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Mitochondrial genetic medicine

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Inherited mitochondrial DNA (mtDNA) diseases were discovered 30 years ago, and their characterization has provided a new perspective on the etiology of the common metabolic and degenerative diseases, cancer, and aging. The maternally inherited mtDNA contains 37 critical bioenergetic genes that are present in hundreds of copies per cell, but the 'mitochondrial genome' encompasses an additional 1,000–2,000 nuclear DNA (nDNA) mitochondrial genes. The interaction between these two mitochondrial genetic systems provides explanations for phenomena such as the non-Mendelian transmission of the common 'complex' diseases, age-related disease risk and progression, variable penetrance and expressivity, and gene–environment interactions. Thus, mtDNA genetics contributes to the quantitative and environmental components of human genetics that cannot be explained by Mendelian genetics. Because mtDNA is maternally inherited and cytoplasmic, it has fostered the first germline gene therapy, nuclear transplantation. However, effective interventions are still lacking for existing patients with mitochondrial dysfunction.

The incidence of diabetes, obesity, and autism is rising, and age-related diseases such as Alzheimer's disease, Parkinson's disease, and cancer are increasing as global populations age. Prodigious resources and efforts are being invested to understand and treat these diseases but have had limited success to date. Perhaps some of the difficulty lies in the assumptions that organ-associated symptoms are the result of organ-specific defects and that the clinically relevant genes are located in nDNA. It is now clear that organ-specific symptoms can result from systemic mitochondrial bioenergetic defects, and some of the most important mitochondrial genes are encoded by mtDNA, which is cytoplasmic. Instead of focusing on anatomical genetics, the clinical relevance of bioenergetic genetics may need to be considered.

The human genome's forgotten DNA

The eukaryotic cell arose through the amalgamation of two separate life forms: an archaeon that gave rise to the nucleus and cytosol, and an α-proteobacterium that gave rise to the mitochondrion. Over the approximately 2.5 billion years of eukaryotic-cell evolution, the nucleus became specialized in encoding the anatomical elements of the cell, whereas the mitochondrion became specialized in encoding the core energy elements[1].

The nDNA encompasses thousands of anatomical genes, which include the structural proteins for the mitochondrion and the enzymes for mtDNA maintenance and expression. The mtDNA contains only 13 polypeptide genes, but they are present in hundreds to thousands of copies per cell. The mtDNA polypeptides are central electron- and proton-transport proteins for the mitochondrial energy-generating process, oxidative phosphorylation (OXPHOS). Thus, mtDNA can be thought of as the wiring diagram of the mitochondrial 'power plant'[1].

OXPHOS generates ~90% of the body's energy by oxidizing the hydrogens from food with the oxygen breathed in, thus generating water, via the electron-transport chain (NADH–complex I (or succinate complex II)–coenzyme Q–complex III–cytochrome *c*–complex IV–oxygen). The energy released as electrons traverse complexes I, III, and IV is used to pump protons out across the mitochondrial inner membrane, thereby generating an electrochemical gradient that acts as a capacitor. The potential energy of this capacitor can drive complex V (the ATP synthase) to condense ADP and inorganic phosphate to ATP[1,2].

The mtDNA encodes seven (ND1, ND2, ND3, ND4, ND4L, ND5, and ND6) of the 45 polypeptides of OXPHOS complex I; one (cytochrome *b*) of the 11 polypeptides of complex III; three (COI, COII, and COIII) of the 13 polypeptides of complex IV; and two (ATP6 and ATP8) of the 18 polypeptides of complex V (ref. [3]). The mtDNA also encodes the 22 tRNAs and 12S and 16S rRNA for mitochondrial protein synthesis[1].

Because mitochondrial OXPHOS involves both mtDNA- and nDNA-encoded polypeptides, the genetics of the mitochondrial genome is enormously complex. Coordinate expression of these dispersed mitochondrial genes is achieved through the bidirectional exchange of polypeptides and small molecules between the two compartments[4–7].

