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Mitochondrial Mutations in Left Ventricular Hypertrophy

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1. Introduction

Left ventricular hypertrophy (LVH) is one of the vicious organ damages of essential hypertension. It contributes a lot to high mortality of essential hypertension due to sudden cardiac death, ventricular arrhythmia and heart failure. Multi-factors involve in the pathogenesis of hypertension-induced LVH including inherited variants as well as environmental factors. For the genetic influence, nucleus' involvement has been discussed for years. However, much fewer interest has been put in the other inherited system—mitochondrion. To make clear the relationship of mitochondria and LVH, we try to illustrate the clinical and pathological characteristics of LVH, the structure and function of mitochondria and mitochondrial role in LVH as follows:

2. Left ventricular hypertrophy

2.1 Definition, diagnostic standard, diversity in phenotypes

Left ventricular hypertrophy (LVH) is a common complication of hypertension (the prevalence varies from 14 to 44% screening by echocardiography)[1] with multiple morphological and pathological characteristics which divide to subgroups as eccentric and concentric, asymmetric and symmetric hypertrophy according to heterogeneity in the pattern and extent of left ventricular wall thickening (see Fig. 1.)

Echocardiography is often used as a sensitive screening and surveillance tool for LVH, especially to concentric and symmetric hypertrophy. Based upon a classic equation deduced by Devereux, R.B. (1987)[2]:

$$LV \text{ mass}=1.04[(IVST+LVID+PWT)^3-LVID^3]0.001-13.6$$

$$BSA=0.006H+0.0128W-0.1529$$

$$LVMI=LVM/BSA$$

Left ventricular mass index (LVMI) over 134g/m² in men and above 110g/m² in women are identified left ventricular hypertrophy.

LVMI≤145 g/m² is considered as mild, 145<LVMI≤165 g/m² as moderate, LVMI >165g/m² as severe[3]. Interventricular Septal Thickness(IVST)/Posterior wall

Thickness(PWT)≥1.3 is considered asymmetric hypertrophy; IVST/PWT≤1.3 identified symmetric; End Diastolic Diameter(EDD)>50mm considered eccentric hypertrophy, EDD<50mm identified concentric hypertrophy. In spite of diversity of phenotype LVH encompassed, the morbidity as well as mortality of cardiovascular events increase when induction of LVH.
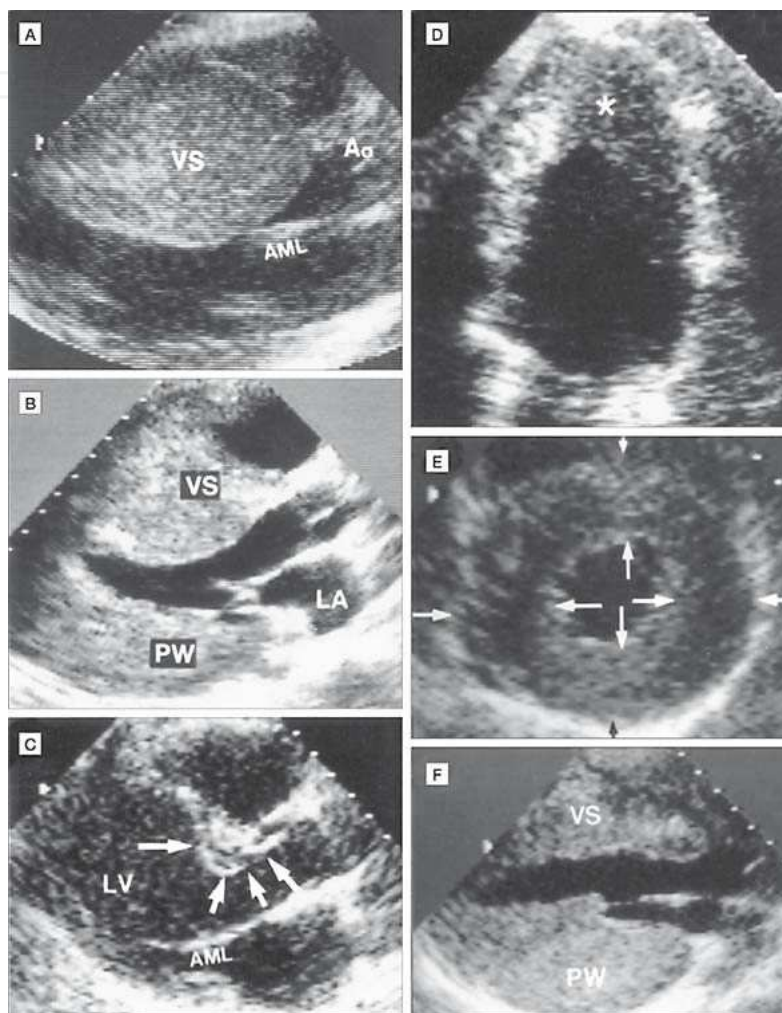

