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Review Article

Mitochondrial Mutations Affect the Cardiovascular System during Aging and Oxidative Stress

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Abstract

Mitochondria are one of the most crucial components of the cell. Aging has a critical impact on mitochondria. Various studies have shown that the relationship between aging and mitochondria is multifaceted. In this review, we focused on mitochondrial DNA mutations and their impact on the cardiovascular system during aging and oxidative stress. While mitochondria contain their own DNA, part of their proteome is encoded by nuclear DNA, which further complicates the inheritance of mitochondrial diseases, making almost all methods of transmission of various pathologies possible. We provide a discussion on mitochondrial DNA mutagenesis and the most common problems associated with mitochondrial DNA mutations.

Introduction

Current hypotheses suggest that mitochondria developed from free-living bacteria and contributed to the evolution of eukaryotic cells through an endosymbiotic process. According to the endosymbiotic theory, the procaryotic ancestor of eukaryotic cells absorbed the primitive mitochondria. Several current theories, however, suggest endosymbiosis with a non-eukaryotic archaeon.[1] Following a massive negative selection caused by gene recombination, these life forms formed beneficial interactions. As a result, mitochondria significantly enhanced the production of cell energy, producing adenosine triphosphate (ATP) through the electron transport chain while the host cell offered a benign environment for bacterial growth.[2]

The discovery of mitochondrial DNA (mtDNA) and an independent translation system in mitochondria in the 1960s confirmed the above-described hypothesis. MtDNA, the mitochondrial genetic material, has the typical properties of bacterial DNA; it is a double-stranded circular genome of approximately 16.6 kb. It is polycistronic and contains no introns.[3] Apart from the D-loop, which is a non-coding region, all the genes are adjacent to each other, although they may partly overlap. In addition, the number of mtDNA copies in the cell is much higher than that of nuclear DNA, corresponding to the energy demand in the tissue.[4] Furthermore, tryptophan and methionine encoded by mtDNA differ from the corresponding codons in nuclear DNA, and the genetic code includes only two stop codons. While the genetic code of mtDNA varies between vertebrates and other metazoans, it is the same for all plants.[5,6] This indicates that the change in the genetic code of mtDNA took place several times throughout evolution, and it cannot explain the mtDNA maintenance in the organelle. The majority of mitochondrial genes were either lost or moved to nuclear DNA during evolution. Currently, only 37 genes are present in mtDNA, including 22 mitochondrial tRNA genes, 11 messenger RNA genes, translated to 13 polypeptides, and 2 ribosomal RNAs (12S and 16S).[7]

Keywords: Mitochondria; Aging; Oxidative stress; mtDNA; Cardiovascular system; Cardiovascular aging.

Abbreviations: ATP, adenosine triphosphate; CVD, cardiovascular disease; CM, cardiomyopathy; IS, ischemic stroke; mtDNA-CN, mtDNA copy number; mtDNA, mitochondrial DNA; MELAS, mitochondrial neuro-gastro-intestinal encephalomyopathy; MUTYH, mutY DNA glycosylase; nDNA, nuclear DNA; OGG1, 8-oxoguanine DNA glycosylase; OS, oxidative stress; OXPHOS, oxidative phosphorylation system; POLG, polymerase subunit gamma; ROS, reactive oxygen species; TFAM, mitochondrial transcription factor A; 8oxoG, 7,8-dihydro-8-oxoguanine.

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Mitochondria

The genetics of mitochondria

In contrast to nuclear DNA, which is governed by Mendelian laws, mitochondrial genetics has the following characteristics: 1) the DNA is inherited only from the mother; 2) the mitochondrial genome exhibits polyploidy; 3) the mitochondrial nucleosome has a specific structure; 4) clonal replication of mtDNA occurs even

within a single mitochondrion; and 5) mitochondrial segregation is random even within the same cell, so that the proportion of mutant mtDNA may change as a result of the segregation.[8] This leads to heteroplasmy, which means that a cell can have a mixture of normal and mutant mitochondrial genomes. These factors contribute to the variability in age- and even tissue-related mitochondrial diseases.