Mitochondrial bioenergetics impinges on virtually every aspect of the cell. In addition to providing most of the energy, the mitochondria generate reactive oxygen species and control cellular redox levels, modulate cytosolic Ca^{2+}, and regulate the intrinsic pathway of apoptosis via the mitochondrial permeability transition pore. The mitochondria also determine the intracellular levels of the intermediates that control the cellular signal-transduction pathways and the epigenome (e.g., ATP, folate plus ATP for *S*-adenosylmethionine, α-ketoglutarate, succinate, and fumarate)[4,5]. Hence, mtDNA variants can affect myriad cell and organismal functions.

mtDNA diseases, adaptation, and germline gene therapy

Human mtDNA is strictly maternally inherited[8,9] and has a much higher mutation rate than that of nDNA[10–12]. When a new mutation arises within a cell, an intracellular mixture of mutant and normal mtDNAs is created, a state known as heteroplasmy (Fig. 1). As the cell undergoes cytokinesis, the proportion of mutant and normal mtDNAs can drift (replicative segregation) until either the mutant or normal mtDNA becomes fixed, a state known as homoplasmy. As the proportion of mutant mtDNAs increases, the mitochondrial energy production declines until the energy level falls below the minimum bioenergetic threshold for that organ to function, and clinical symptoms ensue[1] (Fig. 1). The brain has the highest energy requirement, accounting for

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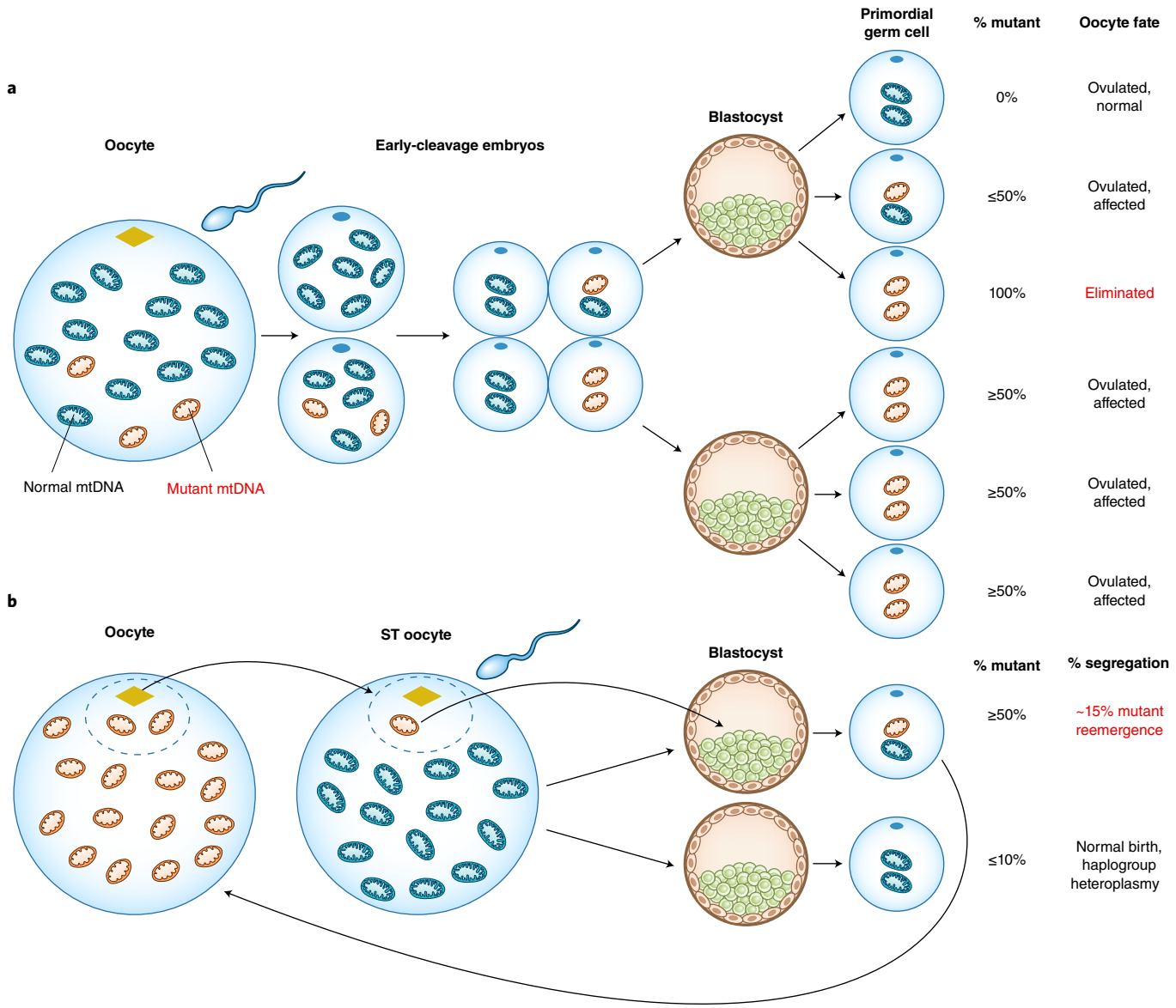

