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Mitochondrial DNA Mutations and Cardiovascular Disease

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Abstract

Purpose of Review—Cardiovascular disease (CVD) is responsible for more morbidity and mortality worldwide than any other ailment. Strategies for reducing CVD prevalence must involve identification of individuals at high risk for these diseases, and the prevention of its initial development. Such preventative efforts are currently limited by an incomplete understanding of the genetic determinants of CVD risk. In this review, evidence for the involvement of inherited mitochondrial mutations in development of CVD is examined.

Recent Findings—Several forms of CVD have been documented in the presence of pathogenic mitochondrial DNA (mtDNA) mutations, both in isolation and as part of larger syndromes. Other “natural” mtDNA polymorphisms not overtly tied to any pathology have also been associated with alterations in mitochondrial function and individual risk for CVD, but until very recently these studies have been merely correlative. Fortunately, novel animal models are now allowing investigators to define a causal relationship between inherited “natural” mtDNA polymorphisms, and cardiovascular function and pathology.

Summary—Cardiovascular involvement is highly prevalent among patients with pathogenic mtDNA mutations. The relationship between CVD susceptibility and “natural” mitochondrial DNA polymorphisms requires further investigation, but will be aided in the near future by several novel experimental models.

Keywords

Cardiovascular disease; mitochondria; mitochondrial DNA; haplogroup; reactive oxygen species; metabolism; bioenergetics

Introduction

Cardiovascular disease (CVD) refers to a class of related disorders that affect the circulatory system. Despite diverse clinical manifestations, these diseases are nonetheless profoundly connected in that the damage generated by one often causes the onset of another. For example, clinically silent forms of CVD, such as hypertension and atherosclerosis, often develop over time and can trigger onset of acute ischemic diseases, such as myocardial

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infarct and stroke [1]. Damage to the heart resulting from either these ischemic events or spontaneous cardiomyopathies can then give rise to arrhythmias and heart failure [2, 3].

Oxidative stress secondary to alterations in mitochondrial function has been repeatedly documented in the setting of CVD [4]. High circulating cholesterol, hyperglycemia, physical inactivity, cigarette smoke exposure, and increased age are all known to increase risk of CVD [5]. Interestingly, each of these risk factors also perturbs mitochondrial function and elevates oxidant production [6, 7]. In this manner, mitochondrial dysfunction and excessive oxidant production have been directly implicated in hypertension, atherosclerosis, myocardial reperfusion damage following ischemia, and heart failure [7–9].

While a role for mitochondrial dysfunction in CVD etiology is established, the role of the mitochondrial genome in this process has not been extensively investigated. Of note, family history and race/ethnicity is known to influence CVD risk, suggesting that there is a heritable modulator of CVD susceptibility [10, 11]. However, attempts to link CVD risk with nuclear gene variation have yielded a seemingly incomplete picture of the genetic underpinnings of this disease [12, 13]. Evidence has recently arisen that naturally occurring variation on the mitochondrial DNA (mtDNA) may play a role in this regard. More specifically, certain inherited mtDNA polymorphisms not directly tied to any form of pathology are now believed to be capable of influencing mitochondrial function [14]. Given the importance of this organelle in CVD, it is possible that mitochondrial genes may represent the long sought after genetic contributor to CVD risk. Furthermore, these mtDNA polymorphisms often vary across different racial and ethnic groups, and therefore offer a genetic explanation for the racial and ethnic disparities observed in CVD risk [10, 15]. This review will summarize the existing evidence that links CVD development with two forms of inherited mitochondrial alterations: mutations known to be pathogenic, and mutations that are currently viewed as non-pathogenic “natural” polymorphisms which nonetheless may alter CVD susceptibility.

The Mitochondrial Genome

Mitochondria are multifunctional organelles descended from an ancient endosymbiotic relationship between primitive prokaryotic host cells and an aerobic α -proteobacteria [16]. Over the course of evolution, the majority of these proteobacteria genes were transferred to the nucleus of the host. However, a remnant of the original α -proteobacteria genome exists in the form of the small, circular, double-stranded mitochondrial DNA which resides on the matrix side of the mitochondrial inner membrane [16, 17].

Far from an obsolete relic of the past, the mammalian mtDNA genome contains 13 functional protein coding genes which encode essential catalytic subunits for electron transport complexes I, III, IV, and ATP synthase [15]. It also encodes its own translational machinery, including the mitochondrial 16S and 12S rRNAs and 22 tRNAs used for mitochondrial protein synthesis. Due to its extra-nuclear localization, the mitochondrial genome does not obey Mendelian laws of inheritance associated with autosomal genes, but instead follows a maternal pattern of inheritance [15].

