Zebrafish's eye muscles give hope for people with muscular dystrophy diseases

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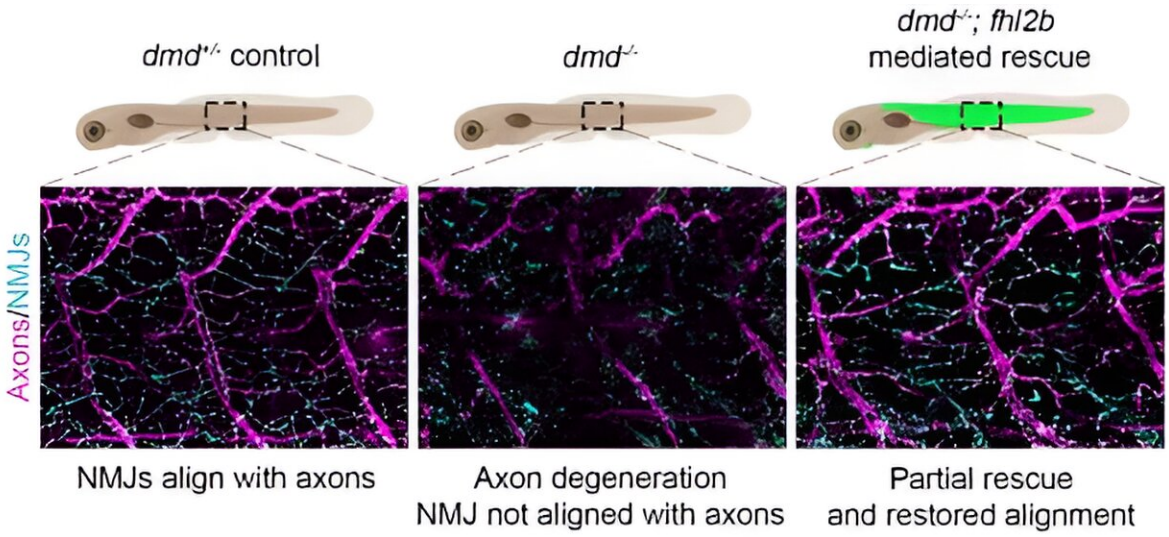

Axon and NMJ integrity is partially rescued by overexpression of fhl2b in trunk muscle of 5 dpf dmd$^{-/-}$ zebrafish larvae. Credit: https://umu.diva-portal.org/smash/get/diva2:1820308/FULLTEXT01.pdf

Muscular dystrophies are a group of diseases in which proteins in the muscles do not function properly, either through inherited or spontaneous mutations. This, in turn, leads to muscle tissue breaking down over time and patients eventually become wheelchair-bound and often die prematurely due to the muscles that help with breathing or the heart stop working.

However, the muscles that control the movements of the eye work well all the way through the course of the disease, which makes it important to study them to try to find out what strategies they use to survive muscular dystrophies.

"In my research, I have studied the zebrafish's eye muscles, which have been shown to have the same properties in muscular dystrophies as humans, and then generated new disease models with the help of the genetic scissors Crispr/Cas9," says Nils Dennhag.

"By reading the gene expression in the eye muscles of zebrafish, both healthy and fish with muscular dystrophies, we have partly succeeded in decoding how the eye muscles handle these diseases—through upregulation of the protein Fhl2."

Healthier muscle fibers

Fhl2 protects the muscle fibers in the eye muscles by preventing cellular breakdown, as well as restraining an unnatural pathological enlargement. Fhl2 is not found naturally in large muscle areas of zebrafish or humans, but by genetically forcing Fhl2 gene expression here as well, the researchers were able to show a large increase in survival in zebrafish with the most lethal type of muscular dystrophy—Duchenne muscular dystrophy.

In addition to better survival, zebrafish with Duchenne muscular dystrophy that also had increased expression of Fhl2, had healthier muscle fibers, markedly better innervation and better swimming ability than sick zebrafish without Fhl2. In addition, the fibers that did break down regenerated faster, which led to a better recovery.

Possible treatment method

"Overall, our studies show that it is possible to use the eye muscles as a kind of template for how to cope with living with muscular dystrophies, which has not been demonstrated to the same extent before. We also believe that this may be a way forward for the treatment of humans, as we have also seen that human eye muscles have muscle fibers that express Fhl2.

"We also believe that we have only scratched the surface of the strategies the eye muscles have to offer, but it is a good step on the way, and shows that this new type of treatment method is possible," says Dennhag.

"We have used the CRISPR/Cas9 genetic scissors to create a number of different models of muscular dystrophies, which are used in the study to study how the eye muscles react when these proteins are removed. We then sequenced RNA from both eye muscles and body muscles to see what differences existed between these tissues under disease conditions.

"When we found that Fhl2 was upregulated in eye muscles, we used circular DNA with the Fhl2 gene, which is linked to a muscle-specific promoter, which was injected into zebrafish with muscular dystrophy. This causes all muscles in the body to express Fhl2, not just the eye muscles, which led to the effects described above," says Dennhag.

Dennhag will defend his doctoral dissertation, "Genetic studies of zebrafish muscles: Clues to protection in muscle disease," on Jan. 26.

More information: Genetic studies of zebrafish muscles: Clues to protection in muscle disease. umu.diva-portal.org/smash/record.jsf?pid=diva2%3A1820308&dswid=5196

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