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NAFLD

Unravelling the path to steatohepatitis

New research published in *Molecular Metabolism* shows that a mitochondrial polymorphism is associated with baseline hepatic mitochondrial dysfunction and susceptibility to diet-induced non-alcoholic steatohepatitis (NASH). The findings support the two-hit hypothesis as a model to explain the progression of nonalcoholic fatty liver disease (NAFLD) from hepatic steatosis (fat accumulation in the liver) to NASH (steatosis combined with inflammation).

The researchers used conplastic C57BL/6J-mt$^{FVB/N}$ mice to investigate the effect of the mitochondrial genome on NAFLD progression. These mice contain a nonsynonymous single nucleotide polymorphism in *Mtatp8* (encoding mitochondrial ATP synthase protein 8) and thus differ only in their mitochondrial genome from C57BL/6J wild-type mice.

Under baseline conditions (standard housing and normocaloric chow feeding), C57BL/6J-mt$^{FVB/N}$ mice exhibited mitochondrial dysfunction (reduced ATP production, increased production of reactive oxygen species and profound alterations in hepatic lipid and acylcarnitine metabolism) compared with wild-type controls. However, no hepatic steatosis or inflammation was evident, even after 12 months. Of note, C57BL/6J-mt$^{FVB/N}$ mice were more susceptible to developing aggravated NASH when fed a western-style diet (high in fat and sugar) than controls. The findings provide initial evidence for a causal role of genetically predetermined mitochondrial dysfunction in regulating susceptibility to NAFLD progression from hepatic steatosis to NASH.

"Although our findings are novel and exciting, validation of their relevance to the human disease is required," cautions lead investigator Christian Sina. "We are currently developing tools to enable us to perform adequate mitochondrial sequencing studies in patients with NAFLD and NASH, with a view to stratifying patients according to their mitochondrial gene polymorphisms for future patient-targeted therapies."

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ORIGINAL ARTICLE Schröder, T. *et al.* Mitochondrial gene polymorphisms alter hepatic energy metabolism and aggravate diet-induced non-alcoholic steatohepatitis. *Mol. Metab.* http://dx.doi.org/10.1016/j.molmet.2016.01.010