Fig. 1. Heterogeneity in the Pattern and Extent of Left Ventricular (LV) Wall Thickening in HCM Echocardiographic parasternal long-axis stop-frame images obtained in diastole showing A, massive asymmetric hypertrophy of ventricular septum (VS) with wall thickness >50 mm; B, pattern of septal hypertrophy in which the distal portion is considerably thicker than the proximal region at mitral valve level; C, hypertrophy sharply confined to basal (proximal) septum just below aortic valve (arrows); D, hypertrophy confined to LV apex (asterisk), consistent with the designation of apical hypertrophic cardiomyopathy (HCM); E, relatively mild hypertrophy in a concentric (symmetric) pattern with each segment of ventricular septum and LV free wall showing similar or identical thicknesses (paired arrows); F, inverted pattern of hypertrophy in which anterior VS is less substantially thickened than the posterior free wall (PW), which is markedly hypertrophied (i.e., 40 mm). Calibration marks are 1 cm apart. AO indicates aorta; AML, anterior mitral leaflet; and LA, left atrium. Reproduced from Maron BJ. Hypertrophic cardiomyopathy: a systematic review. JAMA. 2002, 287(10): 1308-20.
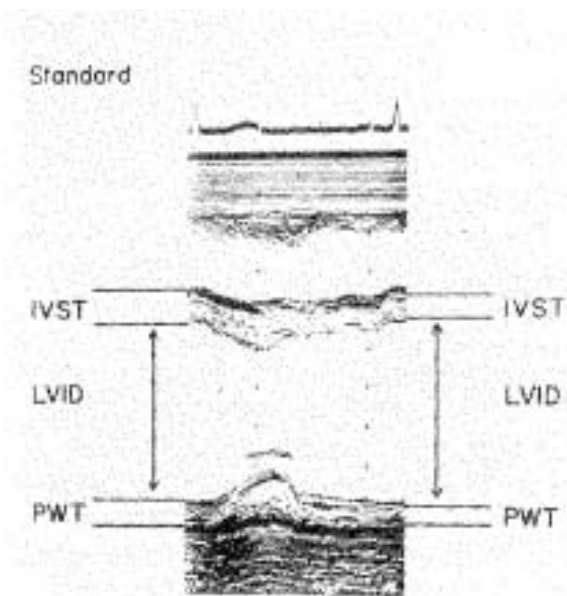
Fig. 2. M-mode echocardiogram of the left ventricle illustrating the standard measurement conventions. IVST= interventricular septal thickness; LVID= left ventricular internal dimension; PWT=posterior wall thickness (Edited from Devereux, R.B. (1987) Detection of left ventricular hypertrophy by M-mode echocardiography. Anatomic validation, standardization, and comparison to other methods. Hypertension., 9 (Suppl II)，II-19-II-26.)

Essential hypertensive patients with left ventricular hypertrophy increase their mortality rates due to all cardiovascular events from 2 to 10 times more than hypertensives without signs of cardiac hypertrophy [4]. Serving as an independent predictor of cardiovascular events in patients with hypertension, LVH is also a prognostic indicator of hypertension. Patients with normal left ventricular geometry have the best prognosis, those with concentric remodeling or eccentric hypertrophy have intermediate, and those with concentric left ventricular hypertrophy are identified the worst prognosis [5].

Given the fact that left ventricular hypertrophy is an end-organ stage of hypertension, scientists have been striving for the pathogenesis and reversal strategies of left ventricular hypertrophy for years.

