Heart Failure Reviews (2019) 24:255–267
https://doi.org/10.1007/s10741-018-9756-2

Mitochondrial membrane transporters and metabolic switch in heart failure

Vikas Kumar[1,2] · T. R. Santhosh Kumar[1,2,3] · C. C. Kartha[1]

Published online: 10 December 2018

Abstract
Mitochondrial dysfunction is widely recognized as a major factor for the progression of cardiac failure. Mitochondrial uptake of metabolic substrates and their utilization for ATP synthesis, electron transport chain activity, reactive oxygen species levels, ion homeostasis, mitochondrial biogenesis, and dynamics as well as levels of reactive oxygen species in the mitochondria are key factors which regulate mitochondrial function in the normal heart. Alterations in these functions contribute to adverse outcomes in heart failure. Iron imbalance and oxidative stress are also major factors for the evolution of cardiac hypertrophy, heart failure, and aging-associated pathological changes in the heart. Mitochondrial ATP–binding cassette (ABC) transporters have a key role in regulating iron metabolism and maintenance of redox status in cells. Deficiency of mitochondrial ABC transporters is associated with an impaired mitochondrial electron transport chain complex activity, iron overload, and increased levels of reactive oxygen species, all of which can result in mitochondrial dysfunction. In this review, we discuss the role of mitochondrial ABC transporters in mitochondrial metabolism and metabolic switch, alterations in the functioning of ABC transporters in heart failure, and mitochondrial ABC transporters as possible targets for therapeutic intervention in cardiac failure.

Keywords Heart failure · Cardiac hypertrophy · Mitochondrial dysfunction · Metabolic shift · Mitochondrial ABC transporters

Introduction

Cardiac failure is a progressive condition in which reduced cardiac output resulting from poor contractility of the heart muscle contributes to the inadequate blood supply to organs and thus an impaired oxygen supply vis a vis demand. Millions of people die from cardiac failure worldwide every year. Beta-blockers, vasodilators, diuretics, and inotropic agents are the major drugs used for management of heart failure. These drugs unload the heart, decrease blood pressure, and maintain the systolic or diastolic function of a compromised heart. Current treatment strategies for heart failure only aid to attenuate cardiac dysfunction and do not reverse the diseased heart to a healthy condition [1]. Mortality and rehospitalization in patients with heart failure are 15 and 35% respectively [1, 2].

Mitochondrial dysfunction is widely recognized as a major accompaniment of heart failure. Alterations in mitochondrial dynamics (fission, fusion, autophagy), membrane potential and ion homeostasis, switch in substrate metabolism, and increase in reactive oxygen species (ROS) and other free radicals (nitric oxide, hydroxyl) are distinct features of mitochondrial dysfunction associated with heart failure [2].

In this review, we examine the mitochondrial alterations in cardiac failure focusing on the role of mitochondrial membrane transporters in mitochondrial dysfunction, metabolic switch, and worsening of cardiac failure.

✉ C. C. Kartha
cckartha@rgcb.res.in

[1] Cardiovascular Diseases and Diabetes Biology group, Rajiv Gandhi Centre for Biotechnology (RGCB), Poojappura, Thycaud Post, Trivandrum, Kerala 695014, India

[2] Graduate Studies, Manipal Academy of Higher Education (MAHE), Manipal, Karnataka, India

[3] Cancer Research Program, Rajiv Gandhi Centre for Biotechnology (RGCB), Trivandrum, Kerala, India

Mitochondrial structure and function in the heart

Normal heart

The mitochondrion, an elliptical organelle is the major source of ATP (approximately 95% of total ATP that the heart utilizes) required for the contractile function of cardiomyocytes.

Mitochondria form approximately 25–30% of the total cell volume in cardiomyocytes [1, 3, 4].

A mitochondrion contains a single double-stranded, circular DNA of 16.5-Kb length. Thirty-seven genes in the mitochondrion code for 13 protein subunits of electron transport chain (ETC) complexes, 22 tRNA, and 2 rRNA. A mitochondrion is a double membrane–bound organelle with inner and outer membranes enclosing a matrix. The heart has three subtypes of mitochondria which are identified depending on their location in cardiomyocytes [5, 6]. These are (i) the subsarcolemmal mitochondria (SSM) which lie beneath the sarcolemma, (ii) intermyofibrillar mitochondria (IFM) which are sandwiched between myofilaments, and (iii) perinuclear mitochondria (PNM) which are located around the nucleus. Mitochondria present at different locations differ in the density of their cristae and matrix composition. IFM have tightly packed cristae and matrix inside and are the most abundant in cardiomyocytes [7–9].

Peroxisome proliferator activator receptor gamma coactivator (PGC1α), a nuclear gene, is the master regulator of biogenesis and replication function of mitochondria. Conditions of high workload, cold temperature, exercise, and fasting induce the expression of PGC1α gene in the heart [10]. PGC1α binds and coactivates nuclear receptor factor (NRF1/2) and induces transcription of mitochondrial genes [11, 12]. PGC1α interacts with estrogen-related receptor-α (ERRα) and regulates glucose and fatty acid transport across mitochondria, ATP synthesis, mitochondrial biogenesis, and quality control function of mitochondria [13–15]. PGC1α-mediated activation of NRF genes also induces mitochondrial transcription factor A (Tfam) which in turn promotes replication of the organelle [11].