Despite being a rather stable molecule, DNA may be modified and mutated as a result of the spontaneous fracturing of nucleic acid structure, as well as an increased presence of reactive oxygen species and their resulting products.[9] MtDNA may be spontaneously transformed, for example, by becoming deaminated as a result of oxidative stress (OS). The most frequent modification type of mtDNA is oxidative modifications in DNA bases or sugar, for example, 8-hydroxyguanine.[10] MtDNA damage as a result of OS was previously associated with mtDNA mutations. However, this was not confirmed by more recent studies. For example, 8-oxoguanine DNA glycosylase (OGG1) knockout mice did not demonstrate cardiac or hepatic mitochondrial respiratory disorders as a result of OGG1 deficiency even in the setting of increased 8-oxo-dG production.[11] Furthermore, mice expressing low fidelity POLG demonstrated considerable accumulation of mtDNA abnormalities, which affected their lifespan despite relatively low levels of OS.[12]

Despite the existence of mtDNA, most genes encoding the mitoproteome are in nuclear DNA, and their inheritance complies with Mendelian inheritance patterns. Almost all patterns of inheritance, including dominant, recessive, and X-linked, were reported.[13] The first mutation in the nuclear mitochondrial gene was reported in the succinate dehydrogenase complex flavoprotein subunit A gene, encoding a structural subunit of complex II, which led the path for a search for candidate genes for mitochondrial disease. Approximately 1,300 nuclear genes participate in mitochondrial maintenance and functioning. These genes are translated by cytosolic translational machinery, and the 5′ mitochondrial targeting sequence enables the translated proteins' transport into the mitochondrion.[14] Defects in more than 250 genes from nuclear DNA were associated with multiple respiratory chain defects and clinical mitochondrial disease.[14]

Mitochondrial diseases

Some mitochondrial diseases are caused by large-scale rearrangements of mtDNA, including single deletions, duplications, or their combination. Among these diseases, chronic progressive external ophthalmoplegia, Kearns–Sayre syndrome, and Pearson's syndrome should be mentioned. Several diseases, such as maternally inherited Leigh syndrome, mitochondrial neuro-gastro-intestinal encephalomyopathy (MELAS), diabetes mellitus, deafness, and Leber's hereditary optic neuropathy, are the result of point mutations in mtDNA.[15] In addition to disorders caused by mtDNA alterations, some diseases are triggered by nuclear mutations, including Wilson's disease (ATP7B), dominant optic atrophy (mutation in OPA1), Barth syndrome (TAZ), and others. Other clinical pathologies linked with mitochondrial dysfunction include neurodegenerative diseases such as Alzheimer's disease, Huntington's disease, and Parkinson's disease, as well as bipolar disorder, schizophrenia, epilepsy, stroke, and cardiovascular disease.[14,16]

Mitochondrial mutations and mutagenic factors

Since the discovery of the first mtDNA mutations, considerable progress has been made in understanding how mtDNA mutations affect the course of mitochondrial disease.[17] The classification of mtDNA mutations includes ancient adaptive mtDNA alterations, new deleterious mutations, and somatic mtDNA abnormalities accumulated in tissues over time.[18]

MtDNA variation caused by mutations has been used in population genetics to identify relatives from various historical periods. Epidemiological studies showed that the prevalence of mtDNA disorder was approximately 1 in 5,000, and 1 in 200 newborns exhibited heteroplasmic mtDNA alterations.[19] The sequence evolution rate, as well as mutation load, is very high in mitochondrial DNA in comparison with nuclear DNA (nuclear DNA vs. mtDNA: 2.5×10^{-8} vs. 3×10^{-6}, ~2.7×10^{-5} per base per generation) as a result of constant replication process and the greater number of mtDNA copies in a cell.[20] The severity of the mutation affects both factors encoded in nuclear DNA and mtDNA, which influence each other and evolve from protein–protein interactions in the oxidative phosphorylation system (OXPHOS), mitochondrial ribosome RNA, and protein-DNA interactions involved in transcription and replication of mitochondria.[21,22]

