Review

Mitochondria in Cardiac Disease: Mechanisms, Therapeutic Targets, and Clinical Progress

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Abstract: Mitochondria regulate cardiac energy metabolism, calcium buffering, reactive oxygen species (ROS) signaling, and programmed cell death, playing a vital role in maintaining heart function and its response to physiological stress. Disruptions in mitochondrial quality control, dynamics, and metabolic signaling contribute fundamentally to the pathogenesis of heart failure, ischemic injury, cardiomyopathy and atrial fibrillation. Over the past five years, growing evidence has linked mitochondrial dysfunction to many cardiac pathologies, spurring research into five key areas: (1) molecular mechanisms, (2) mitochondrial biomarkers, (3) mitochondria-targeted therapies, (4) disease-specific insights, and (5) clinical trials. Below we summarize recent scientific and clinical progress in each area, highlighting emerging mechanisms and especially promising therapeutic directions.

Keywords: mitochondria; reactive oxygen species (ROS); heart failure; metabolism; therapeutic strategies

1. Introduction

Mitochondria have long been recognized as the powerhouse of the cell [1], and in recent years, they have become a major focus in cardiovascular research, not merely for their bioenergetic roles, but also for their dynamic involvement in redox signaling, metabolic regulation, cell survival, and inflammation [2–6]. These core processes shape the fate of the heart under both physiological and pathological conditions. As cardiovascular diseases remain the leading cause of mortality worldwide, the view of mitochondria as passive ATP suppliers has shifted toward a systems-level perspective that positions them at the center of cardiac homeostasis, structural remodeling, and failure [3–7].

Over the past half-decade, this conceptual shift has led to a broadening therapeutic landscape in mitochondrial cardiology. Mounting evidence demonstrates that strategies designed to preserve or restore mitochondrial integrity can directly influence cardiac contractility, metabolic flexibility, and inflammatory balance [8–17]. Emerging therapies include small-molecule redox modulators and cardiolipin stabilizers [8–10,13,18] mitophagy and mitochondrial biogenesis activators [16,17,19] and gene-editing platforms aimed at correcting mitochondrial genome or proteostasis defects [5,10,12]. Precision metabolic reprogramming strategies, including SGLT2 inhibitors and metabolic cardiac conditioning, further highlight mitochondria as therapeutic control points within cardiac energy metabolism [14,15]. Mitochondrial transplantation has also gained attention as a means to restore bioenergetic competence in ischemic myocardium and failing hearts [12,16,18]. These interventions collectively underscore an expanding translational capacity to manipulate mitochondrial structure, dynamics, and signaling in vivo, redefining therapeutic paradigms once limited to metabolic support [8,10,14–16].

At the cardiomyocyte level, mitochondrial quality control (MQC) systems, including mitophagy, fusion–fission dynamics, mitochondrial biogenesis, and proteostasis, play a decisive role in maintaining contractile performance under metabolic or oxidative stress [16,17,19]. Recent work emphasizes that cardiac resilience depends on preserving mitochondrial network architecture, cristae integrity, and organelle–sarcomere spatial coupling rather than ATP production alone [19]. Disruption of MQC contributes to age-related energetic decline, arrhythmogenic remodeling, and heightened vulnerability to ischemic injury [7,19]. Computational and systems biology frameworks, including digital cardiac twins and multi-scale calcium handling models, now integrate mitochondrial energetics into whole-heart simulations to bridge molecular dysfunction with organ-level performance [20–23]. The following section summarizes the core molecular pathways through which

mitochondrial dysfunction drives cardiac injury and remodeling, establishing the mechanistic basis for subsequent clinical and therapeutic advances.

An overview of the evolving review literature from 2020 to 2025, illustrating the relative emphasis placed on major research themes, is shown in Figure 1. Metabolism (27.8%) and cardiac failure (24.8%) are the most prominent topics, highlighting the strong focus on energy homeostasis and clinical cardiac outcomes in recent reviews. Mitochondrial dysfunction (14.3%) and ROS-related mechanisms (13.1%) also account for substantial attention, underscoring their central roles in linking molecular pathology to disease progression. By contrast, mitophagy (4.7%), oxidative phosphorylation (4.6%), biogenesis (3.1%), regeneration (3.0%), AMPK (2.7%), and Nrf2 (1.9%) appear less frequently, suggesting these areas remain comparatively underrepresented and may represent important directions for future investigation.

