Review Article

Mitochondria and left ventricular hypertrophy

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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. Many factors involve in the pathogenesis of hypertension-induced LVH including inherited variants as well as environmental factors. For the genic 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 mitochondrion 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.

Left ventricular hypertrophy definition, diagnostic standard, diversity in phenotypes

LVH is a common complication of hypertension (the prevalence varies from 14 to 44% screening by echocardiography) 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 Figure 1 and Figure 2).

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,(1987):

LV mass=1.04[(IVST+LVID+PWT)3-LVID3]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, and LVMI>165g/m² as severe. Inter-ventricular 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.

Essential hypertensive patients with left ventricular hypertrophy increase their mortality rates due to all cardiovascular events from 2 to 10 times more than hypertensives in patients without LVH.

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Figure 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 thinner 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 (ie, 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.
without signs of cardiac hypertrophy. 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.

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.

Genetic Background

Nuclear Genes

Plthora of evidences support the hypothesis that multiple nuclear genes contribute to left ventricular hypertrophy. 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 et al. reported a genetic locus on chromosome 2 of the spontaneously hypertensive rat affects relative LV mass independently of blood pressure. Tsujita et al. indicated both genes on chromosomes 7 and 17 that influences LVM in a manner dependent on blood pressure. Intrestingly, 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.

Mitochondria

Biogenesis and Bioenergetics

Matrilineal inheritance in LVH pedigrees supports the hypothesis that mitochondrial genes are also implicated in the pathogenesis of LVH. Mitochondria evolved from protobacteria that inhabited primordial eukaryotic cells about 1.5 billion years ago and were first observed more than 100 years ago by Altmann. It’s a small symbiotic (0.5-1 μm) organelle combined with aerobic bacteria and primordial eukaryotic cells. Thirty seven genes make up a mitochondrion within which thousands of mtDNA forming double-stranded 16569 base-pair(Figure. 3). Of these genes, 24 encode RNAs necessary for protein synthesis (22 tRNAs and 2 rRNAs),

The remaining 13 genes encode proteins that are critical subunits of the respiratory chain.

The mitochondrial contains an inner and an outer membranes which define the matrix and the intermembrane space. The outer membrane is permeable to small molecules (up to 10 Å) whereas the inner membrane is freely permeable to oxygen and carbon dioxide. This relative impermeability of the inner membrane is essential for maintaining a proton gradient necessary for the synthesis of adenosine triphosphate (ATP). There are several unique features of mtDNA and mitochondrial genetics which are distinct from the features of nuclear genes and the principles of nuclear inheritance. First, mammalian mtDNA does not contain introns which makes mtDNA mutations affect phenotype of diseases much more easier comparing to nuclear genes.
Second, several mitochondrial genetic codons differ from the universal nuclear genetic code. UCG code for tryptophan and not termination, AUA code for methionine not isoleucine, and AGA and AGG are terminations rather than arginine codons. AUA are possibly AUU are initiation codons as well as AUG. Third, only the mother contributes to the mtDNA pool of the offspring. It dues mostly to the fact to a large extent that sperm contains only 100 mtDNA while egg contains approximately 10,000 mtDNA. Fourth, the fixation of mtDNA mutations is more than 10 times higher in comparison with the nuclear DNA mutation rate. A possible explanation for this difference is the lack of protective histones and the absence of effective DNA repair systems within mitochondria. In addition, by being exposed to tremendous fluxes of oxygen, mtDNA may also be a target for the reactive oxygen species produced as by-products of oxidative phosphorylation. Fifth, an individual may carry several allelic forms of mtDNA, present in different proportions in different tissues. The coexistence of more than one type of mtDNA within a cell, wide-type accompanies with mutant type, is called heteroplasmy. Sixth, there is as yet no conclusive evidence demonstrating that orthodox recombination occurs between individual mtDNA molecules. New mtDNA alleles can thus only arise through spontaneous mutations. In spite of striking difference of morphological and inherited characteristics from nuclear genes, mitochondria have three major functions which associated with pathogenesis of diseases synergically (energetics, reactive oxygen species, and apoptosis).

First, mitochondria offer about 90%-95% energy to cells through oxidative phosphorylation (OXPHOS). Five multipolypeptide enzyme complexes make up OXPHOS (Fig. 4) as follows: Complex 1 (NADH:ubiquinone oxidoreductase), 2 (succinate: ubiquinone oxidoreductase), 3 (ubiquinol: ferrocytochrome C oxidoreductase), 4 (cytochrome C oxidase) constitute electron transport train (ETC). Through ETC, energy is released to pump protons from inside the mitochondrial matrix across the mitochondrial inner membrane into the intermembrane space. And the electrochemical gradient results from ETC offers energy for complex 5 (H+ - translocating ATP synthase) to produce adenosine triphosphate.