Mitochondrial contact site and cristae organizing system (MICOS) is a large multiprotein complex located in the inner mitochondrial membrane at junctions of cristae. MICOS regulates the structure of mitochondrial cristae and composition of the protein complexes at the inner membrane. MICOS in association with TIM (transporter across the inner membrane) complex and SAM (sorting and assembly machinery) complex forms contact sites with the outer membrane of mitochondria. The MICOS/TIM/SAM complex regulates mitochondrial dynamics and function through a well-organized process [16, 17]. These complexes play an essential role in maintaining the mitochondrial homeostasis during cardiac hypertrophy and metabolic reprogramming associated with cardiac failure.

Mitochondria in humans contain over thousands of proteins which are required not only for oxidative phosphorylation–mediated ATP generation but also for the transport of amino acids, fatty acids, NADPH oxidation, and biosynthesis of iron-sulfur cluster and heme. Mitochondria synthesize only 13 proteins which are important components of the electron transport chain; the rest of the proteins are imported from the cytosol.

Mitochondria in the heart differ from those in other organs in topology, matrix composition, mitochondrial DNA replication, and the degree of gene expression [18, 19]. Heart relatively has a higher abundance of mitochondrial transcripts though the mitochondrial DNA copy number per tissue mass is similar in all tissues [19]. Mitochondrial DNA in the heart undergoes a strand-coupled mode of replication. Membrane compositions of proteins and phospholipids in the heart mitochondria also vary from those in other tissues [18].

Heart failure

Mitochondrial dysfunction is a major accompaniment of heart failure and results from structural changes (altered organization and membrane composition, disruption of one or both membranes), impaired dynamics or quality control (deteriorated mitochondrial fission and fusion as well as biogenesis, changes in membrane potential and mitophagy processes), and functional alterations (reduced/diminished ETC complex activity and ATP production). While mitochondria in the normal heart are well organized and have tightly packed cristae and matrix, mitochondria in the failing heart are swollen and have decreased matrix density [20]. Reduced ETC complex activity, myelinization, fragmentation of mitochondrial membranes, and abnormal biogenesis function have also been observed in mitochondria of the heart of dogs with cardiac failure. Mitochondrial turnover and oxidative phosphorylation function are diminished during heart failure and expression of the PGC1α gene in hearts is reduced as well [21].

The presence of mDNA heteroplasmy and mitochondrial diseases are major underlying factors for worsening of symptoms of heart failure [22]. Mitochondrial bioenergetics efficiency is impaired in patients with heart failure (both HFpEF and HFrEF) and the damage is characterized by a decrease in ATP synthesis, phosphocreatine (PCr), and PCr/ATP ratio [23].

Altered fuel preference has also been observed during the cardiac failure in both human and animal models. The normal healthy heart relies majorly (approximately 70–80%) on fatty acid oxidation as an ATP source but switches during heart failure to glycolysis which is approximately 30% more efficient to generate ATP [24, 25]. Downregulation of peroxisome proliferator-activated receptor-α (PPARα) and PPAR-γ coactivator (PGC1α) are observed in the failing heart and are considered as important factors for decreased fatty acid oxidation (FAO). Increased free fatty acid levels are also observed in heart failure [15, 26, 27]. Enhanced plasma catecholamine levels are reported to increase the plasma catecholamine and in turn suppress FAO in energy-starved failing heart [27].

Mitochondrial membrane transporters in the heart

Membrane transporters inlaid with other proteins which span across the mitochondrial membrane assist the transport of molecules or ions across the mitochondrial membranes. Mitochondrial membrane transporters regulate homeostasis of multiple metabolic pathways. Urea and water are freely transported across the mitochondrial membrane; membrane transporters can accelerate their transport [28]. Transport of metabolites across the mitochondria is influenced by changes in both pH and mitochondrial membrane potential [29].

Role of mitochondrial membrane transporters in regulating cardiac metabolism

There are three major types of membrane transport proteins (integral transmembrane proteins) which are classified according to their mechanisms of transport and are highly specific for the substrate to be transported. Integral membrane proteins with transport functions are (i) ATP-powered pumps/ATPase pumps (sodium-potassium pump (Na^+-K^+ ATPase), proton-potassium pump (H^+-K^+ ATPase), and calcium pump (Ca^{2+}-ATPase)); (ii) channel proteins (voltage-gated ion channels, ligand-gated ion channels, and beta-barrel porin/aquaporin); (iii) glucose transporters such as GLUT1; (iv) cytochromes (present at electron transport chain); and (v) ATP-binding cassette (ABC) transporters which transport ions, sugars, amino acids, or water across the phospholipid bilayer to meet the cell's needs. ATPase using energy from ATP hydrolysis pumps against concentration gradients and aids transport of ions or small molecules across the membrane. Channel proteins across the membrane are fast transporters of ions or water molecules (transport at a rate of ~ 10^8 substrates per second) down their concentration gradients or electrical potential. Transporters which transport ions or small molecules in a specific manner function slowly (approx. 10^2–10^4 substrates per second) and transport a few substrates at a time. Alteration of transporter conformation by substrate binding specifies substrate transport across the membrane [28].

