

Organelle homeostasis disruption: A driving force in the progression of cardiomyopathy (Review)

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Abstract. Cardiomyopathy is a complex heart disease with structural and functional defects of the myocardium, often leading to poor clinical outcomes. While traditional research has focused on myofibrillar pathology and ion channel dysfunction, emerging evidence indicates that organelle homeostasis serves a central role in the pathogenesis of the disease. Mitochondrial dysfunction disrupts energy metabolism, calcium handling, dynamics and mitophagy. Golgi fragmentation, impaired glycosylation and abnormal vesicular trafficking jeopardize protein maturation and secretion. Endoplasmic reticulum stress causes myocardial injury via unfolded protein response, calcium dyshomeostasis and disruptions of lipid metabolism. Lysosomal degradation is disrupted by autophagic dysfunction, enzyme dysregulation and calcium signaling abnormalities. Ribosomes regulate proteostasis by defective biogenesis, quality control and translational dysregulation. Nuclear envelope instability and intercalated disc dysfunction disrupt normal mechanical and gene regulation in the development of cardiomyopathy. In combination, these findings support the concept of cardiomyopathy as a multi-organelle network disease driven by coordinated dysfunction of interconnected organelles. This review systematically summarizes current evidence on organelle-specific and inter-organelle mechanisms underlying cardiomyopathy, highlighting how disrupted organelle homeostasis collectively contributes to disease initiation and progression.

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1. Introduction

Cardiomyopathy is a heterogeneous group of conditions with structural and/or functional myocardial lesions, usually in the form of cardiac dilatation, arrhythmias or heart failure (1). Incidence and mortality rates continue to rise globally, making it one of the most notable causes of cardiovascular-related mortality, with the incidence in China reaching 11.76 per 100,000 person-years and an overall mortality rate of 3.38% (2). Cardiomyopathies, based on etiology and clinical presentation, are categorized into dilated, hypertrophic, restrictive and arrhythmogenic right ventricular types (3). The pathological substrate of cardiomyopathy is multifactorial, and comprises genetic mutation, metabolic derangement, inflammatory activation and oxidative stress. Present evidence has highlighted that impaired cellular energy metabolism, calcium dysregulation and apoptosis are the principal molecular processes underlying the onset and progression of the disease (4). Intracellular homeostasis disruption thereby leads to systemic abnormalities in cardiomyocyte energy metabolism, protein quality control and signal transduction and eventually culminates in cardiac remodeling and contractile dysfunction (5).

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Elucidation of these pathogenic mechanisms is important for deciphering the molecular pathogenesis of cardiomyopathy and identifying new therapeutic targets.

The pathological alterations of cardiomyopathy are primarily at the level of cardiomyocytes, whose dysfunction is responsible for the development of the disease. Cardiomyocytes contain different membranous and non-membranous organelles such as mitochondria, endoplasmic reticulum (ER), Golgi apparatus, lysosomes and ribosomes that collectively create a complex intracellular network of organelles to keep cardiac function intact. Prior research has focused on myofibrillar (6,7) and ion channel abnormalities (8,9); however, recent advances in cell biology and high-resolution microscopy have demonstrated that organelle homeostasis serves a major role in the pathogenesis of cardiomyopathy (10-12). Since mitochondrial dysfunction was originally associated with cardiomyopathy during the second half of the twentieth century (13), more evidence has uncovered other mechanisms, including ER stress (14), Golgi apparatus fragmentation (15), lysosomal-autophagic dysfunction (16) and defects in ribosomal quality control (17), which have provided novel insights into the molecular pathophysiology of cardiomyopathy. Organelles not only regulate cardiomyocyte metabolism and survival, but also orchestrate global-cardiac reprogramming of metabolism and stress adaptation, suggesting that the targeting of organelle biology represents a valuable direction for mechanistic exploration and pharmacological identification of novel drugs.

The present review summarized the advances in understanding the functions of several organelles in cardiomyopathy. Mitochondrial energy metabolism disorders, calcium overload and imbalanced dynamics have been reported to be marked contributors to cardiomyocyte dysfunction; ER stress and disturbed ER-mitochondria coupling serve a key role in protein homeostasis and calcium signaling; Golgi fragmentation and aberrant glycosylation are detrimental to membrane protein traffic and signaling pathways; lysosomal dysfunction and impaired autophagic flux compromise intracellular degradation; and ribosome biogenesis and translational regulation defects reveal pathological alterations at the protein synthesis level. Disruption of nuclear envelope integrity and intercalated disc architecture perturbs essential mechanical signaling and gene regulatory programs. Together, these findings indicate that cardiomyopathy is a systemic illness of deranged multi-organelle homeostasis. In the future, the integration of single-cell omics, spatial transcriptomics and high-resolution imaging technologies will enable dynamic dissection of inter-organelle communication and spatiotemporal coordination, thereby redirecting cardiomyopathy research from 'single-organelle pathology' to a 'global organelle network pathology' and paving the way to precision therapeutic strategies.

2. Materials and methods

A systematic literature search was performed in PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) to identify studies related to cardiomyopathy and organelle biology published up to October 2025. The search strategy combined controlled vocabulary (MeSH terms) and free-text keywords. The following Boolean search string was used: ('Cardiomyopathy' OR 'heart failure') AND ('mitochondrial dysfunction' OR 'endoplasmic

reticulum stress' OR 'Golgi apparatus' OR 'lysosome' OR 'ribosome' OR 'nuclear envelope' OR 'intercalated disc' OR 'organelle crosstalk' OR 'proteostasis' OR 'cellular homeostasis'). In addition, MeSH terms including Cardiomyopathies, Mitochondria, Endoplasmic Reticulum, Golgi Apparatus, Lysosomes, Ribosomes, Nuclear envelope and Intercalated disc were incorporated to increase retrieval sensitivity.

Study screening and selection. A total of two independent reviewers conducted a three-stage screening process: i) Title screening; ii) abstract screening; and iii) full-text evaluation. Studies were included if they met the following criteria: i) Investigated organelle structure, function or homeostasis in the context of cardiomyopathy; ii) provided mechanistic evidence at the cellular, animal or human level; and iii) reported molecular, biochemical, ultrastructural or signaling-based insights relevant to cardiac pathophysiology. Studies were excluded if they: i) Lacked relevance to organelle biology or cardiomyopathy mechanisms; ii) did not present mechanistic data (such as commentary, purely descriptive reports); and iii) focused on non-cardiac tissues without cardiovascular implications. The reference lists of key articles were also manually screened to identify additional eligible studies. Any disagreements were resolved through discussion until consensus was reached.

Data extraction and evidence classification. For each included study, data were extracted on the type of organelle investigated, experimental model and mechanistic pathways. Evidence was categorized into three levels: i) Cellular evidence, including *in vitro* experiments, molecular signaling and organelle function assays; ii) animal evidence, including knockout/knock-in models, disease phenotyping, mechanistic validation; and iii) human evidence, including patient tissue, clinical correlations and genetic variants.