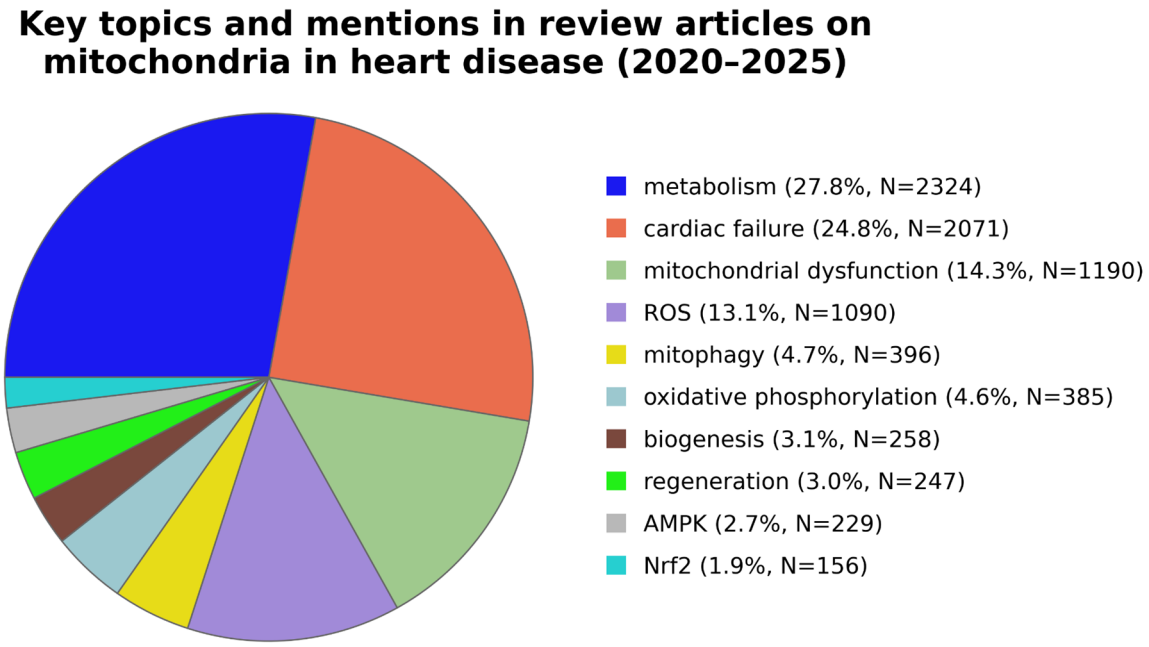

Figure 1. Distribution of major research themes identified in review articles on mitochondria in heart disease published between 2020 and 2025. Percentages represent the proportion of total keyword/topic mentions across the analyzed review corpus.

2. Molecular Mechanisms and Pathways in Cardiac Mitochondrial Dysfunction

High-energy demand makes the heart especially vulnerable to mitochondrial perturbations. In ischemic or severe stress conditions, cardiomyocyte ATP falls rapidly, impairing ion pumps and driving cytosolic Ca^{2+} accumulation that further accelerates energetic collapse [13,23]. Upon reperfusion, mitochondria experience a burst of ROS, classically driven by re-oxidation of ischemia-accumulated succinate via reverse electron transport at complex I, together with mitochondrial Ca^{2+} overload, which cooperatively trigger opening of the mitochondrial permeability transition pore (mPTP), as recently clarified by structural and functional consensus models [23,24]. Sustained mPTP opening collapses $\Delta\psi m$, induces matrix swelling and outer-membrane rupture, and releases pro-death factors, leading to apoptosis or necrosis and irreversible cardiomyocyte loss [25]. These mitochondrial events are widely recognized as central mechanisms of myocardial ischemia/reperfusion (I/R) injury and related acute cardiac insults [25,26].

Chronic cardiac stressors likewise converge on mitochondrial pathways. In heart failure (HF), suppression of fatty acid oxidation (FAO) and increased reliance on glycolysis, together with impaired mitochondrial oxidative phosphorylation, contribute to the classic "energy-starved" myocardium. Mitochondrial biogenesis regulators such as PGC-1α are often depressed, while ROS levels and mitochondrial DNA (mtDNA) damage increase [27]. Notably, failing human hearts show disrupted mitochondrial ultrastructure (e.g., cristae loss) and reduced respiratory chain activity [3,28,29].

Mitochondrial quality control (QC) is disrupted in heart failure and cardiomyopathies. Excessive DRP1-mediated fission promotes mitochondrial fragmentation, cristae disruption, and impaired respiration, while reduced MFN2 and OPA1 weakens network integrity and energetic capacity [2,30,31]. Restoring fusion–fission balance preserves mitochondrial structure, Ca^{2+} handling, and redox homeostasis and limits injury during

ischemia/reperfusion [3,32]. Mitophagy eliminates dysfunctional mitochondria and restrains ROS, but excessive activation can deplete mitochondrial content, impair ATP production, and promote cardiomyocyte death [33,34].

Damage-associated molecular patterns (DAMPs) are endogenous intracellular molecules released during cell injury that activate innate immune receptors and amplify inflammation. Mitochondria act as a major DAMP source in the heart, when membranes rupture, mtDNA escapes into the cytosol and circulation. Cytosolic mtDNA activates cGAS–STING, while extracellular mtDNA engages TLR9, driving inflammatory signaling in myocardial infarction [35,36]. In models of pressure overload, myocardial infarction, and immune-checkpoint-inhibitor myocarditis, cGAS–STING inhibition reduces inflammation, adverse remodeling, and ventricular dysfunction [37–39]. Additionally, mitochondrial DAMPs, including leaked mtDNA and mtROS, activate NLRP3 and TLR9, promoting inflammatory remodeling and fibrosis [40–42].

A third mitochondrial QC layer involves intercellular mitochondrial disposal. Cardiomyocytes release exophers containing damaged mitochondria, which are cleared by MerTK^{+} cardiac macrophages to maintain mitochondrial homeostasis and ventricular performance [43]. Exopher formation is autophagy-dependent and rises with β-adrenergic stimulation or myocardial infarction [43,44]. Loss of macrophage clearance leads to mitochondrial debris accumulation, inflammasome activation, and metabolic decline. In sepsis, TREM2^{hi} macrophages efficiently remove mitochondria-containing exophers; impairing this population worsens injury, while enhancing it improves function [45]. Together, these pathways establish a stress-responsive, macrophage-supported mitochondrial QC network that protects cardiomyocytes [19].

Relatedly, when lysosomal degradation is impaired, the heart increases secretion of mitochondria-containing extracellular vehicles (EVs), which are locally cleared by cardiac macrophages as an alternative disposal route [46]. Conversely, stressed cardiomyocytes can receive functional mitochondria from neighboring supportive cells, including mesenchymal stromal cells (MSCs) or engineered mitochondrial extracellular vesicle (EV)–based delivery systems, which enhances ATP production and improves cell survival and cardiac repair [47–49]. Tunneling nanotubes (TNTs) also mediate direct mitochondrial shuttling between cardiac fibroblasts and cardiomyocytes, transporting mitochondria along microtubules via the kinesin motor KIF5B, thereby improving cardiomyocyte bioenergetics and resistance to hypoxia–reoxygenation injury [50]. The mitochondrial trafficking GTPase MIRO1 further regulates intercellular mitochondrial mobilization; its overexpression in MSCs significantly increases mitochondrial transfer efficiency and enhances cardiomyocyte rescue [51]. Recent work extends this to clinical-grade Wharton's jelly MSCs, where MIRO1 overexpression improves mitochondrial engraftment and functional recovery in injured myocardium [52]. However, mitochondrial export is not uniformly protective: cardiomyocyte-derived small EVs carrying mitochondrial components can be taken up by fibroblasts and activate pro-fibrotic signaling, contributing to maladaptive remodeling [29]. Mitochondrial transplantation (direct delivery of respiration-competent autologous mitochondria) has shown infarct-sparing effects in large-animal ischemia–reperfusion models and has progressed into early pediatric clinical application [53].

