HHS Public Access

Author manuscript

Free Radic Biol Med. Author manuscript; available in PMC 2018 December 28.

Published in final edited form as:

Free Radic Biol Med. 2018 December ; 129: 155–168. doi:10.1016/j.freeradbiomed.2018.09.019.

Targeting mitochondrial dysfunction and oxidative stress in heart failure: challenges and opportunities

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Abstract

Mitochondrial dysfunction characterized by impaired bioenergetics, oxidative stress and aldehydic load is a hallmark of heart failure. Recently, different research groups have provided evidence that selective activation of mitochondrial detoxifying systems that counteract excessive accumulation of ROS, RNS and reactive aldehydes is sufficient to stop cardiac degeneration upon chronic stress, such as heart failure. Therefore, pharmacological and non-pharmacological approaches targeting mitochondria detoxification may play a critical role in the prevention or treatment of heart failure. In this review we discuss the most recent findings on the central role of mitochondrial dysfunction, oxidative stress and aldehydic load in heart failure, highlighting the most recent preclinical and clinical studies using mitochondria-targeted molecules and exercise training as effective tools against heart failure.

Keywords

Mitochondria; Redox imbalance; Aldehydes; Cardiovascular diseases; Therapy; Exercise training

Introduction

Heart failure is a multifactorial degenerative disease, characterized by impaired capacity to fill the left ventricle and/or eject blood to match the demands. It has been considered the final common pathway of several acute and chronic diseases including myocardial infarction, myocarditis, valvular heart disease, hypertension, diabetes, obesity and chemotherapy [1–3]. Despite the advances in pharmacological and non-pharmacological interventions, heart failure continues to be a major public health problem, affecting over 25 million people worldwide [4] and costing about $100 billion/yr in the United States [5].

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Disclosure

DM-R and C-HC hold patents related to Alda and ALDH2, now licensed to Foresee Pharmaceuticals. However, they do not hold stocks of the company and none of this research was supported by the company. The other authors have no disclosure.

Over the last decades, heart failure treatment relied mainly on drugs that reduce cardiac workload by targeting neurohumoral over-activation with drugs such as beta-blockers, ACE inhibitors and AT1 antagonists [6,7]. Although these interventions promote symptom relief, they have a marginal impact on heart failure outcome such as mortality and rehospitalization rates [8]. Therefore, the identification of intrinsic mechanisms responsible for the continuous cardiomyocyte degeneration during the establishment and progression of heart failure is needed for the development of more effective therapies.

Current studies have focused on identifying intracellular targets that act as central nodes in the suppression or retardation of heart failure development and/or progression [9–13]. Many such intracellular candidates have been described in preclinical studies as critical players in cardiomyocyte degeneration during heart failure [14–18]. However, none of them has been translated into the clinic yet. Perhaps it is insufficient to treat heart failure by focusing on individual targets in a condition where a wide range of intracellular pathways is activated at different stages of the disease progression. Yet, identifying the optimal intracellular node(s) that should be inhibited to counteract chronic cardiomyocyte dysfunction and cardiac degeneration remains a major challenge in the heart failure treatment.

Mitochondrial (dys)function in heart failure

Among the myriad of intracellular components, mitochondria have been considered a strategic and dynamic node of influence, with unique biochemical, morphological and spatial features. Mitochondria are double membrane organelles containing over 1200 proteins, mainly encoded by the nucleus, translated in the cytosol and imported through mitochondrial outer and inner membrane (TOM-TIM) complexes. Only 13 proteins (all subunits of the electron transport chain) are encoded by the mitochondrial DNA. Mitochondria use redox oxidation to generate an electrochemical gradient required for ATP synthesis through oxidative phosphorylation. Mitochondrial energy metabolism is also the main source of oxidants; therefore playing a unique role in cardiac redox signaling and oxidative stress. In addition to their central role in ATP synthesis and redox homeostasis, mitochondria are involved in fatty acid and amino acid oxidation; maintenance of metabolites, co-factors and ions homeostasis; and heme and iron-sulfur cluster synthesis [19–21].

There are three different subpopulations of cardiac mitochondria: subsarcolemmal, perinuclear and intermyofibrillar. These mitochondrial subtypes, which account for ~35% of cardiomyocyte volume, differ in their morphology and function [22,23]. Intermyofibrillar mitochondria form a well-organized network of long and dense organelles oriented by the contractile myofilaments. This specific mitochondria architecture along the cardiomyocyte facilitates both physical and chemical interactions between mitochondria and other intracellular structures, such as the sarcoplasmic reticulum, which are critical for the heart physiology [22,23]. Disruption of these interactions is sufficient to reduce cardiomyocyte contractility properties and induce death [24].

Mitochondria have both direct and indirect impact on cardiomyocyte physiology by regulating bioenergetics [cardiomyocytes have high demand for ATP synthesis and oxygen

consumption], redox signaling [physiological response], oxidative stress [pathological response], calcium handling, contractility properties, necrosis and apoptosis. Therefore, maintenance of cardiac mitochondrial function and integrity is critical for human health. Eukaryotic cells have developed several mechanisms of surveillance to protect mitochondrial integrity. The three main levels of surveillance include (1) a multilayer network of detoxifying systems that counteracts excessive accumulation of oxygen- and aldehyde-meditated mitochondrial toxicity; (2) a protein quality control machinery, mediated by chaperones and proteases that are responsible for the maintenance of mitochondrial proteostasis; and (3) an interconnected mitochondrial network that controls mitochondrial morphology and number through mitochondrial fusion and fission, and mitophagy [24]. Pre-clinical studies have demonstrated that activating these mitochondrial surveillance systems is sufficient to protect against heart failure [25].

Several mitochondrial abnormalities have been associated with decompensated heart failure in both humans and experimental animal models [24]. The different types of dysfunction include inefficient energy production, excessive mitochondrial accumulation of ions, ROS and RNS, aldehydic load, disrupted mitochondrial interaction with other organelles (i.e. endoplasmic reticulum) and changes in mitochondrial number, mass and morphology due to unbalanced mitochondrial dynamics and impaired mitophagy [24]. This review is focused solely on detoxifying systems that counteract ROS-, RNS- and aldehyde- meditated mitochondrial toxicity in heart failure. The role of other mitochondrial mechanisms of surveillance in heart failure has been recently reviewed [24,26–28].