Final study set. A total of 166 peer-reviewed articles met the inclusion criteria and were synthesized narratively, with emphasis on mechanistic pathways and organelle-specific contributions to cardiomyopathy.

3. Mitochondrial dysfunction in the pathogenesis of cardiomyopathy

Over the years, accumulating evidence has shed light on the pivotal position occupied by mitochondria in the pathogenesis and progression of cardiomyopathies. Mitochondria not only act as the primary source of cellular energy, but also participate in various biological processes, including calcium homeostasis, control of oxidative stress and apoptosis (18,19). Mitochondrial dysfunction has been shown to induce myocardial disturbances in energy metabolism (20), cellular injury (21) and cardiac failure (22). Therefore, understanding the mechanisms through which mitochondria are implicated in cardiomyopathy is required in order to study its pathogenesis at a deeper level and for the identification of new therapeutic targets.

Mitochondrial metabolic dysfunction. Mitochondria synthesize ATP through oxidative phosphorylation to sustain cardiomyocyte contractile activity (23). Mitochondrial energy

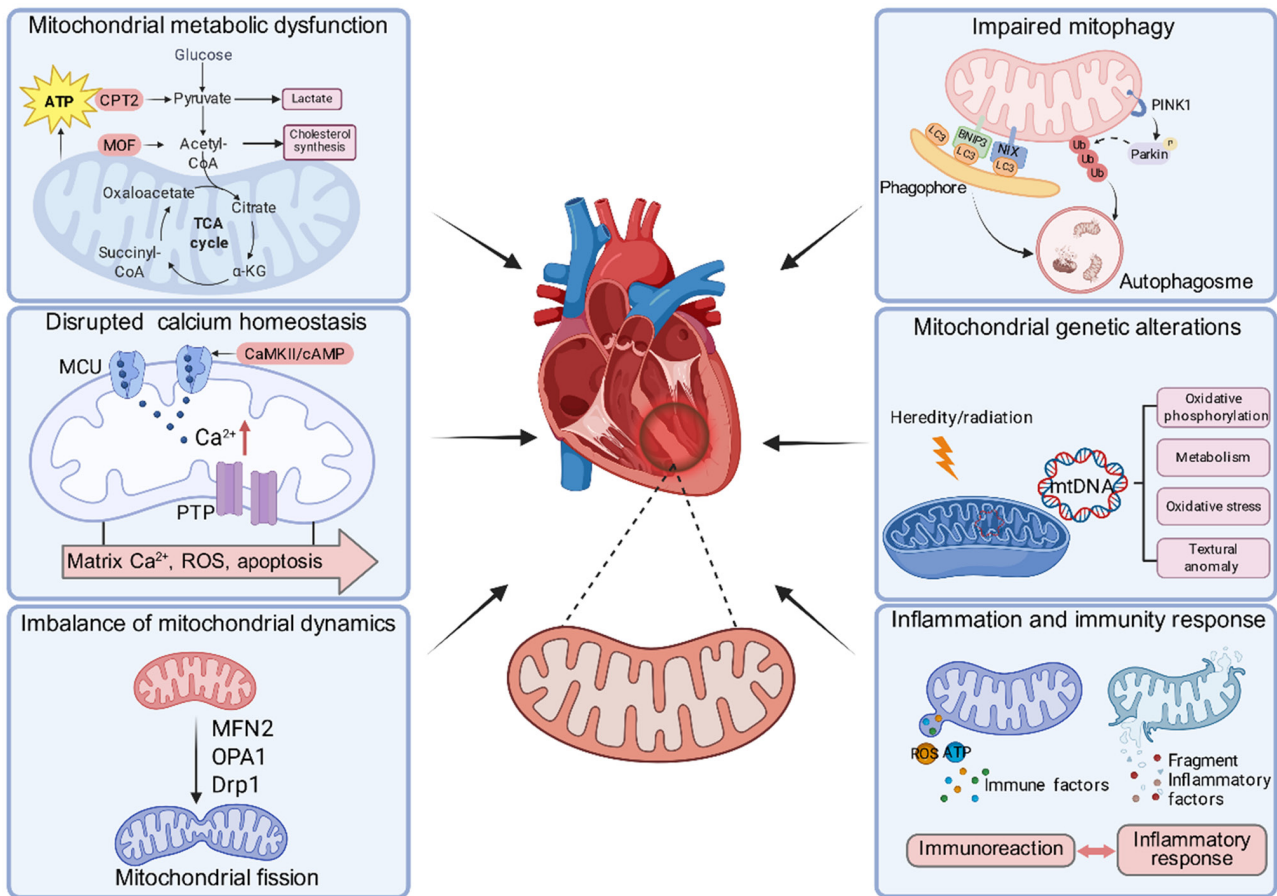


Figure 1. Schematic illustration of mitochondrial dysfunction in the pathogenesis of cardiomyopathy. Defective mitochondrial metabolism and dynamics induce oxidative stress, calcium imbalance, apoptosis and inflammation, ultimately contributing to cardiac remodeling and functional decline. ATP, adenosine triphosphate; MOF, males absent on the first; CPT2, carnitine palmitoyltransferase 2; ROS, reactive oxygen species; mtDNA, mitochondrial DNA; MCU, mitochondrial calcium uniporter; CaMKII, calcium/calmodulin-dependent protein kinase II; cAMP, cyclic adenosine monophosphate; PTP, permeability transition pore; MFN2, mitofusin 2; OPA1, mitochondrial dynamin-like GTPase; Drp1, dynamin-related protein 1; PINK1, PTEN-induced kinase 1.

metabolism disruption is a notable characteristic in cardiomyopathy pathogenesis and development, which is characterized by impaired oxidative phosphorylation and increased glycolysis compensation (24). Previous research has indicated that patients with heart failure exhibit reduced activities of mitochondrial complexes I and IV, in conjunction with loss of mitochondrial membrane potential, suggesting a close association between cardiac failure and mitochondrial metabolic dysfunction (25). Furthermore, reduced activity of the major fatty acid oxidation enzyme carnitine palmitoyltransferase 2 leads to the accumulation of long-chain acylcarnitines, which subsequently inhibit pyruvate dehydrogenase function, impair glucose uptake and contribute to diabetic cardiomyopathy pathogenesis (26,27). In addition, the mitochondrial lysine acetyltransferase MOF is also increased in heart failure; MOF overexpression leads to mitochondrial dysfunction and cardiac remodeling, suggesting that MOF can contribute to cardiomyopathy (28). Overall, these metabolic derangements are accountable for poor energy supply to cardiomyocytes, reduced efficiency of myofilament sliding and causation of cardiac dysfunction (Fig. 1).

