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Cardiac Metabolism and Its Interactions with Contraction, Growth, and Survival of the Cardiomyocte

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Abstract

The network for cardiac fuel metabolism contains intricate sets of interacting pathways that result in both ATP producing and non-ATP producing end-points for each class of energy substrates. The most salient feature of the network is the metabolic flexibility demonstrated in response to various stimuli, including developmental changes and nutritional status. The heart is also capable of remodeling the metabolic pathways in chronic pathophysiological conditions, which results in modulations of myocardial energetics and contractile function. In a quest to understand the complexity of the cardiac metabolic network, pharmacological and genetic tools have been engaged to manipulate cardiac metabolism in a variety of research models. In concert, a host of therapeutic interventions have been tested clinically to target substrate preference, insulin sensitivity, and mitochondrial function. In addition, the contribution of cellular metabolism to growth, survival, and other signaling pathways through the production of metabolic intermediates has been increasingly noted. In this review, we provide an overview of the cardiac metabolic network and highlight alterations observed in cardiac pathologies as well as strategies employed as metabolic therapies in heart failure. Lastly, the ability of metabolic derivatives to intersect growth and survival are also discussed.

Keywords

Cardiac metabolism; cardiac pathology; metabolic signaling; metabolic therapy

Introduction

The mammalian heart must contract incessantly, thus, the requirement for energy to fuel optimal function is immense. As the high energy phosphate storage within the cardiomyocyte is minimal, only sufficient to sustain the heart beat for a few seconds, a tight coupling of ATP production and myocardial contraction is essential for normal cardiac function. Central to the coordinated energy transduction function is the multi-purpose organelle mitochondrion which not only generates more than 95% of ATP utilized by the heart but also regulates intracellular calcium homeostasis, signaling and cell death. While a

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constant supply of substrates through the metabolic network is paramount for mitochondrial conversion of ATP, it is increasingly recognized that metabolites generated by both ATP-producing and non-ATP producing pathways can become critical regulators of cell function. Thus, the importance of substrate metabolism to cardiac pump function is beyond the scope of only modulation of energy supply. In this article, we will provide an overview of changes in cardiac fuel metabolism under pathological conditions followed by recent progress on targeting cardiac metabolism for improving myocardial energetics and function. In addition, we will summarize the emerging role of cardiac metabolism in governing myocardial growth and survival pathways.

Characteristics of Fuel Metabolism in the Heart

The capacity and flexibility of substrate metabolism for ATP production

The heart is capable of utilizing all classes of energy substrates, including carbohydrates, lipids, amino acids and ketone bodies, for ATP production in the mitochondrion (Figure 1, for details see reviews[1-3]). Mitochondria occupy one third of the cell volume in cardiac myocytes making them the cell type with the highest mitochondria content.[4] The robustness of cardiac metabolism is reflected by its highest oxygen consumption rate on the per unit weight basis. For a human heart, the amount of ATP turned over during a one-day period is 15-20 times of its own weight. In a normal heart, mitochondria are largely fueled by fatty acyl-CoA and pyruvate, which are the primary metabolites of fatty acids and carbohydrates, respectively. The entry of long-chain acyl-CoA into the mitochondrion is a regulated process; with the rate-limiting step at the muscle form of the carnitine-palmitoyl transferase I (mCPT-1) reaction. The oxidation of pyruvate is regulated at the pyruvate dehydrogenase (PDH) reaction. Other substrates, including lactate, ketone bodies and amino acids, can enter mitochondria directly for oxidation. Metabolism of ketone bodies yields acetyl-CoA while amino acid catabolism yields keto-acids which are further metabolized to enter the TCA cycle. The contribution of ketone bodies and amino acids to overall cardiac oxidative metabolism is considered to be minor due to the low availability of these substrates under normal physiological conditions.[5-7]

It is widely accepted that fatty acids are the predominant substrate utilized in the adult myocardium. However, the cardiac metabolic network is highly flexible in utilizing other substrates when they become abundantly available (Figure 1). For example, cardiac extraction and oxidation of lactate becomes predominant during exercise as skeletal muscle lactate production increases.[8,9] Prolonged fasting or ketogenic diet increases the blood level of ketone bodies and results in enhanced utilization by the heart.[7] In isolated perfused hearts, the addition of lactate or ketone bodies in the perfusate significantly reduces the oxidation of glucose and fatty acids.[5,10,11] These studies support the concept of metabolic flexibility that confers the advantage of adequately supplying ATP for continual cardiac contraction under a variety of physiological conditions.