3. Mitochondrial Biomarkers in Cardiac Disease: Diagnostic and Therapeutic Windows

Mitochondrial biomarkers in blood offer complementary views into organelle injury, capacity, and metabolic state. These readouts serve three translational roles: risk stratification, mechanistic anchoring, and therapeutic response monitoring.

Circulating cell-free mitochondrial DNA (cf-mtDNA) is increasingly recognized as a DAMP-linked biomarker of mitochondrial membrane injury and inflammatory activation, reflecting cardiomyocyte stress and innate immune signaling in cardiovascular disease [54–56]. Elevated cf-mtDNA likely reflects mitochondrial DAMP release that amplifies sterile inflammation. In a 120-patient cardiometabolic cohort, individuals with heart failure displayed higher circulating cf-mtDNA and a lower ratio of cell-associated mtDNA to cf-mtDNA, which correlated with pulmonary congestion (B-lines) and reduced peak VO_2 (<16 $mL \cdot kg^{-1} \cdot min^{-1}$) after adjustment [55]. Platelet mitochondrial DNA methylation signatures also predict new-onset myocardial infarction and future cardiovascular events, suggesting an epigenetic component to mitochondrial injury signaling [57].

Circulating leukocyte mitochondrial DNA copy number (mtDNA-CN) serves as a surrogate marker of systemic mitochondrial functional reserve, and lower mtDNA-CN is associated with an increased risk of incident heart failure and adverse cardiovascular outcomes [58]. Large cohort studies (ARIC/CHS/MESA) show that lower leukocyte mtDNA-CN independently associates with increased CVD and HF risk. A 2024 meta-analysis of 646,398 participants reported HR 1.27 for CVD and 1.30 for HF in the lowest mtDNA-CN group [59]. Mendelian randomization indicates mtDNA-CN is a risk marker rather than a causal driver, supporting its value for prognosis rather than direct therapeutic targeting.

Mitochondrial biomarkers also signal metabolic status. In Acute coronary syndrome (ACS), both MOTS-c and PGC-1α levels are reduced; MOTS-c correlates with troponin, while PGC-1α inversely tracks glucose and positively associates with HDL, suggesting a blunted mitochondrial stress response [60]. In addition, circulating TCA intermediates, such as citrate, are linked to cardiovascular mortality, underscoring the potential of metabolic fingerprinting in risk stratification [60,61]. These biomarker-to-mechanism pairings form the theragnostic framework guiding the mitochondria-targeted therapies discussed in the next section. Selected examples of mitochondrial biomarker signatures associated with different therapeutic classes are summarized in Table 1.

Table 1. Mechanistic alignment between mitochondrial biomarker signatures and therapy classes, highlighting promising but currently investigational theragnostic directions.

Biomarker	Pathophysiological Significance	Therapeutic Implications
Cytochrome C (increase)	Outer membrane rupture and mitochondrial apoptosis/necrosis	Membrane stabilizers, mPTP modulators
cf-mtDNA (increase)	DAMP release and inflammatory amplification	Anti-inflammatory, mPTP control
mtDNA-CN (decrease)	Low mitochondrial reserve/impaired biogenesis	Biogenesis & mitophagy enhancers (PGC-1α, AMPK, SIRT1/3, NAD^+)
MOTS-c (decrease)	Impaired mitochondrial-encoded stress signaling	MOTS-c peptide replacement, AMPK activators
PGC-1α (decrease)	Suppressed mitochondrial biogenesis master regulator	PGC-1α pathway activation, exercise, AMPK agonists (AICAR/Metformin), SIRT1 activators (Resveratrol/NAD^+ boosting), β-agonist & cold-mimetic pathways

4. Therapeutic Strategies Targeting Mitochondria

Over the past five years, mitochondrial therapeutics in cardiovascular disease have shifted from broad metabolic modulation to direct organelle-targeted intervention. Current strategies modulate complex I–driven redox signaling, Ca^{2+} handling at mitochondria–ER contact sites, mPTP gating, and selective mitophagy pathways. This reflects growing recognition that mitochondrial dysfunction is a primary driver of cardiomyocyte death and heart failure progression, positioning mitochondria as both therapeutic targets and clinically informative biomarkers in translational cardiology [19].

4.1. Redox Modulation at the Source and the Sink

Oxidative stress remains a central target in mitochondrial therapy, with current interventions broadly divided into "sink" and "source" strategies. Sink strategies (e.g., matrix-targeted antioxidants) neutralize excess ROS after formation, while source strategies seek to prevent ROS generation at electron leak sites within the respiratory chain. MitoQ (ubiquinone–TPP^+) and MitoTEMPO accumulate in the mitochondrial matrix where they intercept ROS and mitigate oxidative injury. In diabetic rat hearts, MitoQ restored PINK1/Parkin-mediated mitophagy and improved post-I/R recovery, while MitoTEMPO improved contractile performance in nicotine-primed ischemic myocardium [62,63]. While matrix-targeted antioxidants function as "ROS sinks", more recent approaches aim to prevent ROS generation at its source by selectively blocking specific electron leak sites within the respiratory chain. Site-specific ROS suppression, which is exemplified by S1QELs, represents a more precise strategy. By inhibiting electron leak at complex I's IQ site without disrupting oxidative phosphorylation, S1QEL reduces infarct size, prevents no-reflow, and improves post-ischemic function [64–66]. These studies highlight the therapeutic potential of "redox tuning", rather than blanket antioxidant therapy, for restoring mitochondrial balance in acute and chronic heart injury.

