CRISPR-Cas9-Mediated Upregulation of Utrophin Ameliorates Duchenne Muscular Dystrophy

Maëlle Ralu[1,2 *], Simon Guiraud[1,2 *], Sumitava Dastidar[3,4 †], Paola Galbiati[1,2 †], Emilia Sadaoui[1,2], Fetta Mazed[1,2], Fatima Amor[1,2], Anne de Cian[5], Isabelle Richard[1,2], Kamel Mamchaoui[6], Giuseppe Ronzitti[1,2], Francesco Saverio Tedesco[3,4,7 #], Mario Amendola[1,2,8 #]

Background

Duchenne muscular dystrophy (DMD) is a severe genetic disease that causes muscles to weaken and waste over time. It is caused by the loss of a protein called dystrophin, which normally protects muscle fibers during movement. Without dystrophin, muscles become damaged easily, leading to loss of mobility, breathing difficulties, and heart problems.

The strategy

This project explores an alternative strategy: increasing the amount of utrophin, a natural "backup" for dystrophin already present in our bodies. Very similar to the missing dystrophin protein, utrophin is capable of performing the same protective functions. The major advantage is that this strategy could benefit all individuals living with DMD, regardless of their genetic change.

A new CRISPR based approach

Gene editing is a promising approach to treat DMD as it targets the genetic cause of the condition. Most gene editing focuses on adding a working version of the dystrophin gene. In this study, researchers developed a new gene-editing approach to boost utrophin production. They used a CRISPR tool (“molecular scissors”) to remove a small “repressor” signal in the utrophin gene. This repressor normally limits how much utrophin the body makes. CRISPR acts like molecular scissors, cutting out this signal, which allows the cells to naturally produce more utrophin on their own.

Results

The team tested this strategy in human muscle cells grown in the laboratory, including “lab grown mini muscles” that look more like real muscles. After editing, utrophin levels increased by two- to three-fold. The treated DMD muscle tissues showed clearer improvements in muscle function, including better calcium handling and stronger contractions, both of which are typically affected in DMD.

The researchers then tested the approach in a mouse which has a DMD-like condition. By delivering CRISPR tools with a harmless virus (AAV), they were able to edit the target utrophin

gene in the muscle and increase utrophin levels. Treated muscles showed reduced fibrosis, improved tissue organization, and small improvements in muscle strength.

Conclusions

Although further optimization is needed, this study provides promising evidence that a one-time gene-editing treatment could permanently boost utrophin in muscle. This has the potential to be a treatment option for all people with DMD, regardless of their specific genetic change. This approach may also complement strategies aimed at restoring dystrophin, opening the door to combined therapies in the future. Together, both approaches could slow or even stop the progression of DMD and improve quality of life for families affected by this condition.