Reactive oxygen and nitrogen species in heart failure

ROS and RNS are broad terms used to refer to all the reactive chemical species derived from oxygen and nitrogen, respectively [29], including free radicals (e.g. $OH^{\cdot}$, $O_2^{\cdot -}$, $NO^{\cdot}$) and non-radicals (e.g. H_2O_2). These molecules have different half-life, reactivity and distribution within the cell. Therefore, features such as time, location and concentration should be considered when studying the effect of ROS and RNS in cardiac physiology and disease. Moreover, the method used to detect these species and the secondary products should be specific, suitable and sensitive enough. The current approaches to measure these ROS and RNS directly and indirectly include electron paramagnetic resonance (EPR) spectroscopy, liquid chromatography–mass spectrometry (LC-MS), high-performance liquid chromatography (HPLC) and redox-active probes [30,31].

The role of ROS in tissue degeneration has been studied and reviewed in the last decades [32–34]. But despite the extensive investigation in the field of oxidative stress, commonly defined as the imbalance between ROS generation and antioxidant defense, our current understanding of the so called “equilibrium state” is insufficient; there is a gap in the current knowledge about the physiological role of both oxidants and antioxidants in a time- and location-dependent manner [29]. This gap may have contributed to the difficulty in designing effective interventions and the failure of antioxidants in clinical trials [29]. Most studies have not considered the role of targeted reactive species as signaling molecules as well as the consequences of its scavenging in redox-mediated processes, such as ischemic

preconditioning [35,36]; therefore, reinforcing the need for a better understanding of ROS biological functions.

ROS and RNS have many different intracellular sources, including ETC, xanthine oxidase, NADPH oxidase and nitric oxide synthase (for details see refs [37,38]). In cardiac myocytes, mitochondria have been considered the major source of such products [32]. Mitochondrial respiration generates superoxide ($O_2^{\cdot -}$) through electron leakage at the complexes I and III of the ETC, which are transferred to free O_2. Superoxide is then dismutated to hydrogen peroxide (H_2O_2) by the mitochondrial superoxide dismutase (SOD) and, in the presence of free iron (Fe^{2+}), H_2O_2 can be reduced via Fenton reaction to originate the hydroxyl radical ($OH^{\cdot}$), a highly reactive free radical [39]. Additionally, in the presence of nitric oxide ($NO^{\cdot}$), superoxide can generate peroxynitrite ($ONOO^{\cdot}$). H_2O_2 is eliminated by antioxidant enzymes (e.g. catalase, peroxidase) that mostly require NADPH as an electron donor (Figure 1). ROS can also be produced by the metabolism of drugs and xenobiotics, such as the anti-cancer drug, doxorubicin [29], which has been linked to the development of cardiomyopathies [2]. In fact, cardiac accumulation of ROS and RNS has been reported in several cardiac diseases, including cardiomyopathies (i.e. ischemic, chagasic, dilated, hypertensive and idiopathic) and heart failure in both rodents and humans [40–42].

Due to its important role in energy supply (ATP synthesis) and ROS production/metabolism, mitochondrial dysfunction has been strongly linked to the development of metabolic and oxidative stress related diseases, such as cardiovascular diseases [43]. In fact, increased levels of ROS have been reported in failing hearts [16,44]; however, the cellular mechanisms that trigger its production and accumulation as well as the downstream effects that lead to the disease progression are still elusive, and may differ in distinct cardiomyopathies [40,41]. For example, the accumulation of succinate (a Krebs intermediate) during cardiac ischemia is sufficient to cause massive ROS generation through induction of reverse electron transport in the ETC during reperfusion [45]. This conserved metabolic response has been proposed as a critical process responsible for ischemia-reperfusion injury and, therefore, a promising therapeutic target in ischemic heart diseases [45]. However, its long-term impact on ischemic cardiomyopathy or heart failure remains to be determined.

The source of ROS in heart failure with reduced ejection fraction (HFrEF) seems to be different from heart failure with preserved ejection fraction (HFpEF, also known as diastolic heart failure). While the cardiomyocytes have been described as the main source of ROS in HFrEF [38], the endothelial cells seem to play an important role in ROS generation in HFpEF [46]. In fact, reactive species generated in endothelial cells, as a consequence of coronary microvascular inflammation, have been proposed to propagate the damage to cardiomyocytes through paracrine mechanisms, contributing to the maladaptive cardiac remodeling [38,46]. Notably, the association between ROS production and inflammatory processes has been extensively reported in the literature and may play a role in cardiovascular diseases [47–50].

Mitochondrial calcium overload has also been linked to increased ROS release and reduced ATP production in heart failure [51]. The relationship between Ca^{2+} and ROS generation in mitochondria has been extensively studied and reviewed [38,52–54]. Mitochondrial calcium

activates Krebs cycle dehydrogenases involved in the oxidative phosphorylation, maintaining a pool of reduced NADH and contributing to cellular energy homeostasis and maintenance of adequate cardiac work [55,56]. In heart failure, this process is disrupted, and disturbed mitochondrial Ca^{2+} uptake culminates in NADPH oxidation and ROS generation and accumulation. This effect is partially explained by a shift in the activity of the mitochondrial enzyme nicotinamide nucleotide transhydrogenase (Nnt) in the heart under pressure overload [57]. This enzyme converts NADH to NADPH, an essential substrate for antioxidant enzymes. However, under overload conditions, Nnt catalyzes the opposite reaction, then weakening the cellular antioxidant defense. Other studies have also demonstrated the importance of NADPH for the ROS scavenger enzymes, to provide reduced glutathione, glutaredoxin, and thioredoxin pools [58,59]. Deletion of key enzymes in the generation and/or recycling of NADPH directly impacts cell capacity to remove ROS [59], mainly the H_2O_2, an abundant product in failing cardiomyocytes, involved in hypertrophy signaling [60] and modulation of mitochondrial enzymes activity [61,62] (Figure 1).

Both defective Ca^{2+} and Na^{+} handling were proposed to initiate a vicious cycle leading to changes in NAD(P)H/$NAD(P)^{+}$ redox state and oxidative stress, which potentially affects EC coupling, cardiac dysfunction and heart failure [39,54,57,63]. Accumulation of cytosolic Na^{+}, which has been described in heart failure [39,64], has detrimental effects on mitochondrial Ca^{2+} uptake, once the Ca^{2+} efflux occurs through a Na^{+} /Ca^{2+} exchanger (mNCE). Consistent with this mechanism, inhibition of mNCE rescues mitochondrial Ca^{2+} uptake, prevents ROS accumulation and attenuates cardiac pathological remodeling in a guinea pig model of heart failure [65] (Figure 1).

