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GENETIC VARIATION

Nuclear and mitochondrial genome interplay

ISTOCK

Non-pathogenic variation in mitochondrial DNA (mtDNA) substantially affects metabolism and ageing in mice, reports a new study in *Nature*. This finding could have implications for mitochondrial replacement therapies in humans.

Mitochondrial replacement techniques (MRTs) aim to prevent the transmission of mutant mtDNA by creating embryos containing a mother's unaffected nuclear DNA and non-pathogenic mtDNA from a 'mitochondrial donor'. Human mtDNA exhibits profound within-population sequence variability, but little is known about how this may affect functional interactions with the nuclear genome.

Latorre-Pellicer *et al.* compared metabolic and ageing profiles of wild-type C57BL/6 mice with those of a conplastic mouse strain, which contains the C57BL/6 nuclear genome and mtDNA from the NZB/OlaHsd mouse strain. That is, the two mouse strains share the same nuclear genome but differ in their mitochondrial genome. In brief, conplastic mice exhibited less weight gain, slower metabolic decline and fewer signs of ageing over time — including a lower cancer burden at death — than age-matched wild-type animals. Sequencing of liver mtDNA showed no age-related increase in mtDNA mutations in either mouse strain.

Transcriptomic, metabolomic and proteomic profiles differed between the two mouse strains; for example, conplastic mice show a higher expression of lipid metabolism and lower expression of carbohydrate metabolism and inflammation pathways. An increase in the production of reactive oxygen species (ROS) was noted in hepatic mitochondria of wild-type mice aged >30 weeks. By contrast, conplastic mice exhibited ROS levels that were similar to those of young animals.

Variation in mtDNA also affected glucose and insulin homeostasis, with wild-type mice being slower at clearing plasma glucose or regulating insulin levels than conplastic mice. Concordantly, wild-type mice that were fed a high-fat diet showed greater increases in body weight and white adipocyte size, and an age-related increase in blood cholesterol levels that was not detected in conplastic animals.

Importantly, these findings highlight the interaction between the mitochondrial and the nuclear genome, and reveal that 'healthy' mtDNA variants can have differential effects on mitochondrial function and the cellular adaptive response. These factors may need to be taken into consideration for MRTs.

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ORIGINAL ARTICLE Latorre-Pellicer, A. *et al.* Mitochondrial and nuclear DNA matching shapes metabolism and healthy ageing. *Nature* http://dx.doi.org/10.1038/nature18618 (2016)