3. Genetic background

3.1 Nuclear genes

Plethoras of evidences support the hypothesis that multiple nuclear genes contribute to left ventricular hypertrophy[6]. It is identified that LVH is influenced by polygenic mutations susceptibility to hemodynamic disorders such as salt-sensitivity, obesity and insulin-resistance etc. Brendan AI. reported a genetic locus on chromosome 2 of the spontaneously hypertensive rat affects relative LV mass independently of blood pressure [7].Yasuyuki Tsujita indicated both genes on chromosome 7 and 17 that influences LVM in a manner dependent on blood pressure [8]. Interestingly, left ventricular hypertrophy shared the same pathological changes with hypertrophic cardiomyopathy such as myocyte disarray, interstitial fibrosis and artery wall thickness. Moreover, hypertrophic cardiomyopathy can result from mutations in 11 genes that encode sarcomere proteins, loci where genes

encoding contractile, cytoskeletal, and calcium regulatory proteins. Thus, we can rule out the possibility of indicated genes contribute to hypertrophy cardiomyopathy involving in hypertension-induced left ventricular hypertrophy [9].

4. Mitochondrial and left ventricular hypertrophy

4.1 mtDNA mutations

In the early stage of hypertension-reduced LVH, ventricular hypertrophy is an important compensatory response to increased load, accompanied by increased amounts of mitochondria [10], which makes it likely that upregulation of cardiac energy production is a mechanism allowing increased cardiac work. However, the mitochondrial function is impaired and the efficiency of mtDNA ultimately decreases dramatically with time passing by. Then, the equilibrium between oxygen offering and consuming will be broken as mitochondrial energy under specific thresholds. The hypothesis of biogenesis of LVH has been supported by plethora of mtDNA mutations. Majamaa-Voltti K et al [11] reported that 3243A>G mtDNA mutation is associated with LVH. Lin Z, et al [12] found G8584A mtDNA mutation may influence LVH in hypertensives. In particular, several point mutations such as G4284A [13], A4295G [14], A4269G[15], A4317G[15] and A4300G[16] located in tRNA^{Ile} contribute to hypertrophic cardiomyopathy to certain degree. A systematic and extended mutational screening for the mitochondrial genome has been initiated in a large cohort of Chinese population by the Geriatric Cardiology Clinic at the Chinese PLA General Hospital, Beijing, China. Specific mutations within the mitochondria were further evaluated. Changes of tRNAs were measured by northern blotting using nonradioactive digoxigenin (DIG)-labeled oligodeoxynucleotides specific for each RNA. Rates of oxygen consumption in intact cells were determined with av YSI 5300 oxygraph. Sequence analysis of mitochondrial DNA in one Chinese pedigree identified a novel A-G transition at position 4401 (A4401G) at the junction of tRNA^{Met} and tRNA^{Gln}. The non-coding region mutation appeared to affect the processing of precursors in these mitochondrial tRNAs. The reduction in the rate of respiration and marked decreases in the steady-state levels of tRNA^{Met} and tRNA^{Gln} were detected in the cells carrying this mutation. The novel mutation was absent in 270 Chinese control subjects. In conclusion, the non-coding region (A4401G) mutation was involved in the pathogenesis of left ventricular hypertrophy in Chinese hypertensives[17].

MtDNA mutations can divide into rearrangement mutations and base substitutions. And base substitution mutations are subcategorized into missence mutations (protein coding genes alterations) and protein synthesis mutations (RNAs genes changes).

