

# Energy metabolism homeostasis in cardiovascular diseases

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<https://doi.org/10.11909/j.issn.1671-5411.2021.12.006>

**ABSTRACT** Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the general population. Energy metabolism disturbance is one of the early abnormalities in CVDs, such as coronary heart disease, diabetic cardiomyopathy, and heart failure. To explore the role of myocardial energy homeostasis disturbance in CVDs, it is important to understand myocardial metabolism in the normal heart and their function in the complex pathophysiology of CVDs. In this article, we summarized lipid metabolism/lipotoxicity and glucose metabolism/insulin resistance in the heart, focused on the metabolic regulation during neonatal and ageing heart, proposed potential metabolic mechanisms for cardiac regeneration and degeneration. We provided an overview of emerging molecular network among cardiac proliferation, regeneration, and metabolic disturbance. These novel targets promise a new era for the treatment of CVDs.

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide. Energy metabolism disturbance is found in various CVDs, such as coronary heart disease, diabetic cardiomyopathy and heart failure (HF).<sup>[1]</sup> Maintaining heart energy homeostasis requires a balance among energy supply, energy expenditure, and substrates selection.<sup>[2]</sup> The heart is a very high energy demanding organ and able to metabolize different substrates including fatty acids (FAs), glucose, lactate, and ketones.<sup>[3,4]</sup> It is well known that 60%–80% of cardiac energy metabolism relies on the FA oxidation (FAO), while 20%–40% on glucose, lactate, and ketones in adult healthy heart.<sup>[5]</sup> “Randle cycle”, first defined in 1960s, also called as “glucose-fatty acid cycle”,<sup>[6]</sup> describes that the adult heart has the ability to switch to different substrates for adenosine triphosphate (ATP) generation depending on feeding, hormonal status, and overall nutritional supply.<sup>[7–9]</sup> Myocardial metabolic phenotype can be defined as the substrate preference by the heart at a given metabolic status (e.g., arterial concentrations of glucose, lactate, FAs, insulin, catecholamines, and oxygen), hemodynamic condition (heart rate, preload, afterload, and coronary blood flow), and inotropic state.<sup>[10]</sup> This phenotype is primarily dependent on the enzymes or transporters that facilitate flux through the metabolic path-

ways, the structure and integrity of key cellular organelles, such as mitochondria.<sup>[10]</sup>

In this article, we summarized lipid-, glucose- and pyruvate-related metabolism in the heart, focused on metabolic regulation during neonatal and the ageing heart, proposed possible metabolic mechanisms for cardiac regeneration and degeneration. We also raised some potential targets for keeping heart young through metabolic regulations.

## LIPID METABOLISM AND LIPOTOXICITY IN THE HEART

There are several key proteins involved in triacylglycerol (TAG) synthesis and catabolism in cardiomyocytes. The cardiomyocyte takes up lipids both from circulating non-esterified FAs and esterified FAs bound to lipoproteins, which are hydrolyzed by lipoprotein lipase in the coronary lumen.<sup>[4]</sup> Released FAs enter the cardiomyocyte mainly through the multi-ligand receptor cluster of differentiation 36 (CD36) and are subsequently converted to fatty acyl-coenzyme A esters by long-chain acyl-CoA synthetases (ACSL).<sup>[11]</sup> CD36 serves as the gatekeeper for FAs.<sup>[12]</sup> Movement of circulating FAs to parenchymal cells requires their transfer across the endothelial cell (EC) barrier. It was reported that EC-CD36-KO mice had reduced uptake of radiolabeled long-chain FAs into the heart.<sup>[13]</sup> The cellular fatty-acid uptake

rate is regulated by the subcellular vesicular recycling of CD36 from endosomes to the plasma membrane.<sup>[14]</sup>

The major fates of these FAs are mitochondrial oxidation or incorporation into triglyceride (TG) for temporary storage. TG synthesis is initiated by glycerol-3-phosphate acyltransferase (GPAT) at the mitochondrial and sarcoplasmic reticulum membrane, hearts from GPAT1-/-mice contained 20%–80% less TG than the wildtype controls.<sup>[15,16]</sup> Then, TG synthesis is completed at the sarcoplasmic reticulum by sn-1-acyl-glycerol-3-phosphate acyltransferase (AGPAT), phosphatidic acid phosphatase, and sn-1,2-diacylglycerol acyltransferase (DGAT) reactions. AGPAT contributes to glycerolipid synthesis and plays an important role in regulating lipid metabolism by regulation of peroxisome proliferator-activated receptor- $\alpha$  (PPAR $\alpha$ ).<sup>[17]</sup> The last step in TG synthesis is catalyzed by DGAT which esterifies the diacylglycerol with a FA. Inactivation of DGAT in adult mouse heart results in a moderate suppression of TG synthesis and turnover. Partial inhibition of DGAT activity increases cardiac FAO.<sup>[18]</sup> The newly formed TAG is packaged into cytosolic lipid droplets, which are coated by scaffolding proteins from the perilipin (PLIN) family. The PLIN family are proteins covering the lipid droplets in adipocytes that regulate the coordination of lipid storage and utilization.<sup>[19]</sup> It was found that cardiac PLIN2 and PLIN5 played an important role in the development of dynamic steatosis.<sup>[20,21]</sup>