4.2. Modulating the Mitochondrial Permeability Transition Pore (mPTP)

The mitochondrial permeability transition pore (mPTP) is a decisive mediator of cardiomyocyte death during reperfusion injury. Although broad mPTP inhibitors such as cyclosporine-A failed in large clinical trials (e.g., CIRCUS STEMI), indirect mPTP modulators have renewed therapeutic momentum. Metformin, independent of its systemic metabolic effects, partially inhibits complex I, blunts the reperfusion ROS surge, and limits mPTP opening, reducing infarct size and improving functional recovery [67]. Together, matrix antioxidants, site-specific suppressors, and mPTP modulators now constitute a practical redox-centric therapeutic toolkit that advances from empirical antioxidant use toward mechanism-based modulation of mitochondrial injury [68].

4.3. Enhancing Energetics and Biogenesis

Beyond redox balance, restoring mitochondrial energy production has become a central translational goal. NAD^+ precursors such as NMN and NR replenish depleted cofactor pools in heart failure and aging, enhancing sirtuin signaling and oxidative metabolism in preclinical models, while early clinical studies demonstrate safety and feasibility in patients [69,70].

Among direct bioenergetic enhancers, Elamipretide stabilizes cardiolipin-dependent cristae architecture and improves electron transport efficiency. In failing human myocardium ex vivo, elamipretide increased mitochondrial respiration and supercomplex activity, while chronic dosing improved ventricular function in canine heart failure and reduced I/R injury in large-animal models [71]. Clinical data from the TAZPOWER open-label extension show long-term safety and functional gains, prompting renewed regulatory consideration [72,73].

Trimetazidine (TMZ) optimizes substrate selection by shifting metabolism from fatty acid to glucose oxidation, improving oxygen efficiency. In preclinical models, TMZ activated AMPK, enhanced mitochondrial function, and reduced MCU-dependent Ca^{2+} overload and ROS generation [74,75]. Meta-analysis data support reduced mortality and hospitalization in HFrEF [76]. Collectively, these approaches converge on restoring the bioenergetic competence of the failing heart.

4.4. Systemic Metabolic Therapies with Mitochondrial Benefits

A parallel shift in cardiometabolic pharmacology has revealed that agents originally developed for diabetes exert direct mitochondrial benefits. SGLT2 inhibitors, including empagliflozin and dapagliflozin, consistently reduce heart-failure hospitalization and cardiovascular death across the ejection-fraction spectrum, independent of glycemic status [77–94]. Mechanistic work shows that SGLT2 inhibition activates nutrient-deprivation signaling (SIRT1/AMPK upregulation and HIF-1α suppression), enhances autophagy and mitophagy, normalizes mitochondrial fission–fusion dynamics, and reduces cytosolic sodium and oxidative stress [78,80,95–97]. Figure 2 summarizes the metabolic and mitochondrial pathways through which SGLT2 inhibitors restore cardiac energetic homeostasis.

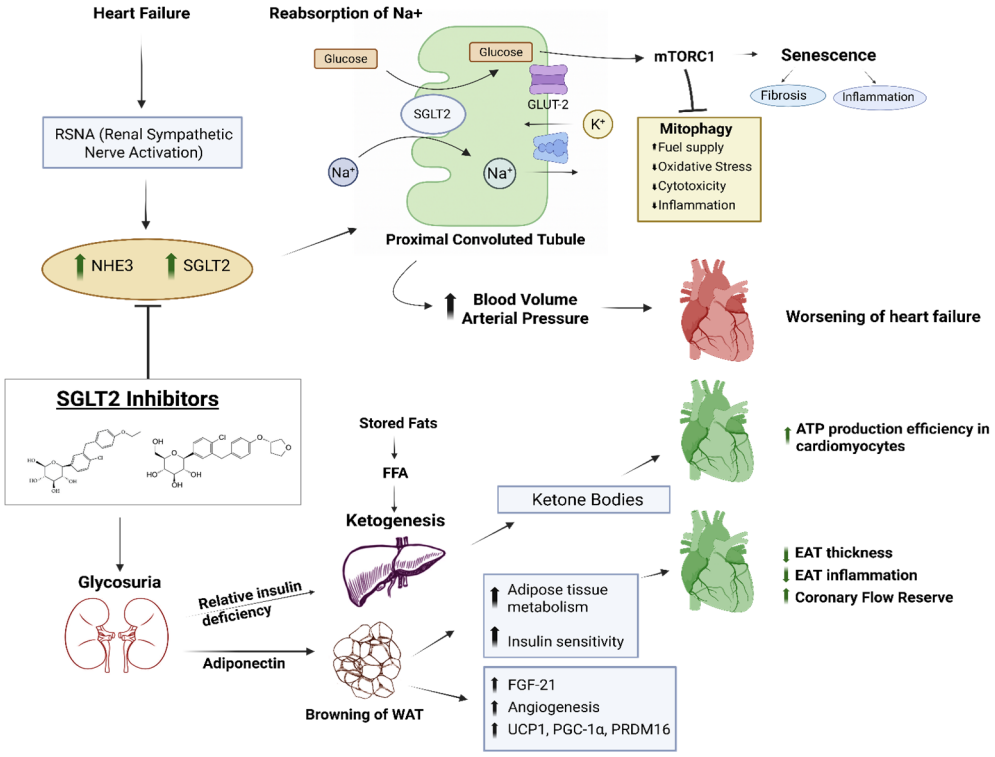

Figure 2. Mechanisms of Action, Metabolic & Mitochondrial Benefits of SGLT2 Inhibition in Heart Failure. SGLT2 inhibitors attenuate proximal tubular Na^+ and glucose reabsorption, reducing renal sodium–hydrogen exchanger 3 (NHE3) activity and maladaptive renal sympathetic nerve activation. These changes improve systemic hemodynamics and mitigate fibrosis and inflammation. At the mitochondrial level, SGLT2 inhibition promotes mitophagy, decreases oxidative stress, and limits cytotoxicity, thereby preserving organelle integrity. Enhanced availability of ketone bodies supports cardiac bioenergetics by improving fuel efficiency and metabolic flexibility. Systemically, SGLT2 inhibitors augment adipose tissue metabolism, insulin sensitivity, and upregulate protective

factors such as FGF21, angiogenic signaling, and thermogenic/oxidative regulators (UCP1, PGC-1α, PRDM16). Together, these mechanisms contribute to improved cardiac structure and function, underscoring the broad cardioprotective benefits of SGLT2 inhibition across the spectrum of heart failure. FFA = free fatty acids, WAT = white adipose tissue, EAT = epicardial adipose tissue.