More than 50 transport processes and 30 or more metabolite transporters which transport different metabolite substrates across the mitochondria have been discovered. Various metabolite transporters which shuttle different metabolites/substrates include (i) Pi carrier/Pi/H^+ compensated carrier (transports inorganic phosphate into matrix of mitochondria [30], (ii) ATP/ADP carrier [31]; (iii) citrate/malate antiporter (transports citrate across mitochondria [32]; (iv) malate/aspartate shuttle (regulates 2-oxoglutarate movement across membrane [33]; (v) fumarate/malate or fumarate/Pi translocators (shuttles fumarate across membrane [34]; (vi) pyruvate/malate, glutamine/malate, and D-lactate/malate carriers (transport malate across the membrane [35]; (vii) proline/glutamate translocator and glutamate/OH- carrier (transports proline or glutamate across the membrane [29]; and (viii) carnitine-acylcarnitine translocase (translocates fatty acyl-CoA across mitochondrial membrane. Ferroportin, frataxin, dimetal transporters (DMT), and ABC transporters are the other major transporters recognized at the mitochondrial membrane [36–39]. These transporters shuttle metabolites and cofactors such as the Fe-S cluster complex across the mitochondrial membrane.

Mitochondrial ABC transporters in normal and diseased heart

Seventeen ATP-binding cassette (ABC) transporters (ABCA2, ABCA3, ABCA5, ABCA6, ABCA8-10, ABCB1, ABCB6, ABCB7, ABCB9, ABCB10, ABCC5, ABCC8, ABCC9, ABCF1, and ABCG2) have been identified to function in the human heart. These transporters in the heart have various functions such as drug efflux, cholesterol/lipid transport, cofactors/iron transport, and biosynthesis of the iron-sulfur cluster and heme [39, 40]. ABCB6, ABCB7, ABCB8, and ABCB10 are inner mitochondrial membrane transporters known to regulate iron transport across the mitochondrial membrane. These transporters regulate heme and Fe-S cluster biosynthesis as well in mitochondria [39–42]. Heme and iron act as cofactors for multiple biochemical pathways such as Fe-S cluster assembly, tricarboxylic acid (TCA) cycle, oxidative phosphorylation process, and nucleotide biosynthesis [43, 44]. In addition to mitochondrial ABC transporters, frataxin and mitoferrin are the other transporters which regulate iron transport and utilization in the mitochondria of cardiomyocytes [45, 46].

In the mitochondrion, ABCB6 is localized in the outer membrane. ABCB6 regulates porphyrin transport across mitochondrial membranes; its function in other locations such as the Golgi complex and the endoplasmic reticulum is not known. ABCB6 knockout in mice results in impaired porphyrin import across the mitochondria. ABCB6 also export porphyrin across the plasma membrane and loss of ABCB6 results in porphyrin accumulation at the plasma membrane [47–51]. An ABCB6 loss in ferrochelatase knockout mice results in protoporphyrin IX accumulation indicating its role in porphyrin transport. The role of ABCB6 in cardiac metabolism has not been deeply investigated. Porphyrin is an essential component of heme or hemoglobin and heme-containing enzymes such as cytochrome P450, which are important molecules of cardiac metabolism [52, 53]. It will hence be interesting to investigate the role of ABCB6 in metabolic remodeling in the failing heart.

The Fe-S cluster assembly is an essential component of multiple mitochondrial and cytosolic enzymes and regulates diverse metabolic pathways in the cell. ABCB7 is an inner mitochondrial membrane transporter which regulates heme

and Fe-S cluster biosynthesis. Human ABCB7 and its ortholog Atm1p in the yeast export mitochondrial metabolites required for cytosolic Fe-S cluster proteins. Mutation of ABCB7 in humans contributes to X-linked sideroblastic anemia with ataxia and developmental hypoplasia in the cerebellum [54–60]. Conditional deletion of exons 9 and 10 in the ABCB7 gene in mice results in accumulation of mitochondrial and cytosolic iron, impaired synthesis of cytosolic Fe-S cluster enzymes, reduced mitochondrial ETC complex II and complex IV activity, and increased expression of ferritin and transferrin receptor in hepatocytes. These mice also have significantly reduced expression and activity of IRP1/2 proteins, the regulators of iron metabolism [61]. We have noted that in severe cardiac hypertrophy, the expression of ABCB7 decreases and is associated with the accumulation of lipid or fatty acid intermediates in the hypertrophied heart. ABCB7 downregulation results in impaired mitochondrial function in hypertrophic cardiomyocytes (Vikas Kumar et al. unpublished observations 2018).

ABCB8, an iron exporter present at the inner mitochondrial membrane, is involved in iron export from mitochondria to cytosol. Deletion of ABCB8 in mice results in iron overload in the mitochondria, induces production of reactive oxygen species (ROS) in mitochondria, decreases ETC complex activity, and reduces the activity of cytosolic enzymes such as xanthine oxidase and glycerol-3-phosphate in the heart. An ABCB8 loss in mice impairs left ventricular function and leads to cardiomyopathy [62, 63]. In contrast to ABCB10, ABCB8 facilitates export of multiple substrates including K^+, iron, glutathione (GSH), and doxorubicin from mitochondria. Downregulation of ABCB8 in cells results in the accumulation of doxorubicin and its metabolites in mitochondria leading to the generation of free radicals and oxidative stress. Earlier, activation of the K^+ATP channel was considered as the basis for the cardioprotective action of ABCB8.

ABCB10 is an inner mitochondrial membrane transporter and is known to regulate iron import. It has been observed that deletion of the ABCB10 gene results in embryonic lethality in mice at the 12.5th day. These mice were found to be anemic at the 10.5th day [64]. Leisa et al. investigated the role ABCB10 in the heart and found that ABCB10$^{+/-}$ mice hearts have normal systolic and diastolic functions, unaltered superoxide/H2O2 levels, and normal mitochondrial function. When these animals are subjected to ischemic-reperfusion injury, progressive heart failure was observed [65]. This observation indicates a cardioprotective function of ABCB10. ABCB10 physically interacts with mitoferrin-1/2 and ferrochelatase, the mitochondrial iron transporters, and, in turn, regulates iron levels across the mitochondria in hematopoietic cells [66, 67]. Its role in heart failure has not yet been unraveled.

