Editorial

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Epigenomics

How mitochondrial DNA-driven changes to chromosomal DNA methylation add a layer of complexity to mitochondrial disease

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Human mitochondrial DNA (mtDNA) is a double-stranded circular molecule of 16,569 bp which, despite its small size, contains genetic material that is of crucial importance to cellular survival. The mtDNA encodes 13 structural subunits of the oxidative phosphorylation system, the cell's most efficient system to generate energy. The other components that make up the five oxidative phosphorylation complexes lie encoded within the nuclear genome and need to be imported from the cytosol. In addition to structural components of oxidative phosphorylation, the mtDNA encodes two rRNAs and 22 tRNAs necessary for intramitochondrial translation processes. mtDNA transcription concomitantly generates large regulatory noncoding sequences which are released upon transcript processing. The importance of mitochondrial efficiency to the cell's wellbeing cannot be overestimated, and defective mitochondria can be caused by both mtDNA and nuclear DNA mutations, and lead to a wide spectrum of human disease.

Cohousing of mtDNA and nuclear DNA within human cells requires sophisticated regulatory processes to harmonize the interconnected activities of the two genomes. Mutual consultation is ensured by bidirectional communication routes: Retrograde communication from mitochondria to the nucleus and anterograde communication from the nucleus to the mitochondria. This way, a cell can successfully align its energy supply with its energy demand. In order to accomplish such dynamic regulation, mtDNA copy numbers need to fluctuate with energetic requirements and should be adapted to the needs of the individual cell types involved. To achieve this, mtDNA copy numbers are strictly regulated by nuclear-encoded mtDNA-specific replication factors, of which the expression is subject to cell-specific DNA methylation [1]. In this respect, polymerase γ (POLG) is a primary factor. *POLG* methylation status appears a particularly potent regulator of mtDNA copy numbers during cell differentiation, a mechanism that ceases its activity in differentiated cells [2]. This illustrates how nuclear DNA transcription is successfully managed by signals generated from the mitochondrion via changes to the nucleus' epigenome. Retrograde communication has, in essence, a truly reversible and dynamic nature, which is clearly shown by the fact that the DNA methylation changes that can be induced by mtDNA depletion are (partially) reversed when mtDNA is re-introduced [3].

Mitochondrial function has a direct effect on nuclear epigenetic markers, nicely illustrated by the modulatory effect of mitochondrial metabolites on methionine adenosyltransferase [4] and S-adenosylmethionine synthetase [5]. The induced changes to the nuclear epigenome elegantly explain how mtDNA mutations can have broad effects on many functions that are nucleus-driven, and the peculiarities unique to the mitochondrial genome could be key to the highly variable phenotype of mitochondrial disease.

First, the mtDNA displays substantial genetic variation that was long thought to be of little functional significance. Based upon mtDNA polymorphic variants, haplogroups of mtDNA have been assigned, which display a continent-specific distribution based upon common ancestry [6,7]. This sequence variation influences the cell's oxidative phosphorylation efficiency and the system's susceptibility to inhibition [8], and haplotypic mtDNA genotype variations affect the nuclear epigenome at the cellular level. J haplogroups exhibit higher mRNA levels of MAT1A [9].

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Overexpression of *MAT1A* indeed might explain the hypermethylation status and lower intracellular ATP levels that can be observed in the J haplogroup. It becomes apparent that via such mechanisms, the haplotype can influence the disease phenotype. Indeed, an association has been recognized between the J haplotype and Leber's hereditary optic neuropathy [10].

Second, human cells can display heteroplasmy of mtDNA, meaning different sequence variants may co-exist in the same cells. When the population of mtDNA with a pathogenic variant exceeds a threshold level, mitochondrial protein synthesis becomes impaired and results in deficiencies of oxidative phosphorylation. A common point mutation encountered in mitochondrial disease is the m.3243G alteration in *MT-TL1*, which is often found in varying amounts alongside the wild-type form m.3243A. The clinical heterogeneity associated with the point mutation is well-recognized, with phenotypes ranging from mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS), Leigh encephalopathy, hypertrophic cardiomyopathy and a wide variety of clinical syndromes that may include diabetes, deafness, ataxia or myopathy. In an *in vitro* setting, it was shown that when cybrids have identical nuclear DNA, increasing percentages of m.3243G lead to accumulated modifications to metabolites and histones [11]. Variations in tissues' mtDNA m.3243A>G mutation levels explain part, but definitely not all of the observed variability of phenotype between individual patients. A study by Pickett *et al.* found that, while age, heteroplasmy and sex were poor predictors of phenotypic severity, hereditary estimate for symptoms such as hearing impairment and cerebellar ataxia was high [12]. The very different symptoms exhibited by patients with similar tissue m.3243A>G heteroplasmy levels may thus boil down to variations in the nuclear answers that are generated. It has been shown that the percentage of m.3243A>G heteroplasmy affects the magnitude of changes to the nuclear epigenome, and subsequent alteration to nuclear gene expression [11]. A plausible assumption is that the susceptibility to such mtDNA-driven epigenetic regulation may differ according to an individual's nuclear background, which could potentially affect vulnerability toward percentages of heteroplasmy. In evidence, monozygotic twins not only show remarkably similar heteroplasmic ratios, but also an extremely similar clinical phenotype of which the equivalent is not seen in regular siblings [13].

It can be concluded that epigenetic changes to the nuclear genome appear an additional mtDNA-driven regulatory link between the patient's genotype and clinical phenotype, illustrating the important role continuous dialogue between the two genomes plays in mitochondrial health. The complex interactions between the two genomes, that we are now only beginning to understand, implicate that caution is warranted when evaluating the possible consequences of assisted reproductive technologies that make use of mitochondrial replacement transfer. In such a protocol, the nuclear genome is removed from an oocyte that contains faulty mtDNA and transferred to a de-nucleated oocyte from a healthy donor. These techniques entail new compositions of mitochondrial and nuclear genome in the offspring, originating from three individuals, and will result in an altered genomic equilibrium. It is therefore worthwhile to continue efforts to grasp the full complexity of retrograde communication and consider its consequences to human health.

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