Journal Club

mtDNA IN THE CROSSROADS OF EVOLUTION AND DISEASE

Mitochondrial DNA (mtDNA) sequences are currently studied mainly by three disciplines: molecular evolution (including anthropology), functional genomics and analyses of genetic disorders. Strangely, these disciplines can use the relatively short sequence of mtDNA in opposing manners, by attributing to it either lack of function, as is the case in (some) molecular evolution studies, or conversely, functional relevance in the aetiology of genetic disorders.

In the field of molecular evolution, mtDNA has been considered an excellent marker for tracing ancient migrations because of its uniparental (maternal) inheritance and lack of recombination. These mtDNA characteristics prompted Rebecca Cann, Mark Stoneking and Allan Wilson to analyse the mtDNA in 147 human samples collected from people representing all major global populations. The most important discovery of their work was that the highest degree of mtDNA variation was found among Africans, attesting to their antiquity. The other finding was that although mtDNA from across the globe contained African types, Africans had many unique mtDNA types.

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These two findings, in addition to other data, prompted Cann et al. (1987) to propose that the origin of all current human populations (at least the maternal lineage) is likely African. Many criticized this study, especially because their African samples originated mainly from Afro-Americans rather than from indigenous African populations. Nevertheless, subsequent studies, which used more advanced techniques and better-sampled populations, supported this pioneering and game-changing work of Cann et al.

In the year following the publication of the above article, Douglas C. Wallace and colleagues published the first report of mtDNA mutations causing a disease — Leber's hereditary optic neuropathy. As disease-causing mutations are amenable to natural selection, how could one consider the mtDNA to be merely a neutral marker? It was this contradiction that drew me into studying mitochondrial biology and to discovering that even common population variants of mtDNA are both subjected to natural selection and alter the tendency to develop genetic disorders.

Dan Mishmar
Department of Life Sciences, Ben-Gurion University of the Negev, Be'er-Sheva, Israel.
e-mail: dmishmar@bgu.ac.il

The author declares no competing interests

ORIGINAL ARTICLES Cann, R. L. et al. Mitochondrial DNA and human evolution. *Nature* **325**, 31–36 (1987) | Wallace, D. C. et al. Mitochondrial DNA mutation associated with Leber's hereditary optic neuropathy. *Science* **242**, 1427–1430 (1988) | Mishmar, D. et al. Natural selection shaped regional mtDNA variation in humans. *Proc. Natl Acad. Sci. USA* **100**, 171–176 (2003) | Marom, S. et al. MtDNA meta-analysis reveals both phenotype specificity and allele heterogeneity: a model for differential association. *Sci. Rep.* **7**, 43449 (2017)

MECHANISMS OF DISEASE

AMPK against NASH

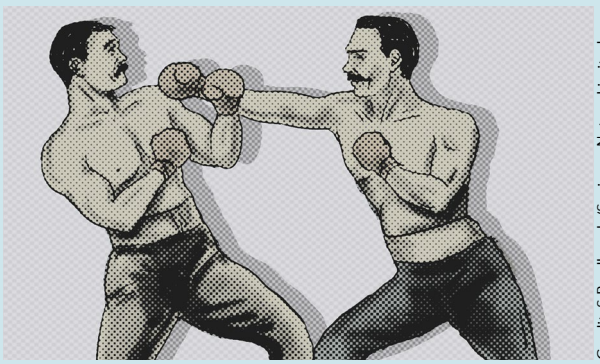
Non-alcoholic steatohepatitis (NASH) is the most severe form of non-alcoholic fatty liver disease (NAFLD), which is tightly linked to overnutrition and obesity. Hepatic cell death, including apoptosis, is an important driver of NASH pathology. Saltiel and colleagues now show that NASH-associated hepatocyte apoptosis is inhibited by AMPK — a major sensor of cellular energy status.

AMPK downregulation was previously associated with NAFLD. In line with this, mice on NASH-inducing diets had reduced AMPK activity. Furthermore, generation of liver-specific AMPK knock-out (LAKO) mice demonstrated that loss of AMPK exaggerates diet-induced NASH pathology, including increased liver damage, fibrosis and cell death — specifically apoptosis.

Apoptosis is driven by the caspase cascade, which involves a series of protein cleavage and activation steps. Cleavage of pro-caspase 6 to its mature form and subsequent caspase 6 activation were elevated in LAKO mice on NASH-inducing diets. Depletion or inhibition of caspase 6 counteracted NASH-associated liver pathology in these mice. Caspase 6 activity was also increased in other mice models of NASH and in liver samples from patients with NASH, indicating a key role of caspase 6 in hepatocyte apoptosis in NASH.

Mechanistically, pro-caspase 6 activation was shown to rely on caspase 3 and caspase 7, which are major executioners of apoptosis. Following activation, caspase 6 promoted the release of cytochrome *c* from mitochondria, thereby supporting activation of the executioner caspases and apoptosis in a feed-forward mechanism.

Pro-caspase 6 was directly phosphorylated by AMPK, and activation of AMPK reduced pro-caspase 6 cleavage in a cell culture model of hepatotoxicity. Together with the data from LAKO mice, this indicated that AMPK is an inhibitor of caspase 6-driven hepatic cell death in NASH.



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> “AMPK is an inhibitor of caspase 6-driven hepatic cell death”

Application of an agonist of AMPK to mice with diet-induced NASH was associated with pro-caspase 6 phosphorylation and with reduced caspase 6 activity. This approach also significantly reduced the number of apoptotic cells and alleviated liver damage. Thus, targeting the AMPK–caspase 6 axis could be explored as a new therapy for NASH.

Paulina Strzyz

ORIGINAL ARTICLE Zhao, P. et al. An AMPK–caspase-6 axis controls liver damage in nonalcoholic steatohepatitis. *Science* **367**, 652–660 (2020)
RELATED ARTICLE Herzig, S. & Shaw, R. J. AMPK: guardian of metabolism and mitochondrial homeostasis. *Nat. Rev. Mol. Cell Biol.* **19**, 121–135 (2018)