Apart from substrate availability, complex regulatory mechanisms contribute to metabolic flexibility at multiple levels, including transcriptional regulation and post-translational modification of key proteins involved in each metabolic pathway as well as allosteric regulation by substrates and their metabolites (Table 1). For example, transcriptional regulation of the proteins involved in fatty acid oxidation (FAO) by the PPAR/ERR/PGC-1 circuit is a major mechanism in the transition of the glycolysis-dependent fetal heart to oxidative metabolism in the adult heart.[12-14] Likewise, transcriptional regulation by HIF1α is responsible for the metabolic adaptation to hypoxic and ischemic conditions.[15] While transcriptional mechanisms contribute to the establishment of the network, post-translational modifications of key enzymes in the metabolic pathways regulate the fluxes. Phosphorylation and inactivation of PDH by pyruvate dehydrogenase kinase 4 (PDK4) plays

a key role in the shift of substrate oxidation between glucose and fatty acid in the heart.[16] The phosphorylation of the branched-chain-α-ketoacid dehydrogenase (BCKD), regulated by BCKD kinase and a mitochondrial localized phosphatase (PP2Cm), governs the oxidation of branch amino acids.[17,18]

Intermediates of glucose metabolism

Although glucose catabolism through glycolysis primarily yields pyruvate for subsequent oxidation, glycolytic intermediates can participate in several additional pathways that do not lend to ATP generation (Figure 2). These pathways are of biological significance in the heart despite the small fluxes. Glucose 6-phosphate (G6P) produced by the hexokinase reaction enters the Pentose Phosphate Pathway (PPP), yielding NADPH during the oxidative phase and 5-carbon sugars in the subsequent non-oxidative phase.[19] The supply of NADPH from the PPP is important for antioxidant defense as NADPH is required for maintaining the level of reduced glutathione.[20] It has been shown that deficiency of G6P dehydrogenase (G6PD), the first and rate-limiting enzyme of the PPP, exacerbates ischemia-reperfusion injury in mice,[21] indicating a protective role of the PPP against oxidative injury. End products of the non-oxidative phase of the PPP are also of significance as ribose 5-phosphate becomes a substrate for nucleotide or nucleic acid synthesis[22] while xylulose 5-phosphate has been suggested as a transcriptional signaling molecule.[23,24]

An alternative fate of G6P is the production of sorbitol, via the enzyme aldose reductase (AR), in the polyol pathway. The role of the polyol pathway in normal cardiac metabolism is unknown. However, increased flux has been noted in diabetic patients and has been associated with abnormal glucose metabolism and cardiac dysfunction.[25,26] Increased AR flux has also been implicated in the myocardial response to ischemia-reperfusion injury.[27,28] Elucidation of the role of the polyol pathway in mouse models should be used with caution as both expression and activity of AR are significantly lower in mice than in humans; however, the use of transgenic mice overexpressing human AR could be translatable.[28]

The glycolytic intermediate fructose 6-phosphate (F6P) can diverge into the hexosamine biosynthetic pathway (HBP), yielding uridine diphosphate-N-acetylglucosamine (UDPGlcNAc), via the enzyme glutamine fructose 6-phosphate amidotransferase (GFAT).[29] UDPGlcNAc is used as the substrate for O-linked-GlcNAc transferase (OGT) which catalyzes the OGlcNAcylation of proteins.[30] Increases in protein O-linked GlcNAcation have been observed in diabetes and proposed to be responsible for altered insulin sensitivity and FAO.[30,31] Recent studies show that protein O-linked GlcNAcation is enhanced during ischemia-reperfusion and represents a cardioprotective mechanism against injury.[32-34]

The turnover of endogenous substrates

The heart stores fuel in the form of glycogen and triacylglycerol (TAG, Figure 1). The turnover rate of the cardiac glycogen pool is rather low under normal conditions in the adult heart.[35,36] Glycogen metabolism has an essential role in the fetal heart as the absence of glycogen due to the deletion of glycogen synthase (GYS), causes abnormal cardiac development.[37] Glucose derived from glycogenolysis also provides a critical energy supply for cell survival during ischemia.[38] Glycogen is also a key energy source to support metabolism during acute increases in cardiac workload.[35]

The turnover of cardiac TAG is more robust compared to the glycogen pool although its functional role has been less understood until recently.[39,40] It has been postulated that fatty acids derived from the myocardial TAG pool can be oxidized and contribute ~10% to the total ATP production under normal physiological conditions.[41,42] A significant loss of TAG turnover was observed in hearts from failing rats[41] while accelerated turnover was noted in

diabetic rats.[43] These results suggest that the intracellular TAG pool is a dynamic entity but the functional significance of altered TAG turnover under pathological conditions is poorly understood.

