Mitonuclear interactions in the control of life history

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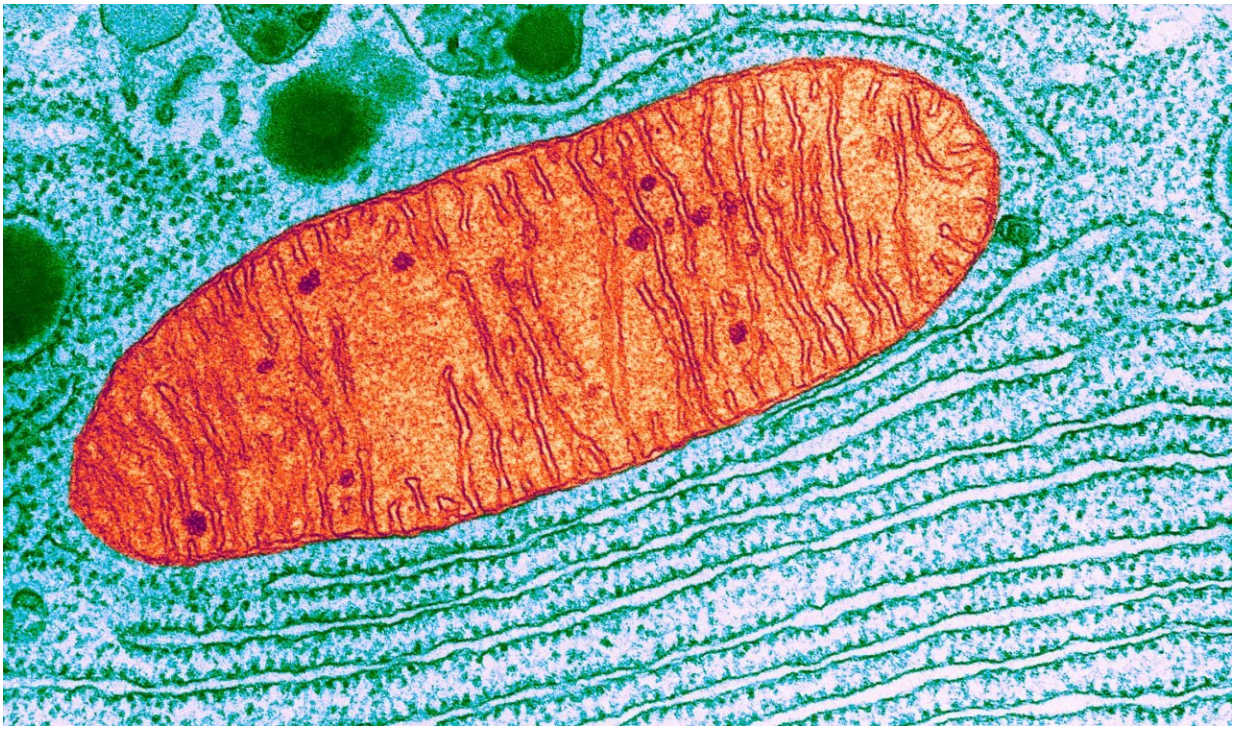

Mitochondrion. Credit: news.cals.wisc.edu/

Mitonuclear interactions are believed to play an important role in the so-called "life history" of Eukaryotic organisms. Unfortunately, no one has come up with any sort of general concrete theory that can predict or even describe these interactions. A recent thematic issue of *Philosophical Transaction of the Royal Society* comprises a series of articles that

attempt the formidable task of linking mitochondrial genotype to phenotype. Of note among them is an article that uses specially crafted populations of fruit flies to explore mitonuclear interactions in life history responses to changes in an organism's environment.

In particular, the paper looks at how diet influences the mitonuclear-controlled conflict between longevity and fecundity that is so often observed in nature. Lead author Florencia Camus and her colleagues at the University College in London assembled their artisanal fly panel by matching 10 mitochondrial haplotypes with two nuclear haplotypes. Fly mitochondrial DNA (mtDNA) varies between different populations on average at around 50 base pair positions. That's about the same variance found in our own 16,000-plus-base-pair-long mtDNA.