The negative impact of ROS in heart failure includes the activation of a wide range of signaling pathways related to cell death [66], proliferation of cardiac fibroblasts, activation of matrix metalloproteinases, mtDNA damage [67], mitochondrial dysfunction [68], impaired calcium handling [69] and contractility [70], and cardiac hypertrophy [15], all of which ultimately leading to maladaptive myocardial remodeling and cardiac dysfunction. For example, the oxidation and activation of the kinase CaMKII (Ca^{2+}-calmodulin–dependent protein kinase) mediated by H_2O_2 triggers mitochondrial permeability transition, oxidative stress-mediated myocardial damage, necrosis and heart failure [62,71]. CaMKII contributes to the regulation of cardiac excitation–contraction coupling, and its delta isoform has been implicated in apoptotic signaling and in mediating the transition to heart failure [72,73].

Furthermore, it has recently been proposed that ROS can directly modify microRNAs [74] and alter its expression [75]; therefore causing both proteome remodeling [76] and metabolic shift in heart failure [76–78]. miRNAs are a class of small non-coding RNA involved in posttranscriptional regulation of protein expression [79]. Therefore, modifications in miRNA expression can lead to expressive changes in protein levels and disrupt down-stream gene regulation in affected tissues. Several microRNAs have been reported to modulate mitochondrial function [80,81]. For example, miR-210 regulates mitochondrial respiration and metabolism during hypoxic stress by repressing the Iron-Sulfur Cluster Assembly Proteins ISCU1/2 [82]. ISCU1/2 facilitates the assembly of [4Fe-4S] and [2Fe-2S] iron-

sulfur clusters required by enzymes such as aconitase (TCA cycle) and the mitochondrial respiratory complexes. Chen et al reported that treatment with miR-210 increases $O_2^{\cdot -}$ and H_2O_2 production in cellular model [83] and several miRNAs were identified in the mitochondrial fraction (mitomiRs) and profiled in failing hearts following TAC (transverse aortic constriction) in mice [84]. However, their functional consequences in heart diseases are still to be elucidated.

In addition to their direct damage of biomolecules and related downstream signaling, increased levels of ROS can induce cellular responses through distinct mechanisms such as the production of other classes of reactive molecules (aldehydes) [85], ROS-induced ROS release [86–88] and the recently described ROS-mediated paracrine signaling [89]. Interestingly, the latter mechanism proposes that ROS indirectly mediates the communication between cardiomyocytes and pericardial cells in the heart. Using *Drosophila*, Lim et al (2014) postulated that cardiac ROS induce downstream signals in the pericardial cells that, in turn, act on the cardiomyocytes in a paracrine way to modulate their function, in a process that does not require diffusion of ROS between cells [89].

For the development of effective therapy for a multifactorial disease as heart failure, it is crucial not to limit our studies to local damage in cardiomyocyte, but also its crosstalk with non-myocytes cells and remote organs. To elucidate the role of ROS as signaling molecules in cardiomyopathies, ROS should be broadly investigated, considering each species own reactivity and stability, cellular concentration and distribution, as well as its sources and metabolism in specific cell types.

Lipid peroxidation and aldehyde metabolism in heart failure

Lipid peroxidation is an oxidative degradation process triggered by a chain reaction of excess ROS attacking cell membrane or subcellular organelle membrane phospholipid and polyunsaturated fatty acid (PUFA) [90]. Lipid peroxidation is characterized by the attack of free radicals (e.g. $OH^{\cdot -}$ and $O_2^{\cdot -}$) on the double bonds of unsaturated lipid to produce lipid peroxide. The result of this chemical reaction is the generation of highly reactive and damaging carbonyls, such as different aldehydes, ketones, alkanes [91]. Two examples of the highly reactive lipid peroxidation aldehydes are 4-hydroxy-nonenal (4HNE) and malondialdehyde (MDA), which are generated from linoleic acid or arachidonic acid [91]. Reactive aldehydes can form adducts with proteins and DNA thus leading to cellular damage. As compared to the average half-life of ROS, which is only micro- to milliseconds *in vivo*, reactive aldehydes are stable for 1–2 seconds, diffuse through cell membranes and amplify the effects of ROS [92]. The damage caused by reactive aldehydes has therefore been implicated in many acute and chronic human diseases such neurodegenerative diseases, alcoholic liver disease, diabetes, cancer and various cardiovascular diseases [27,93–97].

The coupling of oxidative phosphorylation from respiration with electron transport chain across the mitochondria inner membrane is a major site and source of abundant ROS, and consequent, aldehyde generation [98]. The presence of at least six aldehyde dehydrogenase (ALDH) isozymes, among a total of 19 human ALDH isozymes, within the mitochondria highlights the critical protective role of ALDHs for the removal and metabolism of exogenic

and endogenic reactive aldehydes to preserve mitochondrial homeostasis and function [99]. One of the better-characterized ALDH isozyme is the mitochondrial ALDH2 (EC 1.2.1.3). ALDH2 is a tetrameric non-P450 detoxifying enzyme, most efficient in metabolizing short-chain aliphatic aldehydes like acetaldehyde and propionaldehyde. However, ALDH2 also participates in the catalysis of other reactive lipid peroxidation-derived aldehydes, such as 4HNE and MDA [100,101]. Importantly, a common single amino acid substitution variant of ALDH2 (E594K, or the ALDH2*2 allele) that renders the inactive enzyme, exists in about 540 million East Asians and their descendants [102].

Carriers of the ALDH2*2 variant allele typically exhibit the “alcohol flushing syndrome” due to their inability to metabolize acetaldehyde from alcohol drinking efficiently. Accumulation of toxic acetaldehyde not only causes the symptoms of facial flushing, palpitation, headache, vomiting, but it is also highly associated with upperaerodigestive track cancers and liver, colorectal and female breast cancers [102]. In 2007, the WHO International Agency for Research on Cancer (IARC) classified alcoholic beverage as a Group 1 carcinogen (carcinogenic to human), with an emphasis on acetaldehyde toxicity specially for ALDH2*2 enzyme-deficient human subjects [103].

The importance of mitochondrial ALDH2 enzyme for cardiovascular function and cardiovascular diseases is well documented. The subject has been reviewed extensively in recently years [104–113]. Chen et al. first reported a critical role of ALDH2 in εPKC-mediated cardioprotection against ischemia and reperfusion (I/R) injury [114]. A small molecule ALDH2-specific activator, Alda-1, was shown to be effective in reducing I/R injury in an animal model by increasing the ALDH2 enzyme activity directly [114]. X-ray crystal structures showed that Alda-1 binds in the catalytic tunnel site of the ALDH2, close to its substrate site. Alda-1 not only enhances the rate of productive encounter between the aldehyde substrate and the critical active site amino acid residues, but also corrects the conformational defect of the ALDH2*2 mutant enzyme and thus restoring ALDH2*2 activity allosterically [115]. These observations underlie the potential for the development of Alda-1-like compounds as therapeutics for the enhancement of ALDH2 activity and especially for human subjects carrying the defective ALDH2*2 variant [27,108].

