Gene therapy for mitochondrial diseases

27.09.2018 - Mitochondrial disease is now thought to be the second most commonly diagnosed genetic disease worldwide, and, unfortunately, there are still no proven treatment strategies for those diagnosed. Scientists from the Max Planck Institute for Biology of Ageing in Cologne were involved in collaborations to apply gene-therapy approaches in mice to successfully treat an animal model of mitochondrial disease. This may pave the way for future therapeutic strategies for patients.

A remarkable feature of mitochondria is that they contain their own DNA. Mutations in this mitochondrial DNA (mtDNA) can lead to mitochondrial diseases, but whether a person with a mutation develops disease or not is more complex. Many copies of mtDNA are present in each of our cells and, normally, disease-causing mutations are present in only a fraction of them. However, if the fraction of mutated mtDNA molecules rises above a certain threshold, mitochondrial function is compromised resulting in mitochondrial disease. Therefore, reducing the levels of mutated mtDNA molecules is a potential treatment strategy.

However, this treatment strategy is not so straightforward as conventional gene-therapy approaches do not work in mtDNA. Scientists from the University of Cambridge, UK and the University of Miami, USA, developed an approach to specifically degrade mutated mtDNA molecules in cell culture. Using a modified virus, they delivered a gene into the cell nucleus.
that encodes a protein that works as molecular scissors. These molecular scissors are then produced by the cell and targeted to mitochondria, where they specifically cut the mutated mtDNA.

But would the method also work in complex organisms composed of many tissues like mice or humans and actually treat mitochondrial disease? Stewart and his colleagues in Cologne could provide the answer. They had generated a mouse model of mitochondrial disease that contains a specific disease-causing mutation in mtDNA which leads to disorders in cardiac and muscular tissue. They treated the animals with the virus that only infected the heart or the muscles. The virus delivered the molecular scissors to cut the mutated mtDNA in the targeted tissue. And in fact, the approach worked! The levels of mutated mtDNA were reduced and the disease symptoms were alleviated.

“This is the first gene therapy to actually remove the cause of a mitochondrial disease in a living animal” a delighted Stewart tells us. Of course, before the therapy can be applied to human patients more detailed work and safety assessments must be done. Nevertheless, the scientists could prove that they found a way to remove the cause of these mitochondrial diseases. And since there is a link between mitochondrial dysfunction and other conditions like Alzheimer’s disease, Parkinson’s disease, diabetes, and perhaps some cancers, the approach will might even have a higher impact in fighting those disorders in the future.

Original publication:


Sandra R. Bacman, Johanna H.K. Kauppila, Claudia V. Pereira, Nadee Nissanka, Maria Miranda, Melina Pinto, Sion L. Williams, Nils-Göran Larsson, James B. Stewart and Carlos T. Moraes; “MitoTALEN reduces mutant mtDNA load and restores tRNAAla levels in a mouse model of heteroplasmic mtDNA mutation”; Nature Medicine; 2018