4.2 Rearrangement mutations

Rearrangements of mtDNA due to deletions or duplications generally occur in sporadic patients. Duplications are probably not directly pathogenic, but it produces deleted mtDNA molecules, which implicated into different diseases [18,19]. The most prominent multi-systemic disorders involved in cardiomyopathy are Kearn-Sayre Syndrome (KSS) and Chronic Progressive External Ophthalmoplegia(CPEO) The characteristic symptoms of KSS are cardiac conduction block, cardiomyopathy and caridoembolic stroke with ocular damage including ophthalmoplegia, ptosis, pigmentary degeneration of retina. Compared with cardiac conduction blocks, cardiomyopathy is a much less frequent and late-onset symptom in KSS caused by the relatively low abundance of rearranged mtDNA molecules

in the myocardium. Fromenty and colleagues [20] demonstrated that duplications represented an unusually high proportion (41-91%) of all rearranged molecules in hearts from two KSS patients. Because of the preferential accumulation of duplicated rather than deleted mtDNA molecules, the cardiomyopathy may be relatively spared in KSS.CPEO is another rearrangement mtDNA mutation represents a series of abnormalities covering ocular myopathy, mitochondrial myopathy, renal failure and diabetes mellitus [21]. McComish M found the changes of hypertrophy via endomyocardial biopsy on light microscopy[22].

4.3 Missence mutaions

Leigh's syndrome is a most severe missence mutation with neural, spinal and cardiac defects. Hypertrophic cardiomyopathy, as a kind of cardiac defect of Leigh's syndrome，results from series of genes involving OXPHOS including MTAP6, NARP8993G and A3243G mutation[23]. Missence mutations in the gene that encodes γ-2 regulatory subunit of the adenosine monophosphate-activated protein kinase(PRKAG2) have been reported to cause familial Wolff-Parkinson-White syndrome associated with conduction abnormalities and LVH [24,25].

4.4 Protein synthesis mutations

Myoclonic epilepsy with ragged-red fibers (MERRF) is most frequently caused by an A8344G mutation in the tRNA^{Lys} gene. In a review of 62 reported MERRF patients, about one third had clinical cardiomyopathy; 22% had Wolff-Parkinson-White syndrome[26]. Cardiac evaluation of two MERRF patients revealed asymmetric septal hypertrophy with diffuse hypokinesis of the left ventricle. [27] The G8363A mutation has been identified in two families with MERRF[28,29]. However, in two other families harboring this mutation, hypertrophic cardiomyopathy overshadowed the co-existing encephalopathy and hearing loss[30]. Another protein synthesis mutation is mitochondrial myopathy, lactic acidosis, stroke-like episode(MELAS) which accelerates the process of LVH secondary to vasculopathy[31]. After thorough review of database in Medline, we found that there are 16 mitochondrial genes associated with hypertrophic cardiomyopathies derived from isolated or multisystemic disorder indicated in Table 1 . Thirteen point mutations are in tRNA genes, which do have very specific structural properties that allow an optimal positioning of signals for interaction with various partners such as the cognate aminoacyl-tRNA synthetases (the enzymes that charge the correct amino acid to the 3' end of the specific tRNAs), translational initiation or elongation factors, and the ribosomal machinery. Three of these are tRNA$^{Leu(UUR)}$, tRNA^{Ile} and tRNA^{Lys}, seem to be hot spots for cardiomyopathies. It is striking that most mutations in tRNA^{Ile} are associated with diseases that present primarily or exclusively with cardiomyopathy.A prime example of a tRNA$^{Leu(UUR)}$ mutation associated with a multisystem disorder is A3243G, the most common cause of mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome[32,33]. In a review of 110 reported MELAS patients, cardiac manifestations included congestive heart failure in 18%, Wolff-Parkinson-White syndrome in 14%, and cardiac conduction block in 6%[34].The cardiomyopathy is most commonly hypertrophic[35,36]. Atypical presentations of the A3243G mutation have included maternally inherited PEO with RRF and diabetes and deafness[37]. In addition, isolated cardiomyopathy can be the presenting manifestation of this

mutation.[38-40]. Three other point mutations in the tRNA^Leu(UUR) have been associated with cardiomyopathies alone (A3260G, C3303T), associated with myopathy (A3260G, C3303T), or as part of the MELAS syndrome (C3254G, A3260G) [38,41-46], The C4320T mutation was also associated with a multiorgan disorder in a child who died at age 7 months of cardiac failure with hypertrophic cardiomyopathy and a severe encephalopathy manifesting as seizures, nystagmus, and spastic tetraparesis[47]. Intriguingly, the three other point mutations in the tRNA^Ile gene, A4295G, A4300G, and A4317G, have been identified only in patients with isolated hypertrophic cardiomyopathies [15,48-49] .

