IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 21, Issue 1 Ser.3 (January. 2022), PP 07-19
www.iosrjournals.org

Role of Mitochondria in Diabetic Cardiomyopathy and Treatment Challenges for Mitochondrial Dysfunction

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Abstract
Cardiovascular diseases are common among diabetes patients and is an important risk factor for the high mortality in diabetes. Diabetic cardiomyopathy is a significant clinical entity that may occur in diabetes patients independent of hypertension or coronary artery disease. Cardiomyopathy is accompanied by mitochondrial dysfunction, with diminished bioenergetics and oxidative stress. Current research is exploring specific intracellular targets that may be used for the prevention or treatment of heart failure. Mitochondria is a potential target to development new therapy for cardiomyopathy. Numerous strategies focusing on mitochondria pathways with small molecules, targeting peptides, and antioxidants are currently being tested in preclinical studies and clinical trials. This review examines the prospects and challenges in mitochondrial pharmacology for the treatment and prevention of diabetic cardiovascular diseases.

Keywords: *Mitochondria, Diabetes, Cardiovascular diseases, AKT, CoQ10, MitoQ*

Date of Submission: 20-12-2021 Date of Acceptance: 04-01-2022

I. Introduction

Mitochondria are extremely dynamic organelle[71]. They compose a tubular network that continuously alters by fusion and division inside the cell. Both actions are achieved via multielement molecular tools that have a number of dynamin-related GTPases [29, 54]. When mitochondria are removed from cells, the network splits up into fragments that instinctively reseal. Mitochondria are responsible for oxidative phosphorylation and the synthesis of ATP[2]. They preserve their membrane structure, membrane potential ,and organization, besides the capability to fuse [89] and to import proteins [119]. Mitochondria can be recognized by the light microscope, but only electron microscopy shows their particular structural details. The heart serves as a pump to deliver oxygen-loaded blood into the circulation and thus requires adequate ATP production to maintain proper function[106].

Mitochondria morphology in normal and diseased heart

Mitochondria have double membranes arrangement which isolates the organelle into four distinguished compartments the inner membrane, the outer membrane, the intermembrane space, and the matrix. Each part serves different functions. The outer membrane shows various porins which permit free dissemination of molecules into the space between the inner and outer membranes. There are proteins in intermembrane space which located between the two membranes (for example cytochrome c) that assume a major part in apoptosis and mitochondrial energetics. The inner membrane is different from the outer membrane as the inner membrane is very impermeable and many molecules and ions require transporters to cross. The inner membrane has a large part (20%) of the total mitochondrial protein contents, amongst which are transporters for proteins transporting into the matrix (for example translocase of the inward membrane) and the electron transport chain's enzymes. The matrix contains many enzymes which are acting for the cycle reactions of the citric acid [88].

Dysfunction of mitochondria is considering a major accompaniment of heart failure and occurs due to structural changes (altered membrane composition and organization, disruption of one or both membranes). While in the normal heart, the mitochondria are well arranged and have firmly packed cristae and matrix.

Mitochondria are swollen and have diminished matrix density in heart failure [70]. The effectiveness of mitochondrial bioenergetics is impaired in heart failure patients (both HFpEF and HFrEF) and the damage is described by a reduction in ATP synthesis, phosphocreatine (PCR), and PCR/ATP ratio[142]. Changed fuel preference has also been seen during cardiac failure in both animal and human models. When the heart becomes normal healthy, it depends on significantly (approximately 70–80%) on oxidation of the fatty acid as a source of ATP but transformed to glycolysis in the course of heart failure which is around 30% more efficient to produce ATP[6]. Also, the mitochondria morphology is responsive to cardiomyocytes changes. By examining the biopsies of the endocardium from patients with hypertrophic and dilated cardiomyopathy, Baandrup et al.[7]discovered giant mitochondria with diminished matrix density in some cardiomyocytes, accompanied by the increasing numbers of the mitochondrial.

Mitochondrial function in heart diseases

Mitochondria regulate almost every manner of cell function by delivering a sustained supply of adenosine triphosphate (ATP), modulating calcium signal, regulating reactive oxygen species (ROS) production and redox state. Mitochondria may quickly switch from maintaining normal cell function to triggering cell death for tissue remodeling[19, 98]. Myocardial remodeling occurs during the development of cardiomyopathy. To meet the circulatory demand, myocardium may adapt and alter its anatomical configuration in mass and chambers. Microscopic studies have shown myocardial remodeling may be accompanied by myocyte hypertrophy, cell death and fibrosis[109]. Myocardial remodeling can be categorized as adaptive or pathological, depending on its underlying cause.

In the human heart, ATP is mainly produced in the mitochondria, as much as 6 kg ATP can be generated per day[4]. The fetal heart relies on lactate, and glucose as main sources of oxidative phosphorylation. After birth, the heart develops a metabolic remodeling, shifting substrate oxidation from glucose to fatty acids. Thus, β-oxidation of free fatty acids becomes the primary mechanisms for ATP generation, providing nearly 70% of the ATP used by the heart[99].

Mitochondria control basically all aspect of cell function by giving a consistent supply of adenosine triphosphate (ATP), modulation of Ca2+signalling, affecting reactive oxygen species (ROS) levels and regulating redox control (by ROS maintenance and glutathione). Mitochondria may quickly alter from controlling the function of the normal cell to enhance the death of the cell as the organelles also assume a central part in apoptosis and necrosis [46, 98].

In the heart of the human, ATP production is done essentially by mitochondria and is estimated to be as much as 6 kg ATP for each day[4]. Despite during the fetal stage, glucose and lactate are considered the main sources for energy generation, the heart develops a metabolic remodeling at birth, changing substrate oxidation process from glucose to fatty acids. Therefore, oxidative phosphorylation and β-oxidation of free fatty acids become the primary mechanisms for the production of ATP, delivering around 70% of the ATP consumed by the heart [99].

Reactive oxygen species (ROS), for example, hydrogen peroxide (H2O2) and superoxide (O2-), play a significant role in regulating cell growth and cardiac myocytes death. Mitochondria are believed to be both a main source of ROS, besides the main target for ROS damage. Accumulation of ROS is highly enhanced in the myocardial failure, as has been seen in many experimental and clinical researches[136]. Systolic heart failure show increasing in prevalence over the recent decades, in part caused by the successes in the treatment of the coronary disease. The dysfunction of Mitochondria is considering the main part of systolic heart failure and is believed to enhance heart failure advancement by both increased production of reactive oxygen species (ROS) and impaired high energy phosphates production[68]. Suppression of the whole biogenesis pathway of the mitochondria was discovered in HF. First, a reduction in the expression of the cardiac transcription factor PGC-1α was observed in various experiential models of HF[139]. Second, downregulation of mtTFA and NFRs was also discovered, in addition to ETC enzymes and the cycle of tricarboxylic acid [38].

In mankind, the mitochondrial 16,569 DNA base pairs encode for only 37 genes[3]. DNA of the human mitochondrial was the first main part of the human genome to be sequenced. In many species, as in humans, mtDNA is typically inherited exclusively from the mother[83]. Nevertheless, in exceptional conditions, human newborns sometimes get mtDNA from their mothers and their fathers resulting in mtDNA heteroplasmy[83]. The existence of mitochondrial diseases and mtDNA heteroplasmy are the main underlying factors for worsening of heart failure symptoms [8]. However, other studies report a decrease in the phospholipid cardiolipin (CL) content and complex III activity happen acutely after myocardial infarction in both interfibrillar mitochondria (IFM) and cardiac subsarcolemmal mitochondria (SSM), which lead to diminished mitochondrial respiration and increased ROS generation[50]. Losing of CL additionally was discovered in rats with spontaneously hypertensive HF and in humans with dilated cardiomyopathy, and corresponded with the diminished activity of complex IV in both groups of cardiac mitochondria[126]. Additionally, there are

deteriorated dynamics or quality control (impaired fusion and fission of the mitochondria besides biogenesis, changes in membrane potential and mitophagy processes), and functional changes (decreased/reduced ETC complex activity and production of ATP) in heart failure. Decreased activity of ETC complex, fragmentation of mitochondrial membranes, myelinization and abnormal biogenesis function have also been seen in dogs' heart mitochondria with cardiac failure. Oxidative phosphorylation function and Mitochondrial turnover are decreased during heart failure and expression of the PGC1α gene in hearts are decreased as well[115].

Mitochondrial dysfunction in the diabetic heart

Through the last 20 years, our understanding of heart failure pathophysiology has evolved substantially. Heart disease remains one of the leading causes of mortality and morbidity in the industrialized world, affecting more than 27 million people in the United States alone[32]. At the same time, type 2 diabetes has become nearly pandemic, and about 300 million adults will have diabetes mellitus in 2025[32, 65]. Diabetic patients are at particular high risk of cardiovascular-related mortality[61, 77]. The term "diabetic cardiomyopathy" is used to describe the myocardial abnormalities in the diabetic patients who manifest ventricular dysfunction , even in the absence of coronary artery disease and hypertension[24, 53]. Lately, diabetic cardiomyopathy has also been used to explain cardiac dysfunction that is disproportionate to their underlying vascular disease[11]. Because of the important effect of mitochondria on myocardial biology, recent studies have investigated mitochondria structure and function in diabetic cardiomyopathy. The results indicated mitochondria dysfunction likely played a mechanistic role during the development of diabetic cardiomyopathy[118, 122].

Cardiomyopathy in diabetic patients could have resulted from various pathologic mechanisms[122]. It's interesting that most of the proposed mechanisms are accompanied by mitochondrial dysfunction[122]. Previous studies on human and animal models of diabetic cardiomyopathy have reported breakdown of mitochondria structure in myocardium[16, 37, 134]. Diabetic myocardium manifests metabolic abnormalities and mitochondrial dysfunction[121]. Several studied had used antioxidants and ROS scavengers to improve cardiomyocytes survival and reduce cardiac damage in experimental diabetic animal models [73]. Reversing mitochondrial dysfunction may represent an intriguing option to prevent or improve diabetic cardiomyopathy.

The complex interactions between mitochondrial signaling and cytosolic signaling and its pathophysiological effect on bioenergetics in the heart muscle begin to unveil in the last few years. Inhibition of phosphatidylinositol-3 kinase (PI3K)-Akt/PKB signaling pathway could negatively impact the regulating of metabolism, growth, and survival[144]. Insulin receptor signaling through this pathway has a significant effect on maintaining proper oxidative phosphorylation in the myocardium as insulin receptor-deficient myocardium in mice showed reduced oxidative phosphorylation and increased ventricular dysfunction[145] .