Fig. 1 | Germline mtDNA heteroplasmy segregation and removal by nuclear transplantation. Normal mitochondria with functional mtDNAs are blue. Defective mitochondria with mutant mtDNAs are brown. **a**, Oocytes bear hundreds of thousands of mtDNAs. After fertilization of a heteroplasmic oocyte, nDNA replication and cell division form a blastocyst, but the mtDNAs do not replicate and are randomly distributed into daughter cells. Some inner-cell-mass cells become PGCs, which form the oocytes in the female embryos. Each PGC receives only a few functional mtDNA elements, thus generating a broad distribution of PGC mtDNA heteroplasmy levels. The PGCs replicate and increase their mtDNAs, and form proto-oocytes. After hormonal stimulation, multiple oocytes mature toward ovulation. Those proto-oocytes and/or embryos with the most robust mitochondria outcompete those with deficient mitochondria and survive. If all of a woman's PGCs receive a high proportion of mutant mtDNAs, no normal proto-oocytes or embryos are available to outcompete the mutant, and multiple affected offspring result. **b**, Spindle or pronuclear transplantation transfers the chromosomes from the mtDNA-mutant oocyte-zygote to an enucleated oocyte-zygote with 'normal' mtDNAs. These transplanted oocyte-zygotes develop in vitro and are implanted in the mother's uterus. However, a small percentage of mitochondria are also transferred with the spindle and pronuclei, thereby creating heteroplasmy. Approximately 15% of stem cell lines derived from spindle-transfer oocytes revert back to the mother's mutant mtDNA. Additionally, in mouse studies, heteroplasmy of two different mtDNA haplogroups can be deleterious, thus prompting questions regarding the long-term health of heteroplasmic individuals.

2–3% of human body weight but using ~20% of the total mitochondrial energy. The heart, kidney, endocrine tissues, and liver also rely heavily on mitochondrial function. These are the same organs that are impaired in the common metabolic and degenerative diseases[1,13,14]

There are three classes of clinically relevant mtDNA variation: (i) recent maternally inherited deleterious mutations, (ii) ancient adaptive polymorphisms, and (iii) somatic mutations that accumulate during development and in tissues with age[13] (Table 1). The best-studied mitochondrial-gene mutations are those that are sufficiently severe to directly cause a clinical phenotype, termed 'primary mitochondrial diseases'. The minimum prevalence of primary-mtDNA-disease mutations has been estimated to be 1 in 5,000. This prevalence combined with that of primary nDNA mitochondrial-gene mutations results in a frequency of clinical mitochondrial diseases of approximately 1 in 4,300, with mtDNA mutations accounting for more than 75% of adult patients with primary mitochondrial disease[15,16].