There are typically 2–10 copies of mtDNA present per mitochondrion, resulting in 100's – 1000's of mtDNA copies per cell [10, 15]. This plurality means that mutations in mtDNA encoded genes are often present in a heterogeneous mixture within each cell, referred to as “heteroplasmy” [18]. As a consequence, the ability of an mtDNA mutation to have phenotypic consequences is directly related to its prevalence in the mixture, along with the exact nature of the mutation (e.g. missense, frameshift, stop) and the severity of its impact on mitochondrial function [18]. In addition, the specific energy requirements of the parent cell or tissue are also vital in determining the phenotypic influence of any mtDNA alteration. Highly oxidative tissues such as the brain, heart, skeletal muscle and endocrine system are quite sensitive to changes in mitochondrial function, and will display changes in function prior to other tissues less reliant upon mitochondrial function given similar levels of heteroplasmy [18]. These many variables make it difficult to predict the exact level of heteroplasmy required for any mtDNA mutation to influence cell or tissue phenotype. Further complicating matters, heteroplasmy levels often vary between tissues within the same individual due to random segregation of mtDNAs into mature tissues during embryonic development [18].

Maternally Inherited Pathogenic Mutations+

Pathogenic mtDNA mutations are believed to cause disease in 1 of every 5000 individuals [19]. However, the existence of mtDNA heteroplasmy causes significant variation in penetrance and clinical presentation, making these diseases difficult to identify and diagnose [18]. As discussed above, certain tissues are more predisposed to the effects of mitochondrial disease. Due to its reliance on oxidative phosphorylation for ATP, the heart is frequently affected. It is estimated that as many as 40% of victims of mitochondrial disease display cardiovascular involvement [20, 21]. These symptoms can occur either in isolation, or as a component of multisystem disease.

Mitochondrial Cardiomyopathy and Heart Failure

Cardiomyopathy is the most common form of CVD seen mitochondrial disease patients [22]. Its occurrence in this population has already been reviewed extensively, and it will be discussed here only briefly [21–23]. Cardiomyopathy has been recorded to occur in ~25% of adult patients with mitochondrial disease [24]. Recently, a larger study of 260 patients reaffirmed these earlier findings, documenting cardiomyopathy at a rate of 20% in adults with assorted mitochondrial diseases [25**]. Of the different mitochondrial syndromes, Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) is most strongly associated with cardiomyopathy, especially when associated with m.3243A to G mutation in the mtDNA encoded tRNA^{Leu}. This was confirmed in the 260 patient study by Wahbi et al. which demonstrated the presence of cardiomyopathy at a rate of 37% in MELAS patients [25**]. In contrast, only 14% of non-MELAS patients displayed cardiomyopathy in the same study. Several studies have also identified the presence of cardiomyopathy alongside non-syndromic single complex deficiencies. These include cases involving mitochondrial DNA mutations effecting complexes I, III, IV, as well as mutations in the 16S and 12S rRNAs [26–31].

Mitochondrial disease patients typically first present with cardiomyopathy, which then progresses into heart failure [22]. However, there is evidence that ventricular dysfunction and heart failure can occur in isolation, albeit rarely. In a 32 patient study by Malfatti et al., a single individual with ventricular dysfunction in the absence of hypertrophy was identified [32]. Furthermore, of the 260 patients observed by Wahbi et al., isolated left ventricular dysfunction with depressed ejection fraction was present at a rate of 4% [25**]. This suggests that the mitochondrial dysfunction due to mitochondrial disease is capable of causing heart failure in the absence of overt structural alterations, possibly in accordance with the energy starvation hypothesis [33].

Arrhythmias and Conduction Defects

Arrhythmias and conduction defects are another common cardiac manifestation of mitochondrial disease [22]. As with cardiomyopathy, these cardiac symptoms appear to be strongly associated with the m.3243A > G mutation, and several studies have noted asymptomatic sinus arrest, atrial fibrillation, Wolf-Parkinson-White, AV block, bundle-branch-block, and ventricular tachyarrhythmias (VTs) in patients with MELAS [32, 34, 35]. Conduction defects, most notably AV-Block, are also commonly seen in Kearns-Sayre syndrome (KSS) due to mtDNA deletions, and are viewed as pathognomonic [36–38]. KSS patients may also present with *torsades de points* and other VTs [39–40]. Finally, WPW is a common component of Myoclonic epilepsy and ragged-red fiber (MERFF) disease, a disease associated with a mutation in the mtDNA encoded tRNA^{Lys} gene [41].