More recent work indicated that ALDH2 and its polymorphism play a role in the etiology and pathology of heart failure. Two common features of heart failure are oxidative stress and mitochondrial dysfunction, both intricately related to ALDH2 function. In separate studies, downregulation of ALDH2 was associated with cardiac damage in both rat and mouse model of myocardial infarction and pressure overload [116,117], and in tissues obtained from end-stage heart failure patients receiving heart transplantation [116]. In two different genetic models, ALDH2 knockout and dominant-negative ALDH2 mutant overexpression, there was an exacerbated left ventricular dilation and cardiomyocyte death 4 weeks after myocardial infarction [116]. On the other hand, cardiac overexpression of a functional ALDH2 attenuated and protected heart function and remodeling against myocardial infarction [116] and chronic alcohol intake [118].

Therapies targeting mitochondria in heart failure

As previously discussed, mitochondrial dysfunction, oxidative stress and aldehydic load have been linked to the development and progression of heart failure. Therefore, mitochondria may serve as one of the most promising targets for heart failure treatment [25,119,120]. Several strategies targeting mitochondria, such as small molecules [25,115], and mitochondria targeting peptides and antioxidants [121] have been tested in preclinical and clinical studies in heart failure (Table 1). Coenzyme Q10 (CoQ10 or ubiquinone) supplementation has been considered a safe and effective therapeutic option to treat heart failure [122]. CoQ10 is a component of the ETC, mediating the electron transport from Complexes I and II to Complex III. Its reduced form, ubiquinol, acts as an antioxidant inside mitochondria, once it can react with peroxyl radicals and regenerate vitamin E [123], thus protecting the cell against lipid peroxidation.

Preclinical studies have demonstrated a depletion of CoQ10 in different heart failure models [124,125], thus suggesting a role for CoQ10 in the pathophysiology of heart failure. And chronic supplementation with CoQ10 counteracts excessive oxidative stress and cardiomyocyte remodeling in diabetic cardiomyopathy in rodents [125]. Recently, CoQ10 has been tested in patients with chronic heart failure. The clinical trial named Q-SYNBIO was a small study conducted between the years 2003– 2010 in 420 chronic heart failure patients worldwide. Despite its limitations, the study reported promising results, such as reduction in major adverse cardiovascular events and lower rates of hospitalization and mortality among the patients treated with CoQ10 [126]. Another ongoing randomized, double-blind and placebo-controlled design clinical trial currently tests whether ubiquinol treatment (active form of Coenzyme Q10) improves the outcome of heart failure patients with preserved ejection fraction (HFpEF) (estimated enrollment of 250 participants) [127]. In the same direction, short-chain synthetic CoQ analogues have also been developed (e.g. EPI-743 and Idebenone) and tested in genetic mitochondrial disease [128]. An open-label trial demonstrated that sustained treatment with EPI-743 improved quality of life in individuals with genetically-confirmed mitochondrial disease (the study included 13 children and 1 adult) [128].

In 2001, Murphy’s group synthetized a mitochondria targeting antioxidant, named MitoQ, which comprises an exogenous ubiquinone attached to a triphenylphosphonium lipophilic cation [123]. Sustained MitoQ treatment protected hearts against *ex vivo* ischemia-reperfusion injury. This cardioprotection was associated with reduced mitochondrial dysfunction and cell death [129]. MitoQ also reduced mitochondrial ROS production and restored ATP synthesis in a pressure-overload induced heart failure model. However, the treatment was not sufficient to alter the left ventricle function and remodeling [130]. Chronic MitoQ supplementation improved vascular function in healthy older adults (55 subjects enrolled) [131], but not the outcome of Parkinson disease in patients (128 subjects enrolled) [132]. The impact of MitoQ supplementation in heart failure patients remains to be determined.

Another promising strategy for treatment of heart failure relies on targeting the nitric oxide-soluble guanylate cyclase-cyclic guanosine monophosphate (NO-sGC-cGMP) pathway

[133]. Under oxidative stress, this pathway is compromised, and cells present lower levels of cGMP [134]. The downregulation of this signal has been linked to the development of several heart failure symptoms, such as vascular stiffness and reduced coronary blood flow [133]. Among the new molecules being engineered to preserve the cGMP level, the most advanced therapy is the sGC stimulator Vericiguat [135]. The molecule was tested in two parallel phase II studies in both heart failure with reduced (NCT01951625; 456 subjects enrolled) [136] and preserved (NCT01951638; 477 subjects enrolled) [137,138] ejection fraction. The drug was well tolerated in HFrEF patients and, despite no effect on NT-pro-BNP levels, it has been currently tested in a Phase III Study (NCT02861534; ongoing; estimated enrollment: 4872 subjects). In patients with HFpEF, the drug was also ineffective in reducing the levels of the disease severity markers [137,138]. However, as it improved patient's quality of life, the clinical investigation will continue in the recently posted Phase II Trial (NCT03547583; ongoing; estimated enrollment: 735 subjects).

There are other types of antioxidant with potential against cardiac diseases, such as radical scavengers (MCI186/Edaravone, XJB-5–131) and superoxide dismutase mimetics (EUK8/EUK134, M40403, Me2DO2A, MnTBPA) [25]. Notably, edaravone (Radicava) has just received the FDA approval for ALS (amyotrophic lateral sclerosis) treatment and is currently under clinical trial for acute ischemic stroke in Japan. Regarding its application for cardiac diseases, the efforts seem to be concentrated on ischemia-reperfusion injury. Eto et al reported myocardial protection against I/R injury in rabbit hearts treated with edaravone immediately after reperfusion. Using electron paramagnetic resonance (EPR), the authors demonstrated increased $OH^{\cdot}$ production after reperfusion, associated with loss of cardiac function and I/R injury, which was mitigated by edaravone [139]. Furthermore, in a small pilot study carried out in 80 patients with acute myocardial infarction, administration of edaravone prior to reperfusion was associated with a better clinical outcome, such as decrease in reperfusion arrhythmias and myocardial stunning [140].