Table 1 | Range of clinically relevant mtDNA mutations and polymorphisms

Class of variant	Type of mutation	Clinical severity	Phenotypic variability	Prevalence	Common nucleotide mutations	Clinical manifestations
Deleterious mutations: maternally inherited	Base substitutions: recent homoplasmic	Mild deleterious mutations	Stereotypic phenotypes	Classical mutations	3460,11778, 14484, others 1555 4336	LHON, blindness, deafness, AD/PD
	Base substitutions: recent heteroplasmic	Severe deleterious mutations	Variable phenotypes	Classical mutation	3243	MELAS, neuromuscular, DM, perinatal death, ASD
				Classical mutation	8344	MERRF, epilepsy, neuromuscular, DM
				Classical mutation	8993	NARP, Leigh syndrome
				Multiple individual mutations	*MT-CYB* 14747–15887	Mitochondrial myopathies
				Novel mutations	Numerous	MITOMAP
	Large insertions: recent heteroplasmic	Mild to severe	Variable phenotypes	Deletions generated in tissues	Variable positions, one or more tRNAs	DM, CPEO, KSS
Ancient polymorphisms: maternally inherited	Base substitutions: ancient homoplasmic	Neutral to mild	Predisposition to common diseases	Very common but population specific	Numerous positions in linkage-disequilibrium: haplogroups	Diabetes, obesity, AD, PD, cardiovascular disease, et cetera
Somatic mutations: individual and tissue specific	De novo mutations, oocyte and developmental: heteroplasmic	Large deletions: early broadly distributed	Variable	Classical presentations	Removal of one or more tRNAs	Pearson, CPEO, KSS
		Nucleotide, indel, and deletion mutations: late narrowly distributed	Variable	Accumulation with age	Highly variable	Aging, variable penetrance, delayed onset and progression

There are three classes of clinically relevant mtDNA variants: (i) maternally inherited deleterious mutations that generate familial diseases; (ii) ancient haplogroup-associated variants that predispose individuals to common diseases; and (iii) de novo mutations that arise in the oocyte or during development and augment partial mitochondrial defects. (i) Maternally inherited deleterious mutations can be mild and result in clinical manifestations when they are homoplasmic (LHON) or severe, and result in disease when they are heteroplasmic (NARP, MERRF, MELAS, or myopathy). Large insertion mutations can also result in maternally inherited disease because they can undergo rearrangement during development, thus generating deletions causing phenotypes ranging from diabetes to severe CPEO and KSS. (ii) Functional variants associated with mtDNA haplogroups can predispose individuals to metabolic and degenerative diseases, but their physiological effects must be augmented by additional genetic or environmental effects. (iii) De novo mutations can arise in oocytes or during development. Large deletions that remove a tRNA can result in Pearson's syndrome, CPEO, or KSS, depending on the tissue distribution and level of heteroplasmy. Base substitutions and insertion–deletion (indel) mutations accumulate throughout development and life, and progressively erode mitochondrial function. The earlier a mutation occurs, the more widely distributed it becomes. AD, Alzheimer's disease; PD, Parkinson's disease; CPEO, chronic progressive external ophthalmoplegia; DM, diabetes mellitus; KSS, Kearn–Sayre syndrome; LHON, Leber hereditary optic neuropathy; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonic epilepsy and ragged red fibers; NARP, neurogenic muscle weakness, ataxia, and retinitis pigmentosa.

However, a survey of newborn cord blood for the ten most common pathogenic mtDNA mutations has shown that 1 in 200 infants bears a mutation[17,18]. Deep mtDNA sequencing of mother–child pairs has shown that, on average, each individual carries one heteroplasmic mutation, and one in eight individuals bears a disease-associated heteroplasmic mutation at ≥1% heteroplasmy[19].

The most common and well-known pathogenic mtDNA missense mutations are the *MT-ND4* m.11778G>A (p.Arg340His) mutation, which causes sudden-onset blindness, Leber's hereditary optic neuropathy (LHON)[20], and the *MT-ATP6* m.8993T>G (p.Leu156Arg) mutation, which is associated with neurogenic muscle weakness, ataxia, and retinitis pigmentosa (NARP) and Leigh's syndrome[21]. The most common tRNA mutations are the *MT-TK* m.8344A>G mutation, which causes myoclonic epilepsy and ragged red fiber (MERRF) disease[22,23], and the *MT-TL1* m.3243A>G mutation, which causes mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS)[24].