Disrupted mitochondrial calcium homeostasis. Mitochondria uptake cytosolic calcium ions through the mitochondrial calcium uniporter (MCU) to buffer calcium

transients and regulate cellular metabolism (18). In cardiomyopathies, defective sarcoplasmic reticulum release of calcium or MCU malfunction leads to mitochondrial overload of calcium, which leads to faulty opening of the mitochondrial permeability transition and apoptosis or necrosis (29). Previous research has demonstrated that MCU expression is dysregulated in heart failure and cardiac hypertrophy, leading to mitochondrial calcium overload and dysfunctional mitochondria (30). Suppressing abnormal MCU expression inhibits cardiomyocyte hypertrophy and mitochondrial dysfunction, thus improving cardiac performance (31). Furthermore, calcium/calmodulin-dependent protein kinase II and cyclic adenosine monophosphate response element-binding protein signaling pathway are prominent players in angiotensin II-induced cardiac hypertrophy via the facilitation of the transcriptional activation of MCU, leading to exacerbation of mitochondrial calcium overload and oxidative stress (32).

Imbalance of mitochondrial dynamics. Mitochondria preserve structural and functional integrity by performing markedly coordinated and dynamic fission and fusion cycles. Proteins involved in mitochondrial dynamics, such as mitofusin-2, optic atrophy 1 and dyamin-related protein 1 (Drp1), have been demonstrated to serve key roles in the pathogenesis of cardiomyopathies (33). In particular, in diabetic

cardiomyopathy models, dysregulated Drp1-mediated excessive mitochondrial fission leads to increased mitochondrial fragmentation, augmented oxidative stress and deteriorated cardiomyocyte function (31). This type of fragmentation not only reduces the surface area of cristae and the effectiveness of oxidative phosphorylation, but also predisposes mitochondria to membrane potential depolarization, thereby initiating apoptotic mechanisms. Drp1 inhibition was shown to effectively attenuate pressure overload-induced cardiac hypertrophy and heart failure (34). Furthermore, cardiac-specific deletion of Krüppel-like factor 9 (Klf9) causes mitochondrial fragmentation and dysfunction, indicating that Klf9 serves a notable role in mitochondrial dynamic regulation and cardiac function (35).

Impaired mitophagy and mitochondrial quality control. Mitochondrial autophagy (also known as mitophagy) is a critical quality control process where the damaged or dysfunctional mitochondria is targeted and removed, which is mainly controlled by the PTEN induced kinase 1 (PINK1)-Parkin pathway and receptor-dependent mitophagy mechanisms such as BCL2 interacting protein 3 (BNIP3) and FUN13 domain containing 1 (FUNDC1) (36). Diabetic and ischemic cardiomyopathies involve damage to the PINK1-Parkin-mediated mitophagy machinery, leading to a failure to clear the depolarized mitochondria, thereby increasing mitochondrial damage and cellular injury (37). These dysfunctional mitochondria also become major generators of reactive oxygen species (ROS), which in turn further enhance oxidative damage, cause cardiomyocyte contractile dysfunction and disrupt genomic integrity (38). In addition, previous research has revealed that the expression of BNIP3 is abnormally upregulated in the myocardium of patients with dilated cardiomyopathy (DCM), which suggests that BNIP3 is able to induce disease progression by triggering overactive mitophagy or activating noncanonical apoptotic pathways (39).

Mitochondrial genetic alterations in cardiomyopathy. Mutations in mitochondrial DNA (mtDNA) and nuclear-encoded gene mutations of mitochondrial genes are important genetic etiologies of cardiomyopathies of mitochondrial origin (40). Pathogenic mtDNA mutations can prevent oxidative phosphorylation through defective expression or function of respiratory chain complexes of mitochondria, thus compromising myocardial energy homeostasis (41). Hypertrophic cardiomyopathy has a point mutation m.4300A>G, reflecting the pathological metabolic demand and energy dependency of cardiomyocytes (42). In addition, nuclear gene mutations encoding mitochondrial proteins, such as valyl-tRNA synthetase 2, which participate in mitochondrial translation, have been linked to mitochondrial encephalomyopathy, a cardiomyopathy syndrome that is attested to the contribution of nucleo-mitochondrial interactions to preserving cardiac mitochondrial integrity (43,44). In addition, other genomic studies identified a series of rare mtDNA variants in patients with heart failure, some correlating with mitochondrial respiratory competence changes, production of ROS and myocardial contractile performance (45). Furthermore, accumulation of somatic mtDNA mutations caused by age or oxidative stress could also lead to mitochondrial dysfunction, which perpetuates disease progression and adaptive cardiac remodeling (46). Together, these findings

illustrate the intricacies of mitochondrial genetics and cardiac energetics and provide a new understanding of the genetic process of cardiomyopathy as well as hope for novel precision therapeutics for mitochondrial genome integrity.

Mitochondrial regulation of cardiac inflammation and immunity. Mitochondria are central regulators of the innate immunity that interface cellular metabolism and immunological signaling (47). In response to mitochondrial stress or damage, mitochondria induce the release of a variety of molecules such as mtDNA, ATP, cardiolipin and ROS, which act as damage-associated molecular patterns (DAMPs) (19,48). These DAMPs trigger intracellular pattern recognition receptors such as the toll-like receptor 9 and NLR family pyrin domain containing 3 inflammasome to induce vigorous inflammatory cascades (49). These pathway stimulations accelerate immune cell recruitment and invasion, induce pro-fibrotic signaling and generate pathologic myocardial remodeling, a process most notably engaged in the pathogenesis of the progression from viral myocarditis to dilated cardiomyopathy (DCM) (50). Mechanistic research has also shown cristae mitochondrial structural disruption to be a potent inducer of mtDNA release, promoting the cGAS-STING-induced type I interferon response and augmenting inflammatory injury (51). Mitochondrial damage also interacts with oxidative stress and metabolic derangement to synergistically amplify immune activation and cardiomyocyte injury (52). Together, these observations characterize mitochondria not only as energy-generating organelles but also as signaling functional complexes that regulate inflammatory and immune responses in the heart and offer new therapeutic targets for reducing myocardial injury and preventing heart failure.

4. Golgi apparatus as a contributing factor in cardiomyopathy pathogenesis

In complex network of organelles, the Golgi apparatus serves a notable regulatory role in maintaining post-translational modification, protein sorting and vesicular trafficking. Increased evidence supports the Golgi apparatus structural and functional dysfunctions as key to the development and progression of cardiomyopathy. The subsequent section provides brief summaries of research advances in the role of the Golgi apparatus in cardiomyopathies from various pathological process viewpoints.

Golgi fragmentation and structural remodeling. During pressure overload, ischemic injury and hereditary cardiomyopathies, the Golgi apparatus undergoes substantial structural reorganization, with loss of the characteristic flattened stacks of cisternae and presence of scattered, punctate or ring-shaped structures, a phenomenon referred to as ‘Golgi fragmentation’ (53,54). Fragmentation is triggered by different mechanisms such as abnormal gene expression, disruption of the microtubule cytoskeleton and oxidative stress (55). It exerts a direct impact on defective protein secretion, disruption of vesicular transport and dysregulation of signal transduction, which can lead to cell cycle arrest, induction of stress response and even initiation of programmed cell death (56). Previous research has demonstrated that applying combined RNA-sequencing and proteomic analysis on myocardial tissue from patients with DCM can help identify acute dysregulation

of genes essential to the Golgi apparatus architecture. For example, in human hearts with DCM, golgin A2 is notably downregulated and associated with Golgi fragmentation. In addition, its expression level is also closely associated with plasma N-terminal pro-B-type natriuretic peptide concentrations (57). Similarly, in human doxorubicin-treated cardiomyocyte AC16 cells, extensive Golgi fragmentation and increased natriuretic peptide secretion stress were noted (57). In addition, Golgi fragmentation was identified to occur in left atrial biopsies of individuals with chronic atrial fibrillation, and disruption of the microtubule network and activation of CDK5 were closely associated with alterations in the structure of the Golgi apparatus (58).

