Mitochondrial Genetics and Human Systemic Hypertension

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Evolution of biological processes is fascinating and more so the evolutionary reduction of mitochondrial genome. A proteobacterium that invaded the nucleus-containing host cell ∼1.5 billion years ago, as would the endosymbiotic model surmises, ended up enslaved and yet became the essence of life of the invaded cell. And, if so, the invader could not have had a genome that was comprised of only 16569 base pairs (bp), coding for only 13 proteins, 22 transfer (t)RNAs, and 2 ribosomal (r)RNAs (NC_012920). Such a small size would seem to be incompatible with survival of a free-living organism as the smallest known bacterial genome is that of Carsonella Ruddi, which is 159662 bp, i.e., ∼10 times the size of mitochondrial genome, and codes for 182 proteins. Yet, C Ruddi is not a free-living organism but rather an endosymbiont. On the contrary, obligate intracellular lifestyle can exist with as little as 5386 bp, as for fX174, which is smallest known genome. If indeed this organelle, ie, the mitochondrion, was one time a free-living organism with a much larger genome, then, how did it shrink its genome size to the current size and manage to survive? The generation of ATP through oxidative phosphorylation, one of the several mitochondrial functions, alone involves 89 genes and requires a much larger genome to sustain that the mitochondrial (mt)DNA affords. Apparently, the invader could not escape from the evolutionary pressure imposed by the host environment and a symbiotic life. Consequently, mitochondria gradually streamlined its genome by relaxed selection of the genes that were superfluous to its survival. Through yet-to-be defined mechanisms the invader seems to have transferred thousands of sets of mitochondrial polypeptides are not compatible with homologous recombination but rather are tagged with ubiquitin for degradation. Hence, mtDNA has 16 times higher mutation rate than the nDNA. Mutations could initiate a vicious cycle of impaired mitochondrial functions, increased ROS, higher error rates of DNA polymerases and editing enzymes and further accumulation of mutated mtDNA. Given the presence of thousands of copies of mtDNA in each cell, mutations generate an admixture of wild type and mutant mtDNA, which is referred to as heteroplasmy, as opposed to homoplasmy, when all copies of mtDNA are identical. Heteroplasmy in mtDNA in somatic cells, as the mitochondria replicates, increases with age. Accordingly mitochondrial mutations and dysfunctions have been implicated in various age-dependent phenotypes including cellular senescence and metabolic disorders. Likewise, most pathogenic mtDNA mutations are heteroplasmic. However, phenotypic consequences of heteroplasmic mtDNA vary according to effects on mitochondrial functions (mutation type and involved gene) and the characteristics of the host cells, such as their energy dependence and metabolism. Thus, the heteroplasmic threshold that causes a phenotype is expected to be lower for organs such as heart, skeletal muscle, brain and endocrine glands that have high dependence on electron chain transport for ATP generation.

An intriguing aspect of mtDNA mutations is maternal (maternal) inheritance. Whereas sperm and ovum nDNA equally contribute to composition of nDNA in a fertilized zygote, mtDNA almost exclusively is inherited from the ovum. The biological rationale and basis for the uniparental inheritance of mtDNA are not fully understood. Nonetheless, a few copies of paternal mtDNA that might enter the zygote during fertilization neither multiply nor recombine with the ovum mtDNA through homologous recombination but rather are tagged with ubiquitin for degradation. Perhaps, the evolutionary pressure has so meticulously optimized reconstitutions of the oxidative phosphorylation complexes that any homologous recombination between different sets of mtDNA or reconstitution of different sets of 13 mitochondrial polypeptides are not compatible with functional mitochondria. Alternatively, dilution by a shear number of mtDNA in each ovum, which is estimated to be several hundred thousands as opposed to a few hundred copies of mtDNA in the sperm, offers a simple explanation. The process, nevertheless, restricts the opportunity for homologous recombination between 2 sources of mtDNA and, consequently,
haplotypic diversity of humans. Accordingly, humans have a limited number of mtDNA lineages, which are often used to infer evolutionary history of different ethnic populations.

The maternal inheritance of mtDNA imprints a peculiar signature in familial mitochondrial diseases, because the inheritance of the phenotype in the offspring, whether male or female, is solely from mother and never from father. The pattern, whenever observed in a family, provides a clear indication of an mtDNA mutation being responsible for the phenotype. Likewise, given the invincible role of mitochondria in various organs, mtDNA mutations typically but not always affect multiple organs and often exhibit systemic manifestations. Nevertheless, often the predominant phenotype involves heart, skeletal muscles, brain, and metabolism. It is important to note, however, that mitochondrial diseases are not solely restricted to mutations in mtDNA. Mutations in nDNA, which encodes the majority of the mitochondrial proteins, are major causes of mitochondrial disorders. In such situations, the mode of inheritance follows Mendelian transmission.

