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Press information

A Gene Therapy Tested in the Treatment of Myotubular Myopathy

Inserm and CNRS researchers from the Institute of Genetics and Molecular and Cellular Biology (Inserm/CNRS/Université de Strasbourg) have discovered how myotubularin - a protein deficient in myotubular myopathy - interacts with amphiphysin 2 and suggest targeting the latter in order to treat patients. This research was published on March 20, 2019 in *Science Translational Medicine*.

Myotubular myopathy is a rare genetic disease affecting around one in 50,000 children. Linked to a mutation in the MTM1 gene located on the X-chromosome, it manifests as reduced muscle-cell adhesion and an alteration of the muscle fibers. This phenomenon causes major muscle weakness - including at the respiratory level - and leads to premature death with two thirds of patients not surviving beyond two years of age. At present, there is no treatment.

When exploring the interactions of myotubularin (coded by the MTM1 gene) with another protein, amphiphysin 2 (coded by the BIN1 gene), which is also expressed in the muscles and involved in similar myopathies, Inserm's "Pathophysiology of neuromuscular diseases" team, in conjunction with the CNRS at the Institute of Genetics and Molecular and Cellular Biology (CNRS/Inserm/Université de Strasbourg), discovered how these proteins work together and suggests a new therapeutic target. Previous research had shown that myotubularin and amphiphysin 2 can physically interact by binding to each other.

To explore this functional link between the two, the researchers developed a model of MTM1-deficient transgenic mice and crossed these animals with other mice - some of which do not express BIN1 and some of which, on the contrary, overexpress it. They were unable to obtain any animals deficient in both MTM1 and BIN1, proving that at least one of the two proteins is necessary for muscle-fiber development and fetal survival. Conversely - and this came as a pleasant surprise - the overexpression of BIN1 made it possible to correct the myopathy linked to the MTM1 deficiency and obtain life expectancy equivalent to that of wild animals. Upon closer analysis of the muscles, the researchers observed satisfactory muscle-fiber organization and size with good cell adhesion, thereby leading to the hypothesis that MTM1 is an in vivo activator of the bin1 protein and that large quantities of the latter could make it possible to "do without" MTM1.

To verify whether BIN1 is a good therapeutic target, the researchers went on to conduct a gene therapy experiment in MTM1-deficient mice. They administered the human BIN1 gene using an AAV viral vector by systemic (intraperitoneal) injection following the birth of the rodents. A procedure that markedly reduced the symptoms of the condition and increased the survival of the diseased mice to that of healthy mice. *"There we have the proof of concept that the human BIN1 gene offers major potential in the treatment of myotubular myopathy linked to myotubularin deficiency, with spectacular results in mice. We would now like to continue this development in the form of preclinical trials and hope in the long-term to be able to propose a*

treatment for patients currently facing a therapeutic desert", concludes Jocelyn Laporte, head of the Inserm team having performed this research.

Sources

Amphiphysin 2 (BIN1) modulation rescues MTM1 myotubular myopathy and prevents focal adhesion defects
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