Akt is best known for its effect in regulating cell metabolism. Akt activates translocation of GLUT4 and glucose uptake by the AS160-Rab pathway and promotes glycolysis[13]. The signaling of cytosolic Akt might increase ATP generation by alternating hexokinase[42], and elimination of Akt drastically decreased ATP content in fibroblasts[45]. Insulin receptor number is upregulated in the myocardium and receptor signaling to PI 3-kinase/Akt is enhanced in the insulin-deficient streptozotocin (STZ)-diabetes model[145]. On the other hand, Type 2 diabetes models are accompanied by insulin resistance and down-regulation of insulin receptor signaling [15]. Previous research on PI3K-Akt signaling in the heart was mostly focused on cytoplasmic compartment. Therefore, how Akt signaling modulated mitochondria function was not dissected in these studies. Our laboratory has reported that, upon insulin stimulation, Akt could be translocated from cytosol to mitochondria and modulated mitochondria function in the heart[145], which may explain the effect of insulin on mitochondria through a direct mechanism in mitochondria. In the STZ-diabetes model, the translocation of phospho-Akt to mitochondria was undetectable because of insulin deficiency[145]. In the diet-induced Type 2 diabetes model, insulin-stimulated Akt translocation to mitochondria was diminished because of insulin resistance. Thus both Type 1 and Type 2 diabetes model showed dysregulation of mitochondrial Akt singling, which led to impaired mitochondria respiration, oxidative stress, reduced ATP generation and increased cardiomyocytes apoptosis[145].

Cardiovascular systems Abnormalities are commonly seen in diabetic patients, and the results of cardiac disease in diabetes are destructing[23]. Heart failure and cardiomyopathy are significant general medical problems in the United States and developed countries. Despite there are many contributing factors leading to heart failure development, metabolic dysregulation has a critical role in cardiomyopathy development, and diabetes increases the mortality and morbidity related to heart failure[28]. Diabetes mellitus is described by insulin deficiency and/or insulin resistance, which leads to hyperglycemia, glucose uptake defect, decreased glycolytic oxidative phosphorylation, insufficient energy production, and oxidative stress.

Mitochondria are the main source of production of ATP in the heart through glycolysis and oxidation. Diabetic cardiomyopathy in human is associated with diminished myocardial phosphocreatine/ATP ratio, demonstrating deteriorated the metabolism of high energy phosphate and energy deficit. Deteriorated

mitochondrial oxidative phosphorylation and decrease ATP synthesis rates were also seen in diabetic animal models[144]. This develops a metabolic shift to selectively rely on oxidation, which is accompanied by lipotoxicity and insufficient energy conversion[28]. Reversion of the metabolic abnormalities and restoration of the myocardial energetics prevented consequent development of cardiac dysfunction in diabetic patients. Metabolic dysfunction enhanced mitochondrial reactive oxygen species and prompted heart muscle apoptosis and resulting in myocardial fibrosis development[28, 36]. Despite mitochondria have a vital role in the dysregulation of oxidative stress and bioenergetics, the actual molecular mechanisms underlying dysfunction of mitochondria in diabetic cardiomyopathy are not totally known.

The complex interactions which occur between mitochondrial signaling and cytosolic signaling and its pathophysiological effects on bioenergetics regulation in the heart muscle are largely obscure. Suppression of phosphatidylinositol-3 kinase (PI3K), Akt/PKB is a significant step of signaling for insulin and other receptors of growth factor and has a significant function in the controlling of metabolism, growth, and survival[144]. The signaling of insulin receptor plays a significant function in the regulation of oxidative phosphorylation of the myocardium as KO mice's insulin receptor demonstrated diminished oxidative phosphorylation and increased ventricular dysfunction. In spite of insulin receptor signaling is very complex and interacts with many signaling molecules, the phosphatidylinositol 3-kinase (PI3K)–Akt/protein kinase B (PKB) pathway is responsible for the majority of the insulin metabolic actions and represents a significant network pathway of signaling of insulin[145].

Akt is best recognized for its metabolism regulatory impacts. Akt activates translocation of GLUT4 and glucose uptake by the AS160-Rab pathway and enhances glycolysis[13]. The signaling of cytosolic Akt might increase ATP generation by modulating hexokinase[42], and removal of Akt drastically diminished ATP content in fibroblasts[45]. Our laboratory recently notified acute translocation of Akt into mitochondria through insulin stimulation in the cells of heart muscle[145]. The number of the myocardial insulin receptor is upregulated and signaling of its receptor to PI 3-kinase/Akt is increased in insulin-deficient STZ-DM model[145]. On the other side, Type 2 diabetes models are accompanied by resistance to insulin and down-regulation of insulin receptor signaling[15]. Phospho-Akt translocation to mitochondria which stimulated by Insulin was increased in the STZ-DM model and decreased in the HFF-DM model. The magnitudes of Akt translocation in these two models reflected modifications of insulin receptor signaling to PI3K/Akt in each model, that way suggesting insulin receptor signaling dysregulation to mitochondria mirrored the underlying sensitivity of insulin. Collectively, these findings demonstrated that insulin deficiency (Type 1 DM) and insulin resistance (Type 2 DM) could prompt dysregulation of oxidative phosphorylation by insufficient insulin impact on mitochondria[145].

Current challenges for treatment of mitochondrial dysfunction in cardiovascular diseases

Because of the mechanistic role of mitochondrial dysfunction and oxidative stress in the development and progression of heart failure, efforts have been made to use mitochondria as a target to explore new therapies for cardiomyopathy[58, 67, 123]. To get into mitochondria, therapeutic molecules require to not only get access to particular organs, but also to get over several barriers as an example the cell membrane, and the outer and inner mitochondrial membranes. New strategies to overcome mitochondrial barriers had been explored, specific small molecules and targeting peptides capable of interacting with the structure of mitochondriotropic molecule transporters [33, 105, 140] have been tried in preclinical and clinical studies to improve the function of failing hearts.

Coenzyme Q10

Coenzyme Q10 (CoQ10 or ubiquinone) has drawn interests as a potential therapeutic option for the treatment of cardiomyopathy[120]. CoQ10 is a part of the electron transfer chain, mediating the electron transport from Complexes I and II to Complex III. Its reduced form, ubiquinol, an antioxidant within mitochondria, can react with peroxyl radicals and restore vitamin E[62], to preserve the cell from lipid peroxidation. Preclinical studies have shown a CoQ10 depletion in various heart failure models[14], thus restoring CoQ10 in the failing heart seems a logical strategy. Long-term therapy of CoQ10 suppressed oxidative stress and myocardial remodeling in rodent model of diabetes[14]. Small clinical studies on heart failure patients showed positive effect of CoQ10 in cardiac outcomes, lowered hospitalization rates and improved mortalities in the patients treated with CoQ10[100]. A larger randomized, double-blind and placebo-controlled trial is underway and will determine whether ubiquinol treatment (the active form of Coenzyme Q10) can improve the outcome of heart failure[107]. Short-chain synthetic CoQ analogues have also been developed (such as EPI-743 and Idebenone) and investigated in the genetic mitochondrial diseases and appears to be safe [34]. A small open-label observational trial reported that continuous treatment using EPI-743 improved life quality in genetic mitochondrial disease [34] , but its effect on cardiomyopathy is not known.

A mitochondria-targeting antioxidant MitoQ, linking exogenous ubiquinone to a triphenylphosphonium lipophilic cation, has been developed[62]. Continuous MitoQ treatment protected ex vivo hearts from experimental ischemia-reperfusion injury, accompanied by diminished mitochondrial dysfunction and cell

death[1]. MitoQ also decreased mitochondrial ROS generation and restored synthesis of ATP in the heart failure model induced by pressure overload. However, MitoQ failed to restore left ventricle function and remodeling[112]. A small randomized cross-over trial showed that MitoQ therapy improved vascular function in the healthy elderly subjects[113, 124]. The effect of MitoQ on heart failure is not fully clear and will require further study.

Oxidative stress is classical feature of mitochondria dysfunction. Various antioxidant agents had been developed, including free radical scavengers (MCI186/edaravone, XJB-5–131) and superoxide dismutase mimetics (EUK8/ EUK134, M40403, Me2DO2A, MnTBPA)[58]. Edaravone has received FDA approval for amyotrophic lateral sclerosis treatment and a clinical trial for acute ischemic stroke is currently underway in Japan. In myocardial diseases, a preclinical study showed myocardial protection against ischemia reperfusion injury by edaravone treatment in rabbits . Edaravone mitigated production of OH; myocardial dysfunction and injury[35]. Moreover, in a small pilot study in 80 subjects with acute myocardial infarction, edaravone treatment led to better clinical outcomes, with reduced reperfusion arrhythmias and myocardial stunning[135]. Other strategies focusing on mitochondria disorders involve blocking transition of permeability of mitochondria (cyclosporine A[102], TRO40303[5]), transient inhibition of the ETC (mitoSNO)[91], activation of AMPK (metformin, AICAR, resveratrol)[148], modifying the activity of the mitochondrial enzymes(MA-5[86]) and targeting the inner membrane of mitochondria (SS31, also recognized as MTP-131, Bendavia, Elamipretide)[27].

Cyclosporine A (CsA)

It is known to successfully restore myocardial perfusion after an ST-segment myocardial infarction elevation (STEMI) is the most efficient way of reducing the final infarction size and improving clinical outcome[102]. Experimental and clinical data, however, have shown that reperfusion in itself can have damaging impacts, the "myocardial reperfusion injury," recognized as a cardioprotection[49, 51, 52, 95]. By opening a non-specific high-conductance channel called the mitochondrial transition pore(mPTP), situated in the inner mitochondrial membrane, Mitochondria can play the main role in reperfusion injury. Immediately after the start of myocardial reperfusion, the irreversible opening of the mPTP outcomes in the collapse of the membrane potential, the disconnection of the respiratory chain, and the efflux of proapoptotic factors that can lead to cell death[12]. Experimental data indicates that multiple procedures intended to avoid opening up of mPTP may decrease the extent of myocardial infarction in multiple animal models by an additional 30 to 50 percent. A single pre-reperfusion intravenous bolus of CsA was recorded to decrease the release of creatine kinase (CK) by 40% in 58 STEMI patients treated with primary percutaneous coronary procedures (pPCI) [108], and to decrease the impairment of left ventricular (LV) function in the same patients over 6 months after myocardial infarction (MI)[92]. This proof-of-concept research gave rise to new excitement for targeting cardiac reperfusion with CsA as a prototypical agent[55, 87], while paving the way for bigger multicenter research to check these very promising results before proceeding to a "difficult" clinical endpoints trial. However, in 101 STEMI patients, a double-blind trial showed that CsA provided right before thrombolysis did not reduce the size of MI or improve clinical outcomes[39]. Experimental [79] and clinical data on CsA were found to be inadequate to justify a real phase III trial with hard clinical endpoints, such as the CIRCUS (Cyclosporine and Prognosis in Acute Myocardial Infarction [MI] patients) trial, for which one-year follow-up findings were released[103].