Dysregulation of protein glycosylation. The Golgi apparatus is pivotal to cardiomyocyte homeostasis by orchestrating protein glycosylation, which is a crucial activity in protein correct folding, trafficking and functional maturation. The cardiomyocytes in metabolic cardiomyopathy and amyloid cardiomyopathy undergo an increased burden of protein folding and glycosylation changes (59). As the central protein glycosylation center, the Golgi apparatus is vital to ion channel, receptor and secreted factor integrity and function by maintaining their stability and function. Golgi apparatus impairment can therefore impact cellular signaling and myocardial energy metabolism (60). Consistent with this, MGAT1 N-glycosylation enzyme downregulation has been shown to decrease the glycosylation of integrin β 1, impairing cardiomyocyte-extracellular matrix interactions (61). Furthermore, the enzyme GALNT2 O-glycosylates the cardiac sodium channel Nav1.5, influencing membrane targeting and stability, and is associated with arrhythmia development (62).

Vesicular transport dysfunction and secretory imbalance. As cardiomyopathy develops, the Golgi apparatus not only exhibits morphological fragmentation but also manifests systemic disruption in transport pathways. Transcript and proteome analysis of myocardial tissue from patient with DCM revealed marked upregulation of anterograde transport genes and concurrent downregulation of retrograde transport genes, leading to dysregulated trafficking and secretion processes (57). This transport deficiency leads to abnormal protein accumulation in the vesicles or Golgi lumen and increases ER-Golgi system stress. Secreted factor and vesicle functional assays such as intravesicular accumulation and secretion competence of natriuretic peptides have been used in previous studies as markers for cardiomyopathy or heart failure severity (57,63). At the molecular level, COPII/COPI-mediated secretory machinery as well as microtubule-based ER-Golgi and Golgi-ER retrograde traffic machinery are implicated (64,65), although the proteins dysregulated in the various subtypes of cardiomyopathy remain to be fully elucidated. These findings highlight the critical role of the Golgi apparatus in the regulation of cardiomyocyte secretory homeostasis and cardiac intra- and intercellular signaling.

Golgi-phagy. Evidence indicates that fragmentation of the Golgi apparatus could be a novel autophagic substrate for selective degradation, termed 'Golgi apparatus autophagy' (Golgi-phagy) (66). The Golgi apparatus, in physiological conditions, plays a role in the regulation of autophagy by secreting autophagy-related proteins. In cardiomyopathies, mild Golgi-phagy can be protective, but excessive activation

consumes its functional structure, creating a vicious cycle (67). Previous research has demonstrated that fragmented Golgi apparatus is recognized by autophagy receptors under metabolic or toxin stress, and the YIPF3/YIPF4-ATG8/LC3 complex is at the center in deciding the degradation of the Golgi apparatus components (68,69). Recent evidence further indicates that, under Golgi apparatus stress or post-Golgi trafficking blockade, LC3 can undergo lipidation and be recruited directly to the Golgi apparatus, suggesting that stressed Golgi apparatus may activate adaptive signaling programs instead of being targeted for classical autophagic degradation (70). The Golgi phosphoprotein 3 protein, which resides in the Golgi apparatus, can also regulate the level of O_2^- by modulating autophagy-related processes to impact cardiomyocyte energy metabolism (71). Additionally, as a stress sensor, the Golgi apparatus controls autophagic flux through the CAMP responsive element binding protein 3-ADP ribosylation factor 4 pathway, and transcription factors such as transcription factor EB (TFEB)/TFE3 and has a bivalent function in cardiac remodeling and maintenance of function (72).

In summary, the Golgi apparatus contributes to cardiomyopathies pathogenesis by various molecular pathways, including structural deficiency, defect in protein modification, dysfunction of autophagy, disruption of the metabolism pathways of extracellular matrix and failure in stress response (Fig. 2). These findings further provide insights into cardiomyopathy pathogenesis and potential therapeutic intervention.

5. ER homeostasis and its perturbation in cardiomyopathies

Highly differentiated terminal cardiomyocytes rely on ER homeostasis for structure and function (73). Recent research has shown that ER stress and the resulting unfolded protein response (UPR) are central to the pathogenesis of numerous cardiomyopathies, including dilated, hypertrophic and ischemic cardiomyopathies (74,75). Failure of the ER drives pathological processes such as cardiomyocyte apoptosis, fibrosis and contractile dysfunction through different mechanisms, including impaired protein quality control, disrupted calcium homeostasis and dysregulated inter-organelle communication (76).

ER stress and the UPR. With pathological stresses such as pressure overload, ischemia, oxidative stress or genetic mutations, misfolded proteins accumulate in the ER of cardiomyocytes, triggering ER stress (77). ER stress initiates complex signaling mechanisms to regulate misfolded and unfolded proteins, a process known as the UPR, which attempts to restore protein homeostasis through three major branches: Pancreatic/PKR-like ER kinase (PERK), inositol-requiring kinase 1 α (IRE1 α) and activating transcription factor 6 (ATF6) (78-80). In hypertrophic cardiomyopathy, sustained activation of the PERK-eIF2 α -ATF4 pathway increases cardiomyocyte apoptosis via modulation of C/EBP homologous protein (CHOP) expression (81,82). IRE1 α is activated during ER stress and, through unconventional splicing, generates the transcription factor X-box binding protein 1 (XBP1), participating in a major arm of the UPR that entails protein degradation and adaptive regeneration (83). The ATF6 pathway regulates the expression of ER-associated