GLP-1 receptor agonists (GLP-1RAs) such as liraglutide and semaglutide not only improve cardiovascular outcomes (e.g., LEADER trial) but also preserve mitochondrial integrity and prevent ferroptotic cell death in preclinical cardiac injury models [98–100]. Metformin, similarly, provides acute cardioprotection by partially inhibiting complex I, blunting the reperfusion ROS surge, and limiting mPTP opening [67]. Together, these therapies extend mitochondrial protection from the organelle to the level of whole-body metabolic resilience, positioning mitochondria as a central therapeutic node in systemic cardioprotection.

4.5. Gene Therapy and Mitochondrial Gene Editing

Recent advances in gene editing have opened unprecedented opportunities to correct or compensate for mitochondrial genetic defects. Heteroplasmy-shifting nucleases (mtZFNs, mitoTALENs) selectively degrade mutant mtDNA, allowing repopulation by wild-type genomes and functional recovery in cardiac and skeletal muscle [101]. Next-generation base editors, including DdCBE, HiFi-DdCBE, and TALED systems, now enable precise single-base correction (C→T, A→G) without double-strand breaks, expanding the catalogue of correctable mtDNA variants [102–104].

In parallel, mitochondrial replacement therapy (MRT) has moved from theoretical possibility to clinical reality, preventing transmission of mtDNA disease in humans [105]. Cardiac-directed AAV vectors encoding Ndufs6, cBIN1, or TFAM/Nrf1 demonstrate restoration of complex I function, cristae structure, and contractile performance in experimental models [106]. These studies collectively mark the emergence of mitochondrial gene therapy as a feasible and rapidly evolving domain.

4.6. Mitochondrial Transplantation and Cell-Based Approaches

An alternative regenerative paradigm involves the direct replacement of damaged or dysfunctional mitochondria. Mitochondrial transplantation (MitoTx), the delivery of respiration-competent, isolated mitochondria into injured myocardium, has advanced rapidly from preclinical feasibility to early clinical exploration [49,107–120]. Initial studies demonstrated that exogenous mitochondria, isolated from autologous skeletal muscle or allogeneic sources, can engraft within cardiomyocytes, restore ATP production, and ameliorate ischemia-induced contractile dysfunction [18,121,122]. In large-animal models of I/R injury, mitochondrial delivery via intracoronary or intramyocardial injection resulted in preserved left-ventricular ejection fraction, reduced infarct size, and transcriptomic normalization of metabolic and stress-response pathways, indicating both energetic and signaling recovery [4,12,23]. Importantly, these transplanted mitochondria remain functionally integrated with host tissue and participate in bidirectional signaling with endogenous mitochondrial networks, suggesting more than a transient bioenergetic effect [2,3].

Clinical translation has begun to emerge, with compassionate-use applications in pediatric I/R injury and anthracycline cardiotoxicity reporting improved myocardial contractility and hemodynamics without immune rejection or arrhythmic complications [12]. A first-in-human randomized trial in ST-segment elevation myocardial infarction (STEMI) (n = 30) demonstrated procedural safety, enhanced myocardial strain recovery, and favorable biomarker profiles compared with placebo, establishing early clinical feasibility [114].

Collectively, the growing body of work positions MitoTx as a frontier in regenerative cardiology, linking mitochondrial biology with tissue repair and functional recovery. Continued refinement in delivery precision, immunologic compatibility, and long-term integration will determine its viability as a clinically scalable mitochondrial medicine.

5. Disease-Specific Insights: Ischemic Heart Disease, Heart Failure, Cardiomyopathies, Atrial Fibrillation and Myocarditis

Growing evidence shows that mitochondrial dysfunction underlies a broad spectrum of cardiac diseases, coupling energy failure with inflammatory and structural remodeling. These insights are now guiding therapies tailored to specific mitochondrial mechanisms and disease contexts.

5.1. Ischemic Heart Disease (IHD) and Myocardial Infarction

Reperfusion after coronary occlusion triggers a mitochondria-driven injury cascade. Ischemic ATP collapse and succinate accumulation are followed by rapid succinate oxidation and reverse/forward electron transport at complex I, producing bursts of superoxide/H_2O_2 that drive mPTP opening, Ca^{2+} overload, and myocyte death [23,123–127]. This framing, pinpointing complex I site IQ as a dominant ROS source, has shifted therapeutic focus from non-specific antioxidants to timing-specific redox control during early reperfusion [10,128,129]. Importantly, constraining succinate handling can worsen I/R, underscoring the need for nuanced interventions [130].

In preclinical models, site-specific ROS suppressors (S1QELs, e.g., OP2113) reduce infarct size and microvascular obstruction by dampening complex I–derived ROS without impairing oxidative phosphorylation [129,131] and emerging delivery platforms aim to synchronize redox control to the reperfusion window [132]. MitoQ, a matrix-targeted antioxidant, shows protective signals across cardiometabolic I/R contexts, but human cardiac outcome data remain limited, and recent clinical summaries emphasize mechanism-anchored endpoints and timing [15,133]. Beyond drugs, cardiomyocyte exophers and resident macrophages form an intrinsic mitochondrial quality-control axis that clears damaged mitochondria and tempers post-MI inflammation [134,135], extending earlier *in-situ* evidence of a macrophage network supporting mitochondrial homeostasis in the heart [43]. Finally, mitochondrial transplantation (MT), the delivery of autologous, respiration-competent mitochondria, has progressed from pediatric postcardiotomy rescue [136] to an adult IHD randomized, triple-blinded trial reporting safety and functional benefit signals [114]. Collectively, these data support timing-specific, mitochondria-targeted reperfusion strategies coupled with innate QC pathways as a path forward in IHD.