MtDNA may be especially exposed to mutations for several reasons. 1) The mtDNA is located close to the inner membrane where reactive oxygen species (ROS) are generated. During the replication process, one of the mtDNA strands is lagging and remains much more susceptible to spontaneous mutations compared with double-stranded DNA. 2) Mitochondrial DNA is not concentrated in a single spot and is thus more exposed to various types of damage. Whether the nucleoid of the mitochondrion is located close to the ROS production site is still unclear. 3) Covalent modifications in mtDNA are not easy to detect by mtDNA repair mechanisms because the proteins required to repair damaged DNA are not encoded in the mtDNA, and the DNA polymerase subunit gamma (POLG) in mitochondria has low fidelity.[23–25] MtDNA is more vulnerable to mutations because of its persistent replication. Upon division or renewal of cells, mitochondrial mutations can be passed on during segregation or clonal expansion. The continuous replicative nature of mtDNA has been considered a possible pathogenic factor in subjects with either mtDNA mutations of different types or mtDNA depletion syndrome.[26] Furthermore, metabolic dysfunctions independently cause abnormalities in the bioenergetic processes within mitochondria. This leads to a higher mutation rate, contributes to mtDNA impairments, disrupts the replication of mtDNA, and strengthens mitophagy, eventually resulting in the accumulation of somatic mutations in mtDNA.19,24 Diabetes-related metabolic dysfunctions moderated by cytokines, inflammation, and oxidative stress lead to mtDNA depletion rather than transformation or point mutations in mtDNA. Loss of mtDNA can also be caused by an imbalance of nucleotide pools since large amounts of nucleotides are moved into the mitochondria, and the inner membrane has much more restricted permeability to ions. As a result, nucleotide deficiency in mitochondria may cause misincorporation of nucleotides during mtDNA replication.[27,28]

Recent research identified associations between pharmaceuticals and environmental pollutants with mitochondrial toxicity. Pharmaceutical pollutants have been well investigated. Various mechanisms underlying the effects of these elements on mitochondria were shown to be involved, and different degrees of influence of these factors were shown. Various drugs were reported to have toxic effects on mitochondria. For example, Adriamycin, an anticancer chemotherapy drug, generates ROS and inhibits the production of ATP, causing cardiomyopathy.[29] Studies have shown a variety of environmental pollutants, such as silver nanoparticles, also affect mitochondria. These particles are widely used as bactericidal agents, and they were reported as mitochondrial toxins. This may be because of the similarity of bacteria and mitochondria.[30]

However, endogenous mechanisms were recently reported to affect mitochondria more than environmental factors.[31] Ju *et al.* used mtDNA sequencing and found that errors during mtDNA replication and the lack of repair mechanisms are responsible for causing more mitochondrial mutations than any exogenous factor.[32] This was supported by the finding that most mtDNA mutations act as 'passenger mutations,' with no impact on the cell's characteristics, cancer development, and cancer spread. Melanoma and lung cancer are associated with environmental mutagens, but there was no evidence of an impact of the associated carcinogens (tobacco smoke and UV light, respectively) on mtDNA mutations. Moreover, even in cancer, mitochondria must be functional, otherwise, cancer cells would undergo apoptosis due to less energy production. Nevertheless, the above study involved only cancer patients, and the result cannot be translated to other types of disease, such as Parkinson's disease, epilepsy, and cardiovascular disease.[33]

Aging and mtDNA mutations

Many pieces of evidence suggest that deletions and point mutations in mtDNA accumulate with age in different tissues, including the cardiac muscle, in humans and rodents. A study of the mtDNA D-loop in mice between 2 and 22 months showed no mtDNA mutations in younger mice.[34] However, the mtDNA mutation prevalence in older animals was 1,000 times greater than that of nuclear genes. MtDNA loss in the human heart occurs after the age of 40 and increases with age.[35,36]