ABC transporters especially ABCB7, ABCB8, and ABCB10 maintain iron levels in mitochondria by regulating iron uptake and transport across the mitochondria. ABCB6 and ABCB7 also have a protective role against oxidative stress [68]. It would be interesting to investigate their function during aging-associated cardiac dysfunction for which oxidative stress is a major contributing factor.

Therapeutic drugs used for the treatment of cardiovascular diseases such as digoxin, statins, carvedilol, aspirin, and clopidogrel are known to interact with ABC transporters. Interaction of these transporters with cardiovascular drugs results in variable dose-response, bioavailability, and elimination of the drugs [40, 69].

Mitochondrial transporters thus play an important role in cardiac metabolism (Fig. 1).

Role of mitochondria in metabolic switch during heart failure

The heart is the most metabolically active organ of the body. Uninterrupted and synchronized cardiac contraction and relaxation require an abundant supply of ATP (approx. 8% of total ATP generated per day) from mitochondria. An abundance of mitochondria in the normal heart makes the heart an energy-sufficient organ even under conditions of workload [4, 70, 71]. Mitochondrial homeostasis is thus vital to a bioenergetically efficient function of the heart. The prenatal heart which survives under hypoxic conditions, utilizes anaerobic glycolysis as a source for ATP. Mitochondrial biogenesis, quality control mechanisms, and OXPHOS-mediated ROS level increases immediately after birth in response to changes in the environment [72, 73].

Under intense exercise or mechanical workload, glucose oxidation instead of fatty acid oxidation is recognized as the predominant fuel source for the adult heart [73]. Switching the fuel source from fatty acids to glucose is a compensatory response by the heart to adapt to high workload since carbohydrates are considered as a highly efficient source of ATP per mole of O_2 utilized (approximately 30% higher than fatty acids) [70–76].

Alterations in mitochondrial metabolism are a major hallmark of heart failure in patients. Paolisso G and colleagues demonstrated for the first time, metabolic alterations in patients with congestive heart failure (CHF). They found that in patients with CHF, fasting glucose oxidation and non-oxidative glucose metabolism are decreased in the heart. There was a simultaneous increase in lipid oxidation [77]. Though Rimbaud S and colleagues had observed that there are no unique metabolic alterations linked to physiological and pathological stimulus-induced hypertrophy, there is wide recognition that during pathological cardiac hypertrophy, myocardium adapts to a more efficient energy source such as carbohydrates [78]. The normal adult heart under acute cardiac stress such as pacing and exercise also increases its