Mitocare (TRO40303)

TRO40303 targets mitochondrial transitional permeability pore (mPTP), which is thought to be a promising target to prevent reperfusion injury[9, 56]. TRO40303 inhibits the opening of mPTP and shows a reduction in the size of infarction in animal models of myocardial infarction[72, 117], indicating the ability to mitigate ischemic reperfusion injury and the subsequent adverse impacts. It should be noted that the compound has demonstrated effectiveness in protecting human cells (data not shown), thus promoting a potential human translation[5]. Since January 2011, the MITOCARE consortium, consisting of 17 European teams of professionals specializing in clinical and basic studies, biomarkers, imagery, and computer science, has been researching the effectiveness and safety of TRO40303 as an addition to standard cardiac care to reduce reperfusion injury among patients with early STEMI and undergoing primary PCI[5]. The MITOCARE Phase II study examined the potential of adjunctive TRO40303 to limit reperfusion injury in patients with primary STEMI PCI using state-of-the-art therapeutic principles. The initial endpoint has not been met, and this data suggests that treatment of STEMI patients with instant mechanical revascularization and modern supportive pharmacotherapy does not support TRO40303 to restrict myocardial infarction reperfusion injury. To provide extra insight into the nature of reperfusion injury, further study is needed[5].

Mitochondria-targeted S-Nitrosothiol (MitoSNO)

It has been shown recently that MitoSNO protects against acute ischemia/reperfusion (IR) injury by inhibiting the reactivation of mitochondrial complex I in the first minutes of ischemic tissue reperfusion, thereby stopping free radical development underlying IR injury. But how this transient inhibition of mitochondrial complex I-mediated free radicals at reperfusion impacts long-term heart recovery after IR injury remains unclear[91]. Methner et al. noted that MitoSNO's action at reperfusion decreases infarction size and protects against heart failure after myocardial infarction. Targeted inhibition of mitochondrial complex I in the first minutes of MitoSNO reperfusion is, therefore, a rational therapeutic approach to prevent subsequent heart failure in patients with IR injury[91].

Metformin

Metformin is the first-choice drug for diabetes patients, but its use is discussed in advanced cardiorenal disease patients. Epidemiological data indicate that in patients with and without heart failure, metformin may decrease heart failure According to experimental data, metformin decreases cardiac ischemia-reperfusion injury[148]. Metformin reduces blood glucose through increased insulin sensitivity, increased peripheral glucose uptake, and decreased hepatic glucose production while reducing plasma insulin levels[66]. However, metformin's cardioprotective effects cannot be attributed solely to the glucose-lowering effects[44]. Recent experimental studies have proposed prospective ancillary mechanisms. In particular, the protective impacts can be given via the metformin-activated AMP-activated protein kinase (AMPK) pathway[20, 96, 125]. Metformin has been shown to decrease cardiomyocyte apoptosis in ischemia-reperfusion (I / R) models in particular [63], improve endothelial function by increasing NO production[152], maintain myocardial energy production during ischemia[48], and influence lipid metabolism[127]. Experimental studies using a pressure overload model in mice and a pacing model in dogs showed that metformin inhibits collagen synthesis and attenuates cardiac fibrosis[148].

Strongly recommend these experimental studies that metformin decreases I / R injury. However, there is little data available to support the use of metformin after myocardial infarction (MI) and HF in chronic cardiac remodeling. Metformin was correlated with a decreased all-cause-mortality (adjusted odds ratio 0.72 ; P = 0.003) in a case-control study in patients with diabetes and HF (n = 1.633)[84, 87]. Metformin monotherapy was correlated with a decreased 1-yr mortality compared to sulfonylurea therapy in diabetic patients with newly developed HF (n = 1.305)[21]. In hospital-admitted HF patients (n = 16,417), metformin use was associated with a lower 1-yr mortality compared to insulin or sulfonylurea treatment (24.7 vs. 36.0%, P < 0,0001)[85]. In diabetic patients treated with metformin, all-cause readmission and HF hospitalization were also less prevalent than those not treated with an insulin-sensitizing drug. While there is a lack of outcomes from prospective randomized placebo-controlled clinical studies, these results highly indicate that use of metformin in diabetic patients is associated with a better outcome in clinical HF[148]. As recorded in a dog model of heart failure, metformin was shown to inhibit apoptosis[116]. Anti-apoptotic protein Akt's increased levels are correlated with the suppression of AMPK phosphorylation, which can be restored by metformin[69]. On the other side, Sasaki et al. showed that metformin therapy in failing heart causes reduced Akt phosphorylation which subsequently improves heart function[116].

5-Aminoimidazole-4-Carboxamide Riboside (AICAR)

AICAR , a direct AMPK activator, is an adenosine analog taken by adenosine transporters into cells and phosphorylated by adenosine kinase, producing AMP-mimetic, AICAR monophosphate (ZMP)[25]. Sasaki and colleagues have found that AICAR can activate AMPK and exerting anti-apoptotic impact in the heart. Na+–H+ exchanger 1 (NHE-1) inhibition exerts an anti-hypertrophic impact of the heart by inhibiting the AMPK / glycogen synthase kinase 3β (GSK-3β) pathway in cardiomyocytes by opening the mitochondrial transition pore (mPTP). Furthermore, AICAR also had the same impacts, indicating that inhibition of NHE-1 acts as an anti-hypertrophy target by inhibiting the pathway of AMPK / mPTP [57]. In order to enhance the availability of substrates, AICAR also improves the translocation of GLUT4 and FAT / CD36 [18, 114]. In addition, AICAR mice therapy reduces ROS production through enhanced thioredoxin expression in a mechanism that is FoxO3-dependent[74]. Additional AICAR actions include promoting autophagy and inhibiting cardiac hypertrophy in cardiomyocytes [22] and HF [76] mouse models, reducing apoptosis and enhancing cardiac function during HF. Furthermore, AICAR mediates extra antihypertrophic features by restoring PPAR-α levels[90] that are repressed in HF[150]. These results, therefore, support the concept that even possibly indirect AMPK activators, such as AICAR, may be useful for HF treatment[64].

Resveratrol

Resveratrol is a naturally occurring polyphenol found in numerous dietary sources [138] and has also been shown to be a cardiovascular AMPK indirect activator [20, 30]. Previous studies of resveratrol's impacts

on cardiac AMPK have shown that resveratrol activated cardiac AMPK[30], and enhanced cardiac function in HF mice[60]. Resveratrol activation of AMPK also has antihypertrophic impacts by inhibiting protein synthesis pathways by suppressing p70S6 K and eEF2 and the activated T cell nuclear factor (NFAT). NFAT plays an important part in the progression of pathological cardiac hypertrophy and the activation of AMPK results in its suppression, resulting in reduced transcription of the prohypertrophic gene and reduced synthesis of proteins[20]. Recent results also indicate that resveratrol's capacity to enhance the production of glycolytic ATP is mediated by an AMPK-dependent pathway[10], a finding further enhanced by the reality that AMPK-knockout mice demonstrate resistance to resveratrol's metabolic effects[137]. Additionally, induction by nuclear translocation and activation of SIRT1 of the antioxidant enzyme manganese superoxide dismutase, caused by resveratrol, decreased oxidative stress and promoted cell survival in acute HF in a hamster model[133]. In some cases, resveratrol has been used to treat HF, and by decreasing the size of the infarct can increase survival and reverse cardiac detrimental remodeling[43]. Resveratrol has also been demonstrated to reverse left ventricular remodeling and enhance post-infarct heart function through improved autophagy [43]. For example, when post-infarct hearts were treated with both resveratrol and compound C, a known AMPK inhibitor, the autophagic effects of resveratrol were offset[60]. However, in these models, it has not been widely studied whether resveratrol increases myocardial metabolism through AMPK activation or alternative mechanisms, such as PGC-1α activation. That said, it has been shown that resveratrol activates PGC-1α and increases the cellular biogenesis of the muscle[81, 137], indicating that resveratrol-induced mitochondrial biogenesis may help improve cardiac metabolism and eventually cardiovascular function in HF.

Mitochonic Acid-5 (MA-5)

Mitochonic Acid 5 is an indole-3-acetic acid (IAA) plant hormone derivative[130]. MA-5 increased concentrations of cellular ATP independent of ETC complexes and cross-membrane potential, potentially through modulation of complex formation of ATP synthase. Preclinical studies with this compound have shown promising outcomes in patients with mitochondrial diseases having fibroblasts[130]. Recently, Mitochonic acid-5 upregulated cardiac and renal respiration in the mitochondrial cancer model Mitomouse[97], leading in survival prolongation[129]. MA-5 promotes the production of mitochondrial ATP and decreases ROS independent of ETC by promoting ATP synthase oligomerization and supercomplex mitofilin / Mic60 formation. MA-5 decreased fragmentation of the mitochondria, restoring the shape and dynamics of the crista. MA-5 has the ability to treat different mitochondrial diseases as a drug[86]. It was also noted that in the mitochondrial damaged heart, MA-5 enhanced mitochondrial COX activity and respiration[129]. Suzuki et al . reported MA-5 targets mitochondrial protein mitofilin to facilitate the production of ATP and rescue cardiac and renal mitochondrial respiration[129].

Elamipretide

SS-31 is a peptide that links with cardiolipin (CL), a major component of mitochondrial membranes[131]. CL is an emerging target for drug development because it plays a key role in mitochondrial protein import/export and metabolite transport, including cytochrome c, ETC complexes, and ADP/ATP carrier; thus modulating mitochondrial bioenergetics[104]. Szeto *et, al.* reported that SS-31 ameliorates mitochondrial bioenergetics, enhanced the recovery of ATP after the ischemia and reduced ischemic kidney injury[132]. These investigators suggested that SS-31 protected CL from peroxidation, which might explain its effect on mitochondrial permeability transition pore. In Friedreich ataxia disease, treatment with SS-31 enhanced the enzymatic activity of iron-sulphur enzymes (aconitase, ETC complexes II and III), preserved the transmembrane potential of mitochondrial membrane, and increased ATP content[151]. Preclinical studies have shown protective effect of SS-31 in animal models of heart failure induced by pressure overload and hypertension[82]. In the later study, SS31 was shown to inhibit accumulation of ROS in mitochondria and improve cardiac hypertrophy[26].