The milder mtDNA pathogenic mutations can segregate to homoplasmic; common examples include the LHON mutations (*MT-ND4* m.11778G>A (p.Arg340His)[20], *MT-ND1* m.3460G>A (p.Ala52Thr)[25], and *MT-ND6* m.14484T>C (p.Met64Val)[26]), and the aminoglycoside-induced-deafness variant *MT-RNR1* m.1555A>G[27,28]. More severe mtDNA mutations cause diseases when they are heteroplasmic, such that the percentage of mutant mtDNA affects the severity of the phenotype. Some heteroplasmic mutations can cause a characteristic phenotype; for example, certain cytochrome *b* mutations cause mitochondrial myopathy[29–33], whereas other heteroplasmic mutations result in an array of symptoms commonly affecting the brain, heart, muscle, and other tissues with high energy demand[34,35]. Hundreds of putative pathogenic mtDNA mutations have been reported[36,37] and are accessible through the MITOMAP-MITOMASTER website[38].

Because of the high mtDNA sequence-evolution rate, human mtDNAs bear a rich array of variants. A high mutation rate might

be expected to generate a crippling genetic load, but this is not the case, owing to the novel intracellular mtDNA population genetics of the female germline (Fig. 1).

The mammalian oocyte contains hundreds of thousands of mtDNAs. However, after fertilization, the mtDNAs do not replicate until the blastocyst stage, and the zygote mtDNAs are then distributed throughout the blastocyst cells. Consequently, each female primordial germ cell (PGC) receives a limited number of mtDNAs. This bottleneck causes the mtDNA genotype to drift, such that a heteroplasmic oocyte gives rise to PGCs with widely different mtDNA heteroplasmy ratios (Fig. 1). The number of mtDNAs transmitted through this female-germline bottleneck in mice has been estimated to be ~200 (refs [39–41]). The human mtDNA bottleneck has been variously estimated to be from 9 (ref. [42]) to ~30–35 (range 9–141) (ref. [19]) functional elements, and the size of the bottleneck differs for various pathological mtDNA mutations[43]. The molecular basis of the mtDNA bottleneck may be the physical limitation of the number of mtDNAs transmitted or the preferential replication of a select group of mtDNAs, presumably those in proximity to the nucleus[40,44–46] (Fig. 1). The primordial germ cells then undergo approximately 20–24 cell divisions and increase the numbers of their mtDNAs.

With the appropriate hormonal signal, multiple ovarian proto-oocytes are thought to mature into follicles. However, those follicles or the early embryos that bear deleterious mtDNAs are preferentially lost, and those with more optimal mitochondrial function survive[47–49] (Fig. 1). This process creates an intracellular mtDNA system of high mutation rate, bottleneck segregation, and follicular and early developmental selection, which enriches for the best mtDNAs, thus fostering high genetic diversity while minimizing genetic load. Hence, functional mtDNA variants affecting mitochondrial bioenergetics are continuously being introduced into the human population. This process provides the genetic diversity for adaptation to changing environments, such as differing diets, high-latitude cold stress, high-altitude oxygen deprivation, and challenge by an array of antigenic and infectious agents.

Beneficial mtDNA variants and the mtDNAs on which they arose may segregate to homoplasmy in the founder lineage, thus enhancing survival of the maternal descendants bearing these mtDNAs. As the descendants of these mtDNAs increase, additional mtDNA-sequence changes accumulate along the mtDNA lineage, thereby generating a regional group of related mtDNA haplotypes known as a haplogroup. The result of this process is that indigenous human populations living in different environments bear different functional mtDNA variants and their associated haplogroups.