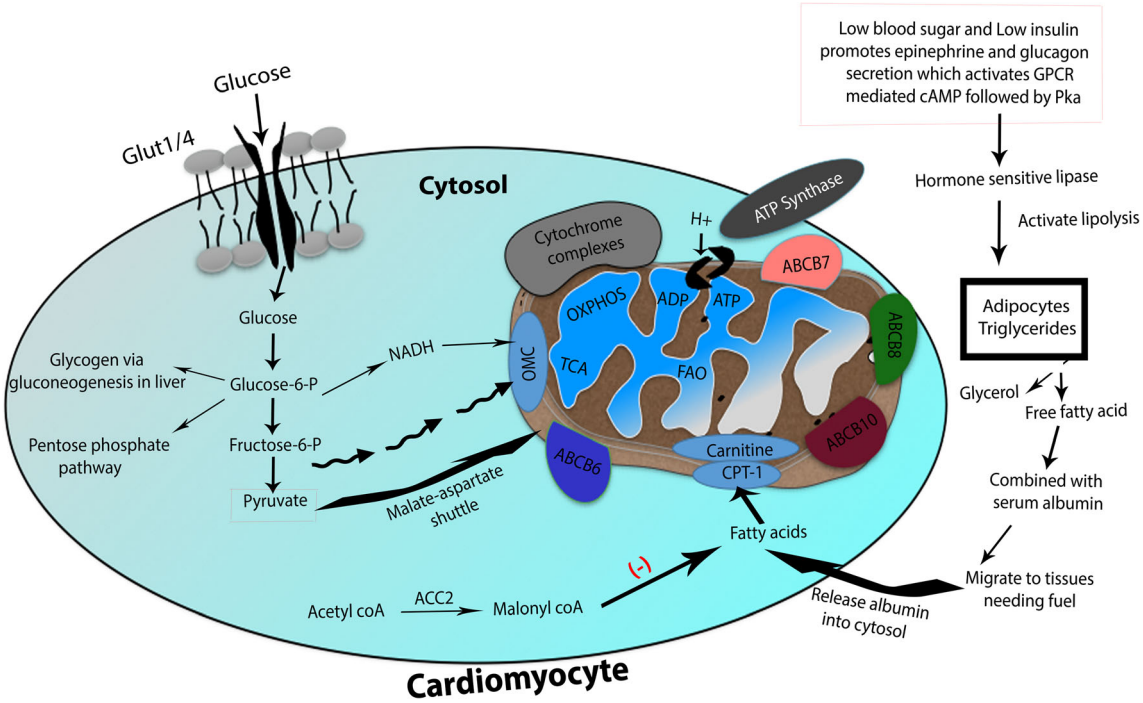

Fig. 1 Role of membrane transporters in cardiac metabolism. Glucose (absorbed from dietary sources) is taken up into cells through glucose transporters 1/4 (Glut1/4) which are localized at the plasma membrane. Glucose then either gets oxidized through the glycolysis pathway to generate ATP/NADH along with pyruvate/lactate or stored as glycogen or utilized by pentose phosphate pathway. NADH, an electron carrier, is then transported into mitochondria by oxaloacetate-malate carrier (OMC) and utilized by cytochrome complexes which enable ATP synthase to produce ATP through oxidative phosphorylation (OXPHOS) pathway. Pyruvate is transported into mitochondria by malate-aspartate shuttle and gets utilized in tricarboxylic acid (TCA) cycle which generates NADH and $FADH_2$. Fatty acid (fatty acyl-CoA) uptake into mitochondrial matrix occurs through carnitine and carnitine palmitoyltransferase I/II carrier molecules. Fatty acyl-CoA molecules undergo beta-oxidation in mitochondria which generate acetyl CoA, which is then utilized by TCA cycle to generate ATP. Mitochondrial ABC transporters localized at the mitochondrial membranes include ABCB6 (at the outer mitochondrial membrane), ABCB7, ABCB8, and ABCB10 (at the inner mitochondrial membrane) and they regulate iron transport, porphyrin synthesis, Fe-S cluster biosynthesis, levels of reactive oxygen species in mitochondria, and metabolism across mitochondria

uptake of glucose and lactate with a decline in the uptake of fatty acid [79, 80].

A decrease in free fatty acid (FFA) uptake and utilization and an elevated glucose uptake have been reported in patients with dilated cardiomyopathy (DCM) as well. Glucose oxidation is not altered in these patients during pacing, in contrast to the increase in glucose oxidation after pacing in normal individuals. Switching from FFA utilization to glucose oxidation is a compensatory response under acute stress which can be deleterious for the heart under moderate stress leading to further deterioration of heart function and to cardiac failure [80].

Using 14(R, S)-[^{18}F]fluoro-6-thia-heptadecanoic acid ([^{18}F]-FTHA), a fatty acid metabolic tracer and [^{18}F] fluoro-2-deoxy-glucose ([^{18}F] FDG) positron emission tomography scans and echocardiographic analysis of patients with heart failure, myocardial free fatty acid uptake, and glucose uptake have been measured. A decrease in myocardial FFA uptake and lower levels of fatty acids were observed in patients with heart failure [81].

Angiotensin II and noradrenaline release are increased in heart failure patients and are reported to decrease oxidative metabolism and impair glucose oxidation. Angiotensin II increase also results in decreased fatty acid oxidation in patients with heart failure [82, 83]. There is however a decrease of 30–40% of total myocardial ATP content and 50–70% of the total creatine pool decreases in failing hearts when compared with normal adult hearts [84, 85].

In one of the earliest studies on cardiac metabolism, Wittlels B et al. demonstrated an impaired palmitate oxidation and decreased carnitine concentration in failing hearts of guinea pigs which had cardiac hypertrophy after banding of the aorta [86]. A decrease in carnitine availability suppresses uptake of fatty acids into mitochondria for a subsequent cycle of oxidation. Wittlels and colleagues did not however discuss glucose metabolism in failing hearts.

Myocardial carnitine palmitoyltransferase 1 (CPT-1) activity is decreased and triglycerides (TG) content is increased in dogs with cardiac failure induced by coronary microembolism [87]. Fatty acid utilization (FAU) increases in rats with cardiac hypertrophy induced by treadmill exercise training–induced hypertrophy. FAU is seen as well to decrease in pregnant (18–19 days of gestation) and spontaneously hypertensive rats (SHR) with cardiac hypertrophy [88].

Compensatory hypertrophy does not involve alterations in citrate synthase, mitochondrial complex I, and cytochrome oxidase function and mitochondrial biogenesis process in the heart while all these are decreased in pathological cardiac hypertrophy [76]. In a recent study, Cannon MV et al. found a decreased glucose uptake and decreased GLUT1 and GLUT4 expression in mice which had aortic constriction induced hypertrophy. These mice also had LXRα deficiency and decreased mitochondrial oxidative phosphorylation capacity and thus an impaired metabolism. LXRα overexpression in hypertrophic hearts of mice results in increased glucose uptake, as well as increased expression of GLUT1 and GLUT4 expression. LXRα overexpression does not however significantly alter hexokinase 2 (the enzyme that catalyzes phosphorylation of glucose), pAMPK (key metabolic regulator under cardiac work), and CD36 (the fatty acid transporter at mitochondrial membrane) proteins in hypertrophic hearts of animals with trans-aortic constriction [89].

We also found a significant decrease in mitochondrial fatty acid oxidation and oxidative phosphorylation in hearts of rats which had cardiac hypertrophy following aortic constriction. Expression of the regulatory enzymes of the glycolysis pathway was not significantly different in hypertrophic hearts when compared with the hearts of sham-operated animals (Vikas Kumar et al. unpublished observations 2018).

It is thus evident that the homeostasis of cardiac metabolism is impaired during pathological cardiac hypertrophy and cardiac failure. Mitochondrial dysfunction such as decreased oxidative capacity of electron transport chain (ETC), downregulated expression of ETC proteins and their super complex assembly, metabolic alterations such as decreased fatty acid oxidation and utilization, and uncoupling of glycolysis to glucose oxidation deteriorate the energy efficiency of the heart affecting the contraction-relaxation cycle and thus contribute to heart failure.