Elamipretide, a SS-31 analog, has been studied in two clinical trials in the heart failure patients with decreased ejection fraction and in the patients with myocardial infarction[40]. Both trials showed acceptable tolerability and safety; yet the phase 2a trial EMBRACE did not demonstrate improvement in primary endpoints after the therapy. New analogs of SS-31 with greater antioxidant activities have also been developed, but its effect on myocardium and cardiovascular function has not yet been studied[17].

Alda-1

A panel of small molecules targeting various mitochondrial pathways have been developed in the last decade. One such molecule is the Alda-1[105], a mitochondrial dehydrogenase 2 (ALDH2) agonist, which mediates oxidation of ethanol[101], protects against oxidative stress[128], and eliminate toxic aldehydes (e.g. acetaldehyde, 4-HNE)[149]. In animal models of ischemic cardiomyopathy, selective ALDH2 activation by Alda-1 reduced the reactive aldehyde overload, restored myocardial mitochondrial bioenergetics, and improved cardiac function[41]. Interestingly, chronic Alda-1 therapy after myocardial ischemia reduced myocardial

fibrosis and ventricular hypertrophy, and improved myocardial remodeling[41]. Moreover, the ALDH2*2 (rs671) polymorphism is an independent risk factor of coronary heart disease in population studies[47, 75, 93, 94, 143]. ALDH2 polymorphisms (GG & GA) were associated with increased serum 4- HNE levels in patients with coronary artery disease and the severity of coronary artery stenosis[146]. In animal model, ALDH2 activation by Alda-1 reduced ROS and reactive aldehydes levels, attenuated calcium overload, and markedly ameliorated survival in post-cardiac arrest cardiomyopathy[141]. These studies not only showed the association between ALDH2 and cardiac function, but also identified ALDH2 as a potential therapeutic target to improve cardiovascular function[147]. Alda-1 therapy seemed safe and did not alter hemodynamic parameters, liver function or kidney function in healthy animals[41]. A phase I clinical study with Alda (FP-045) was completed this year, with acceptable safety and tolerability in healthy individuals[41].

Mixed strategies to approach and treat the oxidative stress and the mitochondrial dysfunction, established on the growing understanding of the part of cellular antioxidants and reactive species, appear to be a promising opportunity to prepare effectively interventions and initiate new therapies for a compound and multifactorial disease such as heart failure.

Gold nanoparticles

Due to their superior physicochemical and pharmacological character, AuNPs have excellent potential in the diagnosis and therapy of multiple illnesses. AuNPs are inert, stable and biocompatible in terms of physicochemical characteristics, which implies small toxicity[110]. AuNPs are a useful candidate for numerous biomedical applications, including drug delivery, cancer therapy, and biomedical imaging. One research found that constant injection into the heart of rats of gold nanofibers coupled with platelet-derived growth factor could decrease myocardial cell death and retain post-MI systolic function[31]. Considering that heart failure is associated with abnormal electrical function, nanofibers have been researched to couple the electrical property. The outcome showed that ex vivo pretreatment of mesenchymal stem cells (MSCs) using 5-azacytidine and AuNPs loaded with conductive nanofibrous construct could enhance cardiomyogenic distinction, leading in protective impacts on the infarcted area [111]. Another study showed that PEG-coated AuNPs could mitigate β-adrenergic receptor-mediated acute cardiac hypertrophy and inflammation through suppressing β1-AR expression and its IL-6 and ERK1/2 downstream effectors[110]. In conclusion, AuNPs have at least two roles to treat heart dysfunction: one is used as a drug vector and the other as an anti-cardiac hypertrophy agent[31].

II. Conclusions

In the last few years, the intracellular drug delivery area has developed quickly with the initial aim of augmenting the therapeutic index of a specific drug moiety via particularly targeting it to relative organelles as example mitochondria. Even before organ specific targeting is taken into account, the transportation of drugs to mitochondria is in itself highly challenging because of the several cellular structures by which the drug has to be transferred, e.g. plasma membranes, cytoplasms, and outer and inner mitochondrial membranes. These compounds are used based on a limited number of research and can be useful only in some mitochondrial disease. Subsequently, mitochondrial diseases therapy keeps highly symptomatic and does not greatly modify the illness course. Though, there is a shortage of therapies for disorders of the mitochondria at the present time, the raised number of clinical studies evaluating molecules target various aspects of the dysfunction of the mitochondrial is promising and is proposed to create more therapeutic solutions for these diseases from this point forward.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1]. Adlam VJ, Harrison JC, Porteous CM, James AM, Smith RAJ, Murphy MP, Sammut IA (2005) Targeting an antioxidant to mitochondria decreases cardiac ischemia- reperfusion injury. FASEB J 19:1088–1095. doi: 10.1096/fj.05-3718com

[2]. Alexandre A, Reynafarje B, Lehninger AL (1978) Stoichiometry of vectorial H+ movements coupled to electron transport and to ATP synthesis in mitochondria. Proc Natl Acad Sci U S A 75:5296–5300. doi: 10.1073/pnas.75.11.5296

[3]. Anderson S, Bankier AT, Barrell BG, de Bruijn MHL, Coulson AR, Drouin J, Eperon IC, Nierlich DP, Roe BA, Sanger F, Schreier PH, Smith AJH, Staden R, Young IG (1981) Sequence and organization of the human mitochondrial genome. Nature 290:457–465. doi: 10.1038/290457a0

[4]. Archer SL (2013) Mitochondrial Dynamics — Mitochondrial Fission and Fusion in Human Diseases. N Engl J Med 369:2236–2251. doi: 10.1056/nejmra1215233

[5]. Atar D, Arheden H, Berdeaux A, Bonnet J-L, Carlsson M, Clemmensen P, Cuvier V, Danchin N, Dubois-Rande J-L, Engblom H, Erlinge D, Firat H, Halvorsen S, Hansen HS, Hauke W, Heiberg E, Koul S, Larsen A-I, Le Corvoisier P, Nordrehaug JE, Paganelli F, Pruss RM, Rousseau H, Schaller S, Sonou G, Tuseth V, Veys J, Vicaut E, Jensen SE (2014) Effect of intravenous TRO40303 as an adjunct to primary percutaneous coronary intervention for acute ST-elevation myocardial infarction: MITOCARE study results. Eur Heart J 36:112–119. doi: 10.1093/eurheartj/ehu331

[6]. Aubert G, Vega RB, Kelly DP (2013) Perturbations in the gene regulatory pathways controlling mitochondrial energy production in the failing heart. Biochim Biophys Acta 1833:840–847. doi: 10.1016/j.bbamcr.2012.08.015

[7]. Baandrup U, Florio RA, Roters F, Olsen EG (1981) Electron microscopic investigation of endomyocardial biopsy samples in hypertrophy and cardiomyopathy. A semiquantitative study in 48 patients. Circulation 63:1289–1298. doi: 10.1161/01.cir.63.6.1289

[8]. Bacman SR, Williams SL, Pinto M, Peralta S, Moraes CT (2013) Specific elimination of mutant mitochondrial genomes in patient-derived cells by mitoTALENs. Nat Med 19:1111–1113. doi: 10.1038/nm.3261

[9]. Baines CP (2009) The mitochondrial permeability transition pore and ischemia-reperfusion injury. Basic Res Cardiol 104:181–188. doi: 10.1007/s00395-009-0004-8

[10]. Beauvieux M-C, Stephant A, Gin H, Serhan N, Couzigou P, Gallis J-L (2013) Resveratrol mainly stimulates the glycolytic ATP synthesis flux and not the mitochondrial one: A saturation transfer NMR study in perfused and isolated rat liver. Pharmacol Res 78:11–17. doi: 10.1016/j.phrs.2013.09.007

[11]. Bell DSH (2003) Heart Failure: The frequent, forgotten, and often fatal complication of diabetes. Diabetes Care 26:2433–2441. doi: 10.2337/diacare.26.8.2433

[12]. Bernardi P, Di Lisa F (2015) The mitochondrial permeability transition pore: molecular nature and role as a target in cardioprotection. J Mol Cell Cardiol 78:100–106. doi: 10.1016/j.yjmcc.2014.09.023

[13]. Bertrand L, Horman S, Beauloye C, Vanoverschelde J-L (2008) Insulin signalling in the heart. Cardiovasc Res 79:238–248. doi: 10.1093/cvr/cvn093

[14]. De Blasio MJ, Huynh K, Qin C, Rosli S, Kiriazis H, Ayer A, Cemerlang N, Stocker R, Du X-J, McMullen JR, Ritchie RH (2015) Therapeutic targeting of oxidative stress with coenzyme Q10 counteracts exaggerated diabetic cardiomyopathy in a mouse model of diabetes with diminished PI3K(p110α) signaling. Free Radic Biol Med 87:137–147. doi: 10.1016/j.freeradbiomed.2015.04.028

[15]. Bonnard C, Durand A, Peyrol S, Chanseaume E, Chauvin M-A, Morio B, Vidal H, Rieusset J (2008) Mitochondrial dysfunction results from oxidative stress in the skeletal muscle of diet-induced insulin-resistant mice. J Clin Invest 118:789–800. doi: 10.1172/JCI32601

[16]. Bugger H, Dale Abel E (2008) Molecular mechanisms for myocardial mitochondrial dysfunction in the metabolic syndrome. Clin Sci 114:195–210. doi: 10.1042/cs20070166

[17]. Cerrato CP, Langel Ü (2017) Effect of a Fusion Peptide by Covalent Conjugation of a Mitochondrial Cell-Penetrating Peptide and a Glutathione Analog Peptide. Mol Ther Methods Clin Dev 5:221–231. doi: 10.1016/j.omtm.2017.04.010

[18]. Chabowski A, Momken I, Coort SLM, Calles-Escandon J, Tandon NN, Glatz JFC, Luiken JJFP, Bonen A (2006) Prolonged AMPK Activation Increases the Expression of Fatty Acid Transporters in Cardiac Myocytes and Perfused Hearts. Mol Cell Biochem 288:201–212. doi: 10.1007/s11010-006-9140-8

[19]. Chalmers S, Olson M, Macmillan D, Rainbow R, Mccarron J (2007) Ion channels in smooth muscle: Regulation by the sarcoplasmic reticulum and mitochondria. Cell Calcium 42:447–466. doi: 10.1016/j.ceca.2007.05.010

[20]. Chan AYM, Dolinsky VW, Soltys C-LM, Viollet B, Baksh S, Light PE, Dyck JRB (2008) Resveratrol inhibits cardiac hypertrophy via AMP-activated protein kinase and Akt. J Biol Chem 283:24194–24201. doi: 10.1074/jbc.M802869200

[21]. Chan AYM, Dyck JRB (2005) Activation of AMP-activated protein kinase (AMPK) inhibits protein synthesis: a potential strategy to prevent the development of cardiac hypertrophy. Can J Physiol Pharmacol 83:24–28. doi: 10.1139/y04-107