Because mtDNAs are related through radiating maternal lineages, the comparison of the mtDNA sequences among indigenous populations has permitted the reconstruction of the ancient origins and migrations of women. All human mtDNAs trace back to a single African mtDNA ancestor from which the African mtDNAs radiated for approximately 200,000 years. This created an array of African mtDNA haplogroups (L0, L1, L2, L3, and so forth), which are subsumed under African macrohaplogroup L. Approximately 65,000 years ago, two mtDNAs arose from haplogroup L3 in northwestern Africa, and only individuals with these two mtDNAs successfully left Africa and colonized the rest of the world. One moved into the temperate zone and gave rise to the European and Asian macrohaplogroup N lineages. The other initially migrated east through Southeast Asia and much later moved north in Asia, and gave rise to the Asian macrohaplogroup M lineages. The European macrohaplogroup N haplogroups include H, I, J, K, T, U, V, W, and X, whereas the Asian haplogoup Ns include A, B, F, and N9a. The Asian macrohaplogroup M haplogroups include C, D, G, and M1–M40. Individuals with three mtDNA haplogroups, A, C, and D, crossed the Bering land bridge and colonized the Americas approximately 20,000 years ago and were subsequently joined by individuals with haplogroups B and X[13].

Although the functional variants associated with haplogroups may be adaptive in the original environment, they can be maladaptive in other environments. As a result, mtDNA haplogroups are now being correlated with a predisposition to a wide range of metabolic and degenerative diseases, cancer, and longevity[13].

For example, the *MT-TQ* m.4336A>G mutation arose between 8,500 and 17,000 years ago in European haplogroup H, thus generating the subhaplogroup H5a. Individuals in this haplogroup are predisposed to late-onset Alzheimer's and Parkinson's diseases[50–52]. Other studies have reported that European mtDNA haplogroups T and J are associated with decreased Alzheimer's disease risk[53–55], whereas haplogroup Uk is associated with increased Alzheimer's disease risk[56]. Similarly, European haplogroups J, T, and Uk are associated with decreased risk of Parkinson's disease[57,58], whereas haplogroup H is associated with increased risk[59]. However, other studies have not observed these same mtDNA haplogroup associations with Alzheimer's disease[60], and a meta-analysis has found associations between mtDNA haplogroups and Parkinson's disease but not Alzheimer's disease[61].

Autism has also been associated with mtDNA haplogroups. Relative to the most common European mtDNA lineage (H+HV), haplogroups I, J, K, T, and U impart an increased risk of developing autism. Each of these haplogroups has an odds ratio of ~2, and together they represent 55% of the European population[62]. The role of mtDNA variation in autism has been corroborated by the observation that somatic-mtDNA mutations are elevated in autism[63].

mtDNA haplogroups have also been shown to correlate with diabetes and metabolic syndrome. For example, Asian haplogroup N9a has been found to be protective against type II diabetes mellitus[64] and myocardial infarction[65]. In another Asian study, haplogroups N9a, F4, and D5 have been associated with decreased risk of diabetes; F4 and N9a have been associated with increased risk of hypertension; and F4 has been associated with increased risk of obesity, although there is considerable variability among metabolic disease studies[66].

This variability among studies of the relative risk of mtDNA haplogroups associated with the common neurodegenerative and metabolic diseases is unsurprising, owing to the regional population specificity of mtDNA haplogroups and their graded physiological effects. Within a specific population, the relative ranking of an interrogated haplogroup for the risk of a particular disease depends on the distribution of the other local haplogroups in that population. Additional variants may also have arisen in the regional haplogroups and modified their relative physiological effects. What is important is the repeated demonstration that mtDNA variation modifies the relative risk of the common neurodegenerative and metabolic diseases. Hence, bioenergetic variation must be an important factor in the etiology of these common diseases.

That mtDNA haplogroup lineages are functionally important has been demonstrated in cell lines created to have the same nucleus but different mtDNAs, in which extensive physiological differences have been documented[13]. Additionally, mice have been generated bearing the same nucleus but different mtDNA lineages and have been shown to have altered phenotypes[67–69].