TG catabolism is performed by a cascade of lipolytic reactions that is initiated by adipose triglyceride lipase (ATGL) in conjunction with its coactivator protein,<sup>[22]</sup> comparative gene identification-58, while inhibited by a protein called G0/G1 switch protein 2.<sup>[23,24]</sup> Hormone-sensitive lipase (HSL) and monoacylglycerol lipase catalyze the hydrolysis of TAG into diacylglycerol (DAG), as well as DAG into monoacylglycerol. The relative FAs hydrolase activity of HSL is 10-fold greater against DAG than TAG *in vitro*.<sup>[19]</sup> The released FAs during TAG catabolism are mainly used for beta-oxidation and subsequent energy (ATP) production via oxidative phosphorylation (OXPHOS) in mitochondria.

FAs transfer from lipid droplets to mitochondria could be regulated by PLIN5, which physically links these organelles. In addition to FAs entering the

cardiomyocyte, FAs released by lipolysis are also suggested to provide ligands or their precursors for PPAR $\alpha$ , which stimulates the transcription of genes involved in FAO and TAG turnover. Besides lipolysis at the lipid droplets, another potential pathway regulating TAG degradation in cardiomyocytes is TAG hydrolysis by lysosomal acid lipase during the process of autophagy, which is also called “lipophagy”.<sup>[25]</sup>

An imbalance between FA uptake and utilization could result in an ectopic lipid accumulation in the heart. Ectopic lipids can disrupt normal cellular signaling and are associated with cardiomyocyte dysfunction and apoptosis, a process termed lipotoxicity.<sup>[26]</sup> Lipotoxic cardiomyopathy, also known as “obesity cardiomyopathy”, is developed independent of hypertension, coronary heart disease or other heart diseases.<sup>[27]</sup> Clinical findings have consolidated the presence of left ventricular (LV) dysfunction in obesity.<sup>[26]</sup> Indeed, contemporary evidence suggests a wide array of cellular and molecular mechanisms underlying the cardiac lipid metabolism disturbance including abnormal FAs transport, synthesis and catabolism, lipotoxicity, and autophagy/mitophagy defect. Cardiac-specific ACSL1 knockout resulted in a shift from FAO toward glycolysis that promoted mechanistic target of rapamycin (mTOR) complex 1 (mTORC1)-mediated substrate switching from FAs to glucose utilization for ATP generation.<sup>[28,29]</sup> ACSL1 redirected long-chain FAs trafficking to ceramide and restoring acyl-CoA, which delayed progressive cardiac remodeling and HF by mitigating cardiac lipotoxicity.<sup>[30]</sup> Cardiomyocyte-specific ATGL deficiency in adult mice was sufficient to promote fibrosis and hypertrophy, and impair myocardial FAO in the absence of markedly reduced PPAR $\alpha$  signaling.<sup>[31]</sup> Overexpression of ATGL was able to ameliorate myocardial TAG accumulation in diabetes-induced lipotoxic cardiomyopathy.<sup>[32]</sup> MiR-320 acted as a small activating RNA in the nucleus at the level of transcription. It induced the expression of CD36, which was responsible for the increased FA uptake, thereby causing lipotoxicity in the heart.<sup>[33]</sup> Autophagy is essentially involved in the recycling/clearing of the damaged organelles, cytoplasmic contents, and aggregates, which are frequently produced in injured cardiomyocytes.<sup>[34]</sup> Cardiac lipophagy is a special form of autophagy to eliminate lipid droplets in cardiomyocytes.<sup>[26]</sup> Mito-



phagy, autophagy for mitochondria, serves as an essential quality control mechanism for mitochondria in the heart. Impairment of mitophagy induces mitochondrial dysfunction and lipid accumulation, thereby exacerbates lipotoxic cardiomyopathy.<sup>[35]</sup> Deletion of acetyl-CoA carboxylase 2 prevented high-fat diet-induced cardiac lipotoxicity via enhancing cardiac FAO, which is mediated, in part, by the maintenance of mitochondria function through regulating Parkin-mediated mitophagy.<sup>[36]</sup>

## GLUCOSE METABOLISM AND INSULIN RESISTANCE IN THE HEART

Glycolytic substrate is derived from exogenous glucose and glycogen stores in the heart.<sup>[10]</sup> Glucose transporting into cardiomyocytes is regulated by the transmembrane glucose gradient and the content of glucose transporter (GLUT) in the sarcolemma (mainly GLUT4, lesser GLUT1).<sup>[37]</sup> Contraction-induced translocation of GLUT4 to the sarcolemma is essential to stimulate cardiac glucose uptake during increased energy demand. Adenosine monophosphate (AMP)-activated protein kinase (AMPK) and its upstream kinases form part of a signaling axis essential for contraction-induced GLUT4 translocation.<sup>[38]</sup> Phosphofructokinase-1 (PFK-1) is a key regulatory enzyme in the glycolytic pathway. PFK-1 utilizes ATP to produce fructose 1,6-bisphosphate, which is the first irreversible step. PFK-1 is activated by adenosine diphosphate, AMP, and Pi, while inhibited by ATP, fructose 1,6-bisphosphate, and a fall in pH.<sup>[10]</sup> Phosphofructokinase-2 (PFK-2)/fructose 2,6-bisphosphate is a bifunctional enzyme. Synthesis of fructose 2,6-bisphosphate by PFK-2 results in an activation of PFK-1. Cardiac PFK-2 is phosphorylated by various protein kinases, including protein kinase B, insulin and AMPK.<sup>[39]</sup>

