Chapter

Emerging Hallmarks of Mitochondrial Biochemistry in Cardiac Trabecular Morphogenesis and Left Ventricular Noncompaction (LVNC)

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Abstract

Functioning as a pivotal platform for energy production and transduction, mitochondria generate ATP to meet the dynamic demands of embryonic development. Consequently, disruption or alteration in mitochondrial activity influences not only cellular status, but also can impact organ formation. Disrupted mitochondrial performance not only impairs cardiovascular function but can also disrupt cardiac maturation through prevention of the myocardium's transition between the trabeculation to the compaction phase. During embryonic development, proliferating cardiomyocytes create a trabecular mesh network. Gradual compaction of this network transforms the intra-trabecular spaces into the capillaries of the coronary circulation. Achievement of functional compaction and ultimately normal cardiac function is dependent in part on mitochondrial well-being with failure to complete remodeling of the inner trabecular layer contributing to disrupted endocardial vasculature and fibrosis, left ventricular noncompaction (LVNC). LVNC, commonly associated with mitochondrial genetic alterations, is speculated to occur due to an interruption during the process of compaction at the early developmental stages of the left ventricle (LV). Mitochondrial mutations, remain the common etiology of LVNC with a wide spectrum of these genes associated with other cardiomyopathies related to LVNC. Understanding the impact that mitochondrial genetic alterations have on the evolution of cardiac noncompaction could provide new treatment opportunities.

Keywords: trabeculation, mitochondria, LVNC, mutations, cardiomyopathy

1. Introduction

Cardiac development consists of four stages including embryonic cardiac chamber maturation [Carnegie stage (CS) 11 in humans and embryonic day (E) 8.5 in mice], trabeculation (at CS 12 in humans and E9.5 in mice), compaction (CS 22 in humans and E14.5 in mice) and cardiomyocyte proliferation (E11-E17.5 in mice). Originating from

embryonic mesodermal germ layer cells that differentiate into mesothelium, endothelium, and myocardium followed by gastrulation, the exterior lining of the heart is made up of mesothelial pericardium. Whereas the interior lining of the heart, lymphatic, and blood vessels, arise from endothelium. During cardiac development, the atrial septation (primary atrial septum formation) begins at E10.5 to E13.5 in mice, which is comparable to Carnegie stages (CS 14 to 18) in humans or estimated gestational age (EGA) of 6 6/7–8 weeks. The ventricular septation proceeds from E11.5 to E13.5 in mice and EGA 8–9 1/7 weeks (CS 18–22) in human fetuses. Outflow septation, the transformation of a right ventricle (RV) single outflow tract into pulmonary and aortic arteries originating from the right and left ventricles, starts at E11.5–E13.5 in the mouse and EGA 7 3/7–8 weeks (CS 16–18) in humans [1]. While the separation of atrioventricular (AV) valves from endocardial cushions at the center of cardiac loop occurs at 9 1/7 weeks (CS 22). By the end of 9 1/7 weeks (CS22), all of the major structures of the heart are formed, with the average spanning period of EGA 6 4/7–9 3/7 weeks [2–4].

During cardiac development, trabeculation followed by a compaction step (CS 12 to CS 22), is vital in the developmental stages of humans (**Figure 1**). Emerging from the developing ventricular wall and stretching into the ventricular lumen, trabeculae projections consist of cardiomyocytes lined by an endothelial layer of the endocardium and are an important element of ordered ventricular formation. Any defects during trabeculation, compaction of remodeling junctions, or cardiac chamber maturation, could lead to the inhibition of well compacted myocardium with persisting trabeculations resulting in the condition left ventricular noncompaction (LVNC).

The trabeculation process is further defined by three sequential steps resulting in fusion with myocardium layer that is compacted and progression into a mature thickened ventricular wall. Initially, the trabecular ridges start to emerge while the myocardial projections progress into the lumen. This is followed by the expansion of trabeculae projections, creating a trabeculae network. In the final remodeling step of trabeculae formation, trabeculae growth ceases and they compact together contributing to ventricular radial thickening [6, 7]. Importantly, the LV of a healthy heart has three distinct trabeculation types (hypertrophic, fibrotic or both) [8] and is less trabeculated than RV [9]. Upon stimulation of ventricular trabeculations during the compaction phase of embryonic development, the growth of trabecula ceases and the ends of the trabecula thicken, with the spaces in between the trabecular buds developing into capillaries [10, 11]. The persistence of a trabecular mesh caused by myocardial noncompaction can occur due to irregularities arising in the maturation process of the cardiac chamber. However, the step of remodeling ventricular trabeculae for compaction is believed to be correlated with congenital or acquired mutations of genes associated with cardiomyocytes and the powerhouse of the cell, mitochondria. Unfortunately, complications arising from disruption in the compaction process, referred to as noncompaction, can result in heart failure and neonatal death [12].

In normal human embryo development, the compaction of myocardium begins after the 5th week of embryonic life. To form a well-developed compacted epicardial and a well-compacted endocardial layer, vascular endothelial growth factor (VEGF) and angiopoietin [13] triggers these loosely interwoven muscle fibers of the myocardium to condense, thus removing the large flattened trabeculae spongy mesh from early embryonic development prior to resolving the intertrabecular recesses into capillaries. This gradual progression of trabeculae compaction occurs faster in the LV than in the RV. However, the etiology of LVNC is poorly understood and occurs as a spectrum of pathological conditions, ranging from asymptomatic to the risk of RV failure and fetal heart failure [14]. Due to its relatively low prevalence in combination