Although the proto-oocyte-selection system permits enrichment for the most robust mtDNAs in a woman's germline, if a deleterious mutation becomes enriched throughout a woman's germ cells, then all of her oocytes will bear a high proportion of mutant mtDNAs, thus negating differential follicle selection (Fig. 1). Consequently, all of her offspring are likely to have devastating multisystem disease[70]. This situation has prompted the development of two oocyte mitochondrial-replacement procedures—zygote pronuclear transfer (PNT) and spindle transfer—to break the maternal transmission of the mutant mtDNAs (Fig. 1). In the PNT procedure, the oocyte of the affected woman is fertilized, and the two pronuclei are transferred by micropipette into an enucleated recipient zygote from a woman with normal mtDNAs[71,72]. In the spindle-transfer procedure,

the spindle from the metaphase II oocyte is transferred into an enucleated oocyte with normal mtDNAs[73–77]. Metaphase II–oocyte polar-body transfer may provide a third approach[78].

Unfortunately, current mitochondrial-replacement procedures cannot eliminate all of the original mother's mutant mtDNAs, because the mutant PNT and spindle-transfer fragments can potentially contribute up to 5% of the embryo's mtDNAs (Fig. 1). Consequently, two types of embryo heteroplasmy result: heteroplasmy for the deleterious mtDNA mutation and heteroplasmy for two maternal mtDNA haplogroups[49,70].

The carryover of mutant mtDNA suggests a possibility that the mutant mtDNA might reemerge. This concern has been validated by monitoring the fates of the two mtDNAs in embryonic stem cell lines derived from spindle-transfer or somatic-cell nuclear-transfer embryos. Up to 15% of the spindle transfer embryos have been estimated to revert to the spindle donor mtDNA (Fig. 1)[75,79,80].

One mechanism through which mtDNA heteroplasmy might revert is if the mutant mtDNA has a replicative advantage, for example a variant in the mtDNA replication origin (CSBII, nt 299–315, G5AG8 versus G6AG8)[75]. Another possibility may be that mtDNAs close to the spindle or zygote nucleus are primed to replicate, whereas those throughout the cytoplasm are not, thus resulting in preferential replication of the mtDNAs carried along with the nucleus or spindle[77]. The reemergence of the mother's mutant mtDNA is potentially problematic not only for reexpression of the mutant phenotype but also because mixing of two different mtDNA haplogroups has been found to be deleterious in mouse-model systems[49,81]

To date, one three-parent-baby has been born and reported in the literature. The mother lost six pregnancies, four through miscarriage and two to Leigh syndrome, in which the infants had high levels of the *MT-ATP6* m.8993T>G (p.Leu156Arg) mutation. The mother's mtDNA haplogroup was 'I', and her 8993G somatic-tissue mutation load was 23% to 34%. However, her oocytes were nearly 100% 8993G mutant. The spindles from her oocytes were transferred to the enucleated oocytes of a woman whose mtDNA was haplogroup L2c. One spindle-transfer blastocyst verified to be euploid and to have low 8993G levels was implanted and resulted in an apparently normal boy. At 2 days of age, the 8993G mtDNA was undetectable in the boy's placenta and umbilical cord, and his tissues ranged from 2% to 9% (refs [79,82]). Hence, at least in one case, spindle transfer has been able to prevent a likely case of Leigh syndrome. However, it has also generated an individual heteroplasmic for two quite different mtDNA haplogroups.

mtDNA mutations, age-related diseases, and aging

The mtDNAs are continuously replicated within cells, and sequence errors occur during replication. Mice in which the mtDNA polymerase has been mutated to be error prone show signs of premature aging[83,84]. Both base substitutions and rearrangement mutations accumulate with age, although rearrangement mutations have been proposed to be more important for age-related decline[85]. Adult somatic-cell-derived induced pluripotent stem cell clones have also been found to bear de novo heteroplasmic mtDNA mutations[86]. The reasons why mtDNA mutations accumulate is unclear, but the decrease in mitochondrial H_2O_2 levels in mice when a mitochondrially targeted catalase is used has been found to decrease mtDNA deletion levels, extend lifespan[87], protect against metabolic disease[88], and impair colorectal tumor induction[89]. Thus, the accumulation of somatic mtDNA mutations may be the aging clock[90–92].