Increased glucose uptake drives glycolysis to convert glucose into pyruvate. The mitochondrial oxidation of pyruvate derived from glucose (glycolysis) is a major source of acetyl-CoA for the tricarboxylic acid (TCA) cycle.<sup>[40]</sup> Pyruvate is then taken up by mitochondria through mitochondrial pyruvate carrier (MPC), then oxidized by pyruvate dehydrogenase (PDH).<sup>[41-43]</sup> MPC1<sup>R97W</sup> mutation perturbs pyruvate transport from cytosol to mitochondrial matrix, resulting in fatal hyperlactic acidemia and

hyperpyruvicemia.<sup>[44]</sup> In case of carbohydrate shortage, mitochondria rapidly adapt to changes in energy supply and demand, then alter their capacity for ATP generation.<sup>[45]</sup> Substrates such as pyruvate, succinate, and malate feed into the TCA cycle to supply the electron transport chain for ATP generation. Loss of pyruvate flux into mitochondria led to a reduction in basal and maximal oxygen consumption rate and total cellular ATP levels, as well as an increase in mitochondrial reactive oxygen species (ROS) levels, finally severe cellular bioenergetic crisis.<sup>[46]</sup> Lactate is a common myocardial fuel that can be converted into pyruvate via the enzyme lactate dehydrogenase, and thereby feed the TCA cycle to produce ATP.<sup>[47]</sup> This consumption of lactate is balanced by the concurrent production of lactate from glycolytic pyruvate in healthy human hearts. During HF, glycolytic pyruvate is preferentially converted into lactate, with a simultaneous decrease in lactate consumption, which termed as interruption balance of the pyruvate-lactate axis.<sup>[43]</sup>

Pyruvate decarboxylation is the key irreversible step in carbohydrate oxidation and is catalyzed by PDH, a multienzyme complex located in mitochondrial matrix.<sup>[48,49]</sup> The activity of PDH is largely regulated by its phosphorylation status. The PDH complex can be phosphorylated and inhibited by pyruvate dehydrogenase kinase (PDK),<sup>[50,51]</sup> while it can be dephosphorylated and activated by pyruvate dehydrogenase phosphatase.<sup>[52,53]</sup> The glycolytic pathway converts glucose 6-phosphate and nicotinamide adenine dinucleotide (NAD<sup>+</sup>) into pyruvate and nicotinamide adenine diphosphate hydride, and generates two ATP for each molecule of glucose, which reduces equivalents for ATP production in the heart. The pyruvate formed from glycolysis has three main fates: conversion to lactate, decarboxylation to acetyl-CoA, or carboxylation to oxaloacetate or malate.<sup>[53]</sup>

Plasma ketone bodies are formed from FAs in the liver, and normally a minor substrate for the myocardium because of the low concentration. During starvation or poorly controlled diabetes mellitus (DM), plasma ketone body concentrations are elevated secondary to low insulin and high FAs, and they become a major substrate for the myocardium.<sup>[54,55]</sup> As with FAs, the uptake and oxidation of glucose and lactate are inhibited by elevated plasma ketone



bodies via PDH.<sup>[10,56]</sup> Oxidation of ketone bodies inhibits myocardial FAO.<sup>[40]</sup> Diabetic myocardium has a high rate of beta-hydroxybutyrate uptake and relatively low rate of FAs uptake,<sup>[54]</sup> suggesting that elevated plasma ketone concentrations can inhibit FAs uptake and oxidation in patients with DM. The FAO contributes the greatest amount to total cardiac ATP production, followed by the oxidation of carbohydrates. HF turns the heart into an “energy-starved” state and induces profound alterations in energy use. Mitochondrial OXPHOS decreases, and glycolysis is uncoupled from glucose oxidation, leaving the heart in an energy-deficient state which increasingly relies on glycolysis as a source of ATP.<sup>[57]</sup> Ketone bodies can serve as an additional energy substrate for the heart. They were first recognized as an important fuel for the heart in the 1930s.<sup>[58]</sup> Alongside FAs, glucose, and lactate, it is now evident that ketone bodies can even become a significant source of fuel for the heart.<sup>[59,60]</sup>