Higher mtDNA mutation rates stimulate aging. The mtDNA mutator mice with ectopic expression of a proofreading-deficient Pol γ accumulated mtDNA alterations in various tissues, including the liver, heart, and brain.[37] The mutation rate was already three to five-fold higher in mutator mice at eight weeks of age compared with wild-type mice. Extensive mtDNA loss was revealed in approximately 30% of the genome. Mutator mice show signs of premature aging, including alopecia, decreased fertility, and osteoporosis.[38] Mutator mice develop diastolic and systolic dysfunction, heart hypertrophy and dilatation, and cardiac fibrosis, and their lifespan is an average of 48 weeks (compared with 72 weeks in wild-type mice). Clinical manifestations of this mutation-related cardiomyopathy include increased oxidative damage to proteins, higher expression of markers indicating apoptosis and senescence, and lower mitochondrial biogenesis.[39,40] These aging phenotypes may be alleviated by increased mitochondrial-targeted catalase, which indicates that the mutation-induced cardiomyopathy is to a certain degree mediated by ROS in mitochondria.[41]

The mtDNA-mutator creates a random set of point mutations in genes of the respiratory chain subunits. According to the oxidative stress aging theory, the mtDNA mutation rate grows exponentially due to the oxidative stress, resulting in a vicious cycle. However, point mutations in mtDNA-mutator mice occur in an approximately linear way, from midgestation to late adult life. Notably, these mice do not exhibit excessive oxidative damage in response to biomolecules, such as DNA, proteins, and lipids. The range of oxidative stress markers was evaluated, and no marker was significantly increased. These markers, including the level of hydrogen peroxide (mitochondrial proteins), protein carbonyls (proteins), F2-isoprostanes (lipids), 8-oxodeoxyguanosine (DNA), and 8-deoxyguanosine (RNA), were within the normal range or exhibited a slight increase.

Moreover, levels of antioxidant defense enzyme expression and aconitase enzyme activity measurements call for the low rate of oxidative stress in tissues from mtDNA-mutator mice. This suggests that the increased levels of mtDNA mutations are not associated with increased ROS production or increased oxidative stress in mtDNA mutator mice. This further suggests that there is no cycle leading to increased oxidative damage.[37,38]

Oxidative stress

Mitochondrial OS and mtDNA mutation in the heart during aging

Studies have shown that mtDNA is subject to increasing oxidative insult in the aging heart. Insufficient supply of histones, inefficient DNA repair, and proximity to ROS production site make mtDNA vulnerable to various deleterious insults, including base pair alterations or DNA point deletions, and a reduced mtDNA copy number (mtDNA-CN).[42] There are different forms of oxidative insults to mtDNA. These include single- and double-strand breaks and base oxidation, such as 7,8-dihydro-8-oxoguanine (8oxoG). Constant replication of mtDNA and its nucleoid structure make mitochondria more susceptible to spontaneous mutations and oxidative insult. The mitochondrial nucleoid is primarily composed of mitochondrial transcription factor A (TFAM), mitochondrial RNA polymerase, Polγ, single-stranded DNA-binding protein, and Twinkle mtDNA helicase.[43] TFAM and DNA Polγ are the main factors moderating metabolism. Their loss or excessive production in transgenic mice can lead to heart failure. Mice with homozygous mutation of mitochondrial Pol γ develop cardiac hypertrophy, show early signs of aging, and accumulate mtDNA deletions and mutations.[44] A product of mtDNA oxidation, 8oxoG is a well-known sign of DNA damage caused by OS. Previous *in vitro* studies showed that TFAM binds to 8oxoG and disrupts the repair processes. The removal of 8oxoG is a complex process that involves proteins encoded by OGG1 and mutY DNA glycosylase (MUTYH) genes. MUTYH removes adenine from 8-oxoG.[45] In the human mitochondria, OGG1 efficiently removes 8oxoG mispaired with adenine by catalyzing the cleaving of the N-glycosidic bond between the impaired 8oxoG base and deoxyribose sugar. OGG1 in the human mitochondria catalyzes the dissociation of an N-glycosidic bond between the impaired 8oxoG base and deoxyribose.[46,47] OGG1 is the main enzyme involved in repairing 8oxoG base lesions. DNA Polγ has a crucial role in replicating mtDNA, in a process that involves Twinkle protein and single-stranded DNA-binding protein, and it is responsible for both mtDNA production and proofreading. Studies have indicated that the proofreading ability may be decreased by ROS, which may cause errors in replication. Therefore, oxidation contributes to abnormalities in mtDNA replication and indirectly leads to mtDNA damage.[48] This suggests that mutations in mtDNA are more often random than transversions, and aging-related mtDNA mutations are likely to be induced by Pol γ oxidation. Thus, mtDNA mutations are largely connected to cardiac aging.[42] See Figure 1 for one of the proposed connections between mtDNA, ROS, and aging.