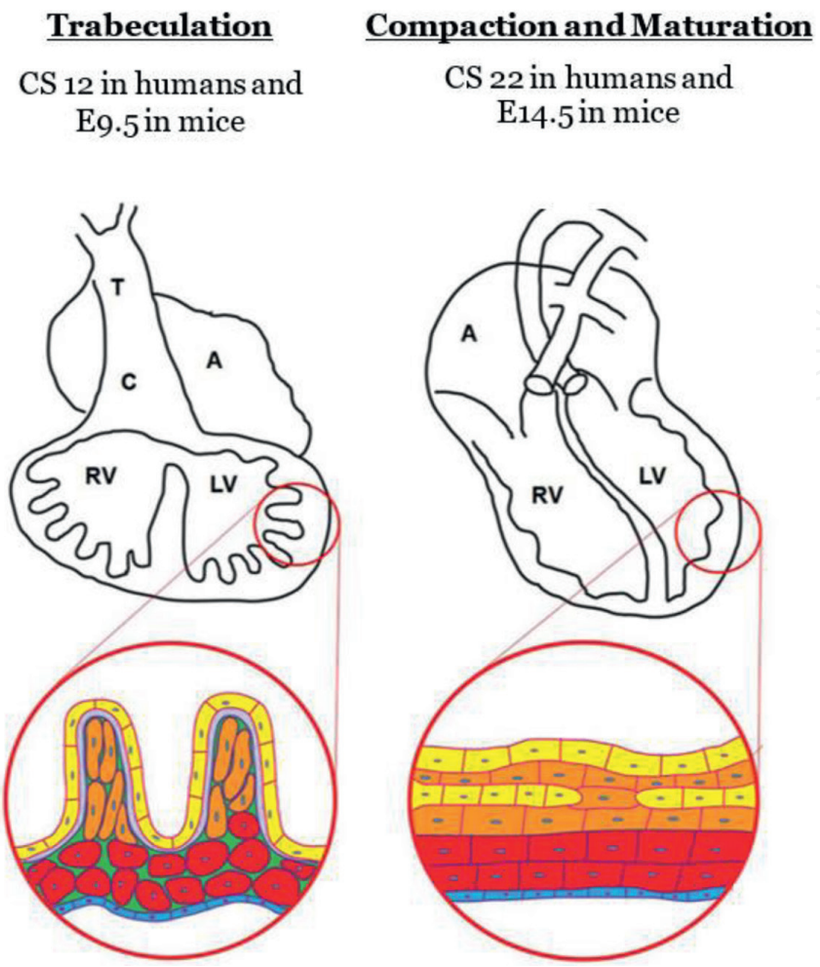

Figure 1.
Progression of left ventricular trabeculation to compaction: Trabeculation and compaction of endocardial cells (yellow), cardiomyocytes (orange in left image, red in right image), cardiac jelly (purple), epicardial cells (blue) of a LV followed by the maturation step in mouse and human are shown (figure adapted and modified from Zhang et al. [5]).

with less sensitive detection techniques for noncompaction, less is known regarding its etiology and therapy compared to other cardiomyopathies. While the occurrence of LVNC is independent of sex or age, the prevalence varies among different ethnic groups: with a greater occurrence within black populations. Lastly, the pathophysiological impact of LV noncompaction is poorly understood, though it is expected to a have an association with altered ventricular systolic and diastolic function [15, 16].

2. Cardiac energy metabolism: role of the mitochondria

Cardiac energy metabolism relies on regular mitochondrial function and energy production. Thus, inborn errors of metabolism impacting the mitochondrial dysfunction are a common pathological factor of LVNC. Mitochondrial cardiomyopathy is a myocardial condition defined by an aberrant heart-muscle structure or function, that involves mitochondrial respiratory chain pathways. Failure in the regulation of these metabolic pathway mechanisms can lead to cardiac dysfunction associated with noncompaction [17]. Thus, the proper functioning of mitochondrial enzyme complexes is crucial for the normal progression of cardiac morphogenesis. This review focuses

specifically on the mitochondrial influence on trabecula morphogenesis and its influence on the compaction of LV myocardium. Moreover, we describe the mechanisms contributing to LVNC and explore the current diagnostic and therapeutic strategies available for this type of mitochondrial myopathy [18, 19].

A double membrane-bound organelle, mitochondria have their own genome and exhibit maternal inheritance patterns. The mitochondrial genome is composed of 22 tRNAs, 2 rRNAs, and 37 genes encoding 13 different proteins that form subunits of enzyme complexes within the oxidative phosphorylation system (OXPHOS). Although comparatively smaller than the nuclear genome, the human mitochondrial genome possesses thousands of mitochondria, each encoding dozens of copies of the mitochondrial genome. Unlike the nuclear genome, mitochondria have higher mutation rates (100 fold higher) due to the absence of a mismatch base repairing mechanism [20]. Notably, deficiencies in NADH-coenzyme Q (CoQ) reductase (complex I) and cytochrome-c oxidase (complex IV) have been commonly studied in many mitochondrial disorders [20, 21]. OXPHOS pathway involves around 80 different proteins to make five electron transport complexes (complex I–V) [22]. Many of the mutations and defects in genes involved in OXPHOS impacts the mitochondrial energy production. As such they are the primary source of reactive oxygen species (ROS) generation. Hence, the overproduction of ROS causes mitochondrial damage through a range of pathologies that affects the rest of the cell (**Figure 2**). In addition to oxidative phosphorylation system, mitochondria also control apoptosis and cytosol calcium concentrations. Importantly within the cardiac muscle, calcium signaling propagated within the cytosol, is trafficked through the mitochondrial membrane via the voltage dependent anion channel (VDAC) and an inner membrane located calcium uniporter or a Na^{+}/Ca^{2+} exchanger. Thus, a vital feature of cellular life any alterations in mitochondrial Ca^{2+} homeostasis can cause profound effects in the mitochondrial function with defects contributing to cell death [23].

Mitochondrial energy production is influenced by maternally inherited mitochondrial DNA (mtDNA) and nuclear DNA [24] with mitochondrial gene mutations causing irregular function. Energy released upon electrons transfer between the 5 enzyme complexes of the mitochondrial electron transport chain (ETC) within the inner mitochondrial membrane, acts as a proton pump across the mitochondrial membrane. This electrochemical gradient is important for cellular energetic homeostasis [25]. Defects in the five enzyme complexes of mitochondrial ETC, some of which are encoded by mitochondrial DNA, can reduce ATP energy generation resulting in an energy insufficiency. Additionally, cardiac mitochondrial function is also coupled with ROS production from oxidative damage during the OXPHOS cycle. Elevated free iron levels and defective ETC as a result of the impaired intramitochondrial metabolism is associated with a vast increase in free radical generation leading to oxidative damage that could impact development.

Cardiomyocytes are composed of bundles of myofibrils containing myofilaments. The distinct, repeating micro units of myofibrils, sarcomeres, are the fundamental contractile units of the myocytes. The mitochondria in cardiomyocytes localized to sarcomeres form intracellular energetic unit (ICEU) [26]. Catabolism favors the movement of the chemical gradient from mitochondria in the form of ATP to sarcomeres. Composed of thin and thick filaments, the thick filamentous myosin motor protein component of the cardiac sarcomere is primarily responsible for force generation. While the structural abnormalities associated with LVNC has been well described, many of the details of its mechanism have yet to be elucidated. However, studies suggest a correlation between LVNC and myocardial abnormalities with