Insulin resistance is defined as the impaired ability of cells to take up glucose from the bloodstream in response to insulin.<sup>[61]</sup> Substrates are likely to switch to metabolites from increased lipolysis, hepatic lipogenesis, and hepatic gluconeogenesis.<sup>[62]</sup> Insulin signaling in the heart plays an important role in modulating cardiac preference for the primary oxidative substrates, mainly glucose and FAs, while myocardial utilization of the minor oxidative substrates ketones and amino acids, are not directly regulated by insulin.<sup>[63]</sup> Insulin causes a switch in cardiac energy substrate preference, by stimulating glucose oxidation and inhibiting FAO.<sup>[53]</sup> Insulin indirectly stimulates glucose oxidation via increasing glucose uptake and subsequent glycolysis that enhances pyruvate supply for mitochondrial glucose oxidation by PDH complex, the rate-limiting enzyme of glucose oxidation.<sup>[64]</sup> Insulin also directly inhibits cardiac FAO via eliminating the inhibitory effect of 5'-AMPK on acetyl-CoA carboxylase and increasing malonyl-CoA, a potent inhibitor of mitochondrial FAs uptake.<sup>[53,65]</sup> There are two key pathways in cellular insulin signaling, one involves insulin receptor substrate 1, phosphatidylinositol 3-kinase (PI3K)-protein kinase B (also known as AKT), the other involves signal transduction via mitogen-activated protein kinase (MAPK). In the past few years, our laboratory revealed that epoxyeicosatri-

enoic acids, metabolites of arachidonic acid metabolized by cytochrome P450 epoxygenases, prevented fructose-induced decreases in insulin receptor signaling (PI3K-AKT and MAPK pathway) in the heart and the aorta.<sup>[66]</sup>

However, myocardial substrate overload decreases substrate oxidation, leading to metabolic maladaptation and myocardial dysfunction through lipo- and glucotoxicity. Several cellular pathways have been implicated in the adverse effects of high glucose in the heart, such as oxidative stress, accumulation of advanced glycation end-products, and chronic hexosamine biosynthetic pathway (HBP) activation. Glucotoxicity impaired the vascular regenerative cell during the progression of type 2 DM (T2DM), which termed as “regenerative cell exhaustion”.<sup>[67]</sup> Maintaining or increasing GLUT4 expression in the context of DM enhances glycolytic function, but exacerbates the decline in glucose oxidation, prevents the increase in FAO, and accelerates the decline in mitochondrial OXPHOS capacity. These changes were associated with post-translational modifications, i.e., O-linked-N-acetylglucosaminylation (O-GlcNAcylation), of mitochondrial proteins and transcription factors that would predict mitochondrial impairment.<sup>[68]</sup> In the heart, chronic activation of the HBP in the heart with DM affects Ca<sup>2+</sup> handling, contractile properties, and mitochondrial function, which promotes stress signaling, such as LV hypertrophy and endoplasmic reticulum stress. Excessive O-GlcNAcylation is a major trigger of the glucotoxic events that affect heart function under chronic hyperglycemia. Recently, it was revealed that sodium-glucose cotransporter 2 inhibitors (SGLT2i) dapagliflozin, a glucose lowering agent, could lower cardiac HBP and improve the cardiac diastolic dysfunction in a mice model with lipodystrophic T2DM.<sup>[69]</sup>

## METABOLIC REGULATION DURING NEONATAL

The heart is a metabolic “omnivore”. The adult heart selects the substrate best suited for each circumstance. FAO preference is to fulfill the high energy demand of myocardium contraction. The fetal heart exists in a hypoxic environment and obtains energy via glycolysis. After birth, the “fetal switch”





to oxidative metabolism of glucose and FAs has been linked to the loss of the regenerative phenotype.<sup>[45]</sup> During the first stages of development, the embryo uses pyruvate as the main energy substrate and glycolysis is undetectable.<sup>[70]</sup> When advancing to the blastocyst stage, oxygen consumption rapidly increases along with glycolysis, while the consumption of pyruvate decreases in subsequent stages. The switch to glycolytic metabolism leads to the restoration of oxygen consumption to normal levels. Fetal cardiomyocytes are highly rely on glycolysis for ATP production, lactate are available for energy production via lactate oxidation as well.<sup>[71]</sup> Especially, immediately after birth, the main energy source is still on glycolysis.<sup>[72]</sup> After alteration of dietary maternal milk and normoxia circumstances, substrates switch from glycolysis-dependence to predominantly FAO in cardiomyocytes.<sup>[73]</sup> Additionally, it was indicated that breast milk, which contained lipids that could not transfer across the placental barrier during prenatal development might also contribute to the substrate availability, and composition change after birth.<sup>[74]</sup> The switch to OXPHOS allows more energy to be spent in order to produce a more efficient contraction of the heart.<sup>[75,76]</sup>