Mutation	Gene	Clinical features	Reference
A3243G	tRNA^Leu(UUR)	MELAS;PEO;DM/De;	[32,33, 38,39]
C3254G	tRNA^Leu(UUR)	Cardiomyopathy(H)	[41]
A3260G	tRNA^Leu(UUR)	MELAS	[42,43]
C3303T	tRNA^Leu(UUR)	Myopathy/cardiomyopathy(H);	[44]
A4269G	tRNA^Ile	MELAS	[50]
G4284A	tRNA^Ile	Encephalocardiomyopathy(H)	[13]
A4295G	tRNA^Ile	Cardiomyopathy(H)	[14]
A4300G	tRNA^Ile	Encephalomyopathy; cardiomyopathy	[16]
A4317G	tRNA^Ile	Cardiomyopathy(H)	[15]
C4320T	tRNA^Ile	Cardiomyopathy(H)	[47]
A8344G	tRNA^Lys	Cardiomyopathy(H+Di)	[51]
G8363A	tRNA^Lys	Cardiomyopathy(H)	[29-31]
G8584A	ATPase 6	Cardiomyopathy(H)/encephalopathy	[12]
T8993G	ATPase 6	MERRF/De/Cardiomyopathy(H)	[52]
T9997C	tRNA^Gly	Encephalopathy/cardiomyopathy(H),	[53]
G15243A	Cyt b	MERRF	[54]
		NARP/MILS; cardiomyopathy	
		Cardiomyopathy(H)/GI dysmotility	
		Cardiomyopathy(H)	

AID, aminoglycoside-induced deafness; De, deafness; Di, dilated (cardiomyopathy); DM, diabetes mellitus; GI, gastrointestinal; H, hypertrophic cardiomyopathy; MELAS, mitochondrial encephaomyopathy, lactic acidosis, and strokelike episodes; MERRF, myoclonus epilepsy with raggedred fibers; MILS, maternally inherited Leigh syndrome; NARP, neuropathy, ataxia, retinitis pigmentosa; PEO, progressive external ophthalmoplegia; (Adatpted from Hirano M et al. Mitochondria and the heart. Current Opinion in Cardiology 2001, 16:201–210.)

Table 1. Mitochondrial DNA point mutations associated with hypertrophic cardiomyopathy alone or as a major component of a multisystem disorder

5. Defects in mtDNA function

In prior reviews, we noted that several of the cardiomyopathy-associated point mutations in tRNA genes accumulated deficiencies in end maturation, including 3′ end cleavage by tRNAase Z and CCA addition by tRNA ucleotidyl-transferase, and in aminoacylation which affected Trna metabolism thus impaired the synthesis of protein in the end[55-58].
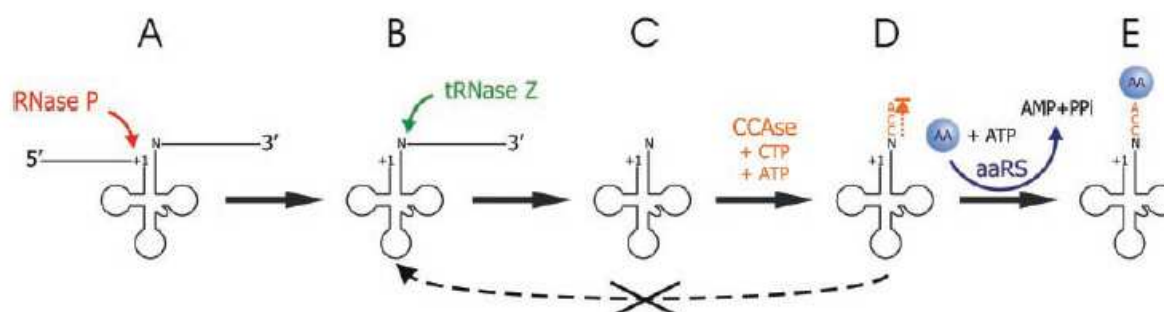
Fig. 3. The tRNA end processing pathway followed by aminoacylation. (A) tRNA is transcribed as a precursor, with a 50 end leader and a 30 end trailer. (B) RNase P has endonucleolytically cleaved the tRNA at +1. (C) tRNAse Z endonucleolytically cleaves the precursor on the 30 side of the discriminator base (N; +73). (D) CCAadding enzyme (CCAse) adds CCA to the 30 end of the tRNA (N) produced by tRNase Z cleavage. (E) tRNA is charged with the cognate amino acid by a specific aminoacyl-tRNA synthetase (aaRS). Dashed line from CCA in (D) to tRNAse Z between (B) and (C) with an X through it indicates that 3'-CCA of mature tRNase Z anti-determinant. (Adapted from Levinger L, et al. Mitochondrial tRNA 3' end metabolism and human disease.Nucleic Acids Res. 2004:11;32(18):5430-41.)