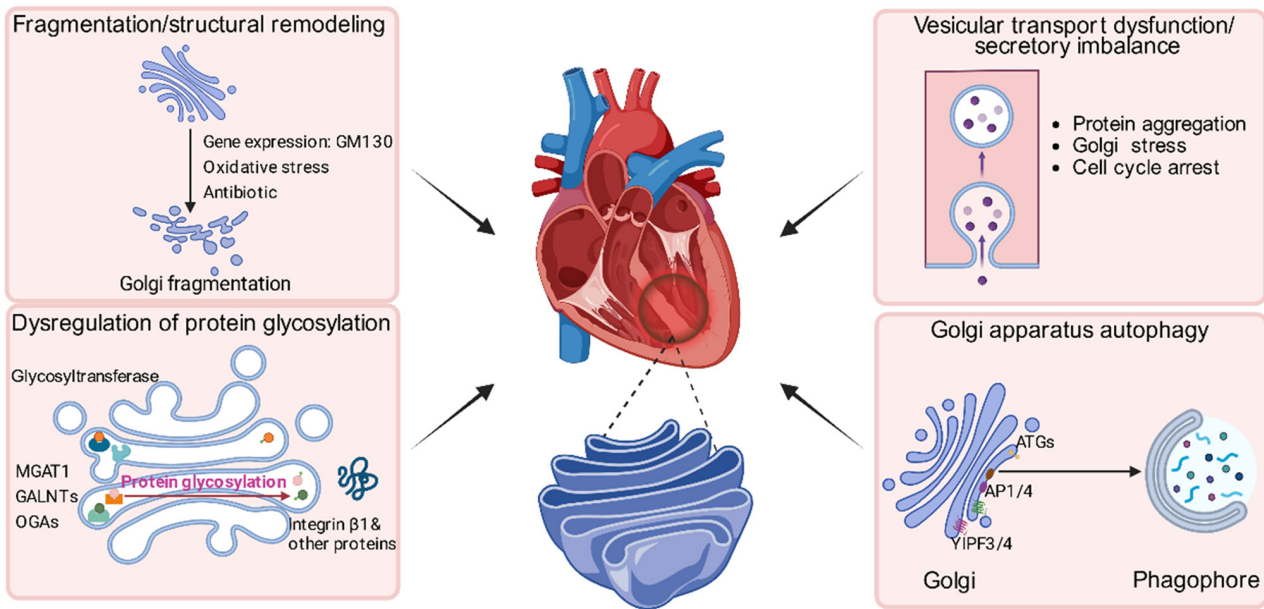


Figure 2. Schematic illustration showing the role of the Golgi apparatus in cardiomyopathy pathogenesis. Golgi apparatus dysfunction disrupts protein trafficking, glycosylation, vesicular transport and autophagy, resulting in endoplasmic reticulum stress, impaired sarcomere organization and altered secretion of extracellular matrix proteins. These alterations contribute to cardiomyocyte hypertrophy, apoptosis and maladaptive cardiac remodeling, ultimately promoting the progression of cardiomyopathy. ROS, reactive oxygen species; MGAT1, α -1,3-mannosyl-glycoprotein 2- β -N-acetylglucosaminyltransferase; GALNT1, polypeptide N-acetylgalactosaminyltransferase 1; OGA, O-GlcNAcase; ATG, autophagy-related protein; YIPF3/4, Yip1 domain family member 3/4; AP1/4, adaptor protein complex 1/4.

degradation components with impacts on the efficiency of misfolded protein clearance (84). Furthermore, previous research in animal and cellular models indicated that overactivated or prolonged ER stress induces cardiomyocyte apoptosis and cardiac failure by CHOP, but maintains or increases the levels of XBP1s to enhance myocardial energy metabolism and angiogenesis with cardioprotective action (85). In a heart failure with preserved ejection fraction (HFpEF) model, XBP1s overexpression promotes FoxO1 ubiquitin-mediated degradation, thereby reducing myocardial lipid accumulation and improving contractile function (86), suggesting that XBP1s may exert multifaceted cardioprotective effects.

ER-mitochondrial coupling and calcium homeostasis. ER and mitochondria also form structural and functional couplings by mitochondria-associated ER membranes (MAMs) that precisely regulate calcium transfer and energy metabolism (87). In cardiomyopathy models, ER stress disrupts the integrity of MAMs, leading to abnormal calcium release, mitochondrial calcium overload, ROS bursts and mPTP opening (88,89). In neonatal mouse cardiomyocytes, knockout of the MAMs-regulating protein FUNDC1 has been shown to exacerbate pressure overload-induced cardiac dysfunction (90). Under ischemia, the voltage-gated calcium channels in cardiomyocytes open and trigger a large calcium influx from the ER to mitochondria through the inositol 1,4,5-triphosphate receptor/glucose-regulated protein 75/voltage dependent anion channel complex at MAMs, which results in mitochondrial calcium overload (91). Excessive mitochondrial Ca^{2+} accumulation over time induces various pathological changes, including mitochondrial membrane potential collapse, mitochondrial swelling and release of pro-apoptotic molecules such as cytochrome *c*. All these

mechanisms together contribute to cardiomyocyte apoptosis, a critical mechanism of ischemia-reperfusion injury (92). Furthermore, in heart failure, sarcoplasmic/ER Ca^{2+} ATPase 2a (SERCA2a) expression or activity is reduced (93), reducing ER calcium sequestration and storage, prolonging myocardial relaxation, impairing contractile performance and accelerating the development of heart failure (93). On this basis, adeno-associated virus 1/SERCA2a gene therapy is being evaluated as a promising new therapeutic approach for the treatment of chronic heart failure in clinical trials (94,95), with notable translational implications for future treatments.

ER-autophagy (ER-phagy) dysregulation. ER-phagy is a selective degradation process dedicated to the identification and elimination of unwanted or aberrant ER components to maintain ER homeostasis and cellular proteostasis, and its dysregulation is increasingly implicated in the progression of cardiomyopathy and cardiac dysfunction (96). Induction of ER stress-related signaling cascades by pathological stresses, particularly those mediated by PERK or c-Jun N-terminal kinase, triggers autophagosome formation that sequesters aberrant ER fragments and ultimately delivers them to lysosomes for breakdown and recycling, thereby restoring ER homeostasis (97). Family with sequence similarity 134 member B (FAM134B) was determined to be the first ER-phagy receptor characterized in mammals, and its identification was the foundation of the molecular control of selective ER turnover through autophagy (98). FAM134B induces ER curvature and fragmentation through its LC3-interacting motif and reticulon homology domain, which targets it for lysosomal transport and results in ER degradation, contributing to the pathogenesis of liver cancer (99). Previous research showed that cardiotoxic compounds such as doxorubicin induce an

interaction between FAM134B and autophagy protein LC3, leading to cardiomyocyte autophagy, apoptosis and myocardial toxicity augmentation (100). However, in a model of doxorubicin-induced cardiotoxicity, ER-phagy plays a protective role in the myocardium through the mediation of the receptor cell cycle progression gene 1 (96). ER-phagy is also notably activated in models of atrial fibrillation, and ER-phagy inhibition can be effectively utilized for alleviating atrial remodeling (101). Sirtuin 1 (SIRT1) deacetylase activation also initiates ER stress-induced autophagy; mechanistically, SIRT1 was determined to cause autophagy under stress conditions through the activation of the eEF2K/eEF2 pathway and thereby promoting the survival of cardiomyocytes. The regulatory pathway not only uncovers the cytoprotective role of SIRT1 but also provides valuable mechanistic insight into the development of new therapeutic strategies against cardiac injury (102).