Hypoxia-inducible factor 1alpha (HIF-1 $\alpha$ ) is the main regulator of responses to hypoxia.<sup>[77]</sup> HIF-1 signaling directly or indirectly targets several genes, which are responsible for the switch from OXPHOS to glycolysis. Physiologic hypoxic regions occur in normally developing embryos, especially in the developing neural tube, heart, and intersomitic mesenchyme.<sup>[78]</sup> There are a number of oxygen sensing pathways, such as the energy and nutrient sensor mTOR, and the nuclear factor kappa B transcriptional response, and the HIF-1 transcription system.<sup>[79]</sup> The shift in metabolism might be not only time dependent, but also tissue specific. At mid-gestation, HIF-1 $\alpha$  is expressed in the compact myocardium but not in the trabeculae,<sup>[80]</sup> which leads to a metabolic shift from glycolysis in the compact myocardium whereas oxidative metabolism increases in the trabeculae. The maturation of cardiac oxidative metabolism is completed after birth, an increased amount of oxygen, resulting from decreased HIF-1 signaling, is thought to be the main impulse for the shift. The neonatal beta-myosin heavy chain isoform to adult alpha-myosin heavy chain isoform switch is

probably driven by a decrease in HIF-1 signaling.<sup>[81]</sup> Transcription factor Hand1, up-regulated by HIF signaling, inhibits the expression of a few genes involved in cardiomyocyte lipid metabolism. Hand1 reduces cellular oxygen consumption and cardiomyocyte vulnerability to ischaemia.<sup>[82]</sup> MicroRNAs (miRNAs) represent an additional regulatory mechanism in which HIF-1 $\alpha$  action contributes to development.<sup>[83]</sup> Recently, the miRNA cluster miR-199a and miR-214 was implicated as a mediator that integrates hypoxic signaling and altered mitochondrial metabolism in HF.<sup>[84]</sup> What's more, miR-199a targets both HIF-1 $\alpha$  and Sirtuin-1 (SIRT1), which make it an important regulator of both the cardiac hypoxic preconditioning as well as cardiac metabolism.<sup>[85]</sup>

The above examples indicate a strong link between the hypoxic response and alterations in cardiac energy metabolism. It becomes clear that hypoxia during neonatal facilitates the metabolic shift from FAs utilization in the myocardium. It is accompanied by direct or indirect regulation of HIF-1 $\alpha$  signaling, which serves to fine-tune the balance between FAO versus glucose oxidation and glycolysis.

## METABOLIC REGULATION DURING AGEING

Ageing is able to induce adverse metabolic conditions, such as obesity, DM, insulin resistance and dyslipidemia, which are associated with senescent features of the vascular and the heart. This highlights a dynamic interaction among ageing, metabolism, and CVDs. As to senescent cardiomyocytes, decreased contractility, ventricular enlargement, mitochondrial dysfunction, and telomere shortening negatively affects myocardial function. As these poorly functioning senescent cells accumulate with age, they interfere with intercellular communication, contribute to compromised tissue function, and promote chronic inflammation, lead to cell death and cardiomyocyte loss.<sup>[86,87]</sup>

Metabolic pathways are important regulatory mechanisms controlling senescent cardiac homeostasis. AMPK is a central regulator of key effectors involved in metabolic processes and ageing. The age-related surge of ROS arising primarily from the accumulation of dysfunctional mitochondria causes



nuclear DNA damage.<sup>[88]</sup> It is notable that SIRT proteins have robust functions in modulating cardiac ROS production under I/R stress, which are critical to maintaining redox homeostasis via regulating substrate metabolism and inflammation in ageing.<sup>[89,90]</sup> SIRT1 can significantly activate AMPK via liver kinase B1 (LKB1) deacetylation, thereby ameliorate ischemic injury in aged hearts.<sup>[91,92]</sup> Pharmacological approaches to inhibit SIRT1 have been shown to prevent maladaptive pathways which might promote ageing, and metabolic abnormalities and CVDs.<sup>[93,94]</sup> SIRT1-LKB1-AMPK pathway leads to energy imbalance, cellular stress and activation of the apoptotic machinery, thus contributes to cardiac ageing.<sup>[95]</sup>

mTORC1, the downstream of AMPK, induces autophagy to ensure heart function during fasting, nutrition enrichment and senescence. The vital roles of general and selective autophagy in the setting of cardiac ageing and CVDs make this cellular process highly attractive for developing targeted therapeutic approaches. Calorie restriction (CR), defined as a reduction in food intake without malnutrition, is among the most powerful inducers of autophagy.<sup>[96]</sup> Emerging evidence suggests that activation of autophagy elicits a pro-survival response in cardiomyocytes. Inhibition of mTOR signaling ameliorated laminopathy-based cardiac symptoms through upregulation of autophagy.<sup>[97]</sup> Upregulation of AMPK-mTORC signaling facilitated lipid autophagy in the heart to eliminate cardiac lipid droplets.<sup>[26]</sup> Unfortunately, the adverse effects of pharmacological mTOR inhibitors preclude their development as anti-ageing treatments, although low doses of one rapalogue safely improved immune function in elderly patients.<sup>[98]</sup> A lifelong 40% of CR increased the autophagic flux in the heart of old rats via suppression of mechanistic target of mTORC signaling.<sup>[99]</sup> This suppression was accompanied by reduced myocardial lipofuscin accumulation, decreased cardiomyocyte apoptosis, and preserved of LV diastolic function.<sup>[88,100]</sup>