The other genes situated in anticodon stem resulted in missense changes of mitochondria herein influence function of protein variably and implicated in pathogenesis of cardiomyopathy. Of these mtDNA mutations, OXPHOS, ROS and apoptosis, three basic function of mtDNA are estimated as culprits of LVH.

6. Oxidative phosphorylation (OXPHOS)

In the early stage of LVH, genes involved in energy transportation including electron transportation chain, tricarboxylic acid (TCA) cycle , glycolysis , fatty acid(FA) metabolism downregulate, while genes devoted to mitochondrial protein transportation and synthesis upregulate. As a result, the expression of cytoskeletal genes increases as well as fetal genes which in line with enhancement of left ventricular mass and size[59]. The compensatory LVH is associated with normalization of myocardial oxygen consumption at the expense of a decrease in the ratio between cardiac work and oxygen consumption (efficiency) [60]. With the time passing by, cardiac working efficiency decreases to a lowest level and heart failure occurs.

7. Reactive oxidative species

Since ETC is inhibited, the electrons accumulate in the early stage of the ETC-generating $CoQ_{10}H$: This ubisemiquinone can then donate electrons directly to molecular oxygen (O2) to give superoxide anion(O2$^{.-}$). Superoxide anion is detoxified by the mitochondrial manganese superoxide dismutase(MnSOD, EC 1.15.1.1) to give H_2O_2, and H_2O_2 is converted to H_2O by glutathione peroxidase-1(EC1.11.1.9). H_2O_2, in the presence of reduced transition metals, can also be converted to the highly reactive hydroxyl radical ($\cdot$OH). Reactive Oxidative Species potentially has both adaptive and maladaptive signaling consequences. Role of oxidative stress and nitric oxide synthase Growth initiators including angiotensin II,

α-agonists, TNF-α, and mechanical strain also promote the formation of reactive oxygen species (ROS) [61]. ROS hypertrophic response at low rates of ROS production to fibrosis [62] and myocyte death at high rates[63]. ROS formation is also stimulated by endothelial nitric oxide synthase (eNOS). In a transgenic eNOS knockout model with low ROS production, severely pressure-loaded hearts developed only modest concentric hypertrophy with little fibrosis and without left-ventricular cavity dilation.61 Consonant with overall knowledge[63], high rates of ROS production can thus contribute to the transition from left-ventricular hypertrophy to heart failure. Although these findings may be controversial [64], there has been recent confirmation of the concept [65]. Notably, plasma and pericardial markers of oxidative stress are increased in patients with chronic systolic failure of the left ventricle, with these increases related to the clinical severity of heart failure. Controversies in ventricular remodeling.[66]

The chronic release of ROS has been recently linked to the development of left ventricular hypertrophy progression. The chronic release of ROS appears to derive from the nonphagocytic NAD(P)H oxidase and mitochondria. The experimental data are accumulating suggesting that abnormal activation of the nonphagocytic NAD(P)H oxidase in response to neurohormones (angiotensin II, norepinephrine, tumor necrosis factor-a) contribute to cardiac myocyte hypertrophy. In conclusion, the fibrosis, collagen deposition, and metalloproteinase activation involved in the remodeling of failing myocardium are dependent on ROS released. In animal model of chronic pressure overload, apoptosis has revealed as a pivotal trait of myocardial damage together with overproduction of extracellular matrix.