Role of mitochondrial membrane transporters in the metabolic switch associated with cardiac dysfunction

Several studies have provided evidence for the role of mitochondrial membrane transporters in the metabolic switch associated with different cardiac pathological conditions [90]. The role of mitochondrial membrane transporters in remodeling of metabolism during cardiac failure however has not been adequately investigated.

ADP/ATP translocase or ANT1 (adenine nucleotide translocase, an isoform of ADP/ATP carrier) deficiency and associated decreased transportation of ADP and ATP across inner mitochondrial membrane have been linked to deterioration of cardiac function. ANT1 overexpression in hearts results in improved cardiac output and decreased cardiac hypertrophy and fibrosis in rats with renin-induced hypertension. Ejection fraction remains unaltered in these animals. ANT1 overexpressed animals have an increased activity of mitochondrial complexes II and IV. The deficiency of complex III and V activity induced by renin over expression is prevented by ANT1 over expression. After ANT1 overexpression, a decrease in apoptosis of myocytes decreased the release of caspase 3, increased mitochondrial DNA copy number, and improved survival rate are all observed in rats with renin-induced hypertension. ANT1 overexpression also reduces MPTP opening, and TGF-β treatment induced an apoptotic response in cardiomyocytes [91].

Carnitine/acylcarnitine translocase maintains the fatty acid oxidation process in mitochondria by regulating the transport of cytosolic fatty acyl-CoA into the mitochondrial matrix. Deficiency of this translocase in the mitochondria results in an impaired fatty acid oxidation pathway, the major energy source in the adult heart [92, 93].

In a recent study, Gibb et al. investigated in mice the effect of exercise on cardiac metabolism. A single bout of exercise for 40 min resulted in a decreased glycolytic rate and increased glycogen content in the hearts of mice. These changes were correlated with decreased phosphofructokinase-2 (PFK2) activity in the heart. A cardiac-specific kinase (PFK2)-deficient mice when subjected to chronic exercise have decreased glycolytic rate and adaptive hypertrophic changes in the heart. Increased PFK2 activity, however, increases the glycolysis flux and enhances pathological changes in phosphatase-deficient mice heart. Alteration in PFK2 activity seems to lead to metabolic inflexibility (low rate of glycolysis activates transcriptional genes regulating cardiac growth) and mitochondrial dysfunction [94]. In this context, it would be interesting to investigate the relationship among glycolytic flux, PFK activity, and mitochondrial membrane transporters.

In addition to the protein or metabolite transport machinery discussed above, mitochondria also have a well-organized transport system for maintaining the homeostasis of cofactors or transition metals (iron, copper, zinc, chromium, cobalt, and manganese) across the mitochondrial membrane, both in the matrix and cytosolic compartments of the cell [95]. These transition metals with their ability to transition between oxidation and reduced states catalyze the rigorous metabolic reactions in cardiomyocytes. Cellular and systemic levels of these metals must be regulated and tightly controlled; deficiency or overload of free metals/metal ions can result in the production of reactive oxygen species, an impaired quality control mechanism, and ultimately cell death [95]. Transition metals especially iron, copper, and manganese act as cofactors for multiple metabolic pathways such as glycolysis, TCA cycle, fatty acid oxidation, and oxidative phosphorylation.

Iron homeostasis is important for maintenance of normal cardiac function. Imbalance in iron levels or free iron levels catalyzes the generation of reactive oxygen species leading to

mitochondrial dysfunction and heart failure. Cellular iron is utilized for iron-sulfur cluster assembly and for heme biosynthesis which are essential components of several mitochondrial or non-mitochondrial enzymes such as electron transport chain complexes I, II, III, IV (enables ATP synthase to produce ATP in mitochondria), aconitase, citrate synthase (catalyzes TCA cycle and produces reducing equivalent NADPH into the mitochondria), ferrochelatase, and xanthine oxidase (cytosolic Fe-S cluster enzyme) [96]. Iron metabolism is thus important for homeostasis in the cell and specific regulatory mechanisms maintain the balance in the levels of iron (free/bound state). Two iron regulatory proteins (IRP1 and IRP2) bind to the iron response element (IRE) region of the transcripts of classic iron transporters such as ferroportin, transferrin, and ferritin and non-classical iron transporters, i.e., L-type calcium channels and regulate iron levels in the heart [39, 97]. IRP1/2 deficiency in cardiomyocytes results in enhanced expression of ferroportin, ferritin, and reduced expression of transferring receptor in transgenic mice. IRP deficiency in mice is also associated with impaired iron homeostasis, decreased respiratory capacity, increased ATP demand, and enhanced expression of ABCB7 in cardiomyocytes, predisposing the animals to develop cardiac failure when the animals are exposed to dobutamine challenge or when they have myocardial infarction [39]. Both iron overload and iron deficiency can lead to cardiomyopathy [97–100]. The mechanism of iron regulation (iron uptake and utilization) in the hemodynamically stressed heart is under-explored.

Copper is another active redox metal which transitions between reduced Cu^{1+} and the oxidized form Cu^{2+}. In mitochondria, copper acts as an essential component of ETC complex IV or cytochrome oxidase and deficiency of copper in the cell has been linked with defects in cytochrome oxidase subunit transport across the mitochondria [101]. Several studies have found that copper deficiency is associated with increased ROS, oxidative damage, impaired mitochondrial membrane function, and reduced mitochondrial biogenesis and cardiomyopathy [102]. Copper deficiency induced by dietary restriction is associated with lipid accumulation, mitochondrial dysfunction, and cardiac hypertrophy in mice whereas copper repletion rescues these changes in cardiomyocytes [102–105]. Copper-specific transporter has not been to date identified in mitochondria. The role of copper regulators and copper transporters in the metabolic switch in heart diseases also warrant scrutiny.