Other strategies targeting mitochondria disorders include blocking the mitochondrial permeability transition (cyclosporine A [141,142], TRO40303 [143]), transient inhibition of the ETC (mitoSNO) [144], AMPK activation (metformin, AICAR, resveratrol) [145–148], modulating mitochondrial enzymes activity (MA-5 [149]) and targeting the mitochondrial inner membrane (SS31, also known as MTP-131, Bendavia, Elamipretide) [9,14]. Among this list, one attractive compound is the SS-31, a peptide that associates with cardiolipin (CL), a phospholipid that localizes in the mitochondrial inner membrane [150]. Lately, CL has been considered a critical target for drug development as it has been shown to interact with several mitochondrial proteins and metabolite carriers, such as the ETC complexes, cytochrome c and ADP/ATP carrier; therefore affecting mitochondrial bioenergetics [151]. Szeto et al demonstrated that SS-31 improves mitochondrial bioenergetics, accelerating ATP recovery after ischemia and reducing ischemic kidney injury [152]. The authors proposed that SS-31 protects CL from peroxidation, which could explain the MTP inhibition. Similarly, in Friedreich ataxia disease, SS-31 treatment increased the enzymatic activity of iron-sulphur enzymes (aconitase, ETC complexes II and III), accompanied by an improvement in the mitochondrial membrane potential and ATP content [153].

Preclinical studies have demonstrated a protective effect of SS-31 in animal models of pressure overload-induced heart failure[154,155] and hypertensive cardiomyopathy. In the latter study, SS31 was shown to prevent ROS accumulation in the mitochondria and ameliorate angiotensin II-induced cardiac hypertrophy and diastolic dysfunction [156]. Additionally, Elamipretide (or Bendavia), a drug form of SS-31, has recently been tested in two clinical trials in patients with heart failure with reduced ejection fraction (HFrEF, 36 patients enrolled) (NCT02388464) and patients with ST-segment elevation myocardial infarction (STEMI, 300 patients enrolled) (NCT01572909 - EMBRACE) [14,157]. Both trials demonstrated acceptable safety and tolerability; however, the phase 2a trial EMBRACE did not show an improvement in the primary endpoint after treatment (myocardial infarct size). It is worth mentioning that Cerrato's group has developed two modified versions of the peptide SS-31, called mtCPP-1 [158] and mtgCPP [159], in the last two years. In preliminary studies, both peptides have shown greater efficiency and antioxidant capacity (2–3 fold) than SS-31. Despite its potential to become new drug candidates, studies on cardiomyopathies have not yet been described.

Finally, small molecules targeting mitochondria have emerged as promising therapeutic strategies in the last decade. One example is the previously mentioned Alda-1 [115], an agonist of the mitochondrial enzyme aldehyde dehydrogenase 2 (ALDH2), which accumulate functions in the ethanol metabolism [97] and redox biology [160], removing intracellular toxic aldehydes (e.g. acetaldehyde, 4-HNE) [161]. Notably, in an animal model of myocardial infarction-induced heart failure, selective activation of ALDH2 by Alda-1 improves the clinical outcome of heart failure by decreasing the overload of reactive aldehydes and preserving mitochondrial bioenergetics [162].

In a rat model of post-myocardial infarction-induced cardiomyopathy, Gomes et al., also showed a protective role of ALDH2. Without an intervention, ALDH2 activity was reduced by 80% within the first two week of coronary artery ligation with a concomitant increase of aldehydic loads and loss in cardiac mitochondria function in the myocardium [163]. However, a sustained treatment with Alda-1 for 4 weeks starting 24 hours after the coronary artery ligation increased ALDH2 activity, reduced lipid peroxidation, 4HNE protein adducts, and prevented mitochondria damage [163]. Furthermore, sustained activation of ALDH2 by Alda-1, from week 4 to week 10, was effective in preventing myocardial hypertrophy, fibrosis and cardiac dysfunction [162]. The absence of 4HNE-protein adducts accumulation and preservation of mitochondria function was clearly associated with the improvement of heart failure outcome [162].

The ALDH2*2 (rs671) variant is an independent risk factor of coronary heart disease in many population-based studies [164–168]. In 248 patients with coronary heart disease, the variant ALDH2 genotypes (GG & GA) were associated with increased serum levels of 4-HNE, severity of coronary artery stenosis and atherosclerosis [169]. Oxidized low-density lipoprotein induces ER stress, apoptosis and 4-HNE protein adducts production in mouse smooth muscle cells. Using an *in vitro* model of atherosclerosis, Alda-1 was effective in reducing 4-HNE-protein adducts, ER stress and apoptosis in smooth muscle cells [169]. In addition, activation of ALDH2 by Alda-1 reduced ROS and reactive aldehydes levels, mitigated calcium overload and dramatically improved resuscitation survival in an *in vivo*

model of post-myocardial arrest dysfunction [170]. These studies established a critical connection between ALDH2 activity, cardiac function and heart failure. These studies also identified ALDH2 as a potential target for intervention and suggest that ALDH2 activators, such as the small molecule Alda-1, as a therapeutic for heart failure [108,113,171] (Figure 2).

Mitochonic Acid 5 (MA-5) is another recently described molecule [172], which consists in a synthetic derivative of the plant hormone, indole-3-acetic acid (IAA). MA-5 increases cellular ATP levels independently of the membrane potential and ETC complexes, possibly through the facilitation of ATP synthase oligomerization. The first studies with this compound reported promising results in fibroblasts from patients with mitochondrial diseases, and its protective effects on animal models of heart failure are to be evaluated [149,172].

To date, there are few studies describing the toxicity (pre-clinical studies) and safety (clinical trials) of the molecules depicted in Table 1. Sustained Alda-1 treatment (for 6 weeks) did not change hemodynamic parameters, circulating aspartate aminotransferase and alanine aminotransferase activities, as well as serum uric acid and creatinine levels in healthy animals [162]. Regarding its use in patients, Alda (FP-045) has successfully completed the Phase I Clinical Study this year, showing safety and tolerability in a dose escalation study in healthy humans (24 subjects). The trial is registered by Foresee Pharmaceuticals in the ANZCTR (Australian New Zealand Clinical Trials Registry) (Trial code: ACTRN12618000195257p). Despite the recent and ongoing clinical tests with MitoQ supplementation (NCT02597023, 55 subjects enrolled; NCT03586414, planned enrolment: 60 subjects), recent studies have raised some concerns regarding the drug toxicity, as it has been reported to inhibit mitochondrial respiratory chain complexes [173] and cause mitochondrial depolarization [174]. In the same direction, the free radical scavenger MCI-186 (Edavarone), which has been considered safe in clinical trials (FDA, NDA: 209176), can be toxic when administered by continuous intravenous infusion.

Remarkably, great efforts have been made not only to identify and address mitochondrial targets, but many studies have also focused on developing effective strategies to increase tissue and cell permeability [159] and deliver molecules inside mitochondria [175,176] as well as alternative ways of drug administration [177]. Combined strategies to approach and treat oxidative stress and mitochondrial dysfunction, based on the increasing understanding of the role of reactive species and cellular antioxidants, seem to be a promising way to design effective interventions and develop new therapies for a complex and multifactorial disease such as heart failure.