The level of somatic mtDNA mutation is further elevated in age-related diseases, such as in brain tissue in individuals with Alzheimer's[93–95], Parkinson's[96], and Huntington's diseases[97] and in heart tissue in individuals with cardiovascular disease[98]. Because the same heteroplasmic mtDNA mutation has been found in both the brain and blood of patients with Alzheimer's disease[95], some somatic mutations must arise early in development. Thus, both ancient homoplasmic mtDNA haplogroup variation and heteroplasmic mtDNA mutations can be associated with a predisposition to neurological diseases (Table 1).

Individuals born with genetic variants causing partial mitochondrial deficiency (specific mtDNA haplogroups, germline heteroplasmic mtDNA mutations, or heterozygous nDNA loss-of-function or copy number variants) may still have sufficient energy to appear normal. However, the age-related accumulation of somatic mtDNA mutations may further erode energetics until it falls below the minimum for high-energy organs to properly function, and clinical symptoms manifest. This scenario may explain why age is the most important risk factor for many metabolic and neurodegenerative diseases, and cancer.

The mitochondria, environment, and inflammation

Mitochondrial function is subject to a broad range of environmental influences. These include the type and availability of calories in the diet; the energy demands of exercise and pregnancy; the availability of oxygen at high altitudes[99]; the presence of toxins, such as those from smoking, which lead to chronic obstructive pulmonary disease[100], or from pesticides causing neurological disease[101,102]; trauma[103,104]; and infectious agents leading to sepsis and AIDS progression[105–107].

Inflammation has been associated with many of these environmental influences and is also a near-universal feature of complex diseases, cancers, and aging. Inflammation is frequently initiated by the elaboration of pathogen-associated molecular patterns or damage-associated molecular patterns (DAMPs), and some of the most potent DAMPs are the bacteria-like molecules of the mitochondrion, including the mtDNA, *N*-formyl mitochondrial translation products, and mitochondrial inner-membrane cardiolipin[108–110]. Cellular damage, including reactive oxygen species toxicity, can activate the release of mitochondrial DAMPs into the cytosol, where they interact with the inflammasome, which is associated with mitochondria. The inflammasome contains nucleotide-binding domain–leucine-rich repeat proteins such as NLRP3 plus the adaptor protein and pro-caspase-1. The inflammasome interacts with the interferon-inducible protein AIM2, which binds double-stranded DNA including mtDNA. DNA binding activates the inflammasome caspase 1, which then cleaves pro-IL-1β to active IL-1β. IL-1 then activates the NF-κB/AP-1 pathway and induces inflammation[111,112]

Mitochondria also modulate inflammation through the differential energetics of T regulatory cells and M2 anti-inflammatory macrophages, which are primarily oxidative, versus T effector cells and the M1 proinflammatory macrophages, which are predominantly glycolytic[113,114]. Therefore, inhibition of mitochondrial function may preferentially inhibit the T regulatory cells and M2 macrophages, thus permitting the hyperactivation of the T effector cells and M1 macrophages and increasing inflammation. If mitochondrial dysfunction is an important factor in the etiology of both rare and common diseases and aging, then mitochondrial dysfunction may explain why inflammation is commonly associated with common disease, cancer, and aging.

Conclusion

The common diseases have complex genetics and a strong environmental component. The large numbers of nDNA and mtDNA mitochondrial genes, the quantitative nature of mtDNA genetics, the age-related accumulation of somatic mtDNA mutations, the tissue specificity of bioenergetics defects, and the sensitivity of mitochondrial function to environmental oscillations provide explanations for many of the features of common diseases that cannot be explained by anatomical and Mendelian paradigms of disease.

Although germline gene therapy might help prevent the inheritance of primary mtDNA diseases, it is not a solution for existing

patients. Therefore, there is a great need for development of both metabolic and genetic therapies for patients with primary mitochondrial disease. Fortunately, the demonstration of the importance of mitochondrial dysfunction in the etiology of common metabolic and degenerative diseases suggests that therapies developed for primary mitochondrial diseases may pave the way for developing therapies for common diseases.

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Competing interests

The author declares no competing interests.

Additional information

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