1016/j.ymthe.2018.02.008.

2. Cowling BS, Prokic I, Tasfaout H, Rabai A, Humbert F, Rinaldi B, Nicot AS, Kretz C, Friant S, Roux A, Laporte J. Amphiphysin (BIN1) negatively regulates dynamin 2 for normal muscle maturation. J Clin Invest. 2017 Dec 1;127(12):4477-4487. doi: 10.1172/JCI90542.

3. Raess MA, Cowling BS, Bertazzi DL, Kretz C, Rinaldi B, Xuereb JM, Kessler P, Romero NB, Payrastre B, Friant S, Laporte J. Expression of the neuropathy-associated MTMR2 gene rescues MTM1-associated myopathy. Hum Mol Genet. 2017 Oct 1;26(19):3736-3748. doi: 10.1093/hmg/ddx258.

4. Tasfaout H, Buono S, Guo S, Kretz C, Messaddeq N, Booten S, Greenlee S, Monia BP, Cowling BS, Laporte J. Antisense oligonucleotide-mediated Dnm2 knockdown prevents and reverts myotubular myopathy in mice. Nat Commun. 2017 Jun 7;8:15661. doi: 10.1038/ncomms15661.

5. Raess MA, Friant S, Cowling BS, Laporte J. WANTED - Dead or alive: Myotubularins, a large disease-associated protein family. Adv Biol Regul. 2017 Jan;63:49-58. doi: 10.1016/j.jbior.2016.09.001.

6. Arbogast T, Ouagazzal AM, Chevalier C, Kopanitsa M, Afinowi N, Migliavacca E, Cowling BS, Birling MC, Champy MF, Reymond A, Herault Y. Reciprocal Effects on Neurocognitive and Metabolic Phenotypes in Mouse Models of 16p11.2 Deletion and Duplication Syndromes. PLoS Genet. 2016 Feb 12;12(2):e1005709. doi: 10.1371/journal.pgen.1005709.

7. Lo HP, Nixon SJ, Hall TE, Cowling BS, Ferguson C, Morgan GP, Schieber NL, Fernandez-Rojo MA, Bastiani M, Floetenmeyer M, Martel N, Laporte J, Pilch PF, Parton RG. The caveolin-cavin system plays a conserved and critical role in mechanoprotection of skeletal muscle. J Cell Biol. 2015 Aug 31;210(5):833-49. doi: 10.1083/jcb.201501046.

8. Cowling BS, Chevremont T, Prokic I, Kretz C, Ferry A, Coirault C, Koutsopoulos O, Laugel V, Romero NB, Laporte J. Reducing dynamin 2 expression rescues X-linked centronuclear myopathy. J Clin Invest. 2014 Mar;124(3):1350-63. doi: 10.1172/JCI71206.