Peroxisome proliferator-activated receptor co-activator 1alpha (PGC-1 $\alpha$ ) is the central factor of mitochondrial biogenesis and another downstream target of AMPK.<sup>[101,102]</sup> Mitochondrial biosynthesis is featured by normal mitochondrial density, mass, and DNA copy number. Mitochondrial biosynthesis, providing enough energy for cellular metabolism,

can intensify cellular tolerance to harmful stimuli and maintain myocardial homeostasis. In the heart, PGC-1 $\alpha$  is induced at birth to support the metabolic shift in substrate preference from glucose and lactate during the fetal period to FAs after birth.<sup>[103]</sup> Older animals and humans use relatively fewer FAs and more glucose.<sup>[104]</sup> The transcriptional factors, including PPAR $\alpha$ , steroid hormone receptor, the estrogen receptor-related receptor 1, and nuclear respiratory factor 1, are all under the control of PGC-1 $\alpha$ .<sup>[105]</sup> Hydrogen sulfide has been indicated as an important regulator of cardiac mitochondrial content and an inducer of mitochondrial biogenesis via a AMPK-PGC-1 $\alpha$  signaling cascade.<sup>[106]</sup> PGC-1 $\alpha$  promoted mitochondrial and cardiac function in three-month-old wildtype and a third generation of telomerase-deficient mice, but accelerated cardiac ageing and significantly shortened lifespan in twelve-month-old wildtype mice, partially of which due to age-dependent defect in mitophagy.<sup>[102]</sup> Cardiac mitochondriogenesis is a complex nuclear-mitochondrial process that orchestrates both genome transcription and replication.<sup>[107]</sup>

SIRT1-LKB1-AMPK-mTOR/PGC-1 $\alpha$  signaling pathways are crucial for the ageing heart homeostasis, which maintain the balance of mitochondrial biogenesis and clearance of senescent cellular organelle to keep heart young.

## METABOLIC REGULATION DURING DEGENERATION AND REGENERATION

Cardiac degeneration induced HF remains huge threats to health and longevity. Unlike other high-turnover tissues, renascence of cardiomyocytes cannot be realized due to the lack of adult cardiac stem cells in the post-mitotic heart.<sup>[108–110]</sup> It shows that the cardiomyocyte turnover rate is approximately 0.5%–1% per year and almost 45% of cardiomyocytes are renewed throughout the human lifetime.<sup>[111]</sup> The adult mammalian heart lacks regenerative capacity, which is a contributing factor during HF after myocardial injury. However, neonatal cardiomyocytes can proliferate and promote regenerative cardiac repair following injury in rodents and swine.<sup>[112]</sup> In some vertebrates, such as newts and zebrafish, there is a capacity for cardiac regenerative repair and cardiomyocyte proliferation throughout life.<sup>[113,114]</sup>



Myocardial infarction (MI) is the most common CVDs. Patients who suffered from MI usually develop ejection fraction reduced HF. The low rate of myocyte turnover that occurs in the adult heart is insufficient for the reconstitution of cardiac function in injured hearts.<sup>[111]</sup> Recent attempts to restore the injured heart have focused on the development of new strategies to replace fibrotic cells with healthy cardiomyocytes through the activation of cardiomyocyte proliferation or regeneration. Targeting on the mechanisms of cell cycle arrest in the early postnatal period may reverse cell cycle arrest in the adult, which may bring hope to restore cardiac function after myocardial injury.<sup>[102,115]</sup>

The neonatal mammalian heart is capable of regeneration following injury within a brief window of time after birth. Removal of up to 15% of the LV apex of postnatal day 1 mice results in regeneration by postnatal days 21.<sup>[116]</sup> Remarkably, the heart systolic functional of one-day-old mice with ischemic heart disease fully recovers within twenty-one days, because of a robust regenerative response through proliferation of preexisting cardiomyocytes.<sup>[117]</sup> This regenerative response is mediated by proliferation of preexisting cardiomyocytes and is lost when cardiomyocytes permanently exit the cell cycle shortly after birth.<sup>[112]</sup> However, this regenerative capacity lost coincides with a postnatal shift from anaerobic glycolysis to mitochondrial OXPHOS.<sup>[118]</sup> As we know, the energy advantage of FAs beta-oxidation, cardiac mitochondria produce elevated rates of ROS when utilizing FAs. Elevated ROS level is thought to play a role in cardiomyocyte cell cycle arrest through induction of DNA damage and activation of DNA damage response pathway, which thereby trigger activation of a cell cycle checkpoint and arrest of the cell cycle.<sup>[73,119,120]</sup>

Interestingly, the mammalian heart's adaptability to high-concentration oxygen supply is synchronized with the stagnation of cardiomyocyte proliferation. Hypoxia induces a variety of cellular responses including cell proliferation, metabolic changes, and alterations in gene expression. HIF-1 signaling is thought to be the key regulator for the shift. Another important regulator of cardiomyocyte metabolism and proliferation is the Hippo-YAP (Yes-associated protein) signaling pathway, which could promote the glycolysis.<sup>[121]</sup> Wnt-beta-

catenin and ERK-Myc signaling pathways also promote glycolysis as well as induce cell proliferation via upregulation of cyclin-dependent kinase/cyclin complexes in neonatal murine cardiomyocytes or human induced pluripotent stem cell-derived immature cardiomyocytes.<sup>[122]</sup> The pyruvate kinase muscle isoenzyme 2 (PKM2) is a glycolytic enzyme directly interacts with HIF-1 $\alpha$  and acts as a transcriptional coactivator. PKM2 not only directly mediates glucose metabolic flux, but also promotes cardiomyocyte proliferation by binding to beta-catenin and thereby increasing expression of genes for cell cycle regulators such as cyclin D1 and c-Myc in the injured zebrafish heart, as well as the neonatal and adult murine heart.<sup>[123,124]</sup>