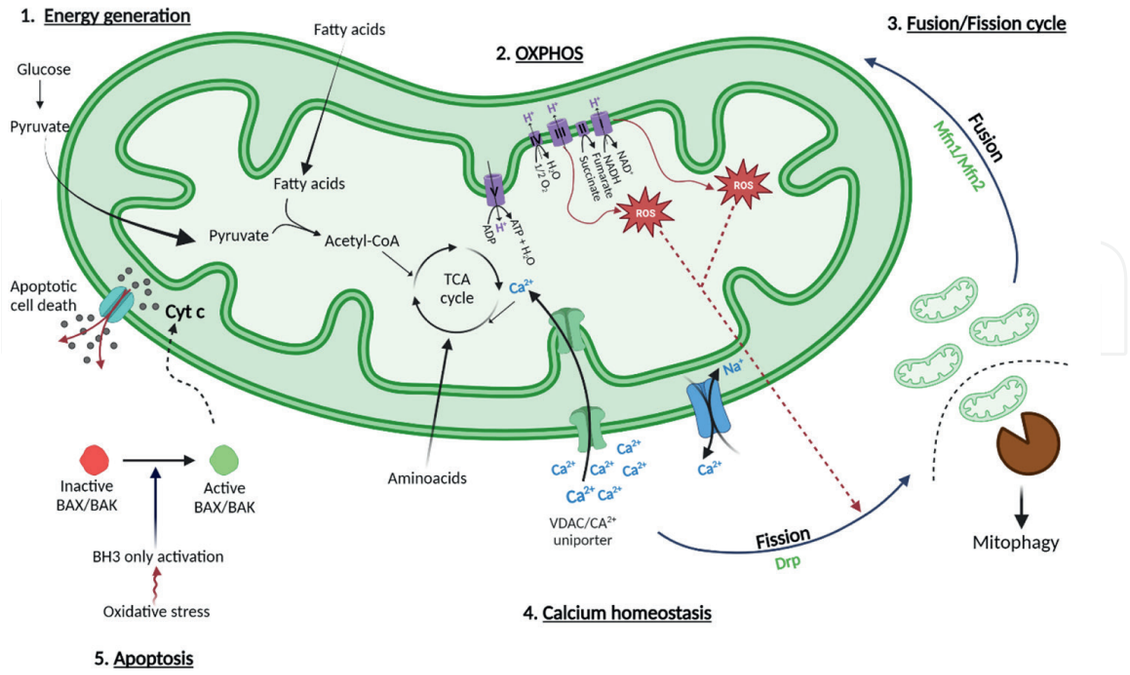

Figure 2.
A variety of roles played by Mitochondria are critical for cellular maintenance: Energy production ("powerhouse of the cell"), OXPHOS pathway, alters between fusion and fission cycle, Ca^{2+} level control and apoptosis.

energy generation, transfer and utilization as possible contributing factors to the irregular contraction and relaxation of cardiac muscles. As such, the impact of mitochondrial related gene deletion, mitochondrial function, and energy production cannot be overstated in light of the disorders arising from disruption of these processes and their impact on compaction at the early development of the LV myocardium.

3. Left ventricular noncompaction (LVNC)

Left ventricular noncompaction (LVNC), also knowns as left ventricular hyper trabeculation (LVHT) or spongy myocardium, is a rare congenital myocardial dysfunction resulting from the arrest of the compaction phase during embryogenesis. Gross histology of this heterogeneous disease condition is characterized by a spongy left ventricle (LV) myocardium, abnormal prominent trabeculations at the ventricular apex, and intra-trabeculae recesses adjacent to a well compacted LV myocardium during the final stages of cardiac development [27]. Within the ventricular cavity the double-layered ventricular myocardium consisting of epicardial and endocardial layers, there appears finger-like protrusions from the myocardium with intertrabecular recesses separating trabeculations. Pathologically these anatomical features of a noncompacted heart demonstrate a tremendously thickened endocardial layer with abnormal trabeculation and a compacted thin epicardial layer. In 1984, the first case of LVNC was described in a newborn that was also associated complications of atresia of semilunar valves and intact ventricular septum [28]. Since then, of the different phenotypes of LVNC (8 different subtypes identified to date) [29], isolated LVNCs (first reported in 1926 occurring as a result of trabeculae morphogenesis interference in the absence of any cardiac abnormalities) and congenital LVNCs are the most

commonly studied. With the latter type of LVNC being associated with systemic diseases including metabolic or mitochondrial diseases, cardiomyopathies such as hypertrophic, dilated, restrictive, and arrhythmogenic, congenital heart diseases, and complex syndromes affecting vast majority of the organs and tissue [30].

While rare forms of LVNC can occur from acquired mutations, commonly LVNCs are from genetic alterations transmitted through generations [31] with around 50% of the identified LVNC patients having either autosomal dominant, autosomal recessive, or X-linked genetic inheritance patterns with multiple genes modifications [32–34] (**Figure 3**). Predominate genetic variants associated with LV noncompaction include defects in mitochondrial, sarcomeric, and cardiac genes. In addition to mitochondrial DNA mutations [35], a wide variety of mitochondrial abnormalities significantly influence LVNC including but not limited to mitochondrial dysfunction [36], metabolic myopathy altered by mitochondrial energy production [37], dysmorphic mitochondria [31, 38], mitochondrial DNA transitions (a type of DNA mutation where a purine or pyrimidine nucleotide is replaced with its complementary purine or pyrimidines, respectively) [39, 40], deficiencies in mitochondrial respiratory chain function [41], mutations in overlapping regions [42], and mitochondrial genome mutations [43]. Further supporting mitochondrial involvement, mitochondrial numbers are enriched in the cardiac muscles of individuals with LVNC, and mitochondrial DNA (mtDNA) content and copy number are also largely altered in non-compacted hearts.

4. Diagnostics and therapeutic aspects of LVNC

The occurrence of LVNC has increased in recent years with a prevalence of 0.01–0.3%, a mortality rate of 5–12%, and is predominately found in males [44]. While most LVNC patients are asymptomatic or noted to have mild symptoms of chest pain, later stages of LVNC can lead to sudden cardiac death due to compromised systolic function. Although the initial diagnosis can be at any stage in life, most individuals with LVNC go undiagnosed until the 5th decade of life. Symptoms are diverse in patients with LVNC and can include heart failure, cardiac arrhythmias, fatigue, excessive sweating, breathing difficulties, compromised growth, and abnormal weight gain, while others do not exhibit any symptoms [44–46]. Hence, early diagnosis is key for timely supportive care.

Common diagnostic tools available for LVNC include echocardiography (echo), cardiac magnetic resonance imaging (cardiac MRI or CMR), electrocardiogram (ECG), cardiac computed tomography (CT), coronary angiograms and myocardial biopsy based on the myocardial thickening [47]. In most cases the first-line diagnostic testing of any heart diseases is echo, due to its availability and being low-cost in nature. Echo criteria include (1) noncompacted/compacted ratio of the two-layered endocardium of >2, (2) left ventricular deep endomyocardial trabeculations, and (3) deep recesses filled with blood visualized on color Doppler [48, 49]. However, the detection of LVNC in its early stage of development are challenging, with only around 0.3% of the patients being referred for an echo [50, 51]. Additionally, echo diagnostics are sometimes considered to be a 'too sensitive of a method' as overdiagnosis frequently occurs, particularly in the black patient population. Therefore, serial echo diagnosis is recommended in LVNC [52].