ER lipid metabolism disorders. The occurrence of enlarged lipid droplets further constitutes a threat to metabolic dysregulation with lipolysis being the activation and transport of lipases (103). Previous research has demonstrated that the transport of adipose triglyceride lipase is mediated by oxysterol-binding protein-like 2 through anchoring the ER to lipid droplets and interaction with coat protein complex I subunit β 1 (104). Research has revealed that, in metabolic stress-related heart failure, the level of spliced transcription factor spliceosome XBP1s is reduced (105). XBP1s-deficient or ER degradation-enhancing α -mannosidase-like protein 2 (EDEM2)-deficient mice exhibited increased vulnerability to metabolic stress, with enhanced myocardial lipotoxicity and impaired cardiac function. Mechanistically, XBP1s inhibits myocardial lipotoxicity under metabolic stress by regulating EDEM2, which increases SEC23A-dependent ATGL transport and blocks the degradation of ATGL, thereby improving cardiac function in HFpEF (106). Collectively, these findings highlight cardiac lipotoxicity as a key pathogenic mechanism underlying metabolic cardiomyopathy, particularly heart failure with HFpEF, and suggest that targeting the XBP1s-EDEM2-ATGL axis represents a promising therapeutic strategy to prevent or attenuate cardiomyopathy progression.

6. Lysosomal regulation and dysfunction in cardiomyopathies

Lysosomes play roles in the maintenance of cardiomyocyte homeostasis through processes such as regulation of autophagy, protein homeostasis, energy metabolism and regulation of calcium signaling. Lysosomal disease is strongly linked to various forms of cardiomyopathy, most prominently hypertrophic and restrictive cardiomyopathy observed in lysosomal storage disorders. Beyond these inherited conditions, impaired lysosomal degradation and autophagic flux have also been linked to maladaptive cardiac remodeling in pressure overload-induced hypertrophy, ischemic cardiomyopathy and metabolic cardiomyopathy, although the strongest and most direct association is observed in lysosomal storage disease-associated cardiomyopathies. Mutations in lysosome-related genes may potentially influence cardiac structure and function directly. The present section is aimed at critically discussing the advances in elucidating the role of lysosomes in

cardiomyopathy pathogenesis and reporting new information regarding their underlying molecular and pathophysiological mechanisms.

Autophagy-lysosome system dysfunction. Under autophagy, autophagosomes merge with lysosomes, and the functional integrity of lysosomes determines the fate of autophagic activity (107). In conditions such as ischemia, pressure overload or metabolic stress, cardiomyocytes first trigger autophagy as a compensatory mechanism (108); however, prolonged or severe stress is known to damage autophagic flux at the lysosomal level, in which autophagic vesicles and autophagosomes accumulate as a result of failure to degrade (109).

A previous study demonstrated that downregulation of the lysosome-associated membrane protein LAMP2 in hypertrophic cardiomyopathy models leads to autophagosome-lysosome fusion defects and increases cardiomyocyte apoptosis (110). Conversely, exogenous LAMP2B expression has been shown to normalize autophagic processing in myocardial ischemia-reperfusion injury (111). Danon disease, an X-linked dominant disorder caused by mutations in the LAMP2 gene, is characterized by giant lysosomes in cardiomyocytes and severe myocardial hypertrophy (112). Pan *et al* (113) also established a cardiac proteinopathy mouse model and showed that TFEB activation enhances autophagic flux by activating the autophagy-lysosome axis, thereby promoting the lysosomal breakdown of ubiquitinated proteins and minimizing cardiomyocyte proteotoxicity. In myocardial ischemia-reperfusion injury, lysosomal inhibition and depletion are also reported, whereas a rise in TFEB expression or an increase in its nuclear translocation augments lysosomal biogenesis and recovers lysosomal function (114). Overall, these findings highlight the pivotal role played by the lysosomal-autophagy system in securing cardiac homeostasis, and place a focus on its potential as an active therapeutic target in the prevention and treatment of cardiomyopathies.

Lysosomal enzyme deficiency and impaired acidification. Genetic deficiencies in lysosomal hydrolases cause lysosomal storage disorders (LSDs), a biochemically heterogeneous group of inherited metabolic disorders that result in the progressive accumulation of undegraded substrates with eventual widespread cellular dysfunction and multi-organ pathology, as exemplified by Gaucher disease, mucopolysaccharidoses and Niemann-Pick disease (115,116). In cardiac muscle, LSDs frequently are accompanied by cardiomyopathic change; for example, Fabry disease, caused by causative mutations in the GLA gene that impair α -galactosidase A activity, leads to glycosphingolipid pathological accumulation in lysosomes, and induces myocardial fibrosis, abnormal electrical conduction and cardiac remodeling progression (117). In addition, Pompe disease, caused by a reduction in lysosomal acid α -1,4-glucosidase levels, induces an over-accumulation of glycogen in cardiomyocytes, impairs energy metabolism and ultimately leads to severe cardiac hypertrophy or heart failure (118).

Lysosomal acidification, which is maintained by the vacuolar H^+ -ATPase (V-ATPase), and resident hydrolase activity have opposite effects on cardiomyocyte fate. Impaired acidification or increased lysosomal membrane permeability can reduce enzymatic activity and autophagic degradation, leading

to the accumulation of defective mitochondria and proteins. By contrast, following disruption of lysosomal membranes, ectopic release of cathepsins into the cytosol triggers inflammatory responses, NLRP3 inflammasome activation and programmed cell death, which contribute to myocardial fibrosis and functional impairment (119). It has been shown that a reduction in lysosomal ATP6V1B2 and ATP6V1D proteins in cardiomyocytes lead to defective V-ATPase function, lysosomal acidification and lysosomal dysfunction, which play a role in the pathogenesis of hypertrophic cardiomyopathy (120). Furthermore, specific deletion of ATP6AP2 in cardiomyocytes causes V-ATPase assembly disruption and subsequent lysosomal acidification loss, eventually resulting in terminal heart failure (121). These findings emphasize the key pathological role of lysosomal acidification in maintaining enzymatic activity and cardiac homeostasis.

Disturbed lysosomal calcium homeostasis. Lysosomes support intracellular quality control through autophagy and via ion channels such as mucolipin TRP cation channel 1 (TRPML1) that mediate Ca^{2+} release (122,123). Lysosomal TRPML1 channels have been shown to activate calcineurin, CaMKK β and AMPK in a calcium-dependent manner, thereby guaranteeing the nuclear translocation of the transcription factor TFEB. This event stimulates autophagy and elevates the expression of lysosomal and autophagy-related genes, including ULK1 and VPS34, inducing spontaneous formation of autophagosomes and long-term regulation of lysosomal biogenesis and recycling of mitochondria (124). In multiple experimental systems, pharmacological or genetic activation of TRPML1 has been shown to recover lysosomal function, enhance mitochondrial homeostasis and alleviate tissue damage (125), with lysosome-initiated Ca^{2+} signaling as a central node connecting cellular metabolism and stress responses to organ function. In the heart, disruption of this TRPML1-TFEB-autophagy axis compromises cardiomyocyte proteostasis, mitochondrial quality control and stress adaptability, thereby promoting maladaptive remodeling and contributing to the development and progression of cardiomyopathy.

In summary, lysosomes maintain cardiomyocyte homeostasis not only through degradation but also as key signaling hubs coordinating diverse pathophysiological processes. Lysosomal deficiency impinges upon autophagic flux, energy metabolism, calcium homeostasis and signal transduction, all synergistically acting to initiate and advance cardiomyopathies. With continuous research progresses in this field, lysosome-targeted therapy has the potential to be a novel treatment method for patients with cardiomyopathy.