In addition to hypoxia, recent studies have revealed that damaged hearts in MI are able to acquire regenerative potential by targeting some key signal pathways that induce cardiomyocytes to re-enter the cell cycle.<sup>[125]</sup> With the adult zebrafish heart regeneration model, Fukuda, *et al.*<sup>[126]</sup> found cardiomyocyte-specific loss- and gain-of-function manipulations of pyruvate metabolism using PDK3 as well as a catalytic subunit of the pyruvate dehydrogenase complex (PDC), which are important in cardiomyocyte dedifferentiation and proliferation after injury. Moreover, PDK regulates glycolysis and pyruvate metabolism of cardiomyocytes of the border area in zebrafish after injury. Loss of PDK4 can increase the proliferation of cardiomyocytes and improve LV function after MI and reduce remodeling.<sup>[119]</sup> PDK activity can modulate cell cycle progression and protrusive activity in mammalian cardiomyocytes in culture (PDK-PDC axis).<sup>[126]</sup> Additionally, mice overexpressing the nuclear receptor PPARbeta/delta can increase the expression of GLUT4 in the myocardium to promote glucose utilization, and significantly reduce myocardial damage caused by I/R injury.<sup>[127]</sup> Pharmacologic and genetic activation of PPAR $\alpha$ -mediated FAs beta-oxidation promoted hypertrophic cardiomyocyte growth and maturation, which induced cytokinesis failure and cell cycle exit. The etomoxir-mediates inhibition of myocardium FA beta-oxidation metabolism enhanced glycolysis and maintained cardiac proliferation in newborn mouse hearts at postnatal days 5 and postnatal days 7.<sup>[128]</sup> Kruppel-like factor 1 (KLF1/EKLF), which is induced in adult zebrafish myocar-



dium upon injury. Myocardial inhibition of KLF1 function severely impairs regeneration.<sup>[129]</sup> Induction of the p53 isoform delta133p53 in cardiomyocytes at the resection site promotes heart regeneration by increasing the expression of antioxidant genes to maintain redox homeostasis.<sup>[130]</sup>

Regeneration and degeneration are two ends of the cardiac homeostasis, which both regulated by energy substrate preferences. Here, we provided an overview of emerging molecular pathways implicated in the interplay between cardiac proliferation, regeneration, and metabolic disturbances. These novel targets might represent a new direction for the treatment of MI and HF over the next decades.

## POTENTIAL THERAPEUTIC STRATEGIES FOR ENERGY DISTURBANCE IN THE HEART

HF is the leading cause of death in patients with CVD, especially in patients with DM. Cardiac energy metabolism disturbance contributes to the severity of HF. Here, we summarized several pharmacological targets of the energy metabolic pathways, which may improve cardiac efficiency, decrease the energy deficit, and improve cardiac function in the failing heart.

Metformin is the first-line drug for the treatment of T2DM. Metformin is primarily used to lower blood glucose, stimulate insulin action, decrease inflammation, and improve myocardial energy metabolism.<sup>[131]</sup> Metformin inhibits respiratory chain enzymes (complex I) in mitochondria, hence decreases ATP production with a parallel increase in AMP. This inhibits glucose synthesis from pyruvate, thereby reduces hepatocytes gluconeogenesis. Furthermore, increased AMP stimulates AMPK, which inhibits acetyl-CoA carboxylase, malonyl-CoA, lipid and cholesterol synthesis.<sup>[132]</sup> Compared to diet alone, in the group of 342 newly diagnosed overweight patients with T2DM treated with metformin, MI was reduced by 39%, coronary deaths was reduced by 50%, stroke was reduced by 41%, and all-cause mortality was reduced by 36% after a median follow-up of 10.7 years.<sup>[133]</sup> A recent systematic review on metformin suggested some beneficial effects, but the overall evidence was not strong enough to make a solid conclusion about metformin decreasing HF severity in patients with DM.<sup>[134]</sup>