Exercise and mitochondrial dysfunction in heart failure

Exercise intolerance is a hallmark of heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). Over the last decades, it has been proposed that exercise intolerance is not only a consequence of heart failure but it indeed has a major contribution to cardiac degeneration and heart failure progression [178–180]. Therefore, exercise has been used as a diagnostic, prognostic and therapeutic tool in heart

failure [181,182]. More recently, exercise training has been included in the European Society of Cardiology (ESC) Guideline recommendations for treatment of heart failure as an important strategy in prevention and treatment of heart failure, as a non-pharmacological adjuvant therapy [178–181,183].

Overall, exercise training can improve the outcome of patients with heart failure by improving quality of life, reducing hospitalization and relieving symptoms [184–186]. The cardiovascular benefits of exercise training include reduction of neurohumoral activation (both SNS and RAS), decrease of inflammatory markers, better vascular function, physiological cardiac remodeling effect and improve of skeletal muscle mass and contractility properties [187–190]. Intrinsically, the positive effects of exercise training in cardiomyocytes are associated, but not limited, to increased levels of calcium-handling-related proteins [191], contractility properties [70,192], antioxidant capacity [188,193] and protein quality control [11,187,194]. However, these intracellular adjustments still need to be validated as causal mechanisms of exercise benefits in heart failure. Therefore, the causal molecular mechanism underlying the benefits of exercise training in failing hearts remains unknown.

Over the last decade, several studies have demonstrated that changes in mitochondrial function are critical to induce exercise benefits in heart failure [195]. Overall, exercise training improves the efficiency of mitochondrial oxidative phosphorylation [68], reduces mitochondrial permeability transition [68], increases the mitochondrial clearance of toxic molecules including ROS and aldehydes [196,197] and increases mitochondria number, size and clearance [68] in heart failure. In this context, exercise training would improve left ventricular function in heart failure animals by reestablishing mitochondrial functionality.

The mitochondrial benefits of exercise training have been demonstrated in both animal models and patients with heart failure. Aerobic exercise improves mitochondrial dysfunction in a rat model of heart failure induced by myocardial infarction [11,68]. This response is mainly characterized by the rescue of mitochondrial oxygen consumption, reduction of mitochondrial hydrogen peroxide release and calcium-induced mitochondrial permeability transition, and reestablishment of mitochondrial number and size in failing hearts [11,68]. Indeed, these exercise-induced mitochondrial changes positively affect cardiac protein quality control machinery in heart failure [11]. Short-term aerobic exercise training also prevents mitochondrial dysfunction and oxidative stress in an animal model of doxorubicin-induced heart failure [198]. Low-intensity aerobic intermittent training attenuates mitochondrial dysfunction with a positive impact on cardiac function and remodeling in animal model of myocardial infarction-induced heart failure [199] and pressure overload-induced heart failure [200].

Cardiac and skeletal muscle mitochondrial abnormalities lead to the metabolic dysfunction seen in heart failure patients; therefore contributing to disease progression [25]. Therefore, increasing energy expenditure during exercise should have a direct and positive impact on mitochondrial bioenergetic efficiency and lately increase the peak oxygen consumption (a predictor of mortality in heart failure patients [201,202]). In fact, even modest increase in peak oxygen consumption (an indicator of mitochondrial metabolism) induced by a 3 month

aerobic exercise training is sufficient to lower the risk of cardiovascular mortality, hospitalization and all-cause mortality in patients with chronic systolic heart failure [203].

Exercise training is also effective in improving peak oxygen consumption with a positive impact on diastolic function and quality of life in patients with heart failure with preserved ejection fraction [182]. The latest Cochrane review, which included 33 trials with 4740 people with heart failure (predominantly with HFrEF and New York Heart Association classes II and III) provides evidence that exercise training reduces the risk of hospital admissions and confers improvements in quality of life of heart failure patients [204].

In summary, the ability of exercise training to improve mitochondria functionality with a clear impact on cardiomyocyte viability highlights an important intracellular node underlying the benefits of exercise training in heart failure. However, further integrative studies comparing different exercise training protocols and time as well as studies investigating the role of mitochondrial metabolism and its extension to cytosolic systems and whether this connectivity is required to improve cardiac fitness induced by exercise in heart failure are needed.

Conclusions

As discussed here, heart failure is a degenerative disease that affects millions of people worldwide. Although extensive efforts have been made over the last decades in the development of better drugs, the available therapies (mainly targeting neurohumoral hyperactivity) still have a marginal effect on heart failure outcome such as mortality. Therefore, identifying the optimal intracellular node(s) that slow down, stop or even reverse cardiomyocyte dysfunction and cardiac degeneration remains a major challenge for developing better therapies.

Recently, mitochondria have attracted considerable attention from both academia and industry, since mitochondrial dysfunction is a hallmark of many diseases, including heart failure. However, are mitochondrial dysfunction benign or do they actually contribute to heart failure? In this review, we examined the evidence from animal studies and from human clinical trials, and it seems that intrinsic mitochondrial changes in the affected cardiomyocyte are critical to heart failure pathophysiology. Overall, these studies support a decisive role for (but not restricted to) impaired cardiac mitochondrial electron transport chain activity, oxidative stress and aldehydic load in cardiomyocyte dysfunction and consequent heart failure establishment/progression.

But, why is there such a central role for mitochondria in heart failure? First, mitochondria are the powerhouse of the cell. Second, mitochondria account for ~35% of cardiomyocyte volume and form a long, dynamic and well-organized network, which facilitates both physical and chemical interactions between mitochondria and other intracellular structures. Third, exciting body of recent research focusing on the cellular and molecular mechanisms involved in heart failure pathophysiology indicates mitochondria as strategic and dynamic nodes of influence, virtually affecting every single biochemical process in cardiac cells. In that sense, dysfunctional mitochondria can quickly propagate damage within cardiomyocyte

in failing hearts, where mitochondrial surveillance mechanisms are usually disrupted. Therefore, different emerging therapeutic strategies including small molecules and peptides individually targeting such mitochondrial abnormalities have the potential to improve the function of the failing heart. In fact, several preclinical studies have succeeded in improving heart failure outcome. Some of these molecules are now in clinical trials.

