Clinical Research

Mitochondrial DNA mutation in essential hypertension

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Abstract Essential hypertension (EH) is an escalating problem for developed and developing countries. It is currently seen as a ‘complex’ genetic trait caused by multiple susceptibility genes which are modulated by gene-environment and gene-gene interactions. Over the past 10 years, mitochondrial defects have been implicated in a wide variety of degenerative diseases, aging, and cancer. Recently several studies showed that human essential hypertension has excess maternal transmission which suggests a possible mitochondrial involvement. However, the exact pathophysiology of mitochondrial DNA mutation (mtDNA) in essential hypertension still remains perplexing. With the application of a variety of imaging approaches and successive mouse model of mitochondrial diseases we convince that these problems will be resolved in the near future.

(Key Words) mitochondrial DNA, essential hypertension, maternal, genetic trait, modulated

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Introduction

The diseases caused by mitochondrial dysfunctions first described 40 years ago have become an important field of human pathology. This area has seen striking developments in the past fifteen years as a result of the elucidation of the structure and function of the human mitochondrial genome and the first understanding of inherited Leber’s hereditary optic neuropathy (HON) resulting from pathogenic mitochondrial DNA (mtDNA) deletions and point mutations. By far almost 100 mtDNA point mutations, a large number of mtDNA rearrangements (including large deletions and duplications) and more recently, as well as numerous nuclear gene mutations have been shown to be associated with a variety of disorders affecting the skeletal muscles, the brain, the heart, the liver, the cochlea and other organs. Dysfunctional mitochondria seem to contribute to the pathophysiology of hypertension, cardiac failure, the metabolic syndrome, obesity, diabetes mellitus, renal disease, atherosclerosis, and aging. And the advances in our knowledge of the basic processes, in turn, have provided new insights into the way in which alterations in the processes caused by mitochondrial mutations, result in pathological or aging-related phenotypes.

Essential hypertension, accounting for 95% of all cases of hypertension, affects over 50 million adults in the United States and approximately 1 billion individuals worldwide. Hypertension is also a major risk factor for coronary heart disease, stroke, congestive heart failure and renal disease. Currently EH is regarded as a multifactorial disease, the onset and severity of which are influenced by both genetic and environmental factors. The role of genetic factors in the etiology of hypertension is supported by cross-sectional studies that document familial aggregation of the disorder despite different environmental factors. Estimates of genetic variance range from 20–50%. The findings of both maternal pattern as mother–children and paternal pattern as father–children have all been reported. Significant BP correlations between mothers and offspring or excess maternal transmission of hypertension have been noted in several early investigations, whereas such correlations between fathers and offspring were either marginal or absent in these studies. Here we concluded the contribution, epidemiology and pathophysiology et al. of pathogenetic mtDNA mutation in essential hypertension.

EH with maternal inheritance in Framingham Heart Study

As we all know that mitochondria (containing thousands of mtDNAs) within each cell’s cytoplasm are transmitted through the oocyte’s cytoplasm at fertilization and thus are strictly maternally inherited. Yang et al. reported the result of the investigation of the contribution of mitochondrial genome to hypertension and quantitative blood pressure (BP) phenotypes in the Framingham Heart Study cohort. In this study they included 6421 participants from 1593 families for SBP and 4409 participants for DBP. For the 6421 participants (46% were men) the mean age of participants was 53, the mean long-term averaged SBP/DBP was 136/82mmHg. For the 4409 participants used in the analysis of DBP, the mean age was 44.8, the mean long-term averaged SBP/DBP was 128/81mmHg. The proportion of individuals with hypertension (defined as SBP of at least 140mmHg or DBP of at least 90mmHg or current drug treatment for high BP present) among participants with long-term averaged SBP and DBP was 42 and 34%, respectively. They used the method described by Sun et al. to do vari-
ance components analyses of quantitative BP on 6421 participants from 1593 families, including 2447 mother–child pairs, 3061 sibpairs, 65 maternal grandparent–grandchild pairs, 1094 maternal avuncular pairs and 375 maternal first-cousin pairs. Estimated heritability effect of maternal trait (mitochondrial) was 5% for multivariable-adjusted long-term average SBP. The heritability of DBP due to maternal effects was 4%.

