Mice point to a therapy for Charcot-Marie-Tooth disease

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VIB researchers have developed a mouse model for Charcot-Marie-Tooth (CMT) neuropathy, a hereditary disease of the peripheral nervous system. They also found a potential therapy for this incurable disease. The treatment not only halted the damage to the nerves and the atrophy of the muscles, it even succeeded in reversing the symptoms.

The research was conducted under supervision of Wim Robberecht en Ludo Van Den Bosch from VIB-K.U.Leuven, in collaboration with the team of Vincent Timmerman at VIB-University of Antwerp. The study was published in Nature Medicine.

CMT: a collection of neuropathies

Charcot-Marie-Tooth (CMT) disease is the name for a collection of hereditary disorders and affects approximately one in 2,500 individuals, making it the most common inherited disorder of the peripheral nervous system. CMT is characterized by loss of muscle tissue due to denervation and by sensory abnormalities, both predominantly in feet and legs but also in the hands and arms in advanced stages of the disease. Persons with CMT can be affected moderately to quite severely. It is presently not possible to cure or prevent CMT, which affects both children and adults. Research into the molecular biological process leading to CMT is important, because it contributes to the development of good diagnosis and offers possible treatments.

Earlier work by VIB researchers showed that some CMT patients have mutations in HSPB1, a gene coding for the 27 kDa small heat shock protein B1, a protein that plays a role in many stress-related molecular processes in the body. Until now, it was unclear how mutations in HSPB1 could lead to degeneration of the nerve bundles and to muscular weakness.

Mouse model for CMT

The core of the study by Constantin van Outryve d'Ydewalle consists of the construction of a mouse model for CMT. The researchers expressed the mutated human HSPB1 gene in mouse neurons. The mouse model develops motor symptoms, muscle atrophy and weakness, foot deformities and steppage gait, all very similar to symptoms observed in affected individuals. Furthermore, the mice develop sensory problems that also occur in CMT patients. Pathological examination of the nerves of the CMT mice shows that the contact between the nerve endings and muscles is disturbed.

Axonal transport deficits

The CMT mice provide the unique possibility to isolate and culture affected nerve cells, making it possible to investigate what exactly goes wrong in the sick nerves. It was discovered that the transport of mitochondria (the cellular power plants) within the axons is severely disturbed in the neurons from symptomatic CMT mice, most likely because the tracks along which the mitochondria are transported (microtubules) are damaged. This could lead to a chronic lack of sufficient mitochondria and other transported cargoes at the nerve endings, causing the nerves to degenerate.

Possible treatment of CMT by HDAC6 inhibitors

These new insights also open possibilities for treatment, because the mitochondrial transport in nerve fibers is known to be affected by tubulin deacetylation, a posttranslational modification of the building blocks of microtubules catalyzed by histone deacetylase 6 (HDAC6). Inhibitors of HDAC6 do not only reverse the axonal transport deficits in vitro, treatment of the CMT mice with HDAC6 inhibitors also halts the damage to the nerves and even succeeds in reversing the symptoms, most likely by muscle reinnervation. The most specific therapeutic molecule used in this study (Tubastatin A) was made by Alan Kozikowski from the University of Illinois at Chicago (USA).

Mouse medicine is not the same as human medicine

There is still a long way to go before these drugs will become available for patients. Many experimental drugs – even those that are successful in animal models – fail during clinical trials due to problems with safety or the lack of therapeutic effectiveness. Still, the results of this study are important not only because of the CMT mouse model that replicates the symptoms of the human disease; it also opens perspectives for possible new treatments of an incurable disease.

Other diseases?

Reduced axonal transport in neurons is also observed in other neurodegenerative or neurological diseases, opening the door for further investigations into the effects of this new therapeutic strategy in other diseases. Further scientific research is crucial to solve this issue.

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