8. Programme cell death

Besides contractile disturbances of cardiomyocytes and interstitial and perivascular fibrosis, cardiomyocyte loss is now being considered as one of the determinants of the maladaptive processes implicated in the transition from compensated to decompensate left ventricular hypertrophy. A number of experimental evidence suggests that exaggerated apoptosis may account for the loss of cardiomyocytes in the hypertensive left ventricle. Furthermore, some factors intrinsic and extrinsic to the cardiomyocyte emerge as potential candidates to trigger apoptosis. Increased exposure of ROS accompany with decline in OXPHOS result in the opening of mtPTP, herein, apoptosis-initiated factors leak from inner membrane of mitochondrial to outer membrane. And apoptosis-related factors including procaspase and TNF-α are activated which cause a series pathway of apoptosis[67].

9. Variability of phenotypes in left ventricular hypertrophy

Phenotype of LVH is variable even for a same mtDNA mutation due to multiple causes. First, diversity in frequency and efficiency of mitochondria transit from eggs to zygotes. The more mutated mitochondria inherited from mother eggs, the higher probability phenotype will present. Second, difference in mutation load within separated organs cause the diversity in phenotype. Cells will not lose their function until high load of pathogenic mtDNA mutations are present, ranging from 60% to 90%, symptoms arise once mutations over certain threshold and lead to impaired mitochondrial protein synthesis, as well as a severe respiratory chain deficiency. Third, variability of influences derived from nuclear

genome. Mitochondrial diseases may result from nuclear DNA mutation (Mendelian mutation) or mitochondrial mutation(maternal inheritance).Mitochondrial synthesis and function require estimated 1000 polypeptides, 37 of which are encoded by mitochondrial (mt) DNA, the rest by nuclear (n) DNA.The nuclear DNA background might also influence phenotypic expression of mtDNA polymorphisms. In fact, Arbustini and colleagues have demonstrated the coexistence of mutations in mtDNA and β-myosin heavy chain (βMHC) in patients with hypertrophic cardiomyopathy, in which mtDNA mutations may contribute to the phenotypic variability of mendelian hypertrophic cardiomyopathies[68].
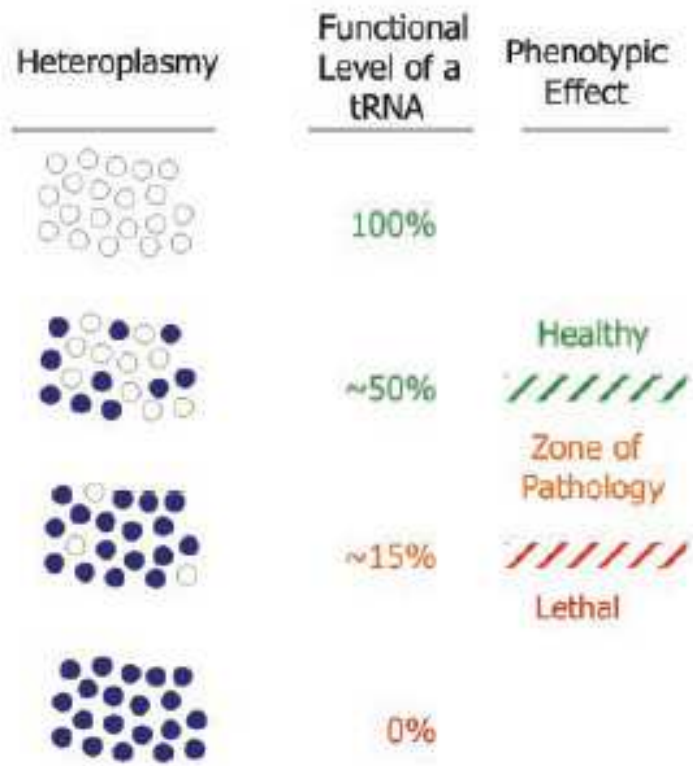

Fig. 4. Heteroplasmy: Mixed (heteroplasmic) populations of wild-type and mutant mitochondrial genomes are present. Filled circles indicate mutant mitochondrial genomes and open circles indicate wild-type. Thresholds: The thresholds for pathology are typically between 15 and 50% of mitochondrial tRNA function, affected by the extent of heteroplasmy. A lower functional level would be lethal and a higher level would be without a phenotype. (Adapted from Levinger L, et al. Mitochondrial tRNA 3' end metabolism and human disease.Nucleic Acids Res. 2004:11;32(18):5430-41.)