As last note, improving mitochondrial functionality by using mitochondria-targeted therapeutics might be an important strategy to enhance the effectiveness of nonpharmacological therapies, such as exercise. Exercise is a well-known and very effective intervention, improving cardiac mitochondrial metabolism in both health and disease. However, it should be performed at a moderate to high intensity to maximize its impact on cardiac physiology. Considering the exercise limitations observed in heart failure patients, its benefits are only marginal in this population. We believe that the optimal management of heart failure requires a combination of pharmacological and nonpharmacological therapies that synergistically potentiates mitochondrial functionality with a positive impact on cardiac performance and patient healthspan and lifespan.

Acknowledgments

Funding

This work was supported by Fundação de Amparo à Pesquisa do Estado de São Paulo [FAPESP 2012/05765–2, 2013/07937–8, 2015/20783–5, 2015/22814–5, 2017/16694–2 to JCBF]; Conselho Nacional de Pesquisa e Desenvolvimento – Brasil [CNPq 303281/2015–4, 470880/2012–0, 407306/2013–7 to JCBF]; and National Institutes of Health [NIAAA MERIT Award AA011147 to D-MR]. LA holds fellowship from FAPESP [2016/00900–0 and 2017/14426–0] and RAP holds fellowship from Capes. This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001.

Abbreviations

4-HNE	4-hydroxynonenal ISCU 1/2 iron-sulfur cluster assembly protein 1/2
ACE	angiotensin converting enzyme
ALDH2	aldehyde dehydrogenase 2
ALS	amyotrophic lateral sclerosis
AMPK	AMP-activated protein kinase
BCL-2	b-cell lymphoma 2
CaMKII	Ca2+-calmodulin-dependent protein kinase
CL	cardiolipin
CoQ10	coenzyme q10
EC	excitation contraction
εPKC	protein kinase C epsilon

EPR	electron paramagnetic resonance
ER	endoplasmic reticulum
ETC	electron transport chain
FDA	Food and Drug Administration
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
HFpEF	heart failure with preserved ejection fraction
HPLC	high-performance liquid chromatography
HSP70	heat shock protein 70
IARC	International Agency for Research on Cancer
IR	ischemia reperfusion
ISCU 1/2	iron-sulfur cluster assembly protein ½
JNK	c-Jun N-terminal kinase
LC-MS	liquid chromatography-mass spectrometry
LV	left ventricle
MDA	malonaldehyde
MI	myocardial infarction
miR-210	microRNA210
miRNA	microRNA
mNCE	mitochondrial Na+ Ca2+ exchanger
MPT	mitochondrial permeability transition
Nnt	nicotinamide nucleotide transhydrogenase
NO-sGC-cGMP	nitric oxide-soluble guanylate cyclase-cyclic guanosine monophosphate
p53	cellular tumor antigen p53
PUFA	polyunsaturated fatty acid
RAS	renin-angiotensin system
RNS	reactive nitrogen species
ROS	reactive oxygen species

SOD	superoxide dismutase
STEMI	st-fragment elevation myocardial infarction
SNS	sympathetic nervous system
TAC	transverse aortic constriction
TIM	transporter of inner membrane
TOM	transporter of outer membrane
WHO	World Health Organization

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Highlights

- Heart failure affects over 25 million people worldwide
- Heart failure therapies target mainly neurohumoral over-activation
- Mitochondrial dysfunction and oxidative stress are hallmarks of heart failure
- Mitochondrial-derived aldehydes accumulate in failing hearts
- Therapies targeting mitochondrial detoxification improves heart failure outcome

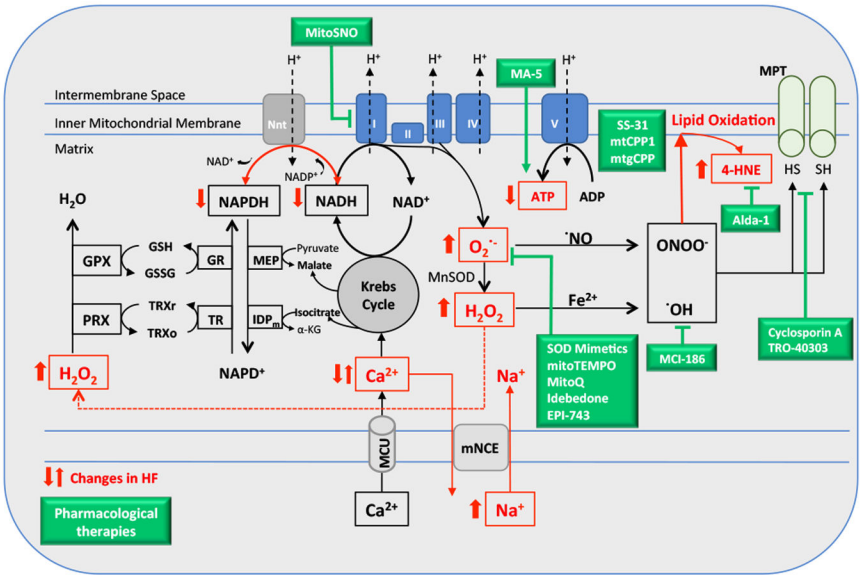

Figure 1.

Proposed model for the sources of reactive oxygen species (ROS) in heart failure based on previous studies [38,57,232], which focused in the interplay between defective Ca^{2+} handling and NAD(P)H/NAD(P)$^{+}$ redox state in mitochondrial ROS generation. In green boxes, the pharmacological therapies listed in Table 1. IDPm, mitochondrial NADP+ dependent isocitrate dehydrogenase; MEP, malic enzyme; Nnt, nicotinamide nucleotide transhydrogenase; GR, glutathione reductase; TR, thioredoxin reductase; MCU, mitochondrial Ca2+ Uniporter; Mn-SOD, Mn2+ dependent superoxide dismutase; PRX, peroxiredoxin; GPX, glutathione peroxidase; TRXr/o, reduced/oxidized thioredoxin; GSH/GSSG, reduced/oxidized glutathione; α-KG, α-ketoglutarate; mNCE, Na+/Ca2+ exchanger; MPT, mitochondrial permeability transition.