Recent studies suggest that the turnover of TAG pool is an important regulatory mechanism of fatty acid metabolism in the myocardium. Genetic manipulation of diacylglycerol acyltransferase (DGAT), the final enzyme in synthesis of TAG from diacylglycerol (DAG), or adipose triglyceride lipase (ATGL), the enzyme responsible for TAG hydrolysis, leads to significant changes of fatty acid uptake and oxidation in the mouse heart. Although deletion of DGAT1, the major isoform of DGAT in the heart, did not significantly decrease total cardiac TAG content, it was associated with decreased FAO and increased glucose uptake.[44] Conversely, DGAT1 overexpression resulted in a two-fold increase in cardiac TAG with both increased uptake and oxidation of exogenous fatty acids.[45] Global deletion of ATGL resulted in massive lipid accumulation and severe cardiomyopathy associated with decreased FAO.[46,47] However, cardiac-specific overexpression of ATGL also led to decreased rates of FAO with increased rates of glucose oxidation suggesting a non-linear relationship between TAG turnover and FAO.[48]

Modulation of Contractile Function by Cardiac Metabolism Under Pathological Conditions

Pathological hypertrophy and failure

It is well established that cardiac metabolism undergoes a reprogramming in response to pathological hypertrophy, characterized by increased reliance on glucose metabolism and decreased FAO (Figures 2 and 3).[49-52] Increased glucose utilization in the hypertrophied heart is predominantly characterized as an upregulation of glucose uptake and glycolysis[50,53] with either no change or a decrease in glucose oxidation.[36,54-56] These changes, combined with decreases in overall FAO, likely represent reduced capacity for mitochondrial oxidative metabolism. In small animal models, the shift in substrate preference is associated with downregulation of the transcriptional mechanisms for FAO and mitochondrial biogenesis mediated via PPARα and PGC-1.[57] Because these changes resemble a reversal of metabolic maturation during the transition from a fetal to adult heart, many have considered the metabolic changes in hypertrophied and failing hearts as a reappearance of the fetal metabolic profile. Is there any advantage of switching to a fetal-like metabolism in the hypertrophied and failing myocardium? A shift from FAO to glucose utilization improves oxygen efficiency for ATP synthesis and is thus considered beneficial.[58,59] This becomes particularly important for heart failure caused by chronic ischemic cardiomyopathy where oxygen supply is limited. There have been concerns whether increased glucose uptake and utilization in adult heart impairs cardiac function since cardiomyocytes cultured in high glucose media develop “glucotoxicity”.[60-63] Transgenic mice with cardiac-specific overexpression of insulin-independent glucose transporter (GLUT1) showed substantial increases of glucose uptake and glycolysis but maintained normal cardiac function and lifespan suggesting that increased glucose utilization does not harm the adult heart in the longterm.[64] A key question remaining is whether metabolic remodeling is adaptive or maladaptive to the high energy demand in the hypertrophied and failing heart. It is known that pathological cardiac hypertrophy is associated with depletion of energy reserves manifested as maintained ATP levels but a reduction of the energy reserve compound, phosphocreatine (PCr).[65,66] This is reflected as a decreased PCr/ATP ratio and eventually, as compensated hypertrophy advances to overt heart failure, significant decreases of ATP are observed.[67,68] The PCr/ATP ratio has been shown to be a superior predictor of mortality as compared to ejection fraction in heart failure patients [69] which is in agreement with the longstanding hypothesis that energy starvation

contributes to the pathogenesis and progression of heart failure (See reviews[67,68,70]). These observations suggest that the fetal-like metabolic profile in cardiac hypertrophy is maladaptive for sustaining myocardial energetics and function (Figure 3).

Animal studies have shown that metabolic remodeling in hypertrophied heart is associated with decreases in the overall ATP synthesis by oxidative metabolism.[50] Although glycolysis is increased, its contribution to total ATP synthesis is limited as glycolytic ATP accounts for less than 5% of total energy used by the heart.[50] Furthermore, glucose entry in the adult heart is controlled by insulin; the co-existing insulin resistance in heart failure would limit the glucose availability and hence compromise the capacity for ATP synthesis.[71,72] A proof of concept study shows that increasing glucose uptake capacity in mouse heart via an insulin-independent mechanism delays the transition of cardiac hypertrophy to failure.[73] Other studies show that cardiac energetics and function can also be preserved in rodent models of heart failure by sustaining FAO or by enhancing ATP synthesis and transfer via the creatine kinase reaction.[74-76] Therefore, the ATP synthesis capacity appears to be more important than the substrate selection for sustaining cardiac energetics and function in these models.