10. Advances in therapy

Reducing heart load, cutting off vicious cycle of hemodynamic disorders as well as thinning hypertrophic myocardium have been accepted as classic methods to treat LVH. As for the pathogenic involvement of mitochondria, gene therapy is a promising way to improve the outcome of treatment. Nevertheless, there's no effective and consent methods to treat mitochondrial disorders so far. One process under way is to reduce the proportion of

mutated mtDNA to subthreshold levels. This could be achieved by adding more wild-type mtDNA, or by removing mutated mtDNA. At the experimental level, some contrary results derived from synthetic wild-type mtDNA transition and gene shifting in skeletal muscles, which help to draw a conclusion that an efficient approach to lead wild-type mtDNA to cells should be further investigated. To remove mutated mtDNA, one approach is to bind specific molecules to mutated mtDNA molecules and prevent them from replicating, while let wild-type mtDNA replication to continue unimpeded. Another approach is to use drugs that select against mutated mtDNA in dividing cells, allowing wild-type mtDNA levels to increase. Otherwise, all the approaches with the goal letting the mutated cells down need to be tested from experimental stages to clinical usage [69]. Recently, antioxidants have been proposed to be important in the pathogenesis of mitochondrial disorders on the basis of ROS involvement [70]. Vitamin B, Vitamin C ,Vitamin E as well as Coenzyme Q has served as scavenger molecules and somewhat has been demonstrated to benefit patients with MELAS and Kearns-Sayre syndrome[71]. Although coenzyme Q10 has shown some early promise in Parkinson's disease and Friedreich's ataxia, such results can only be regarded as provisional at this stage. There have been no large-scale studies to determine the effectiveness of coenzyme Q10 in primary mtDNA diseases [72]. Other molecules involved in ETC may help offering materials for OXPHOS. Moreover, antiapoptosis drugs are beneficial to improving mtDNA diseases in line with the candidate of program cell death.

11. Prospects

Left ventricular hypertrophy is a hot spot for improving the life quality of patients with hypertension. The pathogenesis and progression of LVH are tightly linked to mitochondria as we stated above. However, the mechanism of mitochondria implicated into LVH still remain obscure that much more jobs are needed to disclose the secrets of relationship between mitochondria and left ventricular hypertrophy.1) which mtDNA mutation can be served as a marker to predict and indicate the prognosis of LVH? 2) How nDNA influence mtDNA, and to what extent can we use the methods protecting nDNA from damage to attain the role of protecting mtDNA. 3) What steps may we take to reduce frequency and quantity of mutated mtDNA thus cut off the deterioration pathways of LVH.

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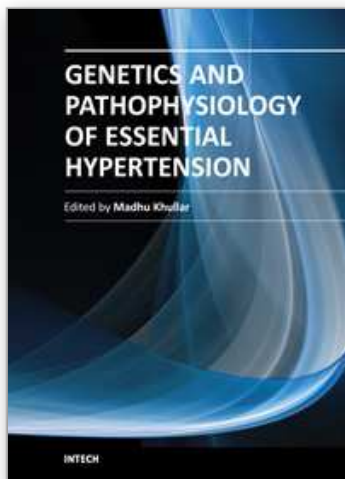
Genetics and Pathophysiology of Essential Hypertension
Edited by Prof. Madhu Khullar

This book, authored by renowned researchers in the field of Hypertension Research, details the state of the art knowledge in genetics, genomics and pathophysiology of Essential hypertension, specifically the genetic determinants of hypertension and role of gene variants in response to anti-hypertensive therapy. Two chapters describe mitochondrial mutations in Essential hypertension and in hypertension associated Left ventricular hypertrophy, one chapter reviews in detail the global gene expression in hypertension, and an up to date treatise on pathophysiology of resistant hypertension is detailed in another chapter. Other topics included in the book are end organ damage, baroreceptor sensitivity and role of music therapy in essential hypertension.

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