By comparison, in some other kinds of organisms (like copepods), the mitochondrial divergence can exceed 20 percent. Crosses between neighboring copepod populations create severe incompatibilities between mitochondrial and nuclear genomes that lead to reproductive failure and arguably even speciation. However, it hasn't been entirely clear whether a little extra mitonuclear diversity would be good or bad for creatures with less divergent mitochondria like ours. In the creation of genetically modified humans like three-parent embryos, the question isn't so much whether we do it as it is which mitochondria to use.

What Camus and her colleagues somewhat surprisingly found is that having the wild type mtDNA and wild type nuclear (nDNA) for any particular fly population always seems to be the worst-case scenario. Corresponding author Nick Lane suggests that having some mismatch is beneficial because it upregulates stress responses that lead to improved health and increased lifespan. The researchers found that there were some flies that got better at everything with a little mismatch—they even became more fecund.

The only way to fully appreciate the devil in the details here is to look at all the individual places where each mtDNA and nDNA haplotype differs from the others. Haptotypes, and for that matter, haplogroups, are nothing more than unique sets of DNA sequences. While biologists often imbue them with special evolutionary significance that explains frequently nebulous migration patterns, they are, in fact, significant only insofar as each reflects their own historical course of discovery by us. They are intrinsically arbitrary.

To illustrate this assertion more clearly, another recent paper dealing with fly mitochondria found that the 250 fly lines used in their study parsed into 12 unique haplotypes. Florence mentioned to me that fruit flies are believed to have radiated from Africa and only colonized some places like Australia some 200 years ago. Already, 15 haplotypes clustering into two haplogroups have been found on the Eastern Australian coast alone.

To establish some kind of physical meaning for "mitonuclear haplotypes," it is necessary to build real-world functional links between them. For example, in the Sherpa population of Tibet, there are many nuclear and mitochondrial SNPs that independently confer specific advantages in environments above 4000 ft where oxygen levels are reduced almost by half. The frequencies of the SNPs T3394C and G7697A, which are the definition sites of mitochondrial haplogroup M9a1a1c1b, are significantly more common in these high-altitude populations. The G7697A allele in particular is found within the gene for respiratory complex IV subunit II, where it appears to directly influence the utilization of oxygen there.

On the nDNA side, Sherpa variants in genes encoding EGLN1, PPAR1, and hypoxia-inducible factor EPAS1 have been offered as good candidates to explain key adaptive features of Tibetans. Genes like these may eventually provide the presumed mitonuclear links we seek and

perhaps even provide direct links to an actual oxygen utilization site. Under hypoxic conditions, EPAS regulates erythropoietin, vascular endothelial growth factor and eNOS situations. Complex IV itself directly employs several nuclear encoded subunits, assembly factors and miscellaneous performance-altering proteins which have yet to be fully explored in Tibetan populations.

Perhaps the most important question we currently face in arena of mitonuclear compatibility is a huge black box called mitochondrial heteroplasmy. In addition to the regular autosomes, any whole-genome analysis worth its salt also reports on 'chromosome M," ie., the mitochondria. The problem here is that most or at least many of us actually have more than one mitochondrial genome floating around in our cells. Human mitochondrial heteroplasmy typically ranges from one to 14 heteroplasmies. Furthermore, different organs tend to have different levels of heteroplasmy.

To be of any real value, a thorough genetic analysis including chromosome M will also report the heteroplasmy at each site obtained from a particular sample. One confounding factor here is that our nDNA contains numerous remnant copies of mtDNA that have, over time, become embedded at several sites in many of our chromosomes. Known as NUMTs, these partial mtDNA acquisitions from long ago make determining our actual heteroplasmy much more difficult.

Only recently has it become possible to account for the interference that NUMTs present. In a nutshell, to be sure you have got bonafide mtDNA and not NUMTs, sequencing to a depth of at least 3000x is required for minor allele frequencies up to 3 percent to avoid false positives or negatives. Even that may not be enough if you happen to have SNPs within your NUMTs sequences themselves. A further complication to the heteroplasmy picture is that many completely normal individuals are actually mosaics—they are built from more than one complete set of

nDNA.