Alternatively, CMR is a well-established, high resolution, noninvasive, albeit more expensive approach, to confirm LVNC after an initial diagnostic echo. CMR

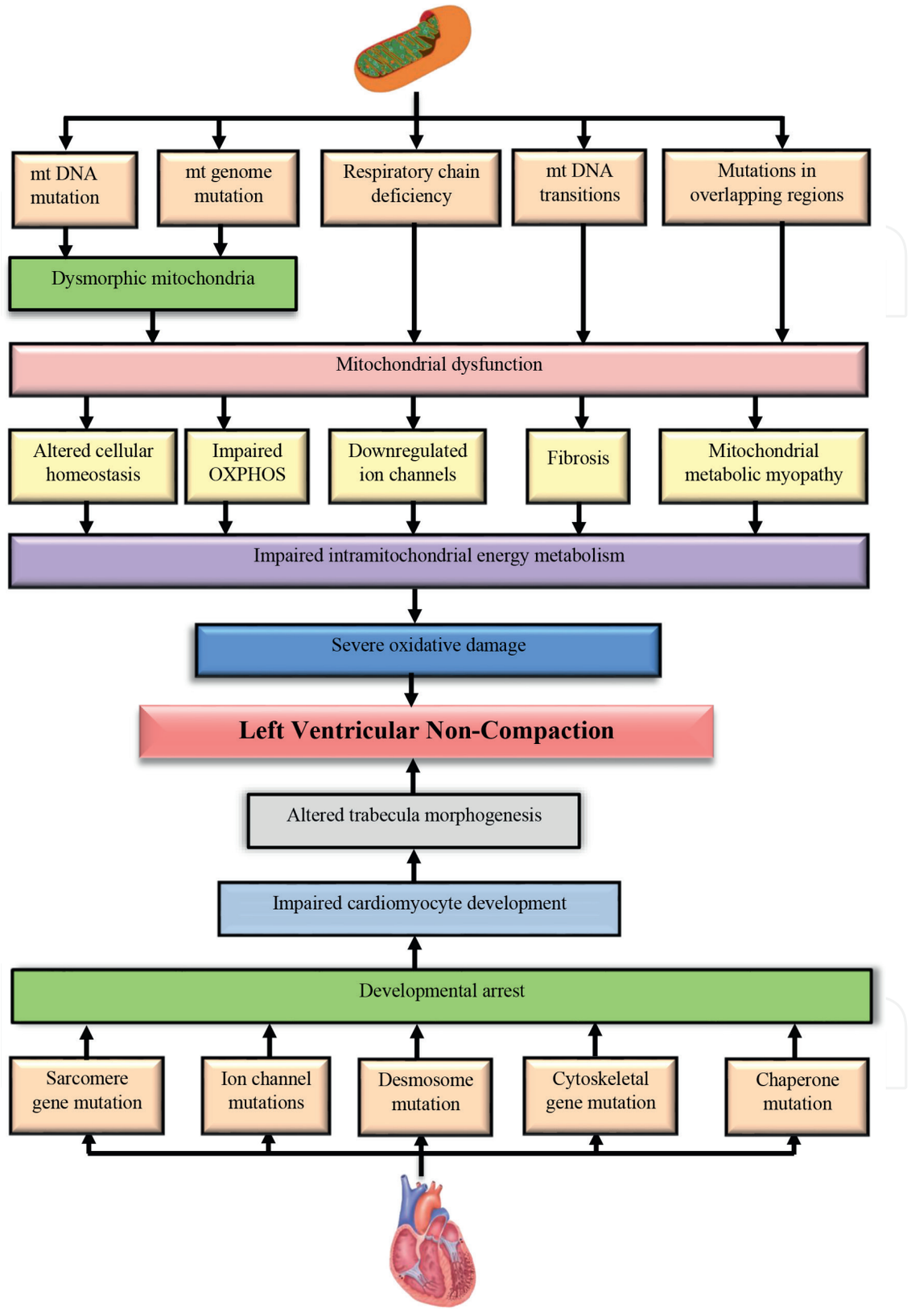

Figure 3.
Schematic overview of influencing factors in myocardial noncompaction: Differential contribution of mitochondria towards LVNC via mitochondrial dysfunction (mtDNA mutations, transitions, ETC defects, mt genome mutations) and involvement of genes associated with cardiomyopathies (sarcomeres, ion channels, cytoskeletal, chaperones, desmosomes).

offers an enhanced sensitivity, as CMR can detect myocardial trabeculations that can be enhanced with steady-state free-precession (SSFP) cine imaging [53, 54]. In CMR, the myocardial trabeculations, apex region and end-diastole ratio can be well monitored over time. Although CMR is associated with many challenges including a wide diagnostic testing timeline, high costs, and availability, it still remains the best approach as a diagnostic tool for LVNC. Unlike echo and CMR, CT imaging is less commonly used due to the ionizing radiation and lower detection ability of myocardial tissues. Nevertheless, this tool is widely used in evaluating other disease processes such as coronary arteries. Apart from the above-mentioned diagnostic tools, advances using blood for whole exome sequencing (PGxome diagnostic exome test) and copy number variation detection can be performed to study single gene defect or defects in gene sets associated with LVNC [55].

In research settings and invasive cardiac catheterization techniques, a more invasive method of histologic examination of cardiac muscle tissue biopsies is assessed. Histological analysis can identify abnormalities in the mitochondrial appearance as ragged red fibers, indicative of mitochondrial dysfunction, are suggestive of mitochondrial anomalies (Gomori Trichrome stain, **Figure 4**). A typical drawback of Gomori Trichrome Staining is the absence of these ragged red fibers in children, and therefore, it fails to detect mitochondrial disorders in neonates at early stages [56, 57]. An alternative method of early detection is the examination of cardiac tissue under electron microscopy for swollen disorganized mitochondria containing irregular cristae [57].

Importantly, around 40% of patients identified with LVNC are determined to have a familial genetic defect that impacts only cardiac function. However, while many genetic syndromes, metabolic disorders, and mitochondrial related anomalies are also associated with LVNC, in many cases the cause of LVNC is still unknown. As there is no cure to date, routine cardiac screening is an important part of the treatment of familial LVNC, with supportive therapy for LVNC patients being dependent on individual symptoms. Supportive therapy targeted to improved quality of life and overcome cardiac dysfunction includes medications to treat heart failure such as angiotensin-converting enzyme inhibitor, beta blockers, blood thinners, diuretics, and digoxin. In severe cases of LVNC, pacemaker implantation, cardioverter defibrillator, or heart transplantation is recommended. A recent case study in 2018 by Kimura

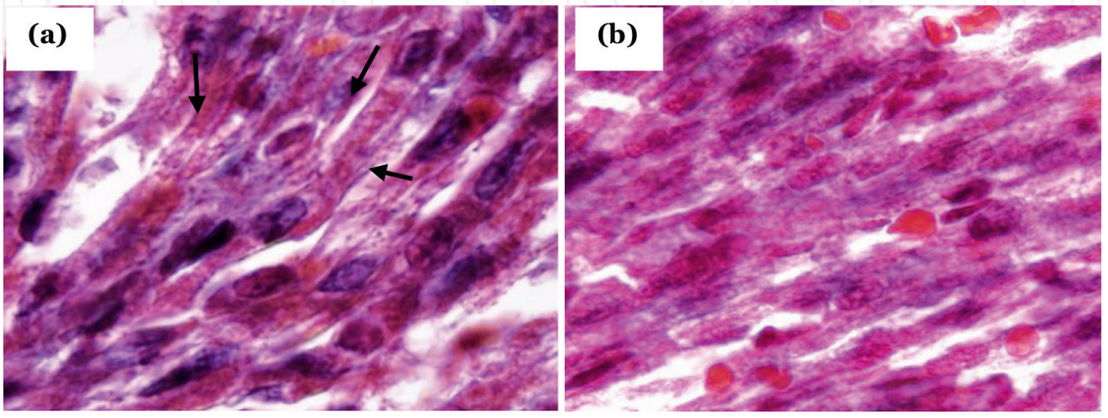

Figure 4.
Gomori Trichrome staining of cardiac tissue from an (a) hyper trabeculated heart and a (b) healthy heart: (a) arrows indicating dysmorphic mitochondria scattered as red-ragged fibers below the matrix of the membrane, (b) mitochondria appear organized and distributed across the cardiac tissue.

