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Abstract

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The Mitochondrial Genome in Human Adaptive Radiation and Disease; on the Road to Therapeutics and Performance Enhancement

The human mitochondrial (mt) genome consists of approximately 1500 genes, 37 encoded by the maternally inherited mtDNA, present in thousands of copies per cell, and the remainder dispersed throughout the chromosomes. The mitochondria burn the calories in our diet with the oxygen that we breathe to produce most of our cellular energy which is used for two main purposes: to produce ATP to do work and to generate heat to maintain our body temperature. The ratio of calories allocated between these two energy outputs is known as the coupling efficiency. The mitochondria also produce much of the cellular reactive oxygen species (ROS) and, in response to energy deficiency and/or oxidative stress, can initiate cellular death (apoptosis) through activation of the mitochondrial permeability transition pore (mtPTP). Mitochondrial ROS mutates the mtDNA, causing new germ line mtDNA mutations that can be associated with a wide range of age-related diseases including chronic muscle and cardiac dysfunction and degeneration. ROS damage also causes the accumulation of somatic mtDNA mutations in post-mitotic tissues that erode energy output with age creating the aging clock. Moreover, as our ancestors migrated out of tropical Africa into temperate Eurasia and arctic Siberia and northern Europe, adaptive mtDNA mutations became established that shifted the mitochondrial energy balance from predominantly ATP production in the tropics to greater heat production in the temperate and arctic zones. These ancient variants are still affecting individual exercise performance and heat-cold tolerance today. Sequence variants in nDNA-encoded mitochondrial genes have also been found to affect mitochondrial function. Based on these discoveries, we can now envision both metabolic and genetic interventions that could enhance individual performance, most of which are currently being developed to treat mitochondrial disease. Metabolic interventions are directed at increasing energy output, reducing ROS production, and stabilizing the mtPTP. Genetic therapies currently include modification of the mtDNA by introduction of nucleic acids into the mitochondrion, modification of the nDNA-encoded mitochondrial genes by standard gene therapy approaches, and introduction of engineered mtDNA-encoded genes into the nucleus. While such approaches could be used to enhance individual performance and would be virtually undetectable, they might also compromise our species' ability to adapt to environmental catastrophe in the future.