Second, toxic by-products, reactive oxygen species (ROS) including O2-, H2O2 and .OH, derived from mitochondrial OXPHOS do harm to cells to variable extents according to different period of time exposure to ROS. Short-term exposure to ROS can reduce the activity of ETC and slow down the metabolism while long-term exposure will induce irreversible oxidative damage thus cause markedly reduction of mitochondrial function.
Third, mitochondria are implicated in the initiation of apoptosis in specific circumstances through opening mitochondrial permeability transition pore (mtPTP) within the membrane. Programmed cell death activates for the leaking of apoptosis-promoting factors located in matrix such as cytochrome c apoptosis-initiation factor (AIF) and kinds of caspases by mtPTP.

Mitochondria and heart diseases

For the three basic functions of mitochondria indicated above, the hypothesis of mitochondria participating in pathogenesis of heart diseases has been supported by both experimental and clinical evidences.

In 1988, the first disease-causing mutation of mtDNA was found that patients with mitochondrial myopathy identified a variety of functional defects of the mitochondrial respiratory chain, predominantly affecting complex ζη (NADH-CoQ reductase) or complex ζε (ubiquinol–cytochrome c reductase) in adult cases.14, 15 This discovery led to a rapid surge in the research into mitochondrial disorders, and there are now more than 200 different mtDNA mutations linked to human disease (http://www.mitomap.org). Given the fact that heart is a second largest oxygen-consumed organ within body with 12% oxygen necessary to work averagely just less than brain, it follows that heart should be a harrowing victim for oxygen deficiency in vivo. Actually, every heart beat consumes 2% of total cellular ATP. And 90% of its ATP is produced by mitochondrial oxidative phosphorylation. Thus, mitochondria are assumed to be implicated in the pathogenesis of multiple cardiovascular diseases, with regard to the basic functions of the organelle.16

Mitochondria are found to influence all of the four major features of cardiomyocytes: excitability, contractility, conductivity and autorhythmicity to certain degree. The rate and force of contraction of heart muscle change according to ATP utilization. Patients with mtDNA deletions named sporadic rearrangements often develop atrioventricular blocks, which progress from mild to severe (type ζη to type ζε),17, 18 respectively. Kearns-Sayre syndrome (KSS) and Chronic Progressive External Ophthalmoplegia (CPEO) are the major multisystemic disorders which affect cardiac conductive system particularly. Diversity of cardiac conduction defects including prolonged intraventricular conduction time, bundle-branch block, and atrioventricular block often lead to sudden cardiac death. The 4.9kb “common” deletion loci from ATP6 through CO ζε ND3, ND4L, ND4, to ND5 contribute to KSS.19 While A3243G mutation associates with maternally inherited PEO with RRF 20 and diabetes and deafness.21 Aon MA, et al22 introduced a novel conception “mitochondrial criticality” to describe the state in which the mitochondrial network of cardiomyocytes becomes very sensitive to small perturbations in reactive oxygen species (ROS), resulting in the scaling of local mitochondrial uncoupling and Ưx loss to the whole cell, and the myocardial syncytium. The energetic changes are translated into effects on the electrical excitability of the cell, inducing temporal heterogeneity of excitability in the heart, and underlying the genesis of potentially lethal cardiac arrhythmias.

Except for arrhythmia and excitability, mitochondrial dysfunction has also been suggested to reduce contraction of heart thus result in heart failure and age-associated decline in heart function.23-26

Mitochondrial and left ventricular hypertrophy 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,27 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 decrease 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 et al28 reported that 3243A>G mtDNA mutation is associated with LVH. Zhou, et al29 found G8584A mtDNA mutation may influence LVH in hypertensives. In particular, several point mutations such as G4284A, A4295G, A4269G, A4317G32 and A4300G32 located in tRNA Ile contribute to hypertrophic cardiomyopathy to certain degree. mtDNA Mutations can divide into rearrangement mutations and base substitutions. And base substitution mutations are subcategorized into missense mutations (protein coding genes alterations) and protein synthesis mutations (RNAs genes changes).

Rearrangement mutations

Rearrangements of mtDNA due to deletions or duplications generally occur in sporadic patients. Duplications are probably not directly pathogenic, but they produce deleted mtDNA molecules, which implicated into different diseases.34,35 The most prominent multi-systemic disorders involved in cardiomyopathy are KSS and CPEO. The characteristic symptoms of KSS are cardiac conduction block, cardiomyopathy and cardiodebolic stroke with ocular damage including ophthalmoplegia, ptosis, pigmented 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 colleagues36 demonstrated that duplications represented an unusually high proportion (41%-91%) of all rearranged mol-
ecules 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 and rearrangement mtDNA mutation represents a series of abnormalities covering ocular myopathy, mitochondrial myopathy, renal failure and diabetes mellitus.37 McComish et al.38 found the changes of hypertrophy via endomyocardial biopsy on light microscopy.