In addition to glycolysis and pyruvate oxidation, multiple accessory pathways of glucose metabolism (Figure 2) have also been altered in the hypertrophied myocardium. Increased flux of the anaplerotic pathway, primarily via increased malic enzyme, have been reported in hypertrophied rodent heart.[76-78] Such a change is considered maladaptive as it “short-circuits” pyruvate into the second half of the TCA cycle and hence produces less NADH for oxidative phosphorylation. The regulatory enzyme of the PPP, G6PD, was upregulated in the hearts of animals subjected to pressure-overload.[19,74] Increased activity of G6PD in heart failure was linked to excessive NAPDH and increased superoxide production.[79,80] On the other hand, G6PD deficiency deprived NADPH supply for glutathione reduction leading to increased redox stress and exacerbated LV dilation and cardiac dysfunction in mice.[81] It is likely that either excessive or deficient production of NADPH through the G6PD reaction impairs the redox regulation. It is also proposed that increased glucose utilization will augment HBP flux resulting in enhanced O-GlcNAcation.[82] Increased glucose metabolism also elevates the citrate level in the cytosol providing more acetyl-CoA for the acetylation of proteins.[83,84] It remains to be determined whether these changes contribute to the maladaptive nature of increased glucose utilization in heart failure. These pathways have been less investigated because their fluxes are small and they do not contribute to the once ultimate goal of cardiac metabolism, ATP production. However, given the emerging significance of non-ATP producing pathways in cardiac biology, this paradigm is rapidly changing. We shall expect a wealth of information in this regard in the future.

Metabolic cardiomyopathy associated with obesity and diabetes

In obese or diabetic individuals, cardiac dysfunction observed independent of macro- and/or microvascular disease is considered a consequence of “diabetic cardiomyopathy”. Increased fatty acid uptake and oxidation associated with reduced glucose oxidation have been observed in both animal models and patients of type 2 diabetes.[85-87] Cardiac dysfunction in obesity and diabetes has been associated with increased myocardial oxygen consumption (MVO_2), reduced cardiac efficiency, and increased oxidative stress suggesting that increased rates of FAO are detrimental to cardiac function (Figure 3).[85,88,89] As discussed above, one mechanism for the undesirable effect of high FAO is the lower O_2 efficiency,[58,59] as well as the increased presence of fatty acid derivatives that may further reduce the efficiency by uncoupling the mitochondria.[90] In skeletal muscle, increased influx of fatty acid to mitochondria was associated with incomplete oxidation and development of insulin resistance.[91] However, this was not observed in the mouse heart during high fat feeding[92] or

with increased import of long chain fatty acids to the mitochondria due to deletion of acetyl-CoA carboxylase 2 (ACC2).[76]

A unique aspect of cardiac metabolism in obesity and diabetes is that the supply of substrates exceeds the need for ATP synthesis. Despite increased FAO, hearts of obese and diabetic individuals accumulate a significant amount of lipid (Figure 3). A positive correlation of cardiac lipid accumulation and cardiac dysfunction has been shown giving rise to the term "lipotoxic cardiomyopathy".[93-95] Additional studies show that increases of lipid supply in animal models of cardiac lipotoxicity exceed the increases in the rate of oxidation, which eventually leads to downregulation of FAO, accumulation of toxic lipid intermediates, and contractile failure.[95,96] Genetic manipulations in mice that reduce fatty acid uptake or increase the storage capacity of neutral lipids in the heart rescue the lipotoxic phenotype.[45,97,98] These results suggest that the metabolic derangements in lipotoxic cardiomyopathy are rooted in the inappropriate matching of lipid supply and oxidation rather than a simple increase of FAO. The molecular mediator(s) of the cardiomyopathy in this case are largely elusive and likely multifactorial in nature. Although the accumulation of neutral lipids correlates closely with functional phenotype whether it is the cause or a mere reporter of lipotoxicity is not clear. Increases in intramuscular lipid are not always associated with detrimental effects. Both animals and humans increase triglyceride content in the heart and skeletal muscle in response to exercise training, which is associated with improved function.[45,99,100]

Although glucose uptake and utilization for ATP synthesis is reduced, due to insulin resistance and increased FAO, increased flux of the accessary pathways of glucose metabolism has been identified in the diabetic myocardium. In the polyol pathway, increased AR gene expression was observed while AR inhibition improved cardiac function in diabetic patients.[25] In models of diabetic cardiomyoapathy, elevated levels of UDPGlcNAc, O-GlcNAc, and OGT were associated with impaired EC coupling suggesting a role of increased HBP flux in diabetic cardiac dysfunction.[63,101,102] Consistent with these observations, increased expression of O-GlcNAase, the antagonist of OGT, improved cardiac function in diabetic mice.[103]