et al. [58], showed successful treatment of a near-fatal ventricular arrhythmia in an infant with LVNC using cardiac resynchronization therapy (CRT). These studies determined that with the implantation of a cardioverter defibrillator (preventive measure for cardiac arrest), dual chamber pacing initiation and CRT, effectively treated the mechanical dyssynchrony of the heart, with subsequent improvement in cardiac function.

Currently, there are no mechanisms to prevent LVNC or to return gain of cardiac function. While genetic testing can be done to identify gene mutations (**Table 1**) and determine the risk of passing these mutations to offspring, there are not therapeutic options to actively treat these gene mutations [74]. Future therapy that promotes personalized gene therapy could be a useful tool in treating LVNC. However, this approach could be highly challenging due to the complex genetics of LVNC.

5. Genes and related mutations associated with LVNC

A variety of gene mutations studied concerning other cardiomyopathies such as genes coding for sarcomere proteins [75], ion channels, cytoskeletal genes [76], chaperone proteins [77], and cellular signaling pathways have a significant association with LVNC [11, 78]. Specific genetic alterations include genes encoding β-myosin heavy chain (MYH7) [34, 79], α-cardiac actin (ACTC1) [80], and cardiac troponin T (TNNT2) [81], lamin A/C (LMNA) [82], ZASP (LDB3) [83], and taffazin (TAZ) [83, 84], cardiac myosin-binding protein C (MYBPC3) [85], and cardiac troponin I (TNNI3) [86] are associated with LVNC (**Table 2**).

Sarcomere gene mutations can lead to noncompaction with reduced ventricular function and hyper trabeculation [110]. Alpha-cardiac actin gene (ACTC) codes for cardiac muscle-specific alpha-actin protein, present in cardiac sarcomeres and cytoskeletal proteins, and is responsible for heart muscle contraction and generation of force to support the contraction. Novel mutations in the ACTC gene are linked to LVNC cardiomyopathies. Although, the novel protein-level amino acid sequence (A21V) mutations of ACTC1 resulting in familial LVNC are rare, it causes diverse cardiac anomalies. This resulting missense mutation in the ACTC1 gene creates structural changes to sarcomeres and their anchorage. In addition to these changes, these variants also modify the highly conserved nature of actin-like domains of the protein resulting in its destabilization with pathogenic consequences [80]. The MYH7 gene encoding for myosin heavy chain beta (MyHC-β) isoform is another primary sarcomeric protein in the adult heart. The ATPase activity of MYH7 powers the myosin power stroke within the myosin heads to convert energy that propels shortening of the sarcomeres. A heterozygous missense mutation (I467T) in MYH7 found in inherited cardiomyopathies presenting with a high penetrance and sudden death, can result in LVNC and hypertrophic cardiomyopathy (HCM) [111]. As the mutation site in MyH7 is close to the hydrophobic ATP binding pocket of the motor domain, the amino acid replacement of hydrophobic isoleucine with a non-polar threonine alters the structure subsequently effecting the ATPase activity of the motor domain [79, 80]. Cardiac Myosin binding protein C (MYBPC3) is another LVNC linked sarcomere protein. Infants with pathogenic truncating mutations in *MYBPC3* die at birth from HCM and LVNC complications. These mutations are believed to cause alterations in the primary contractile function of the heart and septal defects. However, the absolute relationship of contractile dysfunction to sarcomere protein mutations in the progression and pathophysiology of LVNC remains poorly understood [112].

Age/mean age at diagnosis	Patient gender	Complications observed	Diagnostic approach	Reference
7 years	5 males and 3 females	SVD, VA, SE, PVC, FD	Holter monitoring, intracardiac electrophysiological studies	Chin et al. [59]
47 years	24 males and 41 females	Hypokinesia, Akinesia, Dyskinesia	Echocardiography	Lofiego et al. [60]
Not reported	821 males and 627 females	LV dilatation, hypertrophy, and systolic dysfunction	Transthoracic echocardiography, MRI	Tamborini et al. [61]
33-year-old	Female	Myocardial sinusoids, high systolic ventricular pressure, external dyspnea, sinusoid anomaly	2D-echocardiography	Engberding et al. [28]
11 years	13,306 males and 12,283 females	Lower LVEF, higher LV ESV	Echocardiography	Borresen et al. [51]
47.4 years	183 males and 155 females	Lower LVEF, dyspnea, cardiomyopathy, left atrial enlargement	Transthoracic echocardiography and or MRI	Vaidya et al. [12]
90-year-old	Male	Asymptomatic until heart failure followed by progressive shortness of breath, body weakness	Color-flow Doppler echocardiography, electrocardiogram	Cevik et al. [62]
9 years	8 males and 1 female	Mostly asymptomatic, LVH	Electrocardiogram, chest X-ray, 2D-echocardiogram with Doppler interrogation	Alehan et al. [63]
53 years	71 males and 29 females	LVHT, associated neuromuscular disorders	Echocardiography	Stollberger et al. [64]
≤21 years	24 males and 18 females	Myocardial dysfunction, CVM, DCM, HCM	Echocardiography, Genetic testing (cardiomyopathy gene panel)	Miller et al. [65] (2017)
62-year-old	Female	Congestive heart failure, Bilateral crackles (mild symptoms)	Echocardiography, Color Doppler imaging	Lin et al. [66]
6-month-old	Infant (female)	Incessant ventricular fibrillation, cardiopulmonary arrest, polymorphic ventricular tachycardia, LV hypokinesis	Transthoracic echocardiography, Chest X-ray, Color Doppler imaging	Kimura et al. [58]