[22]. Chan AYM, Soltys C-LM, Young ME, Proud CG, Dyck JRB (2004) Activation of AMP-activated Protein Kinase Inhibits Protein Synthesis Associated with Hypertrophy in the Cardiac Myocyte. J Biol Chem 279:32771–32779. doi: 10.1074/jbc.m403528200

[23]. Chen H-S, Shan Y-X, Yang T-L, Lin H-D, Chen J-W, Lin S-J, Wang PH (2004) Insulin Deficiency Downregulated Heat Shock Protein 60 and IGF-1 Receptor Signaling in Diabetic Myocardium. Diabetes 54:175–181. doi: 10.2337/diabetes.54.1.175

[24]. Cohen-Solal A, Beauvais F, Logeart D (2008) Heart Failure and Diabetes Mellitus: Epidemiology and Management of an Alarming Association. J Card Fail 14:615–625. doi: 10.1016/j.cardfail.2008.04.001

[25]. Corton JM, Gillespie JG, Hawley SA, Hardie DG (1995) 5-Aminoimidazole-4-Carboxamide Ribonucleoside. A Specific Method for Activating AMP-Activated Protein Kinase in Intact Cells? Eur J Biochem 229:558–565. doi: 10.1111/j.1432-1033.1995.tb20498.x

[26]. Dai D-F, Chen T, Szeto H, Nieves-Cintrón M, Kutyavin V, Santana LF, Rabinovitch PS (2011) Mitochondrial targeted antioxidant Peptide ameliorates hypertensive cardiomyopathy. J Am Coll Cardiol 58:73–82. doi: 10.1016/j.jacc.2010.12.044

[27]. Daubert MA, Yow E, Dunn G, Marchev S, Barnhart H, Douglas PS, O'Connor C, Goldstein S, Udelson JE, Sabbah HN (2017) Novel Mitochondria-Targeting Peptide in Heart Failure Treatment. Circ Hear Fail 10. doi: 10.1161/circheartfailure.117.004389

[28]. Deng W, Leu H-B, Chen Y, Chen Y-H, Epperson CM, Juang C, Wang PH (2014) Protein kinase B (PKB/AKT1) formed signaling complexes with mitochondrial proteins and prevented glycolytic energy dysfunction in cultured cardiomyocytes during ischemia-reperfusion injury. Endocrinology 155:1618–1628. doi: 10.1210/en.2013-1817

[29]. Detmer SA, Chan DC (2007) Functions and dysfunctions of mitochondrial dynamics. Nat Rev Mol Cell Biol 8:870–879. doi: 10.1038/nrm2275

[30]. Dolinsky VW, Chakrabarti S, Pereira TJ, Oka T, Levasseur J, Beker D, Zordoky BN, Morton JS, Nagendran J, Lopaschuk GD, Davidge ST, Dyck JRB (2013) Resveratrol prevents hypertension and cardiac hypertrophy in hypertensive rats and mice. Biochim Biophys Acta - Mol Basis Dis 1832:1723–1733. doi: 10.1016/j.bbadis.2013.05.018

[31]. Dong C, Ma A, Shang L (2018) Nanoparticles for postinfarct ventricular remodeling. Nanomedicine 13:3037–3050. doi: 10.2217/nnm-2018-0264

[32]. Engelgau MM, Geiss LS, Saaddine JB, Boyle JP, Benjamin SM, Gregg EW, Tierney EF, Rios-Burrows N, Mokdad AH, Ford ES, Imperatore G, Venkat Narayan KM (2004) The Evolving Diabetes Burden in the United States. Ann Intern Med 140:945. doi: 10.7326/0003-4819-140-11-200406010-00035

[33]. Enns GM (2014) Treatment of Mitochondrial Disorders. J Child Neurol 29:1235–1240. doi: 10.1177/0883073814538509

[34]. Enns GM, Kinsman SL, Perlman SL, Spicer KM, Abdenur JE, Cohen BH, Amagata A, Barnes A, Kheifets V, Shrader WD, Thoolen M, Blankenberg F, Miller G (2012) Initial experience in the treatment of inherited mitochondrial disease with EPI-743. Mol Genet Metab 105:91–102. doi: 10.1016/j.ymgme.2011.10.009

[35]. Eto M, Kajihara N, Morita S, Tominaga R (2011) A novel electron paramagnetic resonance spin-probe technique demonstrates the relation between the production of hydroxyl radicals and ischemia–reperfusion injury. Eur J Cardio-Thoracic Surg 39:465–470. doi: 10.1016/j.ejcts.2010.08.011

[36]. Falcão-Pires I, Leite-Moreira AF (2011) Diabetic cardiomyopathy: understanding the molecular and cellular basis to progress in diagnosis and treatment. Heart Fail Rev 17:325–344. doi: 10.1007/s10741-011-9257-z

[37]. Frustaci A, Kajstura J, Chimenti C, Jakoniuk I, Leri A, Maseri A, Nadal-Ginard B, Anversa P (2000) Myocardial Cell Death in Human Diabetes. Circ Res 87:1123–1132. doi: 10.1161/01.res.87.12.1123

[38]. Garnier A, Fortin D, Deloménie C, Momken I, Veksler V, Ventura-Clapier R (2003) Depressed mitochondrial transcription factors and oxidative capacity in rat failing cardiac and skeletal muscles. J Physiol 551:491–501. doi: 10.1113/jphysiol.2003.045104

[39]. Ghaffari S, Kazemi B, Toluey M, Sepehrvand N (2013) The Effect of Prethrombolytic Cyclosporine-A Injection on Clinical Outcome of Acute Anterior ST-Elevation Myocardial Infarction. Cardiovasc Ther 31:e34–e39. doi: 10.1111/1755-5922.12010

[40]. Gibson CM, Giugliano RP, Kloner RA, Bode C, Tendera M, Jánosi A, Merkely B, Godlewski J, Halaby R, Korjian S, Daaboul Y, Chakrabarti AK, Spielman K, Neal BJ, Weaver WD (2015) EMBRACE STEMI study: a Phase 2a trial to evaluate the safety, tolerability, and efficacy of intravenous MTP-131 on reperfusion injury in patients undergoing primary percutaneous coronary intervention. Eur Heart J 37:1296.1-1303. doi: 10.1093/eurheartj/ehv597

[41]. Gomes KMS, Campos JC, Bechara LRG, Queliconi B, Lima VM, Disatnik M-H, Magno P, Chen C-H, Brum PC, Kowaltowski AJ, Mochly-Rosen D, Ferreira JCB (2014) Aldehyde dehydrogenase 2 activation in heart failure restores mitochondrial function and improves ventricular function and remodelling. Cardiovasc Res 103:498–508. doi: 10.1093/cvr/cvu125

[42]. Gottlob K, Majewski N, Kennedy S, Kandel E, Robey RB, Hay N (2001) Inhibition of early apoptotic events by Akt/PKB is dependent on the first committed step of glycolysis and mitochondrial hexokinase. Genes Dev 15:1406–1418. doi: 10.1101/gad.889901

[43]. Gu XS, Wang ZB, Ye Z, Lei JP, Li L, Su DF, Zheng X (2014) Resveratrol, an activator of SIRT1, upregulates AMPK and improves cardiac function in heart failure. Genet Mol Res 13:323–335. doi: 10.4238/2014.january.17.17

[44]. Gundewar S, Calvert JW, Jha S, Toedt-Pingel I, Ji SY, Nunez D, Ramachandran A, Anaya-Cisneros M, Tian R, Lefer DJ (2009) Activation of AMP-activated protein kinase by metformin improves left ventricular function and survival in heart failure. Circ Res 104:403–411. doi: 10.1161/CIRCRESAHA.108.190918

[45]. Hahn-Windgassen A, Nogueira V, Chen C-C, Skeen JE, Sonenberg N, Hay N (2005) Akt Activates the Mammalian Target of Rapamycin by Regulating Cellular ATP Level and AMPK Activity. J Biol Chem 280:32081–32089. doi: 10.1074/jbc.m502876200

[46]. Hajnóczky G, Hager R, Thomas AP (1999) Mitochondria Suppress Local Feedback Activation of Inositol 1,4,5-Trisphosphate Receptors by Ca2+. J Biol Chem 274:14157–14162. doi: 10.1074/jbc.274.20.14157

[47]. Han H, Wang H, Yin Z, Jiang H, Fang M, Han J (2013) Association of genetic polymorphisms in ADH and ALDH2 with risk of coronary artery disease and myocardial infarction: A meta-analysis. Gene 526:134–141. doi: 10.1016/j.gene.2013.05.002

[48]. Hardie DG (2003) Minireview: The AMP-Activated Protein Kinase Cascade: The Key Sensor of Cellular Energy Status. Endocrinology 144:5179–5183. doi: 10.1210/en.2003-0982

[49]. Hausenloy DJ, Yellon DM (2013) Myocardial ischemia-reperfusion injury: a neglected therapeutic target. J Clin Invest 123:92–100. doi: 10.1172/JCI62874

[50]. Heather LC, Carr CA, Stuckey DJ, Pope S, Morten KJ, Carter EE, Edwards LM, Clarke K (2009) Critical role of complex III in the early metabolic changes following myocardial infarction. Cardiovasc Res 85:127–136. doi: 10.1093/cvr/cvp276

[51]. Vander Heide RS, Steenbergen C (2013) Cardioprotection and myocardial reperfusion: pitfalls to clinical application. Circ Res 113:464–477. doi: 10.1161/CIRCRESAHA.113.300765

[52]. Heusch G (2013) Cardioprotection: chances and challenges of its translation to the clinic. Lancet 381:166–175. doi: 10.1016/s0140-6736(12)60916-7

[53]. Ho KKL, Pinsky JL, Kannel WB, Levy D (1993) The epidemiology of heart failure: The Framingham Study. J Am Coll Cardiol 22:A6–A13. doi: 10.1016/0735-1097(93)90455-a

[54]. Hoppins S, Lackner L, Nunnari J (2007) The Machines that Divide and Fuse Mitochondria. Annu Rev Biochem 76:751–780. doi: 10.1146/annurev.biochem.76.071905.090048

[55]. Ibáñez B, Heusch G, Ovize M, Van de Werf F (2015) Evolving Therapies for Myocardial Ischemia/Reperfusion Injury. J Am Coll Cardiol 65:1454–1471. doi: 10.1016/j.jacc.2015.02.032

[56]. Javadov S, Karmazyn M, Escobales N (2009) Mitochondrial Permeability Transition Pore Opening as a Promising Therapeutic Target in Cardiac Diseases. J Pharmacol Exp Ther 330:670–678. doi: 10.1124/jpet.109.153213