How oxidative stress affects mtDNA-CN

Cellular dysfunction in aging is caused by alterations in mtDNA-CN and accumulated mutations resulting in damaged mtDNA integrity. In a recent study, MtDNA-CN was calculated by the relative ratio of DNA from the subunit of mitochondrial NADH dehydrogenase to the nuclear gene cytochrome P4501A1 in mice with cardiac hypertrophy induced by angiotensin (Ang) II.[49] The calculation revealed a decrease in mtDNA-CN. MtDNA-CN is inversely proportional to cardiovascular disease (CVD) prevalence and occurrence as well as the incidence of sudden cardiac

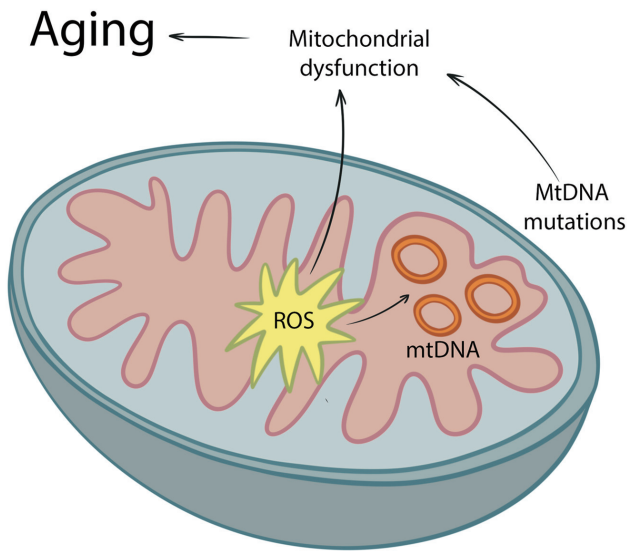

Fig. 1. ROS can affect mtDNA, causing mutations, which lead to mitochondrial dysfunction. Mitochondrial dysfunction is a predisposing factor for aging. mtDNA, mitochondrial DNA; ROS, reactive oxygen species.

death. The number of mtDNA copies can be considered an indirect marker of mitochondrial function. When mtDNA-CN decreases in cells, energy metabolism concomitantly declines, which may be a sign of a lack of OS response.[50] OS response damages enzymes involved in mtDNA replication and thus contributes to further mtDNA loss. In mice with pressure-overload-induced heart failure, overexpression of Twinkle or TFAM reduces left ventricle fibrosis, limits mitochondrial OS and enhances heart function.[51] A study evaluated an inverse correlation between mtDNA-CN and coronary artery disease in a Chinese cohort, particularly among smokers.[52] The study revealed that high mtDNA is inversely related to ROS production. The findings of the study indicate a close association between coronary artery disease, OS and mtDNA-CN. These data suggest that mtDNA may be a potential target for heart damage treatment.[53]

Possible result of mtDNA mutations and its considerations

Mt-tRNA mutations are functionally recessive and may affect the process of mitochondrial translation as they reduce the availability of functional mt-tRNAs. mt-tRNA mischarging occurs more often, and the involved protein gains or loses function.[54–56] Such mutations are the cause of the most investigated mitochondrial diseases, such as mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes, and myoclonus epilepsy with ragged-red fibers. A dominant form of mt-tRNA mutation exists, and some non-pathogenic nucleotide changes may restrain the effects of other detrimental mtDNA mutations. Point mutations in mtDNA-encoded OXPHOS are atypical, which means that they are not inherited maternally in some patients, and they can affect single tissues like skeletal muscle. Several mtDNA and nuclear DNA mutations that cause disease in humans were attributed to common polymorphisms, which suggests that compensatory mutations may have occurred in the same gene or epistatically interacting genes.[57] When a dysfunctional OXPHOS system or mutations of mtDNA impair mitochondrial metabolism, an increase may be observed in mitochondrial biogenesis together with peroxisome proliferator-activated receptor γ coactivator 1α, which compensates for the mitochondrial dysfunction.[58] Furthermore, to better comprehend the partial penetrance of mitochondrial mutations, research has been conducted on nuclear modifier genes often having at minimum two alleles, one aggravating the disease and the other suppressing it. In Figure 2, we summarized the potential scheme of interaction