5.2. Heart Failure (HFrEF and HFpEF)

Heart failure (HF) has long been described as an "energy-starved" syndrome, and mitochondrial biology offers a framework to dissect this concept at the molecular and systems levels. In HFrEF, decades of remodeling culminate in impaired electron transport chain (ETC) activity, cristae disorganization, and loss of metabolic flexibility. Studies in recent years further define how failing myocardium reprograms its fuel utilization, shifting from FAO toward ketone bodies and glycolysis, while suffering persistent deficits in ATP synthesis, NAD^+ balance, and redox buffering [137,138].

In contrast, HFpEF increasingly reveals a peripheral bioenergetic phenotype. The skeletal muscle mitochondrial dysfunction, reduced capillary density, and impaired oxidative phosphorylation are key contributors to exercise intolerance [139]. This shift challenges the notion that HFpEF is primarily a cardiac filling disorder, instead implicating systemic mitochondrial failure as a therapeutic target. In this context, aerobic exercise and caloric restriction restore mitochondrial respiration and improve function, reinforcing lifestyle as mitochondrial medicine [140,141].

Pharmacologically, SGLT2 inhibitors such as empagliflozin and dapagliflozin improve clinical outcomes across EF spectra and demonstrate consistent effects on mitochondrial autophagy, dynamics (↑OPA1, ↓Drp1), and redox signaling (↑AMPK/SIRT1, ↓ROS) [78–97]. Mechanistic analyses from EMMY, DAPA-MI, and EMPACT-MI suggest improved cardiometabolic and mitochondrial profiles post-MI, even as hard endpoints vary by cohort and timing [142,143].

Iron repletion has also emerged as a mitochondria-relevant strategy in HF. Intravenous ferric carboxymaltose (AFFIRM-AHF) and ferric derisomaltose (IRONMAN) significantly improve symptoms and reduce hospitalization in iron-deficient HFrEF, consistent with restoring ETC activity and supporting complex I/III assembly [144,145].

5.3. Cardiomyopathies and Mitochondrial-Specific Disorders

In diabetic cardiomyopathy, chronic glucolipotoxicity, due to elevated glucose and free fatty acids, induces mitochondrial ROS, impairs mitophagy, and accelerates cardiomyocyte apoptosis [146–148]. SGLT2 inhibitors, metformin, and exercise have all shown benefits in reversing this substrate overload and enhancing mitochondrial quality control. Recent studies suggest that early interventions targeting mitochondrial function may delay or even reverse energetic failure in preclinical diabetes-HF models [95,149].

In chemotherapy-induced cardiomyopathy, especially from anthracyclines (e.g., doxorubicin), mitochondrial injury and mtDNA damage drive cardiotoxicity. While dexrazoxane remains the standard prophylaxis, novel approaches focus on preserving mitophagy and stimulating PGC-1α–driven biogenesis, with agents such as elamipretide showing early promise in experimental cardiotoxicity models. Figure 3 presents the pathogenic mechanisms of ROS in cardiomyopathies.

In inherited mitochondrial disorders such as Barth syndrome, which features defective cardiolipin remodeling, mitochondria-targeted therapies are advancing into the clinic. Elamipretide's long-term extension data from TAZPOWER support durable improvements in function and biomarkers. However, generalizing mitochondrial therapeutics to broader HF populations will require phenotype-matched enrollment and mechanism-aligned endpoints, given the variability in mitochondrial dysfunction across etiologies [72,73].

