Mice, mitochondria and myopathy

New research has identified mitochondrial therapies that may benefit people who suffer from certain types of inherited neuromuscular disorders. Neuromuscular disorders affect a large number of children and adults worldwide, and mitochondrial involvement characterizes roughly 1 in 5,000 cases. Currently, treatments for mitochondrial diseases may relieve symptoms but do not target the disease itself.

Carlos T. Moraes and colleagues at the University of Miami School of Medicine (Miami, FL) and Dana-Farber Cancer Institute (Boston, MA) attempted to address mitochondrial myopathy by increasing mitochondrial functional mass. They used mice in which the gene encoding an essential cytochrome oxidase assembly factor was deactivated, resulting in a progressive myopathy with a pattern similar to that observed in human mitochondrial myopathies. The team worked with two different varieties of the knockout mice: a 'severe myopathy' model and a 'mild myopathy' model.

The team studied two different approaches to mitochondrial therapy. Both treatments work by boosting the activity of peroxisome proliferator-activated receptor γ (PPARγ) coactivator α (PGC-1α).

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PGC-1α is a metabolic regulator and is known to have a role in controlling mitochondrial biogenesis.

First, Moraes *et al.* analyzed the effects of induced mitochondrial biogenesis on disease course by crossing both varieties of knockout mice with a third mouse line engineered to express PGC-1α in muscle. Knockout mice expressing PGC-1α survived markedly longer than control knockout mice that did not express the transgene, particularly among female mice (*Cell Metab.* **8**, 249–256; 2008). In addition, muscle impairment took longer to develop in knockout mice expressing PGC-1α than in those without PGC-1α.

In a second approach, Moraes's group investigated whether administering bezafibrate to knockout mice could increase mitochondrial biogenesis. Bezafibrate is a drug that stimulates the PGC-1α/PPAR pathway. Knockout mice that received bezafibrate lived significantly longer than littermates that did not receive the drug. In addition, disease onset was delayed in bezafibrate-fed mice compared with knockouts fed a normal diet.

The researchers concluded that increased mitochondrial proliferation in muscle was able to delay the onset of mitochondrial myopathy in the knockout mice, resulting in a longer lifespan. These benefits were likely due to increased mitochondrial mass in muscle tissue. The authors believe that their therapeutic strategies may also be applicable to other mitochondrial diseases. "The promising results with the bezafibrate-fed myopathy mice clearly identify small-molecule PPAR agonists, already used in humans with metabolic diseases, as a treatment option for mitochondrial diseases," concluded their report.

Monica Harrington

MORE 'EAR HAIR' MAY LEAD TO TREATMENT FOR DEAFNESS

Though hair on the outer ear may become thicker and more bountiful with age, hair cells in the inner ear—which are necessary for hearing—begin to deteriorate and die. Damage to these hair cells, which can result from disease or chronic exposure to loud noise, is the most common cause of hearing loss. One potential approach to restoring auditory function in the hearing impaired is to replace defective hair cells with healthy cells. In a new study led by John Brigande of the Oregon Health and Science University (Portland), researchers used a gene transfer technique to grow large quantities of functional hair cells in the ears of developing mice, proving that such treatment might eventually be possible.

The scientists used an *in utero* technique that they had developed to transfer a transcription factor required for hair-cell development (*Atoh1*) into the inner ears of developing mice (*Nature* published online 27 August 2008; doi:10.1038/nature07265). Transfected progenitor cells later became incorporated into the organ of Corti, which is located in the cochlea of the inner ear and contains the auditory hair cells. The gene transfer resulted in a substantial increase in the number of auditory hair cells in postnatal mice. Auditory function was normal in 1-month-old mice that underwent the *in utero* procedure.

Hair cells in the organ of Corti work by converting mechanical stimuli (sound vibrations) into electrical signals that are relayed to the auditory brainstem and the auditory cortex. To test whether transfected hair cells could function like normal cells, the researchers used an electric current to stimulate hair cell bundles in the tissue of newborn mice. Hair cells that were induced by *Atoh1* misexpression (identified by a green fluorescent protein marker) had the same electrophysiological properties as did hair cells that grew from normal progenitor cells.

Previous studies have shown that additional hair cells can be induced by gene transfer, but this is the first experiment to prove that such cells are functional. According to Brigande, it remains to be seen whether gene transfer into a deaf mouse would be able to restore the mouse's auditory function. Though the gene therapy technique developed in Brigande's lab is probably only feasible in animals, it may provide valuable insights into the function of *Atoh1* and the ability to restore inner ear function through hair cell replacement. Such knowledge is crucial for the development of treatments for human deafness and balance disorders.

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