Such individuals can be either be born as chimeras (through absorption of a twin during development or by the otherwise incidental exchange of cells in-utero), or else become mosaic later in life via organ or bone marrow transplant. A shocking case of mosaicism by transplant was reported in man who recently had his bone marrow wiped by radiation treatment, and then replaced by a donor to treat his leukemia. While the media reported this as a case of "disappeared identity" because his saliva, blood and semen had been totally replaced by the DNA of the donor, some regions (like the hair) retained their previous genetic identity.

In using the word "identity," we are glossing over a critical question: What did they actually test? Curiously, the man happened to work in a forensics department in Nevada. Individuals are typically identified in forensics by using either mtDNA, or by nuclear markers known as short tandem repeats (STRs). The CODIS system, for example, is a well-established set of 13 or 20 STR markers that is used in the U.S., while the U.K. uses a very similar set for their National DNA Database (NDNAD).

Precursor blood cells have a well-known penchant for migrating to other organs, where they anomalously differentiate or even fuse with the local flora. In some cases, Y chromosome-bearing fetal stem cells enter the mother's bloodstream, migrate to her brain, and fuse with the resident neurons to create masculinized cells. These kinds of acquisitions and mergers could possibly explain a situation where the CODIS STR markers changed identity in the man above.

On the other hand, if the mtDNA is what is being evaluated here, all bets are off. For one thing, mitochondria are regularly transmitted between cells throughout the body. Most recently, this kind of transfer was

demonstrated from stromal cells to hematopoietic stem cells in response to infection.

There would be little standing in the way of mitochondria from donor tissue contributing to heteroplasmy in the recipient. Could the mitochondria take over and replace the host stock much like an invasive species in the wild? Consider receiving an organ from another species altogether. As we speak, special retrovirus-free pigs are being created in labs around the world explicitly for that purpose. For example, the Chinese have recently reported success in the creation of pig-monkey embryos, while Spanish researchers have been so bold as to make pig-human embryos.

Nick Lane, who can no doubt be very persuasive in these matters, has assured me that any pig mitochondria that escape their donor organ would not function in a human host. After all, he notes, monkey mitochondria don't even work that well in humans cells. Successful oxidative phosphorylation requires the well-tuned electron transport afforded by closely matched nuclear and mitochondrial respiratory chain subunits. That said, could wayward pig mitochondria replicate in a human host, perhaps by fusion and nucleoid exchange with human mitochondria?

One of Lane's biggest fans is none other than philanthropist and global healthcare advocate Bill Gates. He has favorably reviewed Nick's book, "The Vital Question" on his exhaustive blog, much as we have also reviewed it at Phys.org. In looking to the funding disclosures on the paper reviewed here, I saw the somewhat cryptic source of "research grant from bgc3 to N.L." As it happens, bgc3 is the amply endowed venture capital arm of the Microsoft-Gates Foundation continuum, in any case, excellent funding partners to have in this exciting new work.

Around the globe, countless children suffer from rare orphan diseases

that have neither cure nor proper diagnosis. In some cases, nDNA genes are associated to a particular condition, while in others, a segment of the mtDNA is fingered. What I would like to suggest is that many of these diseases now strictly assumed to be either nuclear or mitochondrial disorders are actually cases of what might be more aptly be termed "mitonuclear rare disease." In other words, a disease only readily apparent under certain specific combined mitonuclear haplotypes.

More information: Camus MF, O'Leary M, Reuter M, Lane N. 2019 Impact of mitonuclear interactions on life-history responses to diet. *Phil. Trans. R. Soc. B* 375: 20190416. dx.doi.org/10.1098/rstb.2019.0416

Bevers, R.P.J., Litovchenko, M., Kapopoulou, A. et al. Mitochondrial haplotypes affect metabolic phenotypes in the Drosophila Genetic Reference Panel. *Nat Metab* (2019) DOI: 10.1038/s42255-019-0147-3