Metabolic Therapies for Heart Failure

Targeting substrate preference

The shift of substrate preference to glucose in pathological hypertrophy was considered adaptive based on the theoretical higher oxygen efficiency of ATP synthesis from glucose.[104] Therefore, various metabolic therapies focusing on the promotion of glucose oxidation have been utilized (Table 2). One strategic target has been mCPT1, the enzyme that is the gateway for long chain fatty acid uptake into the mitochondria. The mCPT1 inhibitors, such as etomoxir, perhexiline, and oxfenicine, have been associated with reduced cardiac FAO and elevated glucose oxidation in both animal models and humans. Etomoxir has been shown to increase expression and activity of the sarcoendoplasmic reticulum (SR) calcium ATPase (SERCA).[105,106] Long term treatment with etomoxir in pressure overloaded hearts improved functional capacity and myocardial performance.[107] The first human clinical trial evaluating etomoxir in patients with chronic heart failure showed improved stroke volume and ejection fraction (EF).[108] A clinical trial evaluated the effect of perhexiline in heart failure patients and observed improved VO_{2max}, EF, and tolerance to dobutamine stress.[109] In hypertrophic cardiomyopathy, perhexiline, in conjunction with medical management, increased the PCr/ATP ratio, corrected energy dependent LV diastolic relaxation, increased VO_2, and improved quality of life.[110] Although not available for human use, oxfenicine treatment in pacing-induced heart failure in dogs, when provided

early, slowed the development of heart failure, prevented LV chamber dilation and LV wall thinning compared to placebo.[111]

Dichloroacetate (DCA) increases PDH activity by inhibiting PDK, and as a consequence promotes glucose oxidation. The efficacy of DCA treatment in functional recovery during reperfusion has been shown in multiple animal models.[112-115] DCA also improves cardiac function in right ventricular hypertrophy and failure.[116,117] In a recent study examining hyperthyroidism and cardiac hypertrophy in rats, DCA administration completely reversed reductions in PDH flux, and significantly reduced cardiac hypertrophy without affecting cardiac output.[118] Although human data are limited due to the chronic neurotoxicity of DCA,[119-121] one study in patients with angina and coronary artery disease revealed that infusion of DCA during left heart catheterization was associated with increased stroke volume and myocardial efficiency index (LV work/myocardial oxygen consumption).[122]

Malonyl CoA decarboxylase (MCD) is a key regulator of malonyl CoA degradation and, thus, its activity relieves the inhibition of fatty acid entry into the mitochondria. Pharmacological inhibition or cardiac-specific deletion of MCD has been shown to limit FAO, increase glucose oxidation and improve cardiac function after ischemia/reperfusion injury in both rodent [123,124] and porcine models.[125] Although clearly effective in treatment of cardiac ischemia, it has not been shown whether targeted inhibition of MCD in heart failure is likewise protective.

While enhancing glucose utilization appears to be beneficial for the failing heart, decreasing fatty acid supply to hypertrophied and failing hearts seems to be detrimental. Acipimox is a nicotinic acid derivative that acutely inhibits lipolysis in adipose tissue and hence decreases plasma free fatty acids (FFA) level. When administered to patients with idiopathic dilated cardiomyopathy, myocardial FFA uptake was reduced by >80% with enhanced glucose uptake. Unfortunately, cardiac work and efficiency declined after acipimox treatment.[126] In long term treatment of heart failure patients with acipimox, increases in whole body glucose utilization and decreased lipid utilization rates were noted, but myocardial function, exercise capacity, and cardiac index scores remained unaffected.[127] These studies suggest that promoting glucose utilization via restriction of fatty acid delivery to the myocardium is not an ideal strategy for enhancement of cardiac function via the optimization of cardiac metabolism.

As oxidation of fatty acids is the predominant and critical energy source for cardiac function, promotion of cardiac FAO would seem to be desirable for long-term treatment. Targeting PPARα, the major regulator of cardiac lipid metabolism, however, has yielded mixed outcomes. Overall, in various animal models of cardiac hypertrophy and heart failure, PPARα agonism maintained expression of genes involved in FAO with significantly improved,[128,129] relatively modest,[130,131] or no benefit on cardiac function.[52] Furthermore, PPARα agonism has been shown to exacerbate post-ischemic injury.[132,133]

Activation of PPARα-mediated transcription has broad effects on lipid metabolism including lipid uptake. Excessive fatty acid uptake relative to the oxidation would contribute to lipotoxicity.[97] In this regard, direct activation of FAO at the level of the mitochondria may provide a more effective therapeutic strategy for sustaining myocardial energetics. Although no drug is available for clinical studies, several proof-of concept studies have been performed in mice. Overexpression of PDK4 in mice promoted cardiac FAO at the expense of glucose but had no effect on cardiac function either under normal or ischemic conditions.[134] However, introduction of the PDK4 transgene into mice expressing a constitutively active form of the phosphatase calcineurin failed to rescue cardiac dysfunction and led to an increase in mortality.[135] In contrary, deletion of ACC2 increased myocardial

