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Animal results may pave way to treating rare mitochondrial diseases in children

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A human drug that both prevents and cures kidney failure in mice sheds light on disabling human mitochondrial disorders, and may represent a potential treatment in people with such illnesses.

"There are no effective cures for mitochondrial diseases, even in animals," said study leader Marni J. Falk, M.D., who cares for children in the Mitochondrial-Genetics Disease Clinic at The Children's Hospital of Philadelphia. "So these striking results in mice may suggest a novel therapy of direct relevance for humans."

Falk and colleagues published their study online May 5 in the journal *EMBO Molecular Medicine*.

Mitochondria are tiny structures that operate as powerhouses within human and animal cells, generating energy from food. As such, they are fundamental to life. Failures of proper mitochondria function impair a wide range of organ systems.

Individually, mitochondrial diseases are very rare. However, because there are hundreds of these disorders, they collectively have a broad impact, affecting at least 1 in 5,000 people, and possibly more. Malfunctioning mitochondria also contribute to complex disorders, including diabetes, epilepsy, Alzheimer's disease and Parkinson's disease .

The current study focused on an inherited genetic deficiency that

prevents the production of coenzyme Q, a critical antioxidant and component of the energy-generating respiratory chain. In humans and in the mutant mice used to model this disease, the deficiency results in fatal kidney failure. The current treatment, which consists of providing regular supplements of the missing enzyme product, coenzyme Q10, is often ineffective.

Falk's team fed the mutant mice probucol, an oral drug formerly used to treat people with high cholesterol (since replaced for that purpose by statin drugs). The drug prevented the mice from developing kidney disease, and also reversed kidney disease in mice that had already developed it. It also raised the levels of coenzyme Q10 within the animals' tissues and corrected signaling abnormalities.

"This drug showed remarkable benefits in the mice, especially when compared to directly feeding the mice supplements of the missing co-factor—coenzyme Q10," said Falk. "If this approach can be safely translated to humans, we may have a more effective treatment for mitochondrial disease than anything currently being used."

Primary coenzyme Q deficiency is vanishingly rare in humans—only a few dozen people are known to have the disease. However, said Falk, the disease is representative of a more common group of inherited, hard-to-treat mitochondrial diseases called respiratory chain (RC) defects.

RC defects share a common cellular failure to properly consume oxygen for the purposes of generating energy. Such defects, caused by a wide range of genetic disorders that affect mitochondria, constitute a common culprit in human mitochondrial disease. "If using probucol or a similar drug can benefit patients with defects in the respiratory chain, this could be a significant advance in treating mitochondrial diseases," said Falk.

At the very least, added Falk, the current study increases basic

understanding of the biology of mitochondrial disease. She noted that continuing research building on her team's findings may set the stage for eventual clinical trials using this approach.

More information: "Probucol ameliorates renal and metabolic sequelae of primary CoQ deficiency in Pdss2 mutant mice," EMBO Molecular Medicine, published online May 5, 2011. doi: 10.1002/emmm.201100149

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