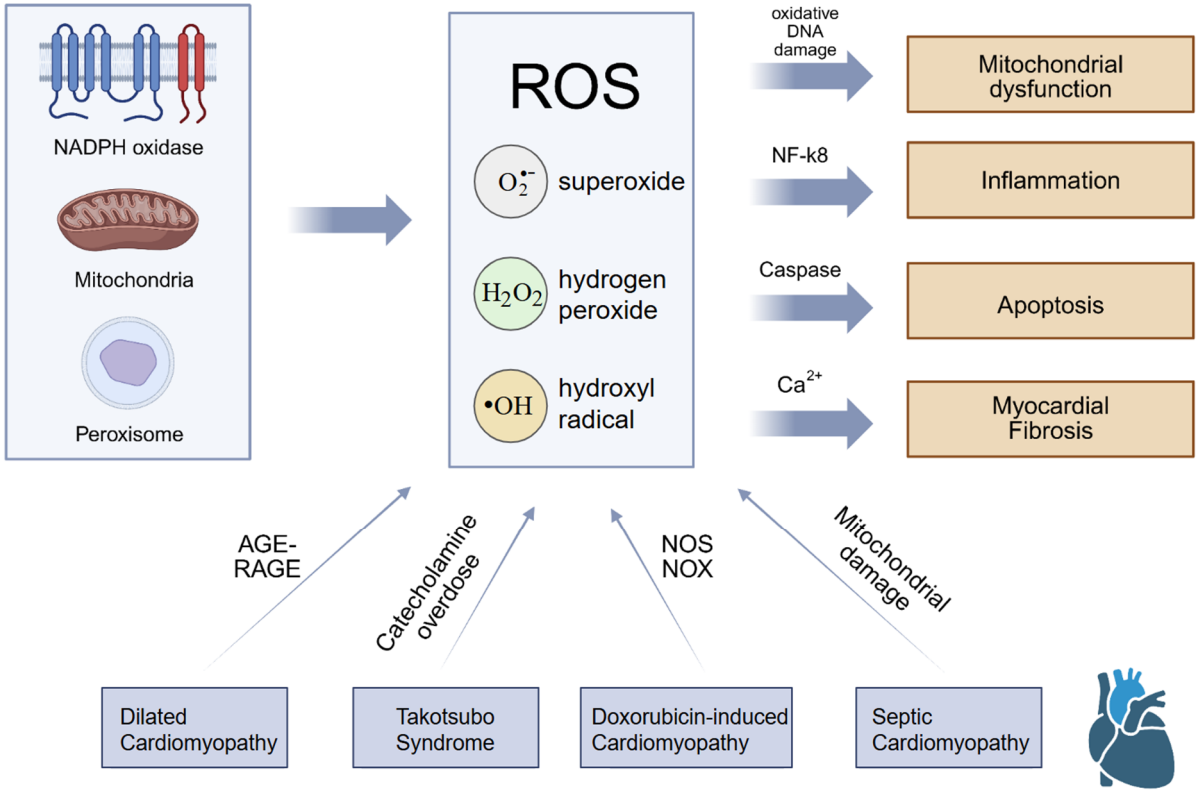

Figure 3. Pathogenic Mechanisms of ROS in Cardiomyopathies. Reactive oxygen species (ROS), including superoxide (O2•−), hydrogen peroxide (H2O2), and hydroxyl radical (•OH), arise from multiple cellular sources, including mitochondria, NADPH oxidases, and peroxisomes. Excessive ROS accumulation damages proteins, lipids, and DNA, leading to mitochondrial dysfunction and activation of NF-κB-mediated inflammatory signaling. This cascade increases mitochondrial membrane permeability, promotes cytochrome c release, and triggers caspase-dependent apoptosis. Distinct cardiomyopathy subtypes exhibit context-specific ROS drivers: in dilated cardiomyopathy (DCM), mitochondrial dysfunction and chronic oxidative stress contribute to disease progression; in Takotsubo syndrome (TTS), catecholamine surges predominate; in doxorubicin-induced cardiomyopathy, NOS and NOX dysregulation amplify oxidative stress; and in septic cardiomyopathy, impaired electron transport exacerbates ROS generation. Persistent oxidative injury establishes a self-perpetuating cycle of mitochondrial damage that drives the progression of cardiomyopathy. Adapted from Xiong et al. [148].

5.4. Atrial Fibrillation (AF) and Myocarditis

Growing evidence indicates that mitochondrial dysfunction in atrial cardiomyocytes contributes directly to the initiation and maintenance of atrial fibrillation (AF) [150]. In human atrial tissue from AF patients, mitochondria show fragmented morphology, impaired oxidative phosphorylation, and elevated ROS generation, leading to oxidative damage of ion channels and sarcomeric proteins [151]. These alterations shorten action potential duration, disrupt $Ca2^{+}$ handling, and facilitate re-entry circuits [152].

Recent transcriptomic and proteomic analyses of atrial tissue indicate that atrial fibrillation is associated with suppressed mitochondrial biogenesis signaling (e.g., reduced PGC-1α expression) and disrupted mitochondrial dynamics, characterized by lower MFN2-mediated fusion and increased DRP1-dependent fission, together with upregulated oxidative-stress pathways. These alterations correlate with structural remodeling and disease progression in AF [150,153]. Mitochondrial Ca^{2+} overload and reduced NAD^{+}/SIRT3 signaling further destabilize atrial energy homeostasis. In atrial fibrillation, SIRT3 down-regulation impairs mitochondrial respiration and increases acetylation of key metabolic enzymes, promoting oxidative stress and contractile dysfunction [152,154].

In parallel, mitochondrial Ca^{2+} imbalance drives Δψm collapse and mPTP opening, amplifying ROS production and electrical remodeling, thereby sustaining the arrhythmogenic substrate [147,150].

Therapeutically, interventions that attenuate mitochondrial ROS, such as MitoTEMPO, reduce atrial oxidative stress, Ca^{2+} alternans, and fibrosis, thereby lowering AF susceptibility in preclinical models [155,156]. Complementing mitochondrial ROS–targeted therapies, strategies that enhance mitochondrial biogenesis and deacetylase signaling, including PGC-1α, SIRT1, and SIRT3 activators or exercise-mimetic metabolic conditioning, restore mitochondrial ATP production, reduce mitochondrial protein hyperacetylation, and limit atrial fibrosis in AF experimental systems [157–159]. Collectively, these findings indicate that the mitochondrial–redox axis is not simply a downstream byproduct of atrial remodeling but a causal driver of AF pathogenesis, highlighting mitochondria as a promising target for rhythm-control and substrate-modifying therapies.

Mitochondria are emerging as central hubs in viral and immune-mediated myocarditis. Viral infections such as SARS-CoV-2 disrupt mitochondrial dynamics and trigger the release of mtDNA and mtRNA, which act as damage-associated molecular patterns (DAMPs) to activate cGAS–STING and NLRP3 inflammasome signaling. This cascade amplifies sterile inflammation and cardiomyocyte death, driving both acute injury and progression to chronic dilated cardiomyopathy [39,160,161]. Preclinical models show that pharmacologic inhibition of cGAS–STING or treatment with mitochondria-protective agents, including TUDCA and MitoQ, can reduce inflammatory cytokine production and preserve mitochondrial membrane potential, highlighting mitochondria as actionable targets in myocarditis [162,163].

6. Clinical Trial Landscape and Translational Progress

Translating mitochondrial-targeted therapies into cardiovascular medicine has proven more complex than anticipated. Although mechanistic rationale is strong, clinical outcomes highlight both notable advances and persistent challenges. Table 2 summarizes mitochondrial-focused clinical trials in heart disease conducted over the past five years, including mechanisms of action and current development status.

Table 2. Clinical trials between 2020–2025 investigating mitochondrial-targeted therapies in heart disease.