[57]. Javadov S, Rajapurohitam V, Kilić A, Zeidan A, Choi A, Karmazyn M (2009) Anti-hypertrophic effect of NHE-1 inhibition involves GSK-3β-dependent attenuation of mitochondrial dysfunction. J Mol Cell Cardiol 46:998–1007. doi: 10.1016/j.yjmcc.2008.12.023

[58]. Ji LL (2019) Faculty Opinions recommendation of Expert consensus document: Mitochondrial function as a therapeutic target in heart failure. Fac. Opin. – Post-Publication Peer Rev. Biomed. Lit. DOI: 10.1038/nrcardio.2016.203

[59]. Kanamori H, Takemura G, Goto K, Tsujimoto A, Ogino A, Takeyama T, Kawaguchi T, Watanabe T, Morishita K, Kawasaki M, Mikami A, Fujiwara T, Fujiwara H, Seishima M, Minatoguchi S (2013) Resveratrol Reverses Remodeling in Hearts with Large, Old Myocardial Infarctions through Enhanced Autophagy-Activating AMP Kinase Pathway. Am J Pathol 182:701–713. doi: 10.1016/j.ajpath.2012.11.009

[60]. Kearney MT (2015) Chronic heart failure and type 2 diabetes mellitus: The last battle? Diabetes Vasc Dis Res 12:226–227. doi: 10.1177/1479164115590324

[61]. Kelso GF, Porteous CM, Coulter C V, Hughes G, Porteous WK, Ledgerwood EC, Smith RAJ, Murphy MP (2000) Selective Targeting of a Redox-active Ubiquinone to Mitochondria within Cells. J Biol Chem 276:4588–4596. doi: 10.1074/jbc.m009093200

[62]. Kewalramani G, Puthanveetil P, Wang F, Kim MS, Deppe S, Abrahani A, Luciani DS, Johnson JD, Rodrigues B (2009) AMP-activated protein kinase confers protection against TNF-α-induced cardiac cell death. Cardiovasc Res 84:42–53. doi: 10.1093/cvr/cvp166

[63]. Kim TT, Dyck JRB (2015) Is AMPK the savior of the failing heart? Trends Endocrinol Metab 26:40–48. doi: 10.1016/j.tem.2014.11.001

[64]. King H, Aubert RE, Herman WH (1998) Global Burden of Diabetes, 1995-2025: Prevalence, numerical estimates, and projections. Diabetes Care 21:1414–1431. doi: 10.2337/diacare.21.9.1414

[65]. Kirpichnikov D, McFarlane SI, Sowers JR (2002) Metformin: An Update. Ann Intern Med 137:25. doi: 10.7326/0003-4819-137-1-200207020-00009

[66]. Kloner RA, Brown DA, Csete M, Dai W, Downey JM, Gottlieb RA, Hale SL, Shi J (2017) New and revisited approaches to preserving the reperfused myocardium. Nat Rev Cardiol 14:679–693. doi: 10.1038/nrcardio.2017.102

[67]. Knowlton AA, Chen L, Malik ZA (2014) Heart failure and mitochondrial dysfunction: the role of mitochondrial fission/fusion abnormalities and new therapeutic strategies. J Cardiovasc Pharmacol 63:196–206. doi: 10.1097/01.fjc.0000432861.55968.a6

[68]. Kovacic S, Soltys C-LM, Barr AJ, Shiojima I, Walsh K, Dyck JRB (2003) Akt Activity Negatively Regulates Phosphorylation of AMP-activated Protein Kinase in the Heart. J Biol Chem 278:39422–39427. doi: 10.1074/jbc.m305371200

[69]. Kumar V, Santhosh Kumar TR, Kartha CC (2018) Mitochondrial membrane transporters and metabolic switch in heart failure. Heart Fail Rev 24:255–267. doi: 10.1007/s10741-018-9756-2

[70]. Lackner LL (2014) Shaping the dynamic mitochondrial network. BMC Biol 12:35. doi: 10.1186/1741-7007-12-35

[71]. Le Lamer S, Paradis S, Rahmouni H, Chaimbault C, Michaud M, Culcasi M, Afxantidis J, Latreille M, Berna P, Berdeaux A, Pietri S, Morin D, Donazzolo Y, Abitbol J-L, Pruss RM, Schaller S (2014) Translation of TRO40303 from myocardial infarction models to demonstration of safety and tolerance in a randomized Phase I trial. J Transl Med 12:38. doi: 10.1186/1479-5876-12-38

[72]. Lathief S, Inzucchi SE (2016) Approach to diabetes management in patients with CVD. Trends Cardiovasc Med 26:165–179. doi: 10.1016/j.tcm.2015.05.005

[73]. Li X-N, Song J, Zhang L, LeMaire SA, Hou X, Zhang C, Coselli JS, Chen L, Wang XL, Zhang Y, Shen YH (2009) Activation of the AMPK-FOXO3 pathway reduces fatty acid-induced increase in intracellular reactive oxygen species by upregulating thioredoxin. Diabetes 58:2246–2257. doi: 10.2337/db08-1512

[74]. Li Y-Y, Wang H, Wu J-J, Kim HJ, Yang X-X, Geng H-Y, Gong G (2018) ALDH2 gene G487A polymorphism and coronary artery disease: a meta-analysis including 5644 participants. J Cell Mol Med 22:1666–1674. doi: 10.1111/jcmm.13443

[75]. Li Y, Chen C, Yao F, Su Q, Liu D, Xue R, Dai G, Fang R, Zeng J, Chen Y, Huang H, Ma Y, Li W, Zhang L, Liu C, Dong Y (2014) AMPK inhibits cardiac hypertrophy by promoting autophagy via mTORC1. Arch Biochem Biophys 558:79–86. doi: 10.1016/j.abb.2014.06.023

[76]. Liang Q, Kobayashi S (2016) Mitochondrial quality control in the diabetic heart. J Mol Cell Cardiol 95:57–69. doi: 10.1016/j.yjmcc.2015.12.025

[77]. Lim WY, Messow CM, Berry C (2012) Cyclosporin variably and inconsistently reduces infarct size in experimental models of reperfused myocardial infarction: a systematic review and meta-analysis. Br J Pharmacol 165:2034–2043. doi: 10.1111/j.1476-5381.2011.01691.x

[78]. Lin J-F, Lin S-M, Chih C-L, Nien M-W, Su H-H, Hu B-R, Huang S-S, Tsai S-K (2008) Resveratrol reduces infarct size and improves ventricular function after myocardial ischemia in rats. Life Sci 83:313–317. doi: 10.1016/j.lfs.2008.06.016

[79]. López-Lluch G, Irusta PM, Navas P, de Cabo R (2008) Mitochondrial biogenesis and healthy aging. Exp Gerontol 43:813–819. doi: 10.1016/j.exger.2008.06.014

[80]. Luo S, Valencia CA, Zhang J, Lee N-C, Slone J, Gui B, Wang X, Li Z, Dell S, Brown J, Chen SM, Chien Y-H, Hwu W-L, Fan P-C, Wong L-J, Atwal PS, Huang T (2018) Biparental Inheritance of Mitochondrial DNA in Humans. Proc Natl Acad Sci U S A 115:13039–13044. doi: 10.1073/pnas.1810946115

[81]. MacDonald MR, Eurich DT, Majumdar SR, Lewsey JD, Bhagra S, Jhund PS, Petrie MC, McMurray JJ V, Petrie JR, McAlister FA (2010) Treatment of type 2 diabetes and outcomes in patients with heart failure: a nested case-control study from the U.K. General Practice Research Database. Diabetes Care 33:1213–1218. doi: 10.2337/dc09-2227

[82]. Masoudi FA, Inzucchi SE, Wang Y, Havranek EP, Foody JM, Krumholz HM (2005) Thiazolidinediones, Metformin, and Outcomes in Older Patients With Diabetes and Heart Failure. Circulation 111:583–590. doi: 10.1161/01.cir.0000154542.13412.b1

[83]. Matsuhashi T, Sato T, Kanno S-I, Suzuki T, Matsuo A, Oba Y, Kikusato M, Ogasawara E, Kudo T, Suzuki K, Ohara O, Shimbo H, Nanto F, Yamaguchi H, Saigusa D, Mukaiyama Y, Watabe A, Kikuchi K, Shima H, Mishima E, Akiyama Y, Oikawa Y, Hsin-Jung HO, Akiyama Y, Suzuki C, Uematsu M, Ogata M, Kumagai N, Toyomizu M, Hozawa A, Mano N, Owada Y, Aiba S, Yanagisawa T, Tomioka Y, Kure S, Ito S, Nakada K, Hayashi K-I, Osaka H, Abe T (2017) Mitochonic Acid 5 (MA-5) Facilitates ATP Synthase Oligomerization and Cell Survival in Various Mitochondrial Diseases. EBioMedicine 20:27–38. doi: 10.1016/j.ebiom.2017.05.016

[84]. Matthews DR, Cull CA, Stratton IM, Holman RR, Turner RC (1998) UKPDS 26: sulphonylurea failure in non-insulin-dependent diabetic patients over six years. Diabet Med 15:297–303. doi: 10.1002/(sici)1096-9136(199804)15:4<297::aid-dia572>3.0.co;2-w

[85]. McCarron JG, Wilson C, Sandison ME, Olson ML, Girkin JM, Saunter C, Chalmers S (2013) From structure to function: mitochondrial morphology, motion and shaping in vascular smooth muscle. J Vasc Res 50:357–371. doi: 10.1159/000353883

[86]. Meeusen S (2004) Mitochondrial Fusion Intermediates Revealed in Vitro. Science (80-) 305:1747–1752. doi: 10.1126/science.1100612

[87]. Meng R, Pei Z, Zhang A, Zhou Y, Cai X, Chen B, Liu G, Mai W, Wei J, Dong Y (2011) AMPK activation enhances PPARα activity to inhibit cardiac hypertrophy via ERK1/2 MAPK signaling pathway. Arch Biochem Biophys 511:1–7. doi: 10.1016/j.abb.2011.04.010

[88]. Methner C, Chouchani ET, Buonincontri G, Pell VR, Sawiak SJ, Murphy MP, Krieg T (2014) Mitochondria selective S-nitrosation by mitochondria-targeted S-nitrosothiol protects against post-infarct heart failure in mouse hearts. Eur J Heart Fail 16:712–717. doi: 10.1002/ejhf.100

[89]. Mewton N, Croisille P, Gahide G, Rioufol G, Bonnefoy E, Sanchez I, Cung TT, Sportouch C, Angoulvant D, Finet G, André-Fouët X, Derumeaux G, Piot C, Vernhet H, Revel D, Ovize M (2010) Effect of Cyclosporine on Left Ventricular Remodeling After Reperfused Myocardial Infarction. J Am Coll Cardiol 55:1200–1205. doi: 10.1016/j.jacc.2009.10.052

