Preventing the production of toxic mitochondrial proteins—a promising treatment target

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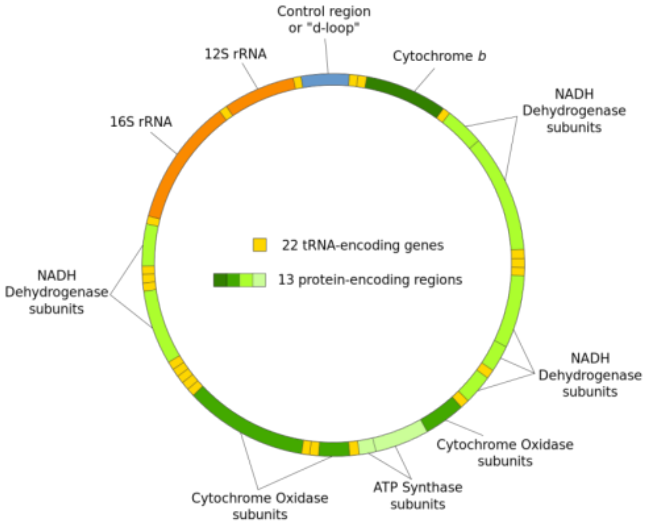

Structure of the human mitochondrial genome. Credit: Wikipedia/CC BY-SA 3.0

Researchers at the University of Helsinki uncovered the mechanisms for a novel cellular stress response arising from the toxicity of newly synthesized proteins. Activation of the stress response is at the epicentre of the molecular events generated by genetic mutations that cause a complex neurological syndrome.

In all living organisms, the ability to translate the genetic code into proteins is the definitive step in gene expression. Mitochondria are known as the powerhouse of the cell and an indispensable organelle with a unique genome and a dedicated protein synthesis machinery. [KEE1] In humans, mitochondrial DNA is only inherited from the mother and encodes only 13 proteins essential for energy metabolism. Defects in the faithful synthesis of these 13 proteins represents the largest group of inherited human mitochondrial disorders, which display exceptional clinical heterogeneity in terms of presentation and severity. Disruptions to energy metabolism alone do not explain the disease mechanism.

"The ability to treat patients has been stymied because of the fragmented understanding of the molecular pathogenesis and thus, bridging this knowledge gap is critical," says Research Director Brendan Battersby from the Insitute of Biotechnology, University of Helsinki.

AFG3L2 genes act as mitochondrial quality control regulator, preventing the accumulation of toxic translation products and thereby keeps the organelle and cell healthy. Mutations in the genes AFG3L2 and paraplegin cause a remodeling of mitochondrial shape and function, which are one of the earliest known cellular phenotypes in the disease. However, the mechanism by which these events arose was so far unknown. The research group of Brendan Battersby, at the Institute of Biotechnology, University of Helsinki, have now solved a molecular puzzle associated with genetic mutations linked to a multifaceted neurological syndrome.

A recently published research of Battersby's group revealed the etiology for the cellular effects was a proteotoxicity arising during the synthesis of new mitochondrial proteins. The group showed how this proteotoxicity was a trigger for a progressive cascade of molecular events as part of a stress response that ultimately remodels mitochondrial form and function.

Excitingly, a clinically approved drug that can cross the blood-brain barrier was also found to block the production of the toxic proteins and the ensuing stress response.

"Since the mitochondrial proteotoxicity lies at the epicentre of the molecular pathogenesis, preventing the production of toxic mitochondrial proteins opens up a promising treatment paradigm to pursue for patients," says Battersby.

Next step in the research is to test the efficacy of the drug in a double-blind preclinical trial in animal models of these diseases.

More information: Uwe Richter et al, Mitochondrial stress response triggered by defects in protein synthesis quality control, *Life Science Alliance* (2019). DOI: 10.26508/lsa.201800219