Trace metal manganese is an essential component of MnSOD/SOD2 and pyruvate carboxylase enzymes in mitochondria. Manganese also maintains the integrity and energy production function of mitochondria through regulation of Mg^{2+}- and Ca^{2+}-dependant mitochondrial enzymes. Mn accumulation contributes to mitochondrial dysfunction. MnSOD, an essential antioxidant enzyme, is requisite to neutralize raising ROS levels [106, 107]. $MnSOD^{+/-}$ mice have enhanced levels of mitochondrial ROS, decreased complex I activity, and increased number of dead cardiomyocytes [108]. Increased mitochondrial respiration, enhanced mitochondrial complex activity, and increased contractility of cardiomyocytes have also been observed in $MnSOD^{+/-}$ mice with type 1 diabetes [109]. Manganese is considered to be transported by proteins such as divalent metal transporter (DMT1) and transferrin receptor (TfR) which transport Fe^{2+} and Ca^{2+} across mitochondria [110]. Specific Mn transporters have not been identified.

Current treatment strategies to improve cardiac metabolism in heart failure

Standard strategies for treatment of heart failure which include clinical use of ACE inhibitors, angiotensin receptor blockers, beta-blockers, and a combination of beta-blockers with ACE inhibitors improve left ventricular dysfunction in the heart and improve the phenotype in patients with heart failure with reduced ejection fraction (HFrEF) [111]. ACE inhibitors and angiotensin receptor blockers have been shown to improve glucose homeostasis as well as increase glucose uptake and fatty acid oxidation in patients with heart failure. Neurohormonal activation/beta-adrenoceptor activation in chronic heart failure patients has been found to promote lipolysis and thus allow them to use free fatty acid rather than glucose as a substrate for energy production. Beta-blockers alter lipolysis while promoting glucose oxidation and utilization, in patients with heart failure [112, 113].

Trimetazidine, a ketoacyl-CoA thiolase inhibitor, decreases fatty acid oxidation and shifts the energy substrate from fatty acids to glucose in heart and skeletal muscles [114, 115]. In a clinical trial in patients with heart failure, trimetazidine was found to improve glucose homeostasis, phosphocreatine to ATP ratio, and myocardial bioenergetics in the heart [116].

Combinatorial treatment of beta-blockers with ACE inhibitors or central sympathetic inhibitors or moxonidine has been tried in patients with heart failure [117, 118]. Combination strategies have yielded improvement in left ventricular function, increased substrate/glucose availability, and decreased fatty acid uptake, thus enhancing myocardial efficiency in patients with heart failure. This observation prompted the suggestion that trimetazidine can be combined with beta-blockers for a synergistic action to reduce free fatty acid availability in plasma and increase glucose oxidation and thus to produce energy sparing effect in the heart [115, 118]. Similar to trimetazidine, CPT-1 inhibitors such as etomoxir and perhexiline also reduce free fatty acid oxidation and improve cardiac energetics in the hypertrophic heart [118].

We examined the role of Ayurvedic medicine, Amalaki rasayana, on the heart in a pressure overload model of cardiac hypertrophy. In rats which had severe left ventricular

hypertrophy, Amalaki rasayana administration increases exercise tolerance capacity, increases ejection fraction, decreases ROS levels, and improves mitochondrial metabolism. Increase in the expression of the enzymes of fatty acid oxidation and oxidative phosphorylation pathways were observed in rats which were orally given Amalaki rasayana. There was however no alteration in the expression of enzymes of the glycolysis pathway. Amalaki rasayana thus attenuated the adverse changes associated with severe cardiac hypertrophy [119].

Thus, there is evidence to indicate that the deficiency of energy in the severely hypertrophic heart and in failing hearts can be corrected in several ways. Maintaining the balance between substrate accumulation and utilization and improving cardiac energetics by manipulation of cardiac energy metabolism is an adjunctive strategy in the management of patients in heart failure.

Mitochondrial ABC transporters as possible therapeutic targets in cardiac failure

Impaired utilization and accumulation of fatty acids and glucose substrates are known to occur in the heart during cardiac failure. Dyssynchrony of glycolysis and decreased efficiency of oxidative phosphorylation process have also been observed in the failing heart. In addition to glucose and fatty acid metabolism, iron metabolism, electron transport chain (ETC) activity, and reactive oxygen species levels are critical for maintenance of mitochondrial function in the normal and pathological hearts [120]. Increased glycolytic flux, iron overload/deficiency, impaired iron utilization, and increased oxidative stress are present in the failing heart. Mitochondria encode for only a few protein subunits of the ETC cycle. The organelle has several transport systems for importing the rest of the amino acids, proteins, metabolic substrates, and metabolites.

ABC transporters in mitochondria are important for regulating iron homeostasis, iron-sulfur cluster assembly (which constitutes protein subunits of ETC), and oxidative stress. ABCB6 ubiquitously expressed in the heart and indirectly regulates the import of protoporphyrin IX/porphyrin into mitochondria. ABCB7 is known to regulate iron-sulfur cluster assembly, heme biosynthesis, and iron homeostasis, and free iron-mediated ROS levels. ABCB7 is ubiquitously expressed in the heart though its role in heart failure has not been investigated.