[90]. Mizuno Y, Harada E, Morita S, Kinoshita K, Hayashida M, Shono M, Morikawa Y, Murohara T, Nakayama M, Yoshimura M, Yasue H (2015) East Asian Variant of Aldehyde Dehydrogenase 2 Is Associated With Coronary Spastic Angina. Circulation 131:1665–1673. doi: 10.1161/circulationaha.114.013120

[91]. Mizuno Y, Hokimoto S, Harada E, Kinoshita K, Nakagawa K, Yoshimura M, Ogawa H, Yasue H (2016) Variant Aldehyde Dehydrogenase 2 (ALDH2*2) Is a Risk Factor for Coronary Spasm and ST-Segment Elevation Myocardial Infarction. J Am Heart Assoc 5:e003247. doi: 10.1161/JAHA.116.003247

[92]. Murry CE, Jennings RB, Reimer KA (1986) Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. Circulation 74:1124–1136. doi: 10.1161/01.cir.74.5.1124

[93]. Musi N, Hirshman MF, Nygren J, Svanfeldt M, Bavenholm P, Rooyackers O, Zhou G, Williamson JM, Ljunqvist O, Efendic S, Moller DE, Thorell A, Goodyear LJ (2002) Metformin Increases AMP-Activated Protein Kinase Activity in Skeletal Muscle of Subjects With Type 2 Diabetes. Diabetes 51:2074–2081. doi: 10.2337/diabetes.51.7.2074

[94]. Nakada K, Inoue K, Ono T, Isobe K, Ogura A, Goto Y-I, Nonaka I, Hayashi J-I (2001) Inter-mitochondrial complementation: Mitochondria-specific system preventing mice from expression of disease phenotypes by mutant mtDNA. Nat Med 7:934–940. doi: 10.1038/90976

[95]. Narayanan D, Xi Q, Pfeffer LM, Jaggar JH (2010) Mitochondria control functional CaV1.2 expression in smooth muscle cells of cerebral arteries. Circ Res 107:631–641. doi: 10.1161/CIRCRESAHA.110.224345

[96]. Neely JR, Morgan HE (1974) Relationship Between Carbohydrate and Lipid Metabolism and the Energy Balance of Heart Muscle. Annu Rev Physiol 36:413–459. doi: 10.1146/annurev.ph.36.030174.002213

[97]. Okonko DO, Shah AM (2014) Mitochondrial dysfunction and oxidative stress in CHF. Nat Rev Cardiol 12:6–8. doi: 10.1038/nrcardio.2014.189

[98]. Ong C, Lim JZZ, Ng C-T, Li JJ, Yung L-YL, Bay B-H (2013) Silver Nanoparticles in Cancer: Therapeutic Efficacy and Toxicity. Curr Med Chem 20:772–781. doi: 10.2174/092986713805076685

[99]. Ottani F, Latini R, Staszewsky L, La Vecchia L, Locuratolo N, Sicuro M, Masson S, Barlera S, Milani V, Lombardi M, Costalunga A, Mollichelli N, Santarelli A, De Cesare N, Sganzerla P, Boi A, Maggioni A Pietro, Limbruno U (2016) Cyclosporine A in Reperfused Myocardial Infarction. J Am Coll Cardiol 67:365–374. doi: 10.1016/j.jacc.2015.10.081

[100]. Ottani F, Latini R, Staszewsky L, La Vecchia L, Locuratolo N, Sicuro M, Masson S, Barlera S, Milani V, Lombardi M, Costalunga A, Mollichelli N, Santarelli A, De Cesare N, Sganzerla P, Boi A, Maggioni A Pietro, Limbruno U (2016) Cyclosporine A in Reperfused Myocardial Infarction: The Multicenter, Controlled, Open-Label CYCLE Trial. J Am Coll Cardiol 67:365–374. doi:

https://doi.org/10.1016/j.jacc.2015.10.081
[101]. Paradies G, Paradies V, De Benedictis V, Ruggiero FM, Petrosillo G (2014) Functional role of cardiolipin in mitochondrial bioenergetics. Biochim Biophys Acta - Bioenerg 1837:408–417. doi: 10.1016/j.bbabio.2013.10.006
[102]. Perez-Miller S, Younus H, Vanam R, Chen C-H, Mochly-Rosen D, Hurley TD (2010) Alda-1 is an agonist and chemical chaperone for the common human aldehyde dehydrogenase 2 variant. Nat Struct Mol Biol 17:159–164. doi: 10.1038/nsmb.1737
[103]. Perkins GA, Frey TG (2000) Recent structural insight into mitochondria gained by microscopy. Micron 31:97–111. doi: 10.1016/s0968-4328(99)00065-7
[104]. Pierce JD, Mahoney DE, Hiebert JB, Thimmesch AR, Diaz FJ, Smith C, Shen Q, Mudaranthakam DP, Clancy RL (2018) Study protocol, randomized controlled trial: reducing symptom burden in patients with heart failure with preserved ejection fraction using ubiquinol and/or D-ribose. BMC Cardiovasc Disord 18:57. doi: 10.1186/s12872-018-0796-2
[105]. Piot C, Croisille P, Staat P, Thibault H, Rioufol G, Mewton N, Elbelghiti R, Cung TT, Bonnefoy E, Angoulvant D, Macia C, Raczka F, Sportouch C, Gahide G, Finet G, André-Fouët X, Revel D, Kirkorian G, Monassier J-P, Derumeaux G, Ovize M (2008) Effect of Cyclosporine on Reperfusion Injury in Acute Myocardial Infarction. N Engl J Med 359:473–481. doi: 10.1056/nejmoa071142
[106]. Porter KE, Turner NA (2009) Cardiac fibroblasts: At the heart of myocardial remodeling. Pharmacol Ther 123:255–278. doi: 10.1016/j.pharmthera.2009.05.002
[107]. Qiao Y, Zhu B, Tian A, Li Z (2017) PEG-coated gold nanoparticles attenuate β-adrenergic receptor-mediated cardiac hypertrophy. Int J Nanomedicine 12:4709–4719. doi: 10.2147/IJN.S130951
[108]. Ravichandran R, Sridhar R, Venugopal JR, Sundarrajan S, Mukherjee S, Ramakrishna S (2013) Gold Nanoparticle Loaded Hybrid Nanofibers for Cardiogenic Differentiation of Stem Cells for Infarcted Myocardium Regeneration. Macromol Biosci 14:515–525. doi: 10.1002/mabi.201300407
[109]. Ribeiro Junior RF, Dabkowski ER, Shekar KC, O Connell KA, Hecker PA, Murphy MP (2018) MitoQ improves mitochondrial dysfunction in heart failure induced by pressure overload. Free Radic Biol Med 117:18–29. doi: 10.1016/j.freeradbiomed.2018.01.012
[110]. Rossman MJ, Santos-Parker JR, Steward CAC, Bispham NZ, Cuevas LM, Rosenberg HL, Woodward KA, Chonchol M, Gioscia-Ryan RA, Murphy MP, Seals DR (2018) Chronic Supplementation With a Mitochondrial Antioxidant (MitoQ) Improves Vascular Function in Healthy Older Adults. Hypertens (Dallas, Tex 1979) 71:1056–1063. doi: 10.1161/HYPERTENSIONAHA.117.10787
[111]. Russell RR, Bergeron R, Shulman GI, Young LH (1999) Translocation of myocardial GLUT-4 and increased glucose uptake through activation of AMPK by AICAR. Am J Physiol Circ Physiol 277:H643–H649. doi: 10.1152/ajpheart.1999.277.2.h643
[112]. Sabbah HN (2016) Targeting mitochondrial dysfunction in the treatment of heart failure. Expert Rev Cardiovasc Ther 14:1305–1313. doi: 10.1080/14779072.2016.1249466
[113]. Sasaki H, Asanuma H, Fujita M, Takahama H, Wakeno M, Ito S, Ogai A, Asakura M, Kim J, Minamino T, Takashima S, Sanada S, Sugimachi M, Komamura K, Mochizuki N, Kitakaze M (2009) Metformin Prevents Progression of Heart Failure in Dogs. Circulation 119:2568–2577. doi: 10.1161/circulationaha.108.798561
[114]. Schaller S, Paradis S, Ngoh GA, Assaly R, Buisson B, Drouot C, Ostuni MA, Lacapere J-J, Bassissi F, Bordet T, Berdeaux A, Jones SP, Morin D, Pruss RM (2010) TRO40303, a New Cardioprotective Compound, Inhibits Mitochondrial Permeability Transition. J Pharmacol Exp Ther 333:696–706. doi: 10.1124/jpet.110.167486
[115]. Schilling JD (2015) The mitochondria in diabetic heart failure: from pathogenesis to therapeutic promise. Antioxid Redox Signal 22:1515–1526. doi: 10.1089/ars.2015.6294
[116]. Schmidt O, Pfanner N, Meisinger C (2010) Mitochondrial protein import: from proteomics to functional mechanisms. Nat Rev Mol Cell Biol 11:655–667. doi: 10.1038/nrm2959
[117]. Sharma A, Fonarow GC, Butler J, Ezekowitz JA, Felker GM (2016) Coenzyme Q10 and Heart Failure. Circ Hear Fail 9:e002639. doi: 10.1161/circheartfailure.115.002639
[118]. Shen X, Zheng S, Metreveli NS, Epstein PN (2006) Protection of Cardiac Mitochondria by Overexpression of MnSOD Reduces Diabetic Cardiomyopathy. Diabetes 55:798–805. doi: 10.2337/diabetes.55.03.06.db05-1039
[119]. Sivitz WI, Yorek MA (2010) Mitochondrial dysfunction in diabetes: from molecular mechanisms to functional significance and therapeutic opportunities. Antioxid Redox Signal 12:537–577. doi: 10.1089/ars.2009.2531
[120]. Smith RAJ, Hartley RC, Cochemé HM, Murphy MP (2012) Mitochondrial pharmacology. Trends Pharmacol Sci 33:341–352. doi: 10.1016/j.tips.2012.03.010
[121]. Snow BJ, Rolfe FL, Lockhart MM, Frampton CM, O'Sullivan JD, Fung V, Smith RAJ, Murphy MP, Taylor KM (2010) A double-blind, placebo-controlled study to assess the mitochondria-targeted antioxidant MitoQ as a disease-modifying therapy in Parkinson's disease. Mov Disord 25:1670–1674. doi: 10.1002/mds.23148
[122]. Solskov L, Løfgren B, Kristiansen SB, Jessen N, Pold R, Nielsen TT, Bøtker HE, Schmitz O, Lund S (2008) Metformin Induces Cardioprotection against Ischaemia/Reperfusion Injury in the Rat Heart 24 Hours after Administration. Basic Clin Pharmacol Toxicol 103:82–87. doi: 10.1111/j.1742-7843.2008.00234.x
[123]. Sparagna GC, Chicco AJ, Murphy RC, Bristow MR, Johnson CA, Rees ML, Maxey ML, McCune SA, Moore RL (2007) Loss of cardiac tetralinoleoyl cardiolipin in human and experimental heart failure. J Lipid Res 48:1559–1570. doi: 10.1194/jlr.m600551-jlr200
[124]. Stumvoll M, Nurjhan N, Perriello G, Dailey G, Gerich JE (1995) Metabolic Effects of Metformin in Non-Insulin-Dependent Diabetes Mellitus. N Engl J Med 333:550–554. doi: 10.1056/nejm199508313330903
[125]. Sun L, Ferreira JCB, Mochly-Rosen D (2011) ALDH2 activator inhibits increased myocardial infarction injury by nitroglycerin tolerance. Sci Transl Med 3:107ra111-107ra111. doi: 10.1126/scitranslmed.3002067
[126]. Suzuki T, Yamaguchi H, Kikusato M, Hashizume O, Nagatoishi S, Matsuo A, Sato T, Kudo T, Matsuhashi T, Murayama K, Ohba Y, Watanabe S, Kanno S-I, Minaki D, Saigusa D, Shinbo H, Mori N, Yuri A, Yokoro M, Mishima E, Shima H, Akiyama Y, Takeuchi Y, Kikuchi K, Toyohara T, Suzuki C, Ichimura T, Anzai J-I, Kohzuki M, Mano N, Kure S, Yanagisawa T, Tomioka Y, Toyomizu M, Tsumoto K, Nakada K, Bonventre J V, Ito S, Osaka H, Hayashi K-I, Abe T (2016) Mitochonic Acid 5 Binds Mitochondria and Ameliorates Renal Tubular and Cardiac Myocyte Damage. J Am Soc Nephrol 27:1925–1932. doi: 10.1681/ASN.2015060623
[127]. Suzuki T, Yamaguchi H, Kikusato M, Matsuhashi T, Matsuo A, Sato T, Oba Y, Watanabe S, Minaki D, Saigusa D, Shimbo H, Mori N, Mishima E, Shima H, Akiyama Y, Takeuchi Y, Yuri A, Kikuchi K, Toyohara T, Suzuki C, Kohzuki M, Anzai J, Mano N, Kure S, Yanagisawa T, Tomioka Y, Toyomizu M, Ito S, Osaka H, Hayashi K, Abe T (2015) Mitochonic Acid 5 (MA-5), a Derivative of the Plant Hormone Indole-3-Acetic Acid, Improves Survival of Fibroblasts from Patients with Mitochondrial Diseases. Tohoku J Exp Med 236:225–232. doi: 10.1620/tjem.236.225
[128]. Szeto HH (2014) First-in-class cardiolipin-protective compound as a therapeutic agent to restore mitochondrial bioenergetics. Br J Pharmacol 171:2029–2050. doi: 10.1111/bph.12461