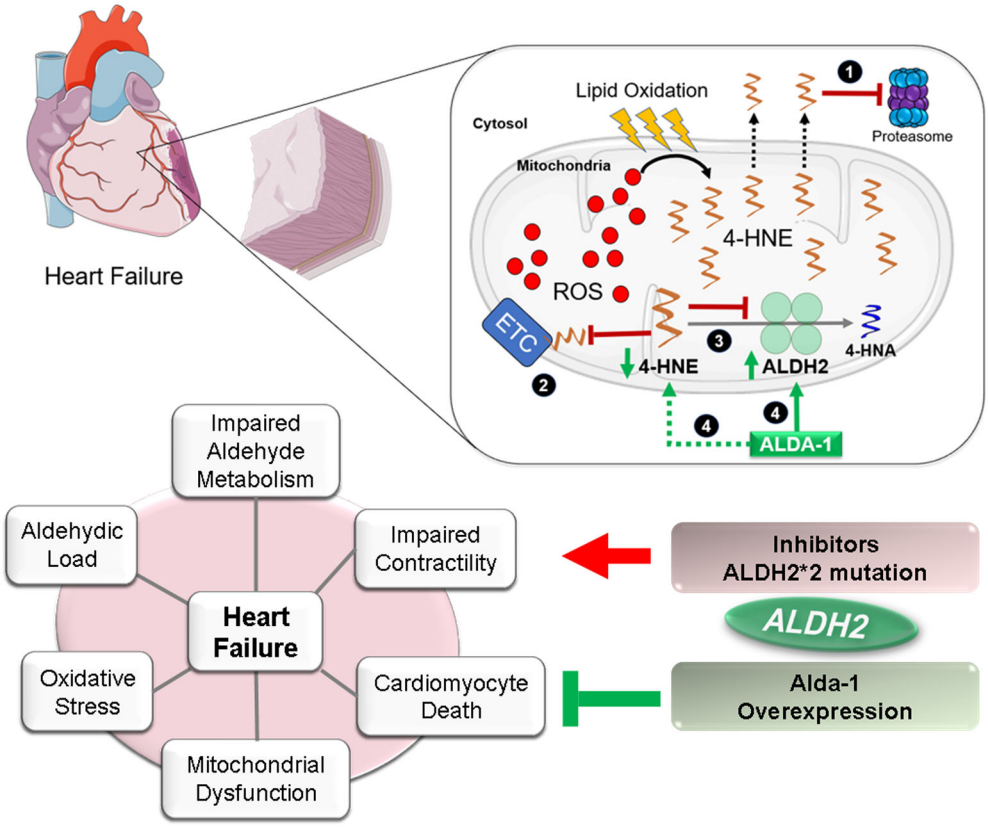

Figure 2.

Proposed model for the aldehydic overload in heart failure and for the role of aldehyde dehydrogenase 2 (ALDH2) in cardiac diseases. In the first scheme, during the progression of post-MI cardiomyopathy, excessive ROS production (free radicals) leads to lipid oxidation and 4-HNE generation and accumulation. The aldehyde inhibits (1) the proteasome [11,233], (2) the electron transport chain [162,234,235], (3) ALDH2, among other intracellular targets [236]. (4) Pharmacological activation of ALDH2 by Alda-1 improves cardiac outcome and 4-HNE removal [162,163,237]. The second scheme summarizes data from preclinical studies using either ALDH2 transgenic mice or pharmacological ALDH2 inhibitors or activators that elucidated the potential pathways regulated by ALDH2 and aldehydic load in cardiac diseases, including heart failure. Activation of ALDH2 or ALDH2 overexpression confer cardiac protection by counteracting aldehydic load, mitochondrial dysfunction, oxidative stress, impaired contractility and death in failing hearts, whereas inactivating mutation in ALDH2 or the use of selective inhibitors of the enzyme, exacerbate all the disease. This figure was produced using Servier Medical Art templates, which are licensed under a Creative Commons Attribution 3.0 Unported License (https://smart.servier.com).

Table 1.

Pharmacological therapies targeting mitochondria in cardiac diseases.

Agent	Chemical Property	Action	Diseases	Clinical Status	References
EUK-8	Synthetic salen-manganese complex	SOD mimetic	Dilated Cardiomyopathy; Pressure overload induced HF	Pre-clinical Pre-clinical	[205] [206]
M40403	Mn^{2+} containing synthetic compound	SOD mimetic	I/R heart injury	Pre-clinical	[207,208]
Me2DO2A	Mn^{2+} containing synthetic compound	SOD mimetic	I/R heart injury	Pre-clinical	[209]
XJB-5-131	Mitochondria-targeted nitroxide	SOD mimetic/ROS scavenger	I/R heart injury; Huntington's Disease	Pre-clinical Pre-clinical	[210,211] [212]
mitoTEMPO	Mitochondria-targeted nitroxide	ROS scavenger	Diabetic cardiomyopathy; Hypertension	Pre-clinical Pre-clinical	[213] [214,215]
MCI-186 (Edaravone)	Small molecule	Free radical scavenger	I/R heart injury; Pressure overload induced HF; Acute Ischemic Stroke; Amyotrophic lateral sclerosis (ALS)	Phase 4 Pre-clinical Phases 2-4 Phases 1-3	[140,216] [217] [218] [219,220]
MitoQ	Ubiquinone derivative	Free radical scavenger	I/R heart injury; Pressure overload; Peripheral Artery Disease (PAD); Cardiovascular Function	Pre-clinical Pre-clinical Clinical Trial Clinical Trial	[123,129] [130] NCT03506633 NCT03586414
EPI-743	Para-benzoquinone analog	Free radical scavenger	Mitochondrial Respiratory Chain Diseases	Phase 2	[128,221]
Idebenone	Short chain quinone	Free radical scavenger	Friedreich's ataxia; Mitochondrial cardiomyopathy	Phase 3 Pre-clinical	[222] [223]
SS-31 (Elamipretide, MPT-131)	Szeto-Schiller tetrapeptide	Cardiolipin protection	Friedreich's ataxia; I/R heart injury; Pressure overload induced HF; HFrEF HFpEF Congestive Heart Failure	Pre-clinical Phase 2 Pre-clinical Phase 2 Phase 2 Phase 1	[153] [157,224,225] [154,155] [9,14] NCT02814097 NCT02914665
mtCPP-1	Peptide	Cardiolipin protection	No studies	Pre-clinical	[158]
mtgCPP	Peptide	Cardiolipin protection	No studies	Pre-clinical	[159]
Cyclosporine A	Small molecule	MPT inhibition	I/R heart injury; Post-MI heart failure	Phase 3	[141,142,226]
TRO-40303	Small molecule	MPT inhibition	I/R heart injury; Post-MI heart failure	Phase 2	[143,227–229]
Alda-1	Small molecule	Increase ALDH2 activity	I/R heart injury; Post-MI heart failure	Phase 1	[114,162,163]
MA-5	Synthetic compound	Increase ATP synthesis	Mitochondrial Diseases	Pre-clinical	[149,172,230]
Metformin	Biguanide	ETC inhibition	I/R heart injury; Post-MI heart failure; HFpEF	Phase 2 Phase 2	[145,231] NCT03629340
Vericiguat	Small molecule	sGC stimulator	HFrEF; HFpEF	Phase 3 Phase 2	[136] [137,138]