FAO in normal mice and prevented the switch to increased glucose reliance during pressure overload induced hypertrophy.[76] Cardiac function and myocardial energetics were also sustained suggesting a benefit of maintaining FAO during pathological hypertrophy. Several recent studies have also demonstrated the effectiveness of high fat diets in protection against the development of heart failure in animal models.[74,136,137]

Taken together, the evidence thus far suggests that enhancing glucose utilization in the hypertrophied and failing heart improves cardiac function and symptoms of heart failure in the short term. Clinical application of metabolic therapy of this kind depends on the ultimate test of its impact on the long-term mortality. However, strategies of enhancing glucose utilization by removing the contribution of fatty acids appear to be less promising. Moreover, recent preclinical studies suggest that sustaining FAO in the hypertrophied heart may be suitable for the preservation of myocardial energetics and function.[74,76,137]

Targeting insulin sensitivity

Insulin resistance has been shown to precede and predict the development of heart failure, independent of established diabetes.[138] Moreover, insulin resistance is positively correlated with NYHA functional class.[139] Since glucose uptake in the adult heart is largely controlled by insulin-sensitive mechanisms, insulin resistance would be an obstacle for measures that seek to enhance myocardial glucose utilization. Although not directly tested, insulin sensitizing agents have been used in heart failure patients with metabolic disturbances (Table 2) and have yielded auspicious results.

Thiazolidinediones (TZD), PPAR gamma agonists including rosiglitazone and pioglitazone, are used as oral hypoglycemic and insulin sensitizing agents. TZDs successfully enhance glucose uptake and oxidation, especially in diabetic animal models, and improve functional recovery after ischemia.[140,141] However, one study showed that rosiglitazone increased mortality post-MI in rats without alterations in LV remodeling.[142] Similarly, rosiglitazone was associated with a higher risk of cardiovascular events including congestive heart failure in the ADOPT trial, as compared to cohorts treated with glyburide or metformin.[143] In the PROACTIVE trial, pioglitazone decreased all-cause mortality, non-fatal MI and stroke, but significantly increased rates of symptomatic edema and CHF in patients with diabetes and cardiovascular disease.[144]

Another widely used insulin-sensitizing drug is metformin that is often used as first line therapy for diabetics. Metformin acts as an AMPK activator in the liver[145] and has been shown to increase glucose uptake both in basal and insulin-stimulated conditions in insulin resistant cardiomyocytes.[146] Of note, activation of AMPK by metformin in human heart has not been reported. In animal studies, metformin improved left ventricular function and remodeling while reducing myocardial lipid accumulation and fibrosis.[147148] Masoudi et al. performed a retrospective cohort analysis on subjects with congestive heart failure and diabetes and found that metformin use for 1 year was associated with a 13% lower mortality compared to sulfonylurea or insulin therapy.[149] Although these results are promising, randomized perspective trials are still needed to evaluate the potential clinical benefits of metformin in heart failure patients with and without diabetes.

Glucagon like peptide-1 (GLP-1) is secreted by intestinal cells in response to the presence of nutrients. Once in the circulation, it stimulates insulin secretion, enhances insulin sensitivity, and promotes glucose utilization in the myocardium. In a canine model of pacing-induced dilated cardiomyopathy, GLP-1 treatment increased myocardial glucose uptake and was associated with decreased LV end-diastolic pressure, increased stroke volume, and increased cardiac output.[150] In heart failure patients, GLP-1, in addition to standard medical therapy, led to improvements in EF and maximal aerobic capacity compared with controls who

received standard medical therapy alone.[151] A study examining patients with an acute myocardial infarction and EF <40% after successful angioplasty treated with 72 hours of GLP-1 infusion demonstrated significantly greater EF associated with improved global and regional wall motion score indices compared to controls.[152]

Targeting mitochondrial function

It is well known that heart failure is associated with mitochondrial dysfunction but therapies specifically targeted to improving mitochondrial function are rather limited. The nitric oxide pathway is a potential stimulator of mitochondrial biogenesis.[153] Modulation of this pathway with phosphodiesterase 5 inhibitors (PDE5I) was related to increased mitochondrial biogenesis.[154] Treatment with the PDE5I, sildenafil, improved cardiac index and right ventricular EF in heart failure patients[155] but additional studies are required to determine whether the benefit can be attributed to increased mitochondrial biogenesis and function.