Age/mean age at diagnosis	Patient gender	Complications observed	Diagnostic approach	Reference
46 years	312 males and 2188 females	Cardiovascular and all-cause mortality, thromboembolic complications, ventricular arrhythmias	Echocardiography, MRI	Aung et al. [30]
41-year-old	Male	Chest pain, biatrial enlargement, right ventricular hypertrophy, global hypokinesis, lower LVEF	Electrocardiogram, MRI	Tian et al. [67]
Not reported (wide range of age groups studied)	6 males and 8 females	VSD, histiocytoid cardiomyopathy, hydrops fetalis, sudden death, heart failure	Echocardiography	Burke et al. [68]
29-year-old	Male	Dyspnea, pulmonary rales, fatigue, cardiomegaly, hepatomegaly, splenomegaly	Twelve-lead electrocardiography, twenty-four-hour Holter monitoring, speckle-tracking echocardiography, MRI, chest X-ray	Toader et al. [69]
57-year-old	Female	Heart failure, onset dyspnea	Echocardiography	Loria et al. [70]
36-year-old	Male	Shortness of breath, exercise intolerance, orthopnea, paroxysmal nocturnal dyspnea	Transesophageal echocardiogram, endomyocardial biopsy, transthoracic echocardiogram	Ayesha et al. [71]
69-year-old	Male	Atrial fibrillation, myocardial fibrosis	Electrocardiogram, post-cardiac arrest transthoracic echocardiogram	Bath et al. [72]
60-year-old	Female	Intermittent chest pain, increasing shortness of breath, decreased appetite, paroxysmal nocturnal dyspnea, orthopnea	Echocardiography, chest X-ray, CT scan	Kalavakunta et al. [73]

Table 1.
Genetic details and characteristics identified in clinical studies.

Notch signaling is a prime mediator of cardiac embryogenesis. Despite the anomalies in other signaling pathways, the dysfunction of the Notch pathway has a notable contribution to LVNC. Germline mutations in human myocardial MIB1 (mind bomb homolog 1) coding for E3 ubiquitin ligase that promotes the endocytosis of Delta and Jagged, (NOTCH ligands) are involved in LV noncompaction [113]. In these studies,

Affected genes	Gene name	Protein type	DNA variant	Cardiac manifestation	Ref no
DTNA	α-Dystrobrevin	Cytoskeletal protein	C362T, N49S	NLVNC, LVNC	[15, 83]*
LAMP2	Lysosome-associated membrane protein-2	Membrane glycoprotein	G928A transition	HCM, skeletal myopathy, DCM	[16, 87]
TAZ (G4.5)	Tafazzin	Phospholipid trans acylase	GIVS8-1C	ILVNC, DCM, BTHS	[75, 83]
HCN4	Hyperpolarization-activated cyclic nucleotide channel 4	Ion channel	G482R, Y481H	Brugada syndrome, Bradycardia, LVNC	[88]
SCN5A	Cardiac sodium channel	Ion channel	H558R	Brugada syndrome, LVNC, DCM	[89]
TMEM70	Transmembrane protein 70	Mitochondrial membrane	Y112X, 578delCA	HCM	[15]*
Nkx2–5	Nkx2-5	Transcription factor	A118S	LVNC, DCM, HF, AVB	[90]
FKBP12 (aka Fkbp1a)	Peptidyl-prolyl cis-trans isomerase	Immunophilin protein family	—	LVNC, VSD, DCM, CHD	[77, 91]
DNJAC19	Mitochondrial import inner membrane translocase subunit TIM14	DnaJ Hsp40 member C19	1G-C transversion in intron 3	DCM, DCMA	[16]*
BMP10	Bone morphogenetic protein 10	TGF-β super family proteins	V407I	LVNC, VSD, HT	[92]
LDB3	LIM-domain binding 3	Z-disk protein	G1876A, G163A	ILVNC, LVNC3, DCM, HCM	[15, 83, 93]
MYBCP3	Myosin binding protein C	Sarcomere thick filament	N948T, G490R, A833T	DCM, LVNC10	[82, 85, 94]*
MYH7	β-Myosin heavy chain 7	Sarcomere thick filament	L1793P, L387F	LVNC5, HCM, DCM	[33, 90, 94–96]*
ACTC	α-cardiac actin	Sarcomere thin filament	A21V, E101K	LVNC4	[97, 98]
TNNT2	Cardiac troponin T, type 2	Sarcomere thin filament	R141W, R131W, E96K	DCM, HCM, RCM, LVNC6, LVD	[75, 81]*
TNNI3	Cardiac troponin I	Sarcomere thin filaments	D190G, A2V	RCM, DCM	[86, 99]
TPM1	Tropomyosin-1	Actin binding protein	E40K, E54K, D159N, L113V	LVNC9, DCM, HCM	[16, 75, 99]*
LMNA	Lamin A/C	Nuclear membrane protein	R644C, R190W, V445E	LVNC	[82, 100]

Affected genes	Gene name	Protein type	DNA variant	Cardiac manifestation	Ref no
MT-ATP6	Mitochondrially encoded ATP synthase membrane subunit 6′	ATP synthase F_o subunit 6	T8528C, G8529A, C8558T, A9058G	LVNC	[101]
MT-ATP8	Mitochondrially encoded ATP synthase membrane subunit 8	ATP synthase F_o subunit 8	A8381G, C8858T	LVNC	[31, 96, 102]
MT-ND1	NADH: ubiquinone oxidoreductase core subunit 1	NADH dehydrogenase 1 enzyme	T3398C, T4216C, G15812A, A3397G	LVNC, MELAS, LHON	[40, 96]
MT-TL1	Mitochondrially encoded tRNA leucine 1	transfer RNA (UUR)	A3243G, A8344G	MELAS, MERRF	[16]
ANT2	Peroxisomal adenine nucleotide transporter-2	ADP/ATP translocase 2	G1409T polymorphism	DCM, LVNC/ LVHT	[103]
MIB1	Mindbomb homolog 1	E3 ubiquitin ligase	V943F, R530X	LVNC7, RVNC, DCM, HF	[78]
PRMD16	PR/SET Domain 16	Transcription regulator	K702X, N816S, P291L, L887P, V1101M, 1573dupC in exon 9	LVNC8, DCM	[75, 104]*
PLEC1	Plectin	Cytoskeletal protein	G4891T, G1019A	ARVC, DCM, LVNC/LVHT	[105]
MT-CYB	Cytochrome B	Component of complex III	T15693C, A15662G	LVNC, HCM	[40, 96]
ACTN2	α-Actinin 2	Cytoskeletal protein	M228T, L727R	HCM, DCM, LVNC	[106]
PRKAG2	Protein kinase AMP-activated non-catalytic subunit gamma 2	AMP-activated protein kinase (AMP-K)	H142A, T400N, N488I, E506K, R302Q	HCM, LVH	[16, 107]
PLN	Phospholamban	Integral membrane protein	R9C, L39X	DCM	[108, 109]

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ILVNC, isolated left ventricular noncompaction; NLVNC, non-isolated left ventricular noncompaction; LVHT, left ventricular hyper trabeculation; RVNC, right ventricular noncompaction; AVB, Atrio ventricular block; HF, heart failure; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; VSD, ventricular septal defect; BTHS, Barth syndrome; DCMA, dilated cardiomyopathy with ataxia syndrome; HT, hyper trabeculation; MELAS, mitochondrial encephalomyopathy; MERRF, myoclonic epilepsy with ragged-red fibers disorder; ARVC, arrhythmogenic right ventricle cardiomyopathy; CHD, congenital heart diseases; LVD, left ventricular dilation; RCM, restrictive cardiomyopathy [33].