Clinical studies of EH associated with mtDNA mutation

Dr. Watson et al. 30 investigated 58 black Americans who have both hypertension and progressed end-stage renal disease (H-ESRD) to assess the possible contribution of mtDNA mutation to susceptibility to hypertension. They used high-resolution restriction analysis 31,32,33 and found six variants as A10398G mutation in the ND3 gene, HaeIII T6620C/G6260A double mutation in the CO1 gene, G2758A mutation in the 16S rRNA gene, T10810C in the ND4 gene, G7028A/T7055C double mutation in the CO1 gene and A10086G in the ND3 gene were significantly higher in the H-ESRD cohort than control. They thought these mtDNA point mutation could possibly contribute to part of susceptibility to hypertension in black Americans who have progressed to ESRD. This is the first report potentially suggests that mtDNA mutation might be a modulator in hypertension. Later after that Shoji et al. 34 investigated single nucleotide polymorphisms (SNPs) in a hypervariable segment of the mitochondrial control region in Japanese hypertension cohort. They found the C16223T genotype was more frequent in hypertensives than normotensives but no significant difference in C16362T variant frequency between the groups. They concluded mtDNA SNPs were enriched in Japanese hypertension and mtDNA C16223 genotype may be one of the genetic susceptibility factors for hypertension. Liu et al. 35 also found mtDNA variation and frequency and density in D-loop region of EH patients were higher than normotensive cohort and patients with polymorphism changes at mitochondrial 152 and 16189 sites could be possibly susceptible to hypertension. More importantly in 2004 Dr. Wilson et al. 36 reported a Caucasian kindred involved 142 relatives presented a cluster of syndrome as hypertension, hypercholesterolemia and hypomagnesemia, which may be associated with T4291C mutation in tRNA\textsubscript{Ile} gene. They further speculated that the loss of mitochondrial function with aging 37, 38 might commonly contribute to all components of the metabolic syndrome.

Pathogenetic mtDNA mutation in EH

Dyshomeostasis of calcium circle associated with mtDNA mutation in EH

Despite numerous efforts, including recent genetic and molecular biology studies, the exact mechanism of elevated blood pressure (BP) in any kind of hypertension has not been satisfactorily explained. As we know clear that cytosolic free Ca\textsuperscript{2+} concentration is closely controlled and Ca\textsuperscript{2+} is important signals in apoptolic, neuronal and hormonal signaling and secretion of insulin 39. Postnov et al. found the exchangeable intracellular calcium in adipose tissue from SHR 40 and patients with essential hypertension 41 were increased which was contracted with early reports. 42,44 Cytosolic Ca\textsuperscript{2+} could be affected by mitochondrial in two ways. The indirect way is ATP dependent transport of Ca\textsuperscript{2+} out of the cell or into intracellular stores (fig. 2). The direct way is uptake Ca\textsuperscript{2+} into mitochondrial through a Ca\textsuperscript{2+}-uniporter by mitochondrial membrane potential. When ATP synthesis caused by mtDNA mutation decreased or the collapse of mitochondrial membrane potential will lead to accumulation of cytosolic Ca\textsuperscript{2+} or calcium dyshomeostasis. Ca\textsuperscript{2+} overload could lead to conduct disorders in heart, systolic/diastolic dysfunction in smooth muscular and apoptosis.45,46 This may partially explain the pathogenesis of hypertension and arrhythmia associated with mtDNA mutation.

Mitochondrial energy conversion defects caused by mtDNA mutation in EH

Although we have no evidence that decreased production of ATP caused by mtDNA mutation is the pivot of pathophysiologic process, we still could insight into it from other researches. 47 Postnov et al. 48, 49 reported rate of ATP synthesis in SHR was significantly lower than normotensive controls (Fig. 1). Another report of Postnov and his colleagues 50 showed that changes in the ultrastructure of cardiomyocyte mitochondria of SHR was similar to those changes under oxidative phosphorylation uncoupling. Defects in complexes I, III or IV disrupt respiration, decrease the mitochondrial proton electrochemical potential gradient and prevent mitochondrial ATP synthesis. Defects due to large mtDNA deletions or tRNA mutations will disrupt the respiratory chain and decrease the ability to form a proton.

**Fig. 1.** Rate of ATP synthesis in isolated mitochondria from the liver and brain of SHR and WKY rats measured in Ca\textsuperscript{2+}-free medium. *p < 0.01. see 48, 49
electrochemical potential gradient as well as the capacity to ATP synthesis. Oxidative phosphorylation defect that completely blocked mitochondrial ATP synthesis would be fatal which has been proved by knocking out transcription factor A (tfatm) in mice. So tissues with variable ATP demand are most susceptible to mtDNA mutation such as pancreatic â-cells which was associated pathogenesis of diabetes. A very important aspect of mtDNA disease is the threshold effect, whereby pathogenic when they were present above a certain level. It is still unclear why the mutant load required to disrupt oxidative phosphorylation varies with cell and tissue type and is also dependent on the nature of the mtDNA mutation (fig. 2).

Besides what we have mentioned above, mitochondrial protein metabolic intermediates participate in other processes. Succinate dehydrogenase also seems to modulate mitochondrial K⁺ transport by taking part in the formation of an inner membrane multiprotein complex that displays ATP-sensitive K⁺-channel activity. Also, cytochrome c participates as a signaling molecule in apoptosis in addition to its key function as a mitochondrial electron carrier. Finally, the citric acid cycle intermediate succinate also acts as a signaling molecule through its binding to G-protein coupled receptors.

Although a variety of hypothesis has been mentioned to explain the mechanism of essential hypertension associated with mtDNA mutation, we still lack concrete data to support these hypotheses. We must clearly realize the complexity of EH with maternal inheritance and fully consider nuclear interaction, environmental factors and ageing et al factors that might have potential action on pathogenesis of EH associated with mtDNA mutation. With development of advanced molecular biochemical methods, especially mouse model of mitochondrial disease, we believe that pathophysiology, prenatal diagnosis, genetic counseling and treatment will become accomplishable in the near future.

**Reference**


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