Tiny mitochondria play outsized role in human evolution and disease

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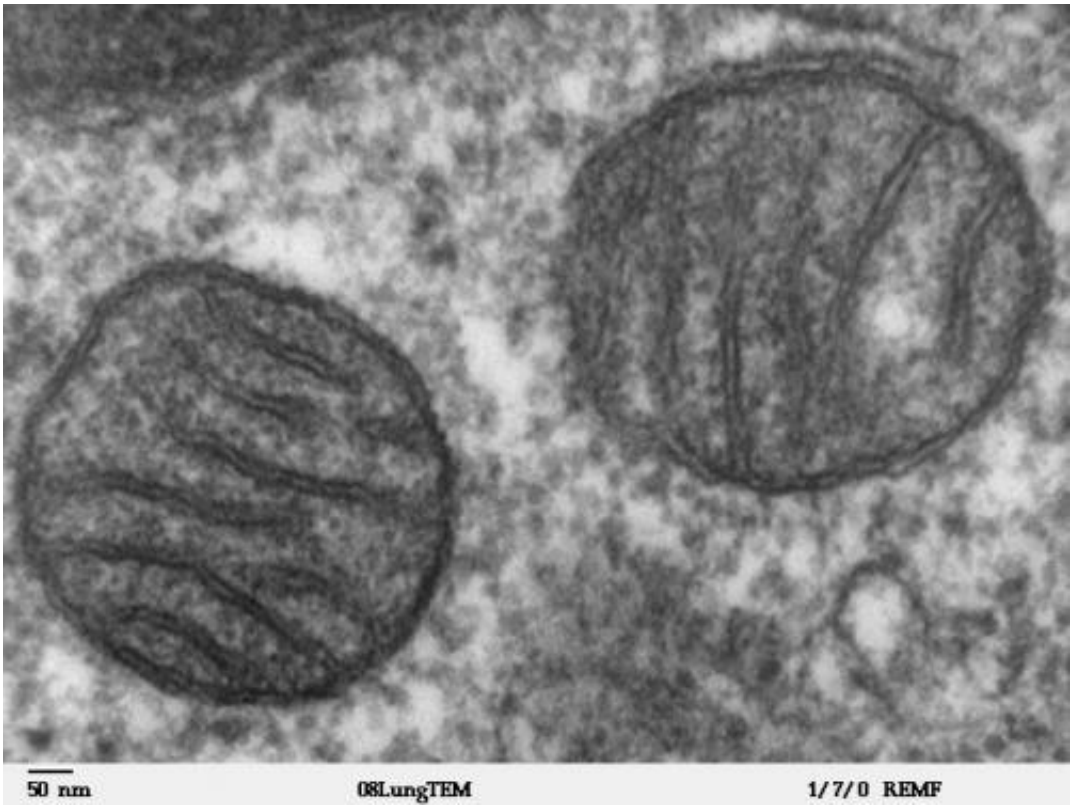

Mitochondria. Credit: Wikipedia commons

Mitochondria are not only the power plants of our cells, these tiny structures also play a central role in our physiology. Furthermore, by enabling flexible physiological responses to new environments, mitochondria have helped humans and other mammals to adapt and evolve throughout the history of life on earth.

A pioneering scientist in mitochondrial biology, Douglas C. Wallace, Ph.D., synthesizes evidence for the importance of mitochondria in a provocative Perspective article today in the journal *Cell*.

Residing in large numbers outside the nucleus of every cell, mitochondria contain their own DNA, with unique features that "may require a reassessment of some of our core assumptions about human genetics and evolutionary theory," concludes Wallace, director of the Center for Mitochondrial and Epigenomic Medicine at The Children's Hospital of Philadelphia.

Wallace has investigated mitochondria for more than 40 years. In 1988, he was the first to show that mutations in mitochondrial DNA (mtDNA) can cause inherited human disease. His body of research has focused on how mtDNA mutations contribute to both rare and common diseases by disrupting bioenergetics—chemical reactions that generate energy at the cellular level.

Wallace and colleagues previously showed in the late 1970s that human mitochondrial DNA is inherited exclusively through the mother. They then used this knowledge to reconstruct the ancient migrations of women by comparing variation in mtDNA among populations throughout the world. From such studies, scientists have concluded that humans arose in Africa about 200,000 years ago and that only two mtDNA lineages successfully left Africa about 65,000 years ago to colonize the rest of the world.

Based on insights from these human migration studies, Wallace takes up a longstanding scientific question raised by Darwinian evolution—both in humans and other species. As subpopulations moved into isolated areas, how did they remain isolated over a long enough time for new species-defining traits to arise in nuclear genes and become enriched by natural selection to permit speciation?

The vast majority of our 20,000 or so genes exist in the DNA within each cell's nucleus, as distinct from the 13 protein-coding genes inside mtDNA. However, Wallace argues that mtDNA mutations provide faster and more flexible adaptations to changing environments than do nuclear DNA mutations. The mtDNA has a much higher mutation rate than nuclear DNA, which by itself might imperil species survival, because most DNA mutations are deleterious. However, mtDNA mutations alter physiology at the single-cell level. Therefore, cells in the mother's ovary that harbor the most deleterious mtDNA mutations can be eliminated by natural selection prior to fertilization. Thus only mild mtDNA variants, a subset of which may be potentially beneficial, are introduced into the population.

The high mutation rate in mtDNA plus ovarian selection thus provides a powerful tool for humans (and animals) to adapt to an environmental change, without endangering a population's overall survival. Mitochondrial DNA also exchanges signals with nuclear DNA, and the interaction helps drive the evolution of physiological processes over time. Populations that expand into a marginal environmental space, Wallace argues, adapt their physiology through mtDNA mutation to better exploit the limited food sources and other resources in that environment. This permits prolonged occupation of the marginal environment, giving sufficient time for nuclear DNA mutations to generate anatomical structures appropriate for exploiting more abundant food resources in the new environment.

To support this hypothesis, Wallace proposes that mitochondria variation can result in crucial energy tradeoffs. At the cellular level, mitochondria convert oxygen and nutrients to the energy-rich chemical ATP, while also producing heat. In tropical climates, this coupling process is maximally effective, permitting more efficient production of ATP with minimal heat production. In the Arctic, the conversion of food to ATP is less efficient, requiring more calories to be consumed for the same

amount of ATP, and this generates more heat. So different patterns of mtDNA variation are likely beneficial in warm versus cold climates. Similarly, certain mtDNA variants are enriched in Tibetan populations, suggesting that mtDNA variation may permit adaptation to the low oxygen tension at high altitude.

Wallace also cites multiple studies that show that regional mtDNA variation correlates with predilection to a wide variety of metabolic and degenerative diseases, including Alzheimer and Parkinson disease, diabetes, obesity, and cardiovascular disease.

Biologists have long known that adaptations that confer an advantage in one environment can become less beneficial in another environment. Wallace suggests an important contributor to this phenomenon could be the physiological adaptation of mtDNA variation. He postulates that as populations migrate and dietary patterns become globalized, people with mtDNA optimized to one environment, where they eat a sub-Saharan African diet, may not be well adapted to another environment, where they may consume a Central European diet. "Because mitochondria have such a crucial role in our physiology, changes in mitochondrial DNA can have profound effects on human biology," he adds.

More information: "Mitochondrial DNA Variation in Human Radiation and Disease," *Cell*, Sept. 24, 2015. doi.org/10.1016/j.cell.2015.08.067

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