Table 2.
Genes and associated mutations in cardiomyopathies.

MIB1 protein was noted to be vital in activating the NOTCH signaling pathway while cardiac deformity managed by two of the MIB1 autosomal dominant mutations (V943F and R530X) causes deregulation of Notch signaling resulting in LVNC. Furthermore, Luxan et al. [78] reported that myocardial inactivation of MIB1 results in the enlargement of the ventricular trabeculae and a thin compact myocardium.

Alterations in cytoskeletal genes have been linked with the LVNC development. The intermediate filament protein, lamin (lamin A/C) or LMNA, maintains the mechanical integrity of the nuclear envelope. Heterozygous LMNA gene mutations (R644C and R190W) are linked to familial and sporadic LVNC, although the mechanisms have not been elucidated to date. Furthermore, lamin A/C V445E mutations were found to be related to sudden death in LVNC patients [82]. Cardiac expressing alpha-dystrobrevin (DTNA) belongs to a dystrophin-related protein family that is significant in intracellular signal transduction. Genetic alterations in DTNA and dystrophin-associated glycoprotein complex (DAPC) located in sarcolemma provoke myocardial disorders targeting the systolic function of the heart [41]. Inactivation of DTNA leads to muscular dystrophy, skeletal myopathy, and cardiomyopathy characterized by deep trabeculations which are always observed in LVNC [76]. Congenital LVNC frequently accompanies neuromuscular disorders in patients with myotonic dystrophy type 1 (MD1), an autosomal dominant type of disorder resulting from a trinucleotide expansion (CTG nucleotide repetitions) in the dystrophia myotonica protein kinase (DMPK) gene [114].

6. Differential contribution of mitochondria towards LVNC

6.1 Mitochondrial DNA (mtDNA) mutations leading to dysmorphic mitochondria

mtDNA sequence variants are maternally inherited point mutations representing a predominate cause of inherited diseases within a tissue or organ. Studies performed on mitochondria isolated from patient's blood and *in vivo* cardiac tissues acknowledged the contribution of mtDNA mutations in the formation of cardiac noncompaction [115, 116]. In these studies, instability of cardiac-specific mtDNA is coupled to metabolic irregularities that impact cardiac functionality in response to a myriad of mitochondrial dysfunctions. Liu et al. [116] determined that hearts with noncompaction present with mitochondrial structural anomalies and have a reduced mtDNA copy number with the G4.5 gene on Xq28 that codes for acyltransferase tafazzin (TAZ); the first gene to be studied in detail in relation to the etiology of LVNC [117]. Tafazzin is a mitochondrial membrane component vital for proper functioning of the electron transport chain. This X-linked TAZ gene encodes for the mitochondrial membrane-associated phospholipid-modifying enzyme that alters cardiolipin through the addition of linoleic acid. As cardiolipin is a major player in the mitochondrial inner membrane and is requisite for the maintenance of mitochondrial shape, protein transport, and energy production within cells, it is essential for maintaining the organization of mitochondrial cristae [57]. TAZ gene mutations resulting in Bath Syndrome, perturbed mitochondrial cardiolipin metabolism and are associated with dilated cardiomyopathy. Inactivation of the TAZ gene produces dysfunctional tafazzin proteins. In this circumstance, linoleic acid is not present to alter cardiolipin. As a result, problems with normal mitochondrial shape and functions such as energy production and protein transport develop. High energy-demanding tissues including heart are more susceptible to cell death due to decreased mitochondrial energy

production [118]. Furthermore, TAZ deficiency impairs cardiolipin remodeling and alters the assembly and stability of mitochondrial super complexes of complex III and IV (intermittently impacting complex V as well) in the inner mitochondrial membrane [119].

These effects occasionally result in respiratory chain activity malfunctions. Mitochondrial transcription factor A (TFAM) is a nuclear-encoded protein that regulates the transcription, packaging, and stability of the mitochondrial genome. TFAM is crucial for the development and differentiation of the mitochondrial genome [120]. It is highly likely that TFAM regulates the mtDNA copy number by binding to the mtDNA promoter region to initiate transcription. Thus, the impact of TFAM on mtDNA copy number illustrates the direct influence of TFAM in mitochondrial function. Carnitine palmitoyl transferases (CPT) are mitochondrial enzymes involved in the transportation of Acyl-CoA to the mitochondrial Matrix for β-oxidation. Located in the outer mitochondrial membrane, CPT I convert fatty acyl CoA into fatty acylcarnitine. Located in the inner mitochondrial membrane, CPT II reconverts fatty acylcarnitine into free carnitine and fatty acyl CoA for β-oxidation for energy generation. Inherited defects in CPT I, II or CPT translocases can result in failure of long-chain fatty acids transportation into the mitochondria for oxidation. This can result in a significant reduction in the ratio of free CoA to acyl CoA thus ultimately disrupting metabolic pathways and decreasing cardiac ATP production [24].

6.2 Mitochondrial dynamics and dysfunction

Adult cardiomyocytes are enriched with hypo-dynamic mitochondria that lack an interconnected reticular network. The fusion-fission cycle of cardiac mitochondria is common in cardiomyocyte mitochondrial dynamics [121]. Regulated by specialized proteins, enzymes, and adapter proteins that physically alter mitochondrial membranes, a delicate balance between mitochondrial fusion and mitochondrial fission is important in the regulation of cellular health. In adult cardiomyocytes progressive mitochondrial fission and fusion cycles occur frequently with the aid of proteins needed for the mitochondrial network remodeling. The key aspects of mitochondrial dynamics can be studied with cardiac-specific ablation of mitochondrial fission and fusion protein genes. As the cardiomyocyte mitochondria exhibit a certain degree of dynamism [122, 123], inability for the fusion or fission process could result in smaller or enlarged mitochondria, respectively. Hence, the imbalance between constant ongoing process of fusion and fission cycle are associated with increased caspases activity and subsequent cell death.

Mitochondrial dysfunction is frequently interrelated with LV noncompaction. Primary mitochondrial dysfunction arises from mutations in mitochondrial proteins involved with OXPHOS. Mitochondrial dysfunction refines mitochondrial dynamics with this phenomenon being associated with a variety of cardiac pathologies. For example, the MYH7 coding myosin protein is associated with the structure and function of cardiac sarcomere. Besides, the mutations in MYH7 linked with HCM and LVNC, makes myosin an important protein in cardiac function as defects in MYH7 expression are a common cause of cardiomyopathy [79]. Friedreich's ataxia (FRDA) is an example of a heart disease arising from mitochondrial dysfunction. FRDA is caused by the trinucleotide GAA expansion in the first intron of FXN gene (codes for mitochondrial matrix iron chaperone protein, frataxin) [123] with this triplet expansion resulting in transcription silencing and diminished frataxin expression. As a result, this mitochondrial localized protein influences iron homeostasis and

respiratory control. Therefore, impaired FXN gene function in FRDA patients is associated with dysfunctional ETC complexes, specifically the complex III with high ROS levels suggesting altered mitochondrial function [124].

