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Mitochondrial diseases: Loss of a protein opens up new therapeutic options

A Cologne-based research team has demonstrated in an animal model that the loss of the protein CLPP alleviates mitochondrial diseases. Targeted inhibition of CLPP could be a new therapeutic approach for these diseases / publication in 'Brain'

Mitochondria are the power plants of our cells. They convert food into energy. Severe dysfunction of the mitochondrial energy production system (OXPHOS) leads to mitochondrial diseases and aging. Researchers led by Professor Dr. Aleksandra Trifunovic at the University of Cologne's Cluster of Excellence for Aging Research CECAD have identified a new target for therapies of mitochondrial diseases in brain cells. The article, 'CLPP deficiency ameliorates neurodegeneration caused by impaired mitochondrial protein synthesis' has been published in *Brain*.

Approximately one in 5,000 individuals is affected by mitochondrial disease. Mitochondrial diseases are genetically and clinically distinct, and symptoms vary widely. Organs that have high energy demands, such as (cardiac) muscle and the brain, are most affected. Current treatment options are limited to dietary supplements and medications aimed at alleviating symptoms, maintaining an acceptable state of health, or preventing a worsening of symptoms during periods of physiological stress.

In a previous paper, Trifunovic's team had already shown that the loss of the mitochondrial matrix protease CLPP has beneficial effects in cells that have defects in the OXPHOS system. The new study now used animal models to examine whether the omission of CLPP is actually beneficial for different types of neurons, including Purkinje cells in the cerebellum and cortical and hippocampal neurons in the forebrain. 'We could see a positive effect when CLPP is no longer in brain cells. Various phenotypes that imply cell limitations, such as the fusion of multiple mitochondria, no longer took place,' said Anastasia Rumyantseva, first author of the study. In addition, the degradation of neurons deficient in the OXPHOS system is delayed when CLPP is not present in cells. This, in turn, leads to a lower inflammatory response and a significant improvement in motor function.

‘Our findings open up the possibility of targeting CLPP activity in many other mitochondrial diseases or brain function damage characterized by OXPHOS instability,’ Trifunovic said. ‘This work shows a clear path for a new therapeutic treatment of primary mitochondrial diseases, but also for other diseases that could benefit from altering mitochondrial quality control, such as aging and metabolic syndrome.’

Mitochondrial dysfunction, particularly mitochondrial OXPHOS instability, is directly related to aging. Therefore, the research team envisions that CLPP protease inhibitors could be used in the future to treat certain age-related diseases characterized by similar features.

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