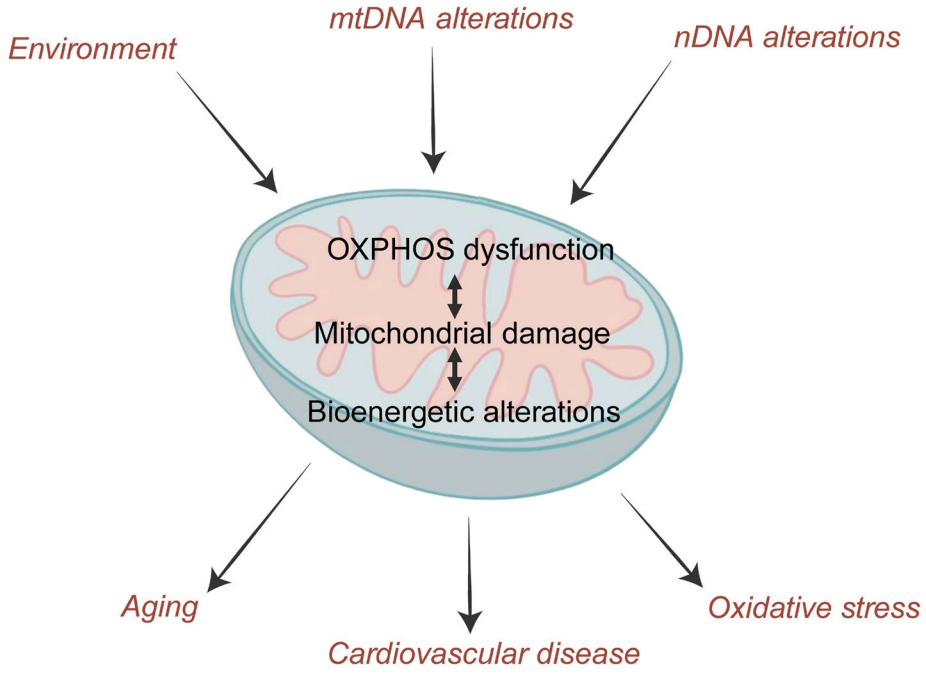

Fig. 2. The scheme of mtDNA mutations and other factors affecting mitochondrial functioning, leads to cardiovascular disease and other detrimental consequences. mtDNA, mitochondrial DNA; nDNA, nuclear DNA; OXPHOS, oxidative phosphorylation system.

of mtDNA mutations, mitochondria functions, and cardiovascular diseases among other detrimental consequences.