6.3 Mitochondrial metabolic myopathy resulting from respiratory chain complex deficiency

Mitochondrial cardiomyopathy, a distinct myocardial condition is denoted by improper cardiac muscle structure and function accompanied by genetic defects in the mitochondrial respiratory chain. Various genetic anomalies are detected in genes regulating mitochondrial activities or in genes coding for ETC complexes or in genes that code for proteins necessary in assembling and transporting.

Peroxisomal adenine nucleotide transporter-1 and 2 (ANT-1 and ANT-2) in humans are ADP/ATP carriers with two main functions; to catalyze mitochondrial-cytosol ATP/ADP exchange and regulation of the mitochondrial inner membrane mitochondrial permeability transition pore (mtPTP). The ATN-1 isoform influencing the mtPTP towards a more open state while ATN-2 is involved in the guiding the closure of the mtPTP. Within the heart, muscles, and brain ANT-1 is the predominant isoform while the second isoform ANT-2 is expressed systemically. However, ablation of ANT-1 isoform does not impair fetal development; but does result in hypertrophic cardiomyopathy in the postnatal period. In contrast, a study published in 2016 by Kokoszka et al. [125] identified the embryonic lethality of ANT-2 null mutations to be associated with a distinct cardiac developmental defect consistent with LVNC/LVHT; characterized by swollen mitochondria in cardiomyocytes and hyperproliferating cardiomyocytes. In these studies, mice with ANT-2 mutations, cardiac maturation progresses during embryonic days E9.5 and E13.5. However, by day E14.5 mice exhibit embryonic lethality. Histologic analysis of the heart revealed hyper-proliferating cardiomyocytes, decreased apoptosis, and swollen mitochondria with few cristae, and mtPTP open for transport. These findings suggest that loss of ANT-2 regulation of mtPTP closure results in cardiomyocytes maintenance in an immature state with a reduction in total number of contractile fibers and loss of organization thus paving the way for the continued immature cardiomyocyte proliferation resulting in LVNC and embryonic lethality [37].

6.4 Mitochondrial genome mutations in LVNC

In most of the reported cases, LVNC is related to the alterations in nuclear DNA encoded mitochondrial genes. Defects in the mediator of a mitochondrial fusion protein, Mitofusins 1 & 2 (MFN 1 & 2) affect the mitochondrial morphology during embryogenesis. Mediated by MFN1 and 2, mitochondrial fusion facilitates the exchange between the contents of mitochondrial membrane and matrix to help in maintaining the mitochondrial function. Mutations in any of the MFN's results in mitochondrial fragmentation that affects the symmetry of fusion and fission events [126]. As cell apoptosis is significantly influenced by the mitochondrial fusion and fission, cells lacking apoptosis related genes such as caspases 3, 7, 8, FADD, and c-FLIP are also susceptible to develop cardiac noncompaction. Caspases 3 and 7 are potential regulators of mitochondrial apoptosis. A3243G transition in tRNALeu(UUR) gene is another common mitochondrial mutation [127, 128].

The tRNALeu(UUR) gene encodes for mitochondrial transfer ribonucleic acid (tRNA) for leucine (tRNALeu) and this nucleotide alteration was studied in both HCM and LVNC [129]. Other studies show that A3243G mutation related disorders

cause alterations in nearly 56 different genes, thus having a broad spectrum of impact. The A to G transition at the 3243rd position in tRNALeu (UUR) gene results in diminished glucose oxidation rate, NADH response, and mitochondrial membrane potential that ultimately affects ATP production [127, 130]. Lastly, a A8381G transition in ATPase subunit 8 genes (ATPase 8) was observed in a patient having LVNC complications [43, 102, 115]. These arising missense mutations impact within the ETC complex V that could alter the ATPase complex stability, directing to reduced ATP production [43, 131].

6.5 Mitochondrial DNA transitions in LVNC

Single mutations arising from mtDNA transitions are responsible for an abnormal diseased phenotype. mtDNA transitions mutations occur when there is a replacement of the complementary nucleotide (A replaced with G, T replaced with C and vice versa). One example is found in the mitochondrially encoded NADH: ubiquinone oxidoreductase core subunit 1 (mt-ND1) encoding gene for the NADH dehydrogenase 1 enzyme that is part of complex ETC complex I, which is active in mitochondria. Here, a single nucleotide transition (T → C) at a highly conserved nucleotide position (T3398C) is within the region of the *ND1* gene of the mt genome. This particular mtDNA transition results in the conversion of methionine to threonine at the 31st amino acid position was identified in patients suffering from cardiomyopathy [39]. A case report presented by Finsterer et al. [40] investigated the combination of A → G transition at the nucleotide position of 15,662 in novel mitochondrial cytochrome B and three of the known mutations (T3398C, T4216C, G15812A) in *ND1* gene. These above-mentioned mutations were found to be in association with left ventricular hyper trabeculation and some clinical conditions. Later studies determined that a homoplasmic A → G transition at the nucleotide position of 8381 in the ATPase8 gene, investigated by Finsterer et al. [129] resulted in an amino acid substitution of alanine to threonine. Their findings revealed the correlation of LVNC with A8381G mtDNA transition that develop later in adulthood.

6.6 Mutations in overlapping regions in LVNC

The ETC complex V, known as ATP synthase, is made up of 13 protein subunits. Two of the gene mutations in mitochondrial genome or the nuclear genes result in complex V deficiency. The mitochondrial-encoded protein subunits of complex V, ATPase 6, and ATPase 8 overlap in the mitochondrial genome and undergo polycistronic fashion of transcription. The nucleotide position 8528 is within the overlapping region that codes for ATPase 6 and ATPase 8 subunits. The phenotypic representation of point mutation affects ATPase 6 and ATPase 8 genes of complex V. This is commonly seen in identical mitochondrial mtDNA mutations in children [42]. Here, the nucleotide alteration of m. T8528C, causes a M1T in the start codon in ATPase 6 subunit (One might expect to have alterations in the protein translation initiation. However, it has not been reported so far, thus making the function of altered ATPase 6 unclear) and W55R missense mutation in ATPase 8 subunit. Additionally, 2 other overlapping mutations in G8529A and C8558T affecting both the subunits have been reported in patients exhibiting cardiomyopathies [101, 115, 132]. This kind of overlapping pathogenic mutations could cause reduced ATP synthesis by affecting mitochondrial energy production and complex I, II and III for which the mechanism is still unknown [42].

7. Conclusion

This review overlays the aspects of gene mutations relevant to mitochondrial energetics, cardiomyocyte function, and LV myocardial noncompaction. Understanding the rudimentary causes of LVNC imparts helpful information in the prognostic evaluation and early diagnosis of LV noncompaction. Further examination of mitochondrial involvement in cardiac noncompaction leading to heart failure would facilitate advances in the therapeutic treatment of this disease process.

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