7. Emerging role of ribosomal homeostasis in cardiomyopathy pathogenesis

The ribosome, a central molecular machinery orchestrating cellular protein synthesis, is a notable regulator of cardiomyocyte homeostasis and cardiac integrity. Previous studies have indicated that ribosomes not only perform the primary activity of protein translation but are also involved in cellular stress adaptation through mechanisms such as ribosome quality control (RQC) and regulation of translational selection (126,127). The following section summarizes advances on

how ribosomes contribute to cardiomyopathy, providing new insights into cardiac disease mechanisms.

Impaired ribosome biogenesis. Mutations in ribosomal protein-encoding genes have been reported to cause defects in ribosome assembly, leading to specific forms of cardiomyopathy, most notably DCM and developmental cardiomyopathies associated with congenital syndromes. The ribosomal protein L3-like gene, for instance, is cardiac muscle-specific, and mutations in this gene disrupt the assembly of the large ribosomal subunit. Furthermore, these mutations alter the rate of elongation of nascent peptides on mRNAs and increase ribosome collisions or stalling events and, therefore, this translational dysregulation selectively reduces the synthesis of proteins essential to cardiac contractility, ultimately leading to abnormal heart function and the development of DCM (128). In addition, gene mutations for ribosomal proteins that are associated with Diamond-Blackfan anemia, such as RPS19 and RPS26, also serve roles in cardiac developmental abnormalities. Specifically, RPS19 deficiency interferes with 18S rRNA maturation and triggers the p53 pathway, resulting in unorganized myocardial and hematopoietic development (129).

Dysregulation of RQC mechanisms. RQC detects aberrant ribosomal particles and facilitates their dissociation along with degrading defective polypeptides and preventing cytoplasmic accumulation of misfolded proteins, which is critical for maintaining cellular homeostasis intact (130,131). Previous research identified central components of the RQC pathway, such as HOIL-1, Vms1 and ZNF598, to have marked functions in regulating cardiomyocyte adaptive and stress-regulated pathways (132). Mutations in the RQC factor HOIL-1 increase cardiomyocyte vulnerability to nutrient and translational stress; this signal converges through the ZAK α pathway to activate ATF4 and xCT, inducing non-canonical cell death and enhancing pressure overload-induced cardiac dysfunction (133). Cardiomyocyte-restricted inactivation of the RQC factor Vms1 leads to an accumulation of ribosomal proteins, activation of the proteasome pathway and eventually cardiomyocyte apoptosis, resulting in cardiomyopathy with reduced contractile function and heart failure (134). Additionally, 14-3-3 proteins interact with ribosomal proteins in cardiomyocytes to regulate protein synthesis and quality control to ensure cellular homeostasis, whereas their dysfunction may interfere with adaptive stress responses and the development of cardiomyopathy (135). These findings show that the ribosome-associated RQC pathway is essential for cardiomyocyte proteostasis and stress adaptation, and its disruption may drive cardiomyopathy through multiple mechanisms.

Abnormal translation regulation. Increased evidence highlights that ribosomal translation is a mechanistic mediator in cardiomyopathy pathogenesis and progression. Of regulatory pathways, the mTORC1-S6K pathway is a central node for regulating the initiation and elongation of translation and is notable in pathological cardiac hypertrophy and energy deficit (136). In a mouse perfusion model of the heart, ischemic preconditioning (IPC) was found to enhance mTORC2 activity, and mTORC2 inhibitor pretreatment abolished IPC-induced cardioprotection, which identifies the central contribution of mTORC2 activation to cardioprotection. Mechanistically, mTORC2 promotes sustained Akt-Ser473 signaling via a ribosome Rps6-dependent mechanism that

is required for cardioprotective effects (137). Conversely, mTORC1/S6K/eIF-4B pathway chronic activation has been shown to increase the activation of cardiac fibroblasts and aggravate myocardial infarction (138). Furthermore, in ischemic cardiomyopathy, eIF2 α phosphorylation suppresses general translation but selectively translates stress-protective genes such as ATF4 through mechanisms involving upstream open reading frames; however, chronic activation of this pathway ultimately causes cardiac dysfunction (139).

Overall, cardiomyocyte ribosomes not only synthesize proteins but also form a central regulatory network governing proteome homeostasis and cardiac function, where disruptions in structure, biogenesis, elongation dynamics or quality control may drive cardiomyopathy. Advances in ribosome profiling and functional genomics will improve molecular subtyping and mechanistic insights, guiding ribosome-targeted therapies for cardiomyopathy.

8. Nuclear and intercalated disc dysfunction in cardiomyopathy

The fine structure of cardiomyocytes is the foundation of their normal contraction and electrophysiological activity. Studies have revealed that the nucleus/nuclear envelope and the intercalated discs are not merely static cellular components, but dynamic signaling hubs, and their dysfunction directly drives the occurrence and progression of various cardiomyopathies.

The nuclear envelope is composed of the inner nuclear membrane, the outer nuclear membrane and the perinuclear space between them and provides mechanical support through a network of nuclear lamina proteins. The *LMNA* gene, which encodes nuclear lamina proteins, is one of the most common causes of autosomal DCM and conduction system diseases, accounting for 5-10% of familial DCM cases and a notably higher proportion (30-40%) in patients with concomitant conduction defects. Mutations in this gene lead to disease primarily by disrupting nuclear membrane stability and function (140). Under pathological conditions, mutated nuclear membrane proteins can trigger nuclear membrane rupture, leading to sustained activation of the DNA damage response and apoptosis of cardiomyocytes, accelerating the progression of heart failure (141). In addition, the nuclear membrane acts as a mechanical sensor, transmitting extracellular mechanical stress to the chromatin and regulating gene expression; LMNA mutations disrupt this function, leading to the activation of pathological gene programs (142). Abnormalities in nuclear membrane-associated proteins such as Emerin are also closely related to Emery-Dreifuss muscular dystrophy, as well as syndromic DCM or arrhythmogenic cardiomyopathy (143,144), highlighting the central role of the nuclear membrane complex in maintaining myocardial integrity.

Intercalated discs are specialized cell-cell junctions that connect cardiac muscle cells, consisting of desmosomes, adherens junctions and gap junctions, and are indispensable for mechanical transmission and electrical coupling (145). Studies on the ultrastructure and proteomics of the stratum corneum have revealed the complexity and plasticity of its composition, particularly highlighting that the structure and regulation of desmosomes serve a key role in maintaining cell adhesion (146-148). Mutations in multiple genes encoding

intercalated disc-related proteins have been confirmed to be closely associated with arrhythmogenic cardiomyopathy (149), including plakophilin-2, desmoplakin, desmoglein-2, desmocollin-2 and plakoglobin, suggesting that intercalated disc instability is one of the core molecular mechanisms of this disease. The intercalated disc not only serves a mechanical connection function but also acts as a 'hub' for mechanical sensing and signal transduction, participating in myocardial stress responses and pathological remodeling through signaling pathways such as Hippo-YAP and Wnt/ β -catenin (150). In addition, abnormal localization and functional changes of intercalated disc proteins have also been reported in dilated and hypertrophic cardiomyopathy (151). Specifically, key intercalated disc components such as connexin 43, plakoglobin and N-cadherin are frequently redistributed from the intercalated discs to the lateral membranes or cytoplasm of cardiomyocytes, accompanied by impaired gap junction coupling, weakened mechanical adhesion and altered electrical conduction. These changes promote electrical instability, contractile dysfunction and adverse cardiac remodeling, indicating that intercalated disc pathology plays a broad disease-promoting role across diverse cardiomyopathy spectra.