**Missense mutations**

Leigh’s syndrome is a most severe missense 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.39 Missense mutations in the gene that encodes |β-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.40,41

**Protein synthesis mutations**

Myoclonic epilepsy with ragged-red fibers (MERRF) is most frequently caused by an A8344G mutation in the tRNA<sup>Lys</sup> gene. In a review of 62 reported MERRF patients, about one third had clinical cardiomyopathy; 22% had Wolff-Parkinson-White syndrome.42 Cardiac evaluation of two MERRF patients revealed asymmetric septal hypertrophy with diffuse hypokinesis of the left ventricle.43 The G8363A mutation has been identified in two families with MERRF.44,45 However, in two other families harboring this mutation, hypertrophic cardiomyopathy overshadowed the co-existing encephalopathy and hearing loss.46 Another protein synthesis mutation is mitochondrial myopathy, lactic acidosis, stroke-like episode (MELAS) which accelerates the process of LVH secondary to vasculopathy.47 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<sup>Leu(UUR)</sup>, tRNA<sup>Val</sup> and tRNA<sup>Lys</sup>, seem to be hot spots for cardiomyopathies. It is striking that most mutations in tRNA<sup>Val</sup> are associated with diseases that present primarily or exclusively with cardiomyopathy. A prime example of a tRNA<sup>Leu(UUR)</sup> mutation associated with a multisystem disorder is A3243G, the most common cause of mi-

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

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Gene</th>
<th>Clinical feature</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>A3243G</td>
<td>tRNA&lt;sup&gt;Leu(UUR)&lt;/sup&gt;</td>
<td>MELAS;PEO;DM/De; Cardiomyopathy(H)</td>
<td>[23,48,49, 54,55]</td>
</tr>
<tr>
<td>C3254G</td>
<td>tRNA&lt;sup&gt;Leu(UUR)&lt;/sup&gt;</td>
<td>MELAS</td>
<td>[57]</td>
</tr>
<tr>
<td>A3260G</td>
<td>tRNA&lt;sup&gt;Leu(UUR)&lt;/sup&gt;</td>
<td>Myopathy/Cardiomyopathy(H); MELAS</td>
<td>[58,59]</td>
</tr>
<tr>
<td>C3303T</td>
<td>tRNA&lt;sup&gt;Leu(UUR)&lt;/sup&gt;</td>
<td>Encephalocardiomyopathy(H)</td>
<td>[60]</td>
</tr>
<tr>
<td>A4269G</td>
<td>tRNA&lt;sup&gt;Leu&lt;/sup&gt;</td>
<td>Cardiomyopathy(H)</td>
<td>[66]</td>
</tr>
<tr>
<td>G4284A</td>
<td>tRNA&lt;sup&gt;Leu&lt;/sup&gt;</td>
<td>Encephalomyopathy; Cardiomyopathy</td>
<td>[30]</td>
</tr>
<tr>
<td>A4295G</td>
<td>tRNA&lt;sup&gt;Leu&lt;/sup&gt;</td>
<td>Cardiomyopathy(H)</td>
<td>[31]</td>
</tr>
<tr>
<td>A4300G</td>
<td>tRNA&lt;sup&gt;Leu&lt;/sup&gt;</td>
<td>Cardiomyopathy(H)</td>
<td>[33]</td>
</tr>
<tr>
<td>A4317G</td>
<td>tRNA&lt;sup&gt;Leu&lt;/sup&gt;</td>
<td>Cardiomyopathy(H+Di)</td>
<td>[32]</td>
</tr>
<tr>
<td>C4320T</td>
<td>tRNA&lt;sup&gt;Leu&lt;/sup&gt;</td>
<td>Cardiomyopathy(H)</td>
<td>[63]</td>
</tr>
<tr>
<td>A8344G</td>
<td>tRNA&lt;sup&gt;Lys&lt;/sup&gt;</td>
<td>Cardiomyopathy(H)/Encephalopathy</td>
<td>[67]</td>
</tr>
<tr>
<td>G8363A</td>
<td>tRNA&lt;sup&gt;Lys&lt;/sup&gt;</td>
<td>MERRF/De/Cardiomyopathy(H)</td>
<td>[45-47]</td>
</tr>
<tr>
<td>G8584A</td>
<td>ATPase 6</td>
<td>Encephalopathy/Cardiomyopathy(H), MERRF</td>
<td>[29]</td>
</tr>
<tr>
<td>T8993G</td>
<td>ATPase 6</td>
<td>NARP/MILS; Cardiomyopathy</td>
<td>[68]</td>
</tr>
<tr>
<td>T9997C</td>
<td>tRNA&lt;sup&gt;Glu&lt;/sup&gt;</td>
<td>Cardiomyopathy(H)/GI dysmotility</td>
<td>[69]</td>
</tr>
<tr>
<td>G15243A</td>
<td>Cyt b</td>
<td>Cardiomyopathy(H)</td>
<td>[70]</td>
</tr>
</tbody>
</table>