Mitochondrial dysfunction in heart failure is associated with increased oxidative stress making mitochondria-targeted ROS scavenging an attractive therapeutic strategy. Several antioxidants that accumulate in the mitochondrial matrix have demonstrated cardioprotective effects in animal models. Mitoquinone (MitoQ) improved functional recovery from ischemia in the isolated rat heart[156] as well as prevented doxorubicin-induced cardiac dysfunction, fibrosis, and apoptosis.[157] MitoTEMPO, a superoxide and alkyl scavenger, demonstrated cardioprotective effects in hypertension and diabetes models.[158,159] EUK–8, a superoxide dismutase and catalase mimetic, rescued cardiac dysfunction in genetic models of increased oxidative stress.[160,161] Finally, Szeto-Schiller (SS) peptides have shown cardiac protection in guinea pig hearts subjected to ischemia-reperfusion injury and mouse models of hypertrophy and failure, in part, by reducing oxidative stress.[162,163] So far, clinical studies using such a strategy are rather limited. However, a Phase IIa clinical trial on the safety and efficacy of the SS-peptide, Bendavia, on reperfusion injury is ongoing.[164]

While mitochondrial specific antioxidants have shown promising results for the treatment of heart failure, general antioxidants in clinical trials have not. Vitamin E, also known as alpha tocopherol, has been extensively studied in heart failure. Large clinical trials revealed that Vitamin E can actually increase the risk of developing heart failure after myocardial infarction.[165] The HOPE and HOPE-TOO trials also suggested that long term vitamin E supplementation increases the risk of heart failure and heart failure exacerbations with no improvement in other cardiovascular outcomes.[166] Further work is needed in order to elucidate the differences between mitochondrial-specific and general antioxidant therapy for heart failure.

Dietary strategies

The benefits of polyunsaturated fatty acids (PUFAs) in decreasing the incidence of coronary artery disease and sudden cardiac death are well accepted. PUFAs also improve various factors related to heart failure including lipid metabolism, mitochondrial function, endothelial function, and inflammation. Clinical evidence now suggests that PUFAs can prevent the development or progression of heart failure. A 12-year study following over 4700 adults found an inverse correlation between incidence of heart failure and dietary consumption of tuna and other fish, with the highest intake of dietary long-chain n-3 fatty acid offering a 37% lower risk of heart failure.[167] A randomized double-blind, placebo controlled trial (GISSI-HF) showed that heart failure patients treated with low dose eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) for a median time of 3.9 years had a significantly lower mortality rate and decreased hospital admissions for cardiovascular causes.[168] A recent meta-analysis involving 7 trials found that fish oil supplementation in non-ischemic heart failure significantly increased left ventricular EF.[169]

In contrary, high levels of long chain monounsaturated fatty acids (LCMUFA) were associated with a greater incidence of congestive heart failure, suggesting potential cardiac toxicity of this lipid species.[170]

Metabolic Modulation of Growth and Survival Pathways

The effects of metabolism on growth, proliferation, and survival pathways have been increasingly recognized in recent years, especially in cancer biology. Although a large fraction of the metabolic fluxes in the heart is devoted to oxidative metabolism for ATP synthesis, substrate metabolism has significant impact on multiple aspects of cardiac biology. Closely related to the topic of cardiac hypertrophy and failure discussed above, here we present the recent development on the role of metabolism in the regulation of cardiomyocyte growth, survival and autophagy (Figure 4).

Regulation of mTOR signaling

Recently, an interesting finding regarding the influence of fatty acids on cardiac myocyte growth was made in Burmese pythons.[171] Elevations in three fatty acids (palmitic acid, myristic acid, and palmitoleic acid) were identified as inducers of reversible cardiac hypertrophy during the feeding period and were associated with increased mammalian Target of Rapamycin (mTOR) phosphorylation. This effect of fatty acids on mTOR has been previously shown in skeletal muscle and liver tissue of rats fed a high fat diet.[172,173] In addition, incubation of myotubes with palmitate increased phosphorylation of S6 kinase (S6K), a downstream target of mTOR.[173] Transgenic mouse models of enhanced lipid metabolism are generally associated with cardiac hypertrophy,[95,96,174,175] but whether the increased uptake of fatty acids contribute to cardiac growth via the mTOR pathway has not been determined.

It has been shown that glucose phosphorylation is required for insulin-dependent activation of mTOR in the heart.[176] A recent study suggested that accumulation of glucose 6-phosphate during mechanical overload activated mTOR and caused contractile dysfunction by triggering ER stress.[177] Since glucose metabolism is increased in the hypertrophied and failing heart it is tempting to hypothesize that altered glucose metabolism is causally linked to the development of hypertrophy and dysfunction.