[129]. Szeto HH, Liu S, Soong Y, Wu D, Darrah SF, Cheng F-Y, Zhao Z, Ganger M, Tow CY, Seshan S V (2011) Mitochondria-targeted peptide accelerates ATP recovery and reduces ischemic kidney injury. J Am Soc Nephrol 22:1041–1052. doi: 10.1681/ASN.2010080808
[130]. Tanno M, Kuno A, Yano T, Miura T, Hisahara S, Ishikawa S, Shimamoto K, Horio Y (2010) Induction of manganese superoxide dismutase by nuclear translocation and activation of SIRT1 promotes cell survival in chronic heart failure. J Biol Chem 285:8375–8382. doi: 10.1074/jbc.M109.090266
[131]. Tomita M, Mukae S, Geshi E, Umetsu K, Nakatani M, Katagiri T (1996) Mitochondrial Respiratory Impairment in Streptozotocin-Induced Diabetic Rat Heart. Jpn Circ J 60:673–682. doi: 10.1253/jcj.60.673
[132]. Tsujita K, Shimomura H, Kawano H, Hokamaki J, Fukuda M, Yamashita T, Hida S, Nakamura Y, Nagayoshi Y, Sakamoto T, Yoshimura M, Arai H, Ogawa H (2004) Effects of edaravone on reperfusion injury in patients with acute myocardial infarction. Am J Cardiol 94:481–484. doi: 10.1016/j.amjcard.2004.05.007
[133]. Tsutsui H, Kinugawa S, Matsushima S (2008) Oxidative Stress and Mitochondrial DNA Damage in Heart Failure. Circ J 72:A31–A37. doi: 10.1253/circj.cj-08-0014
[134]. Um J-H, Park S-J, Kang H, Yang S, Foretz M, McBurney MW, Kim MK, Viollet B, Chung JH (2010) AMP-activated protein kinase-deficient mice are resistant to the metabolic effects of resveratrol. Diabetes 59:554–563. doi: 10.2337/db09-0482
[135]. Wang H, Yang Y-J, Qian H-Y, Zhang Q, Xu H, Li J-J (2011) Resveratrol in cardiovascular disease: what is known from current research? Heart Fail Rev 17:437–448. doi: 10.1007/s10741-011-9260-4
[136]. Watson PA, Reusch JEB, McCune SA, Leinwand LA, Luckey SW, Konhilas JP, Brown DA, Chicco AJ, Sparagna GC, Long CS, Moore RL (2007) Restoration of CREB function is linked to completion and stabilization of adaptive cardiac hypertrophy in response to exercise. Am J Physiol Circ Physiol 293:H246–H259. doi: 10.1152/ajpheart.00734.2006
[137]. Wongrakpanich A, Geary SM, Joiner MA, Anderson ME, Salem AK (2014) Mitochondria-targeting particles. Nanomedicine (Lond) 9:2531–2543. doi: 10.2217/nnm.14.161
[138]. Woods C, Shang C, Taghavi F, Downey P, Zalewski A, Rubio GR, Liu J, Homburger JR, Grunwald Z, Qi W, Bollensdorff C, Thanaporn P, Ali A, Riemer K, Kohl P, Mochly-Rosen D, Gerstenfeld E, Large S, Ali Z, Ashley E (2016) In Vivo Post-Cardiac Arrest Myocardial Dysfunction Is Supported by Ca2+/Calmodulin-Dependent Protein Kinase II-Mediated Calcium Long-Term Potentiation and Mitigated by Alda-1, an Agonist of Aldehyde Dehydrogenase Type 2. Circulation 134:961–977. doi: 10.1161/CIRCULATIONAHA.116.021618
[139]. Wu F, Zhang J, Beard DA (2009) Experimentally observed phenomena on cardiac energetics in heart failure emerge from simulations of cardiac metabolism. Proc Natl Acad Sci U S A 106:7143–7148. doi: 10.1073/pnas.0812768106
[140]. Xu F, Chen YG, Xue L, Li RJ, Zhang H, Bian Y, Zhang C, Lv RJ, Feng JB, Zhang Y (2011) Role of aldehyde dehydrogenase 2 Glu504lys polymorphism in acute coronary syndrome. J Cell Mol Med 15:1955–1962. doi: 10.1111/j.1582-4934.2010.01181.x
[141]. Yang J-Y, Deng W, Chen Y, Fan W, Baldwin KM, Jope RS, Wallace DC, Wang PH (2013) Impaired translocation and activation of mitochondrial Akt1 mitigated mitochondrial oxidative phosphorylation Complex V activity in diabetic myocardium. J Mol Cell Cardiol 59:167–175. doi: 10.1016/j.yjmcc.2013.02.016
[142]. Yang J-Y, Yeh H-Y, Lin K, Wang PH (2009) Insulin stimulates Akt translocation to mitochondria: implications on dysregulation of mitochondrial oxidative phosphorylation in diabetic myocardium. J Mol Cell Cardiol 46:919–926. doi: 10.1016/j.yjmcc.2009.02.015
[143]. Yang M-Y, Wang Y-B, Han B, Yang B, Qiang Y-W, Zhang Y, Wang Z, Huang X, Liu J, Chen Y-D, Ren J, Cao F, Xu Y (2018) Activation of aldehyde dehydrogenase 2 slows down the progression of atherosclerosis via attenuation of ER stress and apoptosis in smooth muscle cells. Acta Pharmacol Sin 39:48–58. doi: 10.1038/aps.2017.81
[144]. Yavari A, Ashrafian H (2014) Potentiating mitochondrial aldehyde dehydrogenase 2 to treat post-infarction heart failure. Cardiovasc Res 103:429–431. doi: 10.1093/cvr/cvu175
[145]. Yin M, van der Horst ICC, van Melle JP, Qian C, van Gilst WH, Silljé HHW, de Boer RA (2011) Metformin improves cardiac function in a nondiabetic rat model of post-MI heart failure. Am J Physiol Circ Physiol 301:H459–H468. doi: 10.1152/ajpheart.00054.2011
[146]. Zambelli VO, Gross ER, Chen C-H, Gutierrez VP, Cury Y, Mochly-Rosen D (2014) Aldehyde dehydrogenase-2 regulates nociception in rodent models of acute inflammatory pain. Sci Transl Med 6:251ra118-251ra118. doi: 10.1126/scitranslmed.3009539
[147]. Zhabyeyev P, Gandhi M, Mori J, Basu R, Kassiri Z, Clanachan A, Lopaschuk GD, Oudit GY (2012) Pressure-overload-induced heart failure induces a selective reduction in glucose oxidation at physiological afterload. Cardiovasc Res 97:676–685. doi: 10.1093/cvr/cvs424
[148]. Zhao H, Li H, Hao S, Chen J, Wu J, Song C, Zhang M, Qiao T, Li K (2017) Peptide SS-31 upregulates frataxin expression and improves the quality of mitochondria: implications in the treatment of Friedreich ataxia. Sci Rep 7:9840. doi: 10.1038/s41598-017-10320-2
[149]. Zou M-H, Kirkpatrick SS, Davis BJ, Nelson JS, Wiles WG, Schlattner U, Neumann D, Brownlee M, Freeman MB, Goldman MH (2004) Activation of the AMP-activated Protein Kinase by the Anti-diabetic Drug Metformin in Vivo. J Biol Chem 279:43940–43951. doi: 10.1074/jbc.m404421200

Mohamed A. Hassany, et. al. "Role of Mitochondria in Diabetic Cardiomyopathy and Treatment Challenges for Mitochondrial Dysfunction." *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 21(01), 2022, pp. 07-19.