MtDNA mutations and heart disorders

Cardiomyocytes, or primary cardiac muscle cells, contain several thousands of mitochondria per cell, which amount to approximately 20–40% of the cell volume. Mitochondrial disorders cause slow deterioration of the infrastructure, limiting the energy supply, which may cause severe complications at localized sites.[59] Thus, mitochondria impair the energy balance, which can be considered both a reason and result of cardiac dysfunction. With the development of technology, it has become possible to identify an increased number of mitochondrial disorders. Recent studies showed that cardiac defects can be closely related to primary and secondary mitochondrial diseases.[60] Genetic disorders can be caused by mtDNA mutations, and a variety of these mutations have been revealed in heart tissue. The disorders are frequently manifested as cardiac muscle fatigue and weakness, and these symptoms are often missed by clinicians. While patients with the same mtDNA mutation may show different cardiac phenotypes, mtDNA mutations may differ among patients who demonstrate similar cardiac impairments.[61] Furthermore, even similar mtDNA mutations can manifest diverse characteristics or phenotypes, such as occurrence, onset age, sex distribution, affectation of other organs, or affectation of cardiac tissue by the mutation. More comprehensive and up-to-date information is available in resources such as the MitoMAP database, Support, and Advocacy groups, researcher and patient forums, and data analysis pipelines. The three main groups of patients with mtDNA mutations linked with cardiac disorders include arrhythmia, cardiomyopathy (CM), and asymptomatic patients.[62] Cardiac diseases that involve mtDNA mutations, also with mtDNA depletion, may present as structural impairments, functional lesions, or both. In children with mitochondrial disorders, the occurrence of CM is over 20–40%. Hypertrophic CM is more frequent (40% of patients) than dilated CM among cardiac disorders related to mtDNA mutations.[63,64] Cardiomyopathies associated with mitochondrial disorders also manifest as left ventricle non-compaction, dilated, histiocytoid, or restrictive CM. They may also involve endocardial fibroelastosis. While histiocytoid CM was previously considered to be caused by a Purkinje fibers abnormality in the cardiac conduction system, it is now regarded as a primary genetic CM, since it is manifested as a mitochondrial impairment resulting from mtDNA mutation.[65]

Cardiac manifestations related to mitochondrial impairment can be classified as hereditary or sporadic diseases. While mitochondrial disorders linked with neurodegeneration or other neurological pathology are usually symptomatic, the onset age for mitochondrial disorders resulting from nuclear gene mutations is early childhood, and diseases resulting from mtDNA mutations become noticeable in late childhood or later in life.[66,67] The occurrence of mitochondrial diseases in children supports the hypothesis that such diseases can affect any tissue and manifest various signs in the course of life. Mitochondrial diseases in children involve progressive cardiac, neurological, and liver impairment and are generally more severe compared with those in patients with onset at adult age.[68]

The clinical symptom outbreak, phenotypic variance, and varying penetrance of mitochondrial disorders depend on numerous factors. First, in the presence of heteroplasmy, the minimal critical percentage of mutated mtDNA must be 60–90% of wild-type DNA before biochemical disorders and tissue dysfunctions are detectable.[69] There is a poor correlation between the severity of clinical symptoms and mtDNA mutation proportion, which explains such a difference in the patients' threshold level. Second, mitochondria in eukaryotic cells differ genetically; thus, during mitosis when eukaryotic cells segregate randomly and generate cells, some contain only mutant or only non-mutant organelles. The mtDNA mutation proportion is different in different cells because mitochondria and their DNA replicate continuously.[70] Third, during aging, mutations in mtDNA can reach especially high levels in non-dividing cells like neurons or muscle cells. MtDNA replication can be perturbed as a result of random intracellular drift, which leads to clonal expansion of single mutations with age.[71] Finally, in germline cells, there is the so-called mtDNA bottleneck phenomenon. MtDNA aggregates or nucleoids may also be responsible for quick changes in the frequency of the mtDNA allele from generation to generation. Mitochondrial diseases induced by nuclear genes affecting the mtDNA stability with both cellular genomes involved are particularly interesting.[72] Thus, primary nuclear gene defects can lead to secondary mtDNA losses or deletion formations. Mitochondrial manifestations caused by a nuclear gene defect sometimes look like those induced by mtDNA mutations. However, they follow a Mendelian type of inheritance, such as paralysis of the eye motor nerves and autosomal dominant progressive external ophthalmoplegia.[73] Factors such as mtDNA heteroplasmy often meet low correlation between genotype and phenotype in individuals, and the complexity of nucleus-mtDNA interactions makes it very difficult to precisely predict or interpret from mtDNA mutation to impairment.

mtDNA in various cardiovascular diseases

mtDNA mutations can be grouped according to their mechanism of action. Mutations in tRNA destabilize base pairing in affected areas, potentially changing the secondary structure of this tRNA and causing its faster degradation and subsequent decrease in the level of mitochondrial protein. Mutations in OXPHOS components decrease ATP synthesis and increase ROS production. Mutations in the D-loop interrupt the normal process of mtDNA replication, resulting in a decrease in the number of mtDNA copies.[13]