9. Discussion

Over the past decade, research on the molecular pathogenesis of cardiomyopathy has progressed from a single-organelle dysfunction-driven paradigm to an integrative system based on systemic homeostatic failure following inter-organelle crosstalk. The present review synthesizes increasing evidence pointing towards mitochondria, ER, Golgi apparatus, lysosomes and ribosomes remodeling their structure and function markedly during the development and progression of cardiomyopathy. These membranous and non-membranous compartments are additionally closely integrated by networks that regulate intracellular signaling, proteostasis, bioenergetic metabolism, calcium signaling and vesicular transport. Perturbations in a single organelle thus cascade through the entire cellular network, spreading metabolic stress and continuing pathological remodeling. In contrast to the old paradigm that attributed cardiomyopathy to abnormalities in isolated metabolic pathways or sarcomeric proteins, the new paradigm of organelle network disease provides an improved explanation of the heterogenous and multifactorial clinical cardiomyopathies.

Mitochondria remain the focal point of remodeling disease in cardiomyopathy. Their dysfunctional metabolism not only affects ATP production and contractile efficiency, but also triggers the endogenous innate immune signaling by releasing DAMPs such as ROS, mtDNA and cardiolipin (152-154). Non-normal oxidative phosphorylation and fatty acid oxidation further exaggerate metabolic stiffness and induce a maladaptive pathway towards inefficient glucose metabolism. This metabolic reprogramming causally directs inflammatory signaling cascades bidirectionally, thus creating a self-perpetuating loop of metabolic stress and immune activation. For instance, mtDNA release into the cytosol is found to stimulate type I interferon responses through cGAS-STING activation (155,156), enhancing the proinflammatory environment and possibly the kinetics of myocardial

fibrosis and structural remodeling. These findings highlight that therapeutic approaches aimed specifically at the rehabilitation of mitochondrial bioenergetics will be likely to provide only transient benefit unless these therapies also control the spread of inflammation and ensuing pathologies. The ER, or the intracellular calcium central reservoir and regulatory site, is functionally interdependent in a complex way with mitochondria via mitochondria-associated membranes, thus integrating energy metabolism and calcium signaling homeostasis (157). In cardiomyopathy, chronic ER stress deteriorates MAM integrity, leading to dysregulation of calcium efflux and ensuing mitochondrial calcium overload, initiating an aberrant positive-feedback cycle of overproduction of ROS and abnormal opening of the mitochondrial permeability transition pore (158,159). SERCA2a abnormality also accelerates the cascade earlier, not only prolonging myocardial relaxation but also decreasing contractile efficiency and accelerating heart failure onset. Therapeutically, attempts to reverse SERCA2a function or to fix MAM structural dynamics are potential therapies for normalization of calcium equilibrium (160). However, accumulating evidence suggests that these interventions are primarily effective during early or compensatory stages of cardiomyopathy.

The Golgi apparatus, previously considered a passive accepting organ for protein targeting and post-translational modification, is now recognized as an active regulatory site functionally integrated within cellular homeostasis (161,162). In cardiomyopathies, Golgi apparatus disruption, manifests as structural fragmentation, defective glycosylation and disruption of vesicular trafficking, which notably compromises the spatial arrangement of membrane proteins and intracellular cascades of signals (163,164). These perturbations disrupt proper receptor and ion channel expression and localization, extracellular matrix turnover and mechanotransductive responsiveness, thus remodeling cardiomyocyte biomechanical properties. Additionally, increasing evidence suggests that Golgi apparatus impairment, ER stress and ribosomal quality-control failure are temporally and mechanistically interdependent (165,166). This spectrum suggests that early dysfunctions of the protein-processing machinery may cause excessive pressure on subsequent surveillance and degradative mechanisms, eventually enhancing proteostatic degradation during cardiac remodeling.

The RQC pathway is a notable protective mechanism against translational blockage and dysregulated accumulation of nascent polypeptides in cardiomyocytes (167). During hemodynamic stress or cardiotoxic injury, dysfunction of integral RQC machinery such as HOIL-1 and Vms1 eliminates co-translational surveillance, resulting in dysregulated accumulation of defective stalled ribosomal complexes and defective proteins (168). This proteostatic deregulation triggers compensatory hyperactivation of the proteasome and ultimately the activation of apoptotic cascades. In addition to ER stress, translational stress in cardiomyocytes is beyond their scope of adaptability, which results in overall failure during sarcomeric assembly, membrane channel expression and integrity of signal transduction. In therapeutic contexts, concerted modulation of RQC function together with site-specific regulation of protein degradation machineries has the potential to provide a novel platform for enhancing

proteostasis and alleviating cardiac dysfunction in the context of precision medicine.

A deep analysis of the causal chain of multi-organelle network imbalance in the development and progression of cardiomyopathy will lay the foundation for precise subtyping and mechanism-guided intervention strategies. First, advances in single-cell multi-omics and spatial transcriptomics have allowed spatiotemporal mapping of organelle interactions and identification of key regulatory nodes, such as mitochondrial-ER calcium coupling, Golgi apparatus-plasma membrane signaling and nuclear mechanosensitive structures. These cross-scale datasets provide a refined framework for molecular subtyping of cardiomyopathy, and offer a basis for developing network-level biomarkers capable of predicting disease progression and therapeutic responsiveness. Second, multi-organelle intervention strategies will become a core direction for future translational research. For example, combined regulation of mitochondrial-ER calcium flux, repair of Golgi glycosylation profiles, enhancement of nuclear membrane stress resilience or remodeling of the RQC-autophagy axis may all achieve multidimensional cardioprotective effects with lower toxicity. Finally, the development of organelle-penetrating drug delivery systems, including organelle-targeted nanocarriers, programmable liposomes and peptides directed to mitochondria or the Golgi apparatus, will be essential for enabling mechanism-based therapy. In parallel, platforms such as patient-derived cardiomyocytes, cardiac organoids and engineered microtissues provide physiologically relevant readouts of organelle function, allowing more accurate prediction of individualized therapeutic responses and accelerating the clinical translation of organelle-targeted interventions.

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Authors' contributions

YH, CL, LM, SL and FH were responsible for the methodology, including literature search strategy design, database selection, study inclusion and exclusion criteria, and methodological framework for evidence synthesis. YH, CL, YC, DZ, MC and QC curated the data. YH and CL wrote the original draft of the manuscript, and YH, YC and QC reviewed and edited the manuscript. YH, SL and FH supervised the project, and YH and QC provided project administration. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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