Glucagon-like peptide-1 (GLP-1) agonists improve glycaemia control in patients with DM by mimicking GLP-1 action. It lowers blood glucose by increasing insulin and decreasing glucagon release, while further decreasing body weight in T2DM patients.<sup>[61]</sup> These include exenatide (a partial structural analogue of GLP-1), liraglutide, lixisenatide and semaglutide. Liraglutide can protect against diabetic cardiomyopathy by inactivating the endoplasmic reticulum stress pathway. The improvement in cardiac function by liraglutide is independent of glucose control.<sup>[135]</sup> GLP-1 receptor agonist (exendin-4) protects cardiac function by inhibiting the Rho-kinase/PPAR $\alpha$  pathway, thereby ameliorating lipotoxicity in diabetic cardiomyopathy.<sup>[136]</sup> Some of these GLP-1 analogues could reduce the HF risk in patients with DM, as shown by results of multiple phase III/IV large scale double-blind randomized clinical trials. Both the EXSCEL trial and the EXLXA trial showed that GLP-1 analogue could not reduce major adverse cardiovascular event in T2DM patients with a recent acute coronary event.<sup>[137,138]</sup> In contrast, the LEADER trial and the SUSTAIN-6 trial revealed that liraglutide lowered the rate of cardiovascular death, non-fatal MI, or non-fatal stroke in T2DM patients with high cardiovascular risk.<sup>[139,140]</sup>

Dipeptidyl peptidase-4 (DPP-4) inhibitor was used to prevent the cleavage and inactivation of GLP-1.<sup>[141]</sup> It is well known that DPP-4 enzyme deactivates GLP-1, thus DPP-4 inhibition extends the function of endogenous GLP-1.<sup>[142]</sup> Current DPP-4 inhibitors include vildagliptin, sitagliptin, and saxagliptin, which increase insulin secretion from pancreatic beta-cells, improve insulin tolerance and glucose control.<sup>[143]</sup> In addition to the glucose-lowering effects, DPP-4 inhibitors might lower the body weight and blood pressure, improve postprandial lipid status and endothelial function, attenuate inflammation and oxidative stress.<sup>[144]</sup> Unlike sulfonylureas and metformin, DPP-4 inhibitors are metabolized by the portal hepatic circulation, which is not affected by impaired renal function. Therefore, the DPP-4 inhibitors are safe in patients with renal dysfunction, including those on dialysis.<sup>[145]</sup> Five major clinical trials have compared the cardiovascular outcomes associated with DPP-4 inhibitors: SAVOR-TIMI 53 (saxagliptin), EXAMINE (alogliptin), TECOS (sitagliptin), CARMELINA (linagliptin), and CARO-





LINA (linagliptin).<sup>[146–148]</sup> The SAVOR-TIMI 53 showed a significant increase in the rate of hospitalization for HF in T2DM patients treated with saxagliptin.<sup>[149]</sup> However, the EXAMINE trial showed non-inferiority of alogliptin to placebo on major cardiovascular events in patients with DM with recent acute coronary syndrome.<sup>[150,151]</sup> Up to date, increase of HF was not observed in the TECOS, CARMELINA, or CAROLINA, suggesting that sitagliptin and linagliptin may have a neutral side-effect profile on HF hospitalization risk, which need more perspective clinical trial to define.<sup>[152]</sup>

SGLT2i prevent glucose reabsorption in the proximal tubules of the kidney, therefore increasing its secretion into the urine and improving glycaemic control.<sup>[153]</sup> Three SGLT2i were approved for clinical use include empagliflozin, dapagliflozin, and canagliflozin. Recently, large-scale clinical trials have shown cardioprotective benefits independent of its antihyperglycaemic effect in both T2DM and non-DM patients. Three large cardiovascular outcomes trials (CVOTs) have been completed for the SGLT2i in T2DM patients to compare the cardiovascular safety: EMPA-REG OUTCOME (empagliflozin), CANVAS (canagliflozin), and DECLARE-TIMI 58 (dapagliflozin).<sup>[154–156]</sup> All three trials showed non-inferiority for cardiovascular safety results compared to placebo, and in some cases showed impressive reductions in adverse cardiovascular outcomes. Two additional trials, CREDENCE (canagliflozin) and DAPA-HF (dapagliflozin), evaluated alternative primary outcomes of renal events and HF events in patients with chronic kidney disease stage II/III and chronic HF, respectively, and analyzed three-point major adverse cardiovascular event as a secondary endpoint. All five CVOTs reported reduction in hospitalization for HF, including DAPA-HF, which evaluated HF hospitalization and cardiovascular death as a composite primary outcome in patients with baseline chronic HF.<sup>[157]</sup>

## CONCLUSIONS

In this article, we summarized lipid metabolism/lipotoxicity and glucose metabolism/insulin resistance in the heart, focused on the metabolic regulation during neonatal and ageing heart, proposed potential metabolic mechanisms for cardiac regeneration and degeneration. We provided an overview of emerging molecular network among cardiac pro-

liferation, regeneration, and metabolic disturbance. These novel targets promise a new era for the treatment of CVDs.

## ACKNOWLEDGMENTS

This study was supported by the National Natural Science Foundation of China (No.81600236 & No. 82170283 & No.81822002 & No.31771264), the Staff Starting Foundation in Tongji Hospital (2020HGR Y013), and the Fundamental Research Funds for the Central Universities (2019kfyXMBZ035). All authors had no conflicts of interest to disclose.

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**Please cite this article as:** WANG LY, CHEN C. Energy metabolism homeostasis in cardiovascular diseases. *J Geriatr Cardiol* 2021; 18(12): 1044–1057. DOI: 10.11909/j.issn.1671-5411.2021.12.006