In this issue of Circulation Research, Wang et al report on a very large Chinese family with matrilineal inheritance of systemic hypertension affecting 15 of 24 adult matrilineal relatives but none of the offspring of affected fathers. The authors sequenced mtDNA and identified a novel point mutation (m.4263A>G) in MT-T1, which codes for mitochondrial tRNA for isoleucine. The A>G transition, which was homoplasmic (within the resolution of restriction enzyme fragments mapping), is located at the tRNAile precursor 5'-end processing site. The mutation also changed codon AGA to AGG in MT-ND1 gene, coding for NADH dehydrogenase subunit 1 of complex I. However, the change was synonymous (stop codon to stop codon). The change is not expected to alter mRNA expression in the intronless mtDNA. Through a series of elegant studies, the authors showed that the mutation reduced processing of the 5' leader sequence on the tRNA precursor by ribonuclease P by approximately 70% and led to a ∼46% reduction in the tRNAile level. The reduction in the tRNAile level was associated with reduced mitochondrial protein synthesis by ∼32% and substrate-dependent oxygen consumption reflective of complex I, III, and IV by 70% to 80%. Finally, to link the changes in mitochondrial to the clinical phenotype, the authors showed that levels of ROS in the lymphoblastoid cell lines derived from 3 mutation carriers were increased.

The study is not the first to report a potential causal role of mtDNA mutation in maternally inherited hypertension, because previous studies have already shown that.18,19 The strength of the study is in robust multilevel mechanistic characterizations of biological and functional significance of the mutated mtDNA. In this aspect the study is exemplary. The findings are sufficiently convincing and strengthen the role of mtDNA mutations in the pathogenesis of systemic hypertension. Notwithstanding the strength of the data, establishing causality in human genetic studies is often not definitive and challenging but less so in large families. Presumably in this large Chinese family, the mutation cosegregated with matrilineal inheritance of the phenotype, although the evidence is apparently based on a limited number of available DNA samples. Moreover, as is the case for most if not all studies, the findings raise substantial questions that remain unanswered, which, to a large extent, are beyond the scope of the present study. This novel mutation, as is the case for many genetic disorders, seems to be infrequent and perhaps even private, because it was found in only 1 family and was absent in 49 other families with matrilineal hypertension. The authors did not elaborate on the presence of other mtDNA mutations in the remaining families, which would be expected to be present. A potential null result in this regard would raise a radical and the broader question of whether matrilineal inheritance is solely restricted to mtDNA, which we currently surmise. The m.4263A>G mutation is not a common cause of matrilineal systemic hypertension, let alone systemic hypertension. Yet, the discoveries of uncommon or rare variants often provide clues into the pathogenesis of common forms of the phenotypes. Could the findings in the present study provide insights into the pathogenesis of common nonmaternally inherited systemic hypertension? The authors provide evidence of increased ROS, which might serve as a mechanism for the pathogenesis of hypertension caused by the m.4263A>G mutation. Could increased ROS alone be responsible for the pathogenesis of matrilineal systemic hypertension or contribute to the pathogenesis of common forms of systemic hypertension? The results of genome-wide association studies (GWASs) do not show an association between variants in genes involved in redox pathways and systemic hypertension.20,21 The null results of GWASs, however, may reflect the small effect sizes of such alleles and the shortcomings of the GWASs.22 Yet, one must consider alternative mechanisms as well. Could the phenotypic consequences of mtDNA mutations be the consequence of epigenetic changes in nDNA? Perhaps, increased ROS production is simply a surrogate indicator of impairment of other mitochondrial functions, such as ATP generation, buffering cytosolic calcium, and apoptosis. Intriguingly, the observed phenotype in this family was restricted to systemic hypertension, as opposed to a compound heterogeneous phenotype involving multiple organs and systems. Even the systemic hypertension in this family appears to be relatively mild. What are the determinants of phenotypic variability and plasticity of mtDNA mutations or phenotypic restriction to a single system or organ, beyond the dependence of the tissue on oxidative phosphorylation? The restrictive and the relatively mild nature of the phenotype are not because of the threshold effect of the heterogeneous mutations, because the m.4263A>G mutation was homoplasmic, indicative of replicative segregation, another fascinating and largely unexplained feature of mtDNA whereby wild-type and mutant mtDNA are segregated during fission. Moreover, it is likely not to be reflective of the nature of the involved gene, because mutations in tRNA genes including tRNAile (MT-T1) are associated with various phenotypes, including cardiomyopathy, ophthalmoplegia, and metabolic disorder.
ders and hearing loss. Perhaps, Darwin’s theory of natural selection rules in Mammalian ovaries as well, wherein oocytes carrying the most deleterious mutations are eliminated, perhaps through apoptosis mediated by excess oxidative stress. Conceivably, the homoplasmic nature of the m.4263A>G mutation in MT-T1 hints to a mild nature of this mutation that is permissive to survival of the oocytes in the ovary, and, hence, the ensuing modest and system restricted phenotypic effect. The genetics of this captive invader will continue to mesmerize the enthusiasts for years to come.

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### References


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