The effects of amino acids on protein synthesis have been well-studied in cultured cells, animal models, and humans.[178-183] Although the exact mechanisms are not known, the presence of amino acids have been shown to activate the mTOR complex and its downstream effectors.[180,182] It has been suggested that amino acids activate mTOR through a calcium dependent mechanism involving class III PI3K, or hVps34, which would combine the interaction of protein synthesis with inhibition of autophagy.[181] Previous work demonstrated that mTOR and its downstream targets are affected by the availability of intracellular amino acids.[184] Additional studies have specifically implicated the branched chain amino acid (BCAA), leucine, in the stimulation of the mTOR pathway.[178,185,186] This has been particularly important in accounting for increased skeletal muscle protein synthesis during the post-exercise recovery period [183,187] and in atrophy associated with aging.[188,189]

The above evidence offers strong support to the notion that mTOR behaves as a “nutrient sensor”. It remains to be determined whether one or multiple metabolites of the aforementioned substrates have a direct binding affinity for the mTOR complex. It is also not known whether different metabolic pathways affect mTOR signaling through distinct mechanisms or via a unifying effector.

Apoptosis and autophagy

Ceramides, a sphingolipid composed of sphingosine and a fatty acid, have been purported to function as a signal which triggers apoptosis in lipotoxic cardiomyopathy.[190] Elevated ceramide levels were found in the hearts of mice overexpressing enzymes of lipid metabolism, including acyl CoA synthetase (ACS),[45,96] lipoprotein lipase (LPL),[174] and PPARγ[175], which was associated with increased apoptosis and/or cardiac dysfunction. However, high fat feeding in rodent models have not consistently recapitulated this observation. Although content of cardiac ceramides was increased in rats fed a high fat diet, no evidence of apoptosis[191] or cardiac dysfunction[192] was found. In addition, 10 or 12 weeks of a high fat diet fed to mice failed to significantly increase ceramide levels.[193,194] Ceramides were elevated in rat hearts subjected to coronary artery ligation but provision of a high fat diet during that interval did not further increase ceramide content.[131]

In studies using cultured cells[195-197] or neonatal rat ventricular myocytes (NRVM),[198,199] addition of palmitate to the media significantly increased measures of apoptosis. Similar findings were observed with addition of stearate, suggesting long chain saturated fatty acids as the culprit.[197,198] Interestingly, co-incubation with the unsaturated fatty acid, oleate, significantly reduced apoptosis measures in cells.[195,198,199] Since the metabolic rate of quiescent cells is vastly different from that of the beating heart, the observation could be confounded by the low oxidation rate of fatty acids in cell culture. However, cells exposed to different species of fatty acids showed differential outcomes suggesting that the chain length and/or the degree of saturation influence the survival of cardiomyocytes under conditions of lipid overload. In rodents fed a high fat diet, a lower ceramide content and reduced apoptotic events were observed in cardiomyocytes from the group receiving predominantly unsaturated versus saturated fatty acids.[137] These studies suggest that elevated cytosolic levels of palmitate are associated with increases in lipid species that have the potential to promote apoptosis. It is also suggested that oleate facilitates palmitate accumulation into the TAG pool,[195] and provision of unsaturated fats in conjunction with saturated fats could promote survival by attenuation of apoptosis.

Recent work in mice demonstrated that a high milk fat based diet resulted in elevated supply of the 14 carbon (C14) saturated fat, myristic acid, which increased the presence of C14-ceramide, and was associated with cardiac hypertrophy, dysfunction, and increased autophagy.[200] However, other studies using high fat feeding models in mice have suggested that autophagy is impaired during the lipid overload condition.[201,202] Furthermore, hearts from a porcine model exposed to a high fat or atherogenic diet revealed progressive decreases in autophagy combined with increases in apoptosis.[203] Whether metabolic derangement in the heart causes cardiac injury via inhibition of autophagy is an open question. Autophagy is critical for protein quality control, cellular homeostasis and survival. However, increased autophagy can be adaptive or maladaptive to cardiac pathologies depending on the circumstances (see for recent reviews[204-208]). While autophagy is known as an evolutionarily conserved response to metabolic stress, the metabolic mediators of autophagy are poorly understood at the molecular level. An expanded knowledge of the metabolic control of autophagy will facilitate targeting autophagy for therapeutics.

In summary, the knowledge on cardiac metabolism and its role in human diseases has increased explosively in recent years. Multi-disciplinary approaches in both experimental and clinical research seem to converge on the concept that the capacity and flexibility of the metabolic network is essential for cardiac function. Although energy transfer is a primary function of cardiac metabolism, the sophistication of the system is being appreciated for its regulatory role through the interactions of the ATP-producing and non-ATP producing pathways. Future advances of the field will elucidate novel disease mechanisms and identify new targets for metabolic therapy.

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Non-standard Abbreviations and Acronyms

EF	ejection fraction
FAO	fatty acid oxidation
mCPT1	carnitine palmitoyl transferase 1, muscle form
NADPH	nicotinamide adenine dinucleotide phosphate
PDH	pyruvate dehydrogenase
PDK4	pyruvate dehydrogenase kinase 4
PPARα	peroxisome proliferator-activated receptor alpha
TAG	triacylglycerol
TCA cycle	tricarboxcylic acid cycle

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