As with heart failure, arrhythmias and conduction defects often arise secondary to cardiomyopathy in mitochondrial disease patients. However, there is also evidence that they occur in isolation – a Chinese study found arrhythmias to be present at rate of 22.2%, as opposed to only 5.6% for cardiomyopathy [42]. More recently, Wahbi et al. observed conduction defects at a high frequency in a cohort of 260 patients. Overall, 26% of patients presented with arrhythmias or conduction defects [25**]. Importantly, this number again exceeded those with diagnosed left ventricular hypertrophy or dysfunction (24%), indicating that mtDNA mutations can give rise to arrhythmias directly.

Diseases of the Vasculature

Several studies have linked pathogenic mtDNA mutations with vascular pathology (Table 1). Pulmonary hypertension, aortic dilation, aortic rupture and carotid stenosis have all been associated with several forms of mitochondrial disease [43–49]. Numerous studies have also associated mtDNA mutations with maternally inherited hypertension and atherosclerosis [50–59]. Recently, Jia et al described a mitochondrial tRNA^{Thr} G15927A mutation that associated with early onset coronary artery disease in a Han Chinese family [56]. Subsequent studies have identified additional mutations in the mitochondrial tRNA^{Thr} and tRNA^{Gln} genes associated with both coronary artery disease and hypertension [57]. Finally, Jiang et al. identified a mutation in the mitochondrial tRNA^{Ala} gene [58*]. This mutation also appears to significantly segregate with maternally inherited hypertension.

Non-Pathogenic Mitochondrial DNA Polymorphisms

The vast majority of mitochondrial genetic variation is not directly tied to pathogenesis of any disease. Instead, different individuals commonly possess co-inherited groups of “natural” mitochondrial DNA polymorphisms, referred to as a haplogroup [15]. Interestingly, the mitochondrial genome does not undergo any form of DNA recombination, and its relative stability enables clustering of similar mitochondrial haplogroups based on their shared maternal ancestry [15, 60]. These clusters are often associated with different racial and ethnic groups, and have been used for decades in molecular anthropology studies to study population dynamics, geographic origins and prehistoric migration patterns of human populations [61, 62]. More recent work suggests that these genetic differences may encode fundamental alterations in the function of the mitochondrion [15].

The Origin of Mitochondrial Haplogroups

It is now known that all contemporary human haplogroups worldwide are genetically descended from haplogroup L, which is endemic to the continent Africa [10, 15]. In prehistoric Africa, it has been hypothesized that the mitochondrial electron transport chain had evolved to maximize the utilization of caloric energy (electron flow) for ATP production since low calorie carbohydrates were the primary source of energy [10]. As early humans migrated northward “out of Africa”, they encountered colder climates and animal fats became a more common component of their diets [63, 64]. This change to a higher calorie diet provided a means for “tolerating” mtDNA mutations that generated new haplogroups and increased the production of heat (energy loss) at the expense of ATP production during electron transport [65–67]. In turn, this greater generation of heat may have conferred a survival and/or reproductive advantage in the face of frigid weather [15, 67]. Data indicating that haplogroups from northern latitudes display a greater frequency of mtDNA missense mutations relative to their African counterparts are consistent with this hypothesis, and moreover, these mutations occur in portions of mitochondrial genes that are highly conserved in African L haplogroups [15, 67]. Interestingly, a consequence of these prehistoric selection events is that different human haplogroups may retain differences in mitochondrial function, and that these differences in mitochondrial function may influence susceptibility to disease [10, 15].

Mitochondrial Haplogroups and Disease Susceptibility

Modern human society is increasingly characterized by reduced physical activity and calorically excessive diets [68, 69]. This lifestyle fosters a positive energy balance that favors oxidant production, and has been hypothesized as a growing cause of cardiovascular disease [70–78]. Reactive oxygen species are normally produced as a byproduct of ATP production within the mitochondria [10]. In this manner, the prehistoric mutations at northern latitudes which fostered heat generation by the mitochondria at the expense of ATP may have also reduced their proclivity for generation of oxidants [10]. As a result, these mitochondrial polymorphisms may influence onset of cardiovascular disease, and explain disparities in CVD risk amongst different human populations.