De, deafness; Di, dilated (cardiomyopathy); DM, diabetes mellitus; GI, gastrointestinal; H, hypertrophic cardiomyopathy; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonus epilepsy with ragged fibers; MILS, maternally inherited Leigh syndrome; NARP, neuropathy, ataxia, retinitis pigmentosa; PEO, progressive external ophthalmoplegia; (Adapted from Hirano M et al. Mitochondria and the heart. Curr Opin Cardiol 2001;16:201-210.)
tochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome. 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%.

The cardiomyopathy is most commonly hypertrophic. Atypical presentations of the A3243G mutation have included maternally inherited PEO with RRF and diabetes and deafness. In addition, isolated cardiomyopathy can be the presenting manifestation of this mutation.

Three other point mutations in the tRNA\textsuperscript{Leu(UUR)} gene have been associated with cardiomyopathies alone (A3260G, C3303T), associated with myopathy (A3260G, C3303T), or as part of the MELAS syndrome (C3254G, A3260G). 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.

Intriguingly, the three other point mutations in the tRNA\textsuperscript{Ile} gene, A4295G, A4300G, and A4317G, have been identified only in patients with isolated hypertrophic cardiomyopathies.

**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 tRNA\textsuperscript{ase Z} and CCA addition by tRNA nucleotidyl-transferase, and in aminoacylation which affected tRNA metabolism thus impaired the synthesis of protein in the end.

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

**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.

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). With the time passing by, cardiac working efficiency decreases to a lowest level and heart failure occurs.

**Reactive oxidative species**

Since ETC is inhibited, the electrons accumulate in the early stage of the ETC-generating \textsubscript{CoQ}\textsubscript{10H}. This ubisemiquinone can then donate electrons directly to molecular oxygen (O\textsubscript{2}) to give superoxide anion (\textsubscript{O2}^-). Superoxide anion is detoxified by the mitochondrial manganese superoxide dismutase (MnSOD, EC 1.15.1.1) to give H\textsubscript{2}O\textsubscript{2}, and H\textsubscript{2}O\textsubscript{2} is converted to H\textsubscript{2}O by glutathione peroxidase-1 (EC 1.11.1.9). H\textsubscript{2}O\textsubscript{2}, in the presence of reduced transition metals, can also be converted to the highly reactive hydroxyl radical (OH). Reactive oxidative species potentially has both adaptive and maladaptive signalling consequences. Role of oxidative stress and nitric oxide synthase Growth initiators including angiotensin \textsubscript{A} \textsubscript{1}-agonists, TNF- \textsubscript{A} and mechanical strain also promote the formation of (ROS). ROS hypertrophic response to fibrosis at low rates of ROS production and to myocyte death at high rates. 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 dilatation. Consonant with overall knowledge, high rates of ROS production can thus contribute to the transition from left-ventricular hypertrophy to heart failure. Although these findings may be controversial, there has been recent confirmation of the concept. 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 remodelling.85

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 non-phagocytic NAD(P)H oxidase and mitochondria. The experimental data are accumulating suggesting that abnormal activation of the non-phagocytic NAD(P)H oxidase in response to neurohormones (angiotensin 2, norepinephrine, tumor necrosis factor-α) 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.

**Programmed 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 decompensated left ventricular hypertrophy. A number of experimental evidence suggest 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 accompanies 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.85

**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 transition of mitochondria 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 causes 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, Fortuno and colleagues have demonstrated the coexistence of mutations in mtDNA and α-myosin heavy chain (αMHC) in patients with hypertrophic cardiomyopathy, in whom mtDNA mutations may contribute to the phenotypic variability of mendelian hypertrophic cardiomyopathies.84

**Advances in therapy**

Fig. 6: 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.)

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. Recently, antioxidants have been proposed to be important in the pathogenesis of mitochondrial disorders on the basis of ROS involvement. Vitamin B, vitamin C, vitamin E as well as coenzyme Q have served as scavenger molecules and somewhat have been demonstrated to benefit patients with MELAS and Kearns-Sayre syndrome.

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. 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 programed cell death.

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 remains 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.

Reference