Trial/Program	Target and MOA	Disease Context	Key Findings	Current Status	References
PROGRESS-HF	Elamipretide (MTP-131)–mitochondria-targeting peptide	Stable HFrEF	Safe, but no improvement in LVESV or EF	Development in HF discontinued	[143]
EMPEROR-Reduced	Empagliflozin–SGLT2 inhibition (↑ketone use, ↓Na^+ load, bioenergetics)	HFrEF	Reduced CV death & HF hospitalization	FDA-approved; guideline standard	[144]
EMPEROR-Preserved	Empagliflozin–SGLT2 inhibition	HFpEF	First therapy to reduce HF events in HFpEF	Approved Standard-of-care	[77]
DELIVER	Dapagliflozin–SGLT2 inhibition	HFpEF	Lowered risk of HF hospitalization/events	Approved Standard-of-care	
TAZPOWER	Elamipretide–stabilizes mitochondrial cardiolipin	Barth syndrome (genetic mitochondrial disorder)	No primary endpoint met; OLE showed ↑6MWT & cardiac function	September 2025, when the FDA granted accelerated approval to Elamipretide (FORZINITY™) [a]	[72,73]

[a] FORZINITY™ was approved as the first treatment for improving muscle strength in Barth syndrome patients ≥30 kg; included here because Barth syndrome has important cardiac manifestations, but this is not a direct heart-failure indication.

6.1. Lessons from Clinical Experience

Early direct mitochondrial therapies, such as mPTP inhibitors, have demonstrated target engagement but limited clinical benefit. Trials in acute I/R (e.g., CIRCUS STEMI) and chronic HFrEF confirmed safety yet failed to improve major outcomes, reflecting suboptimal timing, delivery, and endpoint selection. Conversely, indirect metabolic approaches, especially SGLT2 inhibitors, have achieved robust outcome improvements across HFrEF and HFpEF. Their benefits, attributed in part to enhanced mitochondrial redox balance, substrate flexibility, and mitophagy, illustrate that reinforcing mitochondrial resilience through systemic pathways may be more practical than attempting direct organelle delivery.

6.2. Emerging Directions in Clinical Translation

Recent trials increasingly incorporate mitochondrial biomarkers, such as circulating cell-free mitochondrial DNA (cf-mtDNA), mitochondrial DNA copy number (mtDNA-CN), MOTS-c peptide, and high-resolution respirometry, as pharmacodynamic (PD) endpoints to confirm on-target mitochondrial engagement. This approach has been particularly relevant for Elamipretide (FORZINITY™), which demonstrated improvements in mitochondrial respiration and stabilization of cardiolipin integrity in Barth syndrome patients, as reflected by biomarker trends in the TAZPOWER trial and its open-label extension. The FDA's accelerated approval of Elamipretide in September 2025 marks a milestone, validating mitochondria-targeted therapy and reinforcing the importance of biomarker-driven development. These PD readouts not only confirm mechanistic activity but also enable precision phenotyping, guiding future trials toward endotype-specific enrollment and adaptive designs.

Meanwhile, SGLT2-inhibitor programs continue to integrate mitochondrial readouts to refine mechanistic understanding, reinforcing the role of systemic metabolic modulation in improving mitochondrial resilience. Beyond these successes, early-phase innovations, including gene editing, mitochondrial transplantation, and intercellular mitochondrial transfer, are advancing toward feasibility testing in ischemic and cardiomyopathic contexts. Collectively, these developments signal a shift from large empirical outcome trials toward biomarker-anchored investigations designed to demonstrate mechanistic efficacy and enable precision targeting.

6.3. Precision Alignment and Future Opportunities

Progress in clinical translation will require tighter alignment between mitochondrial mechanism, disease phenotype, and treatment timing. Emerging biomarker frameworks, integrating circulating indices (cf-mtDNA, mtDNA-CN, MOTS-c), metabolic imaging (^{31}P-Magnetic Resonance Spectroscopy (^{31}P-MRS), PCr/ATP), and ex vivo respirometry, enable classification of mitochondrial dysfunction into redox-dominant, bioenergetic-deficient, or inflammatory endotypes. This endotype-guided enrollment may increase therapeutic signal, particularly in contexts such as post-MI cf-mtDNA–high patients receiving cGAS–STING pathway modulation.

Temporal design is equally important. Acute I/R injury appears most responsive to short-term interventions targeting early ROS and mPTP opening, whereas chronic HF benefits from sustained metabolic support, redox buffering, and mitophagy enhancement. Pharmacodynamic markers such as PCr/ATP ratios, MOTS-c, and PGC-1α will be essential to confirm on-target mitochondrial engagement.

Looking forward, gene-editing platforms (e.g., heteroplasmy-shifting nucleases), cardio-tropic delivery vectors, and organelle-based approaches (mitochondrial transplantation, intercellular mitochondrial transfer) offer the possibility of direct mitochondrial correction, while AI-assisted metabolic modeling and adaptive trial designs can reduce trial size and accelerate mechanistic learning. Together, these advances shift the field toward biomarker-anchored, phenotype-matched, and temporally coordinated mitochondrial therapy strategies.

7. Conclusions and Future Outlook

Mitochondrial therapeutics have evolved from systemic metabolic modulators to organelle-level interventions, reflecting the growing recognition of mitochondria as central regulators of cardiac health. Small-molecule redox modulators and peptides, most notably Elamipretide (FORZINITY™), FDA-approved in September 2025, represent an important milestone, demonstrating safety and scalability in clinical use. However, their modest efficacy underscores the challenge of achieving sustained mitochondrial engagement in vivo. Similarly, systemic strategies such as SGLT2 inhibitors and metabolic conditioning have delivered meaningful improvements in cardiac energetics yet act through complex pathways that do not fully correct organelle-specific defects.

Next-generation approaches, including genetic and epigenetic interventions, promise durable correction but face hurdles in delivery efficiency, tissue targeting, and long-term safety. Organelle-based strategies such as mitochondrial transplantation show feasibility in acute injury models but remain constrained by scalability, immune compatibility, and graft persistence.

Future progress will depend on precision alignment between therapeutic mechanism, disease stage, and mitochondrial phenotype. Advances in delivery systems, mitochondrial imaging, and circulating biomarkers will be critical for verifying on-target effects and guiding personalized interventions. Furthermore, integrating computational modeling, digital cardiac twins, and multi-omic profiling could enable predictive frameworks for virtual testing, reducing trial size and accelerating mechanistic learning. As these precision strategies mature, mitochondrial modulation is poised to transition from conceptual promise to clinically actionable cardioprotection, marking a new frontier in system-level cardiovascular medicine.

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