Several studies have linked mtDNA sequence variation to mitochondrial and cardiovascular function [14, 15]. Mitochondria bearing haplogroup H polymorphisms have been observed to possess elevated basal oxygen consumption and oxidant production relative to other European haplogroups, especially haplogroup J [79, 80]. Furthermore, these differences appear to correlated with CVD risk [81–83]. Similarly, Haplogroup T appears to be an independent risk fact for coronary artery disease [84]. In addition, several haplogroups in both Europe and Asia have been associated with increased longevity, likely via reduced oxidant generation which is a driver of the aging process [85–90].

A recent study also attempted to correlate mtDNA haplogroups with the disparity in CVD risk observed between Caucasians and African Americans in the United States [91**]. This study found that fundamental differences in oxygen utilization, maximal respiratory capacity, and oxidant production, exist between human umbilical vein cells (HUVECs) isolated from individuals of haplogroups H (Caucasian) and L (African). Furthermore, peripheral blood from adults in the same study revealed that individuals of African mitochondrial ancestry display a greater burden of mtDNA damage, diminished vascular function, increased pathologic vascular remodeling, and earlier onset of coronary artery disease relative to Caucasians. Unfortunately, these human studies are limited to cells and tissues that differ at both the nuclear and mitochondrial level, rendering them correlative at best. However, several animal models have been recently designed that are capable of defining causal relationships between mitochondrial DNA and cardiovascular function.

Animal Models

Different inbred strains of laboratory mice and rats possess their own unique DNA haplogroups reminiscent of those seen in human populations [92, 93]. Houšť k et al. were the first to report that these mtDNA polymorphisms could influence phenotype in rats [94]. In these studies, congenic rats were generated that possessed the nuclear genome of the Spontaneously Hypertensive Rat (SHR) strain coupled with the mitochondrial genome of a F344 rat strain. In these studies, the F344 mitochondrial genome had small but significant effects on cardiac hypertrophy, endo-systolic diameter, and fractional shortening in the setting of pathologic hypertension [94].

More recently, Latorre-Pellicer et al. used backcrossing to similarly generate congenic C57/BL6 mice harboring a NZB mitochondrial genome (Figure 1A) [95**]. Compared to C57BL/6 wild type mice, the mice possessing the NZB mtDNA showed alterations in mitochondrial oxygen consumption, cellular ATP levels, mitochondrial oxidant production, and mtDNA/nDNA ratio in the heart. Gene expression differences were also present, most notably with regards to “carbohydrate and lipid metabolism”. Furthermore, C57BL/6 mice harboring an NZB mitochondria displayed increased size and content of lipid droplets within their cardiomyocytes, evidence that fundamental differences in lipid metabolism were present. Finally, differences in mitochondrial dynamics within the hearts of these animals were also observed. These studies show that altering mitochondrial genetic background in laboratory mice results in fundamental differences in physiology and oxidant production within the heart. However, these studies are limited in that they never show or describe any

influence on pathology. Also, their technique for derivation of these mice leaves open the opportunity for nuclear genetic drift which could influence their findings.

A second study by Fetterman et al. has helped address some of these issues and further added to the evidence that mitochondrial DNA polymorphisms can influence heart physiology and pathology [96]. The mice in this study were generated using a novel technique referred to Mitochondrial-Nuclear-eXchange (MNX) that resembles the pro-nuclear transfer technique currently in used with human embryos, making it a relevant model system for current mitochondrial health issues (Figure 1B) [97, 98]. Furthermore, it spontaneously generates mice which possess shared nuclear backgrounds, but differing mitochondrial genomes. Thus, it avoids the common caveats associated with the breeding of congenic animals.

In their study, Fetterman et al. generated both C57BL/6 animals with a C3H/HeN mitochondrial genome, as well as C3H/HeN animals with a C57BL/6 mitochondrial genome [96]. The C57BL/6 and C3H/HeN mtDNAs were chosen for comparison in these studies due to the differing susceptibilities of these two inbred mouse strains to atherogenesis [99]. Interestingly, several bioenergetic and metabolic parameters in these animals segregated exclusively with the mitochondrial genetic background. Cardiac mitochondria from animals harboring the C3H/HeN mtDNA consumed a greater amount of oxygen for ATP production irrespective of their nuclear genetic identity. In addition, cultured cardiomyocytes derived from animals harboring C3H/HeN mitochondrial were also found to have reduced mitochondrial membrane potential and oxidant production. Finally, the C3H/HeN mtDNA background also appeared to be remarkably protective in the setting of acute heart failure, which caused pronounced mitochondrial swelling and myofibrillar degeneration in animals harboring C57BL/6 mitochondria.