Hypertension

Hypertension (high blood pressure) is a common public health problem affecting more than 1.28 billion people worldwide. Recent studies have identified multiple mtDNA mutations associated with hypertension and the results suggested maternal transmission. A large-scale study in 2007 determined the proportion of mitochondria-mediated cases among the pedigrees of hypertensive patients at 35.2%.[14] Notably, in northern China, the number of hypertension cases is much higher than the average. Thus, most current research on hypertension has been conducted on this ethnic group (Chinese, Han Chinese, and Mongol-Chinese); in other ethnic groups, the incidence of hypertension may have a different rate and proportion of mitochondria-mediated maternal transmission.[15]

Ischemic stroke

Ischemic stroke (IS) is a multifactorial disease characterized by the sudden loss of blood circulation in a region of the brain due to stenosis or occlusion of a cerebral artery, resulting in cerebral ischemia, hypoxia, or necrosis. Oxidative stress, energy disturbances, excitatory amino acid toxicity, neuroinflammation, and nerve cell death are induced by cerebral ischemia and form a complex network leading to subsequent damage.[16] Mitochondrial dysfunc-

tion is involved in neuronal death and oxidative damage in neurodegenerative and cardiovascular diseases by triggering several molecular mechanisms leading to vascular dysfunction. The identified mtDNA variants can be used as diagnostic and predictive biomarkers of IS. Similarly, the identified IS protective mtDNA mutations may be useful in further studies to better understand the etiology of IS.[17]

Potential therapeutic strategies for CVD treatment

Studying the mechanism of mitochondrial dysfunction in vascular diseases is a challenging task for developing strategies for influencing mitochondria in cardiovascular diseases. One of the promising approaches is mtDNA editing. Mitochondrial gene editing includes four potential approaches: mitochondria-targeted restriction endonuclease technology, zinc finger nuclease technology, transcription activator–like effector nuclease technology, and the CRISPR/Cas9 system.[18] MtDNA editing is a promising therapeutic option for the treatment of heteroplasmic or mutant mtDNA diseases. This approach could theoretically reduce the disease-causing mutation load below a threshold and is a potential mtDNA targeting strategy for the treatment of CVD due to mitochondrial dysfunction and mtDNA mutations.[19]

Another approach is mtDNA replacement therapy. mtDNA replacement therapy is the use of enucleated donor embryos as a source of healthy mtDNA to replace unwanted defective/mutated mtDNA to prevent maternal mitochondrial inheritance. mtDNA replacement therapy is a form of *in vitro* fertilization that includes spindle transfer, prokaryotic transfer, and polar body transfer.[20] Human nuclear transplant embryos may contain low levels of mutant mtDNA, which suggests this source may be suitable for the treatment of degenerative diseases caused by mtDNA mutations. This opens up the possibility of MRI in CVD, a chronic non-communicable degenerative disease. Hyslop *et al.* developed a prokaryotic transfer protocol that promotes efficient development at the blastocyst stage by keeping mtDNA remnants as low as possible.[21]

Conclusion

In this review, we summarized data on the role of mitochondrial mutations in aging and oxidative stress. Based on the specifics of mtDNA inheritance, it is clear that the balance between the number of mutant and "healthy" mtDNA copies in a cell plays a decisive role. TFAM and DNA Polγ are the main factors moderating metabolism, and mutations in these genes are likely associated with oxidative stress and aging. Disturbances in these genes can lead to heart failure in transgenic mice. Due to the complexity of aging, it is very difficult to define the main mutations since each gene plays its role and affects the processes of inflammation, oxidative stress, and the formation of certain cardiovascular diseases. Research is additionally complicated by the number of mtDNA copies.

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Conflict of interest

ANO has been an editorial board member of *Gene Expression* since June 2023. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interests.

Author contributions

ANO and AVP: study concept and design; AVP: drafting of the manuscript; VNS, SSK, AVG and MAP: critical revision of the manuscript for important intellectual content; ANO and VNS: study supervision. All authors have significantly contributed to the study and approved the final manuscript.

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