ABCB8 and ABCB10 are abundantly expressed in the heart and their protective role during ischemia-perfusion injury is recognized. Abrogation or heterozygous deletion of ABCB8 and ABCB10 genes though does not produce alter-

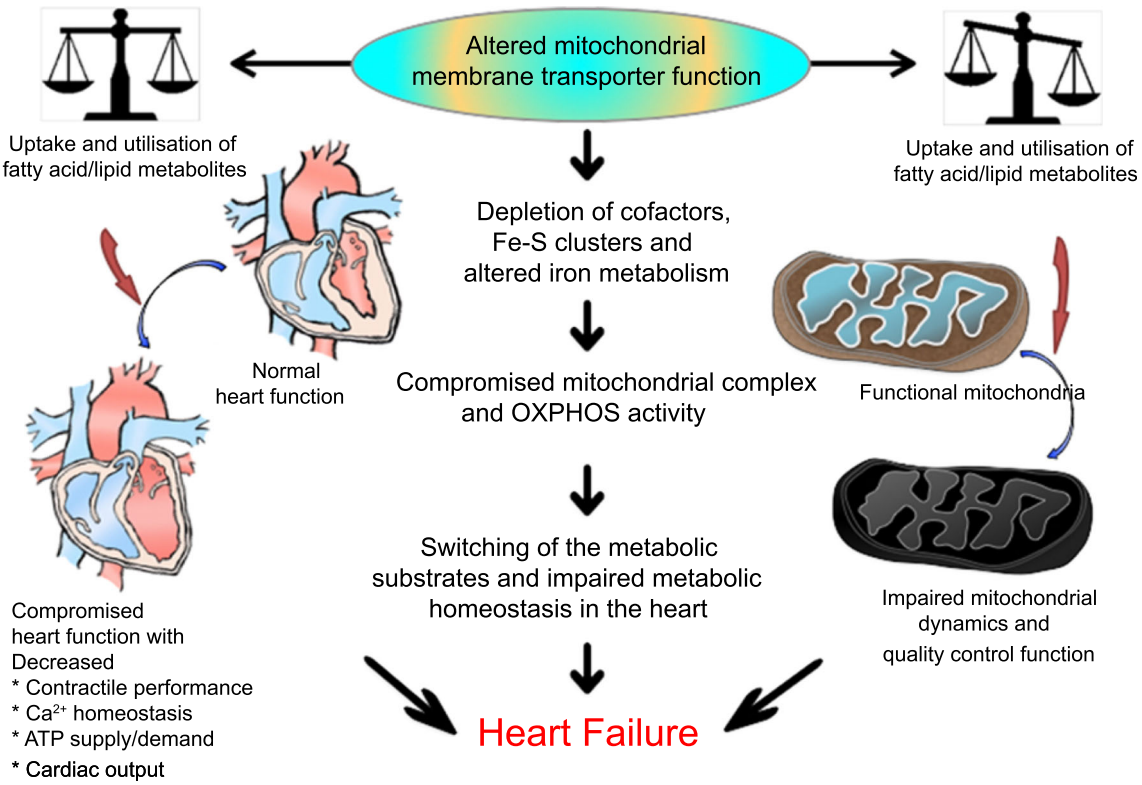

Fig. 2 A schematic diagram of the possible role of mitochondrial membrane transporters especially ABC transporters in heart failure

ations in mitochondrial structure and function in the normal heart; when challenged with ischemia-reperfusion injury, they contribute to diminished mitochondrial biogenesis, impaired ETC activity, decreased total ATP or ATP synthesis, and impaired ROS homeostasis. Whether ABCB8 and ABCB10 have any role in cardiac failure progression is yet to be discerned.

The evidence thus suggest that deficiency of ABC transporters contributes to reduced mitochondrial ETC complex activity, altered mitochondrial dynamics, decreased mitochondrial biogenesis and increased iron overload, lipid accumulation, and increased reactive oxygen species production in the failing heart [59–69]. To what extent dysfunction of mitochondrial ABC transporters contributes to metabolic switch in the heart during heart failure is unknown. Alterations in mitochondrial ABC transporters during heart failure and the role of transporter function in metabolic switch during heart failure have not been adequately investigated. The possible mechanisms through which alterations in mitochondrial membrane transporters could contribute to heart failure are depicted in Fig. 2.

Conclusions

Despite evidence for the dysfunction of mitochondrial ABC membrane transporters in several pathologic conditions of the heart, current therapeutic interventions surprisingly do not target these molecules. We hypothesize that strategies to sustain the function of ABC transporters or reverse the loss of function of ABC transporters can be an adjunct treatment strategy to counter the metabolic inefficiency and mitochondrial dysfunction during cardiac failure. Rescuing the function of ABC transporters could stabilize the mitochondrial ETC complex assembly, maintain mitochondrial membrane potential (by countering the excess ROS and free iron), and also stabilize the activity of other metabolite transporters in the mitochondria of the failing heart.

Acknowledgments We thank the Director, Rajiv Gandhi Centre for Biotechnology, for providing the facilities and funding the study. We thank Ms. Nimmy Francis for the help in the preparation of summary figure and Mr. Aneesh Kumar A for the contribution in the reference style of the manuscript.

Author contributions VK, TRSK, and CCK designed and directed the overall project. VK wrote and drafted the manuscript. CCK revised and edited the manuscript.

Funding We thank the Department of Science and Technology-Science and Engineering Research Board (DST-SERB), Government of India for funding the study. The study was supported by grants (CO/AB/006/2012) from DST-SERB, Government of India and Rajiv Gandhi Centre for Biotechnology (RGCB), Trivandrum, India.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

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