Conclusion

From the literature it is clear that inherited pathogenic mtDNA mutations can trigger onset of several forms of CVD. However, the role that “natural” non-pathogenic mtDNA mutation play in this regard is still incompletely understood. Past studies have been limited by a lack of animals models capable of establishing a causal relationship between mtDNA polymorphisms and disease phenotype. However, the development of novel animal models in recent years may not only prove such a relationship exists, but also be capable of defining the biochemical and cellular mechanisms through which it is possible.

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Summary

- Cardiovascular complications are commonly associated with pathogenic mtDNA mutations and/or damage.
- Mitochondrial genetics is complex, characterized by maternal inheritance and heteroplasmy; due to these features mtDNA mutations can have a varying effects upon cellular/tissue function related to the distribution of mtDNA mutations and the reliance of that organ on mitochondrial function.
- “Natural” mtDNA variation can be linked with changes in mitochondrial function and may influence individual susceptibility to CVD.

Figure 1. Derivation of congenic animals versus the Mitochondrial-Nuclear-eXchange (MNX) technique

Congenic animals (A) were recently used to study the role of mitochondrial genetic variation on mouse phenotype. Parental C57 male and NZB female animals were bred to produce C57/NZB hybrid F1 animals harboring the NZB mtDNA of the mother. F1 females were then backcrossed against parental C57 males to yield offspring bearing a greater proportion of C57 nuclear alleles. Female hybrids were subjected to 19 additional rounds of backcrossing to generate animals which effectively possess the C57 nuclear genome, but retain the mitochondrial genome of the parental NZB female. By comparison, MNX mice (B) are derived via the enucleation of a mouse zygote, and subsequent insertion of a nucleus from a different strain of mouse in its place. The zygote and resulting animal retain the mitochondrial genome of the original zygote, but possesses the nuclear genome of the transferred nucleus without any need for backcrossing. Pictured is the derivation of a C57^{nuclear}.C3H^{mito} MNX mouse.

Table 1

Vascular manifestations associated with pathogenic mtDNA mutations.

Vascular Manifestation	Associated Mutation	Clinical Syndrome	Reference
Aortic Rupture	m.A3243G in tRNA ^{Leu}	MELAS	Tay et al. 2006 [44]
Pulmonary Hypertension	m.A3243G in tRNA ^{Leu}	MELAS	Sproule et al. 2008 [45]
Carotid Artery Stenosis	m.G617A in tRNA ^{Phe}	Non-Syndromic	Iizuka et al. 2009 [46]
Aortic Root Dilation	7.44 kb mtDNA deletion	CPEO	Brunetti-Pierri et al. 2011 [47]
Pulmonary Hypertension	m.A3243G in tRNA ^{Leu}	Non-Syndromic	Hung et al. 2012 [48]
Pulmonary Hypertension	m.A3243G in tRNA ^{Leu}	CPEO	Liu et al. 2012[49]
Essential Hypertension	m.T4291C in tRNA ^{Ile}	Non-Syndromic	Wilson et al. 2004 [50]
Impaired FMD	m.A3243G in tRNA ^{Leu}	MELAS	Koga et al. 2006 [51]
Essential Hypertension	m.A4435G in tRNA ^{Met}	Non-Syndromic	Lu et al. 2011 [52]
Essential Hypertension	m.A4263G in tRNA ^{Ile}	Non-Syndromic	Wang et al. 2011 [53]
Essential Hypertension	m.T4353C in tRNA ^{Glc} m.C593T in tRNA ^{Phe} m.C5553T in tRNA ^{Trp}	Non-Syndromic	Qiu et al. 2012 [54]
Essential Hypertension	m.A1555G in 12S rRNA	Deafness	Chen et al. 2012 [55]
Coronary Artery Disease	m.G15927A in tRNA ^{Thr}	Non-Syndromic	Jia et al. 2013 [56]
Coronary Artery Disease	m.T5592C in tRNA ^{Gln} m.G15927A in tRNA ^{Thr}	Non-Syndromic	Qin et al. 2014 [57]
Essential Hypertension	m.A8701G in ATP6	Non-Syndromic	Zhu et al. 2016 [58]
Essential Hypertension	m.A5655G in tRNA ^{Ala}	Non-Syndromic	Jiang et al. 2016 [59]

Abbreviations: MELAS, Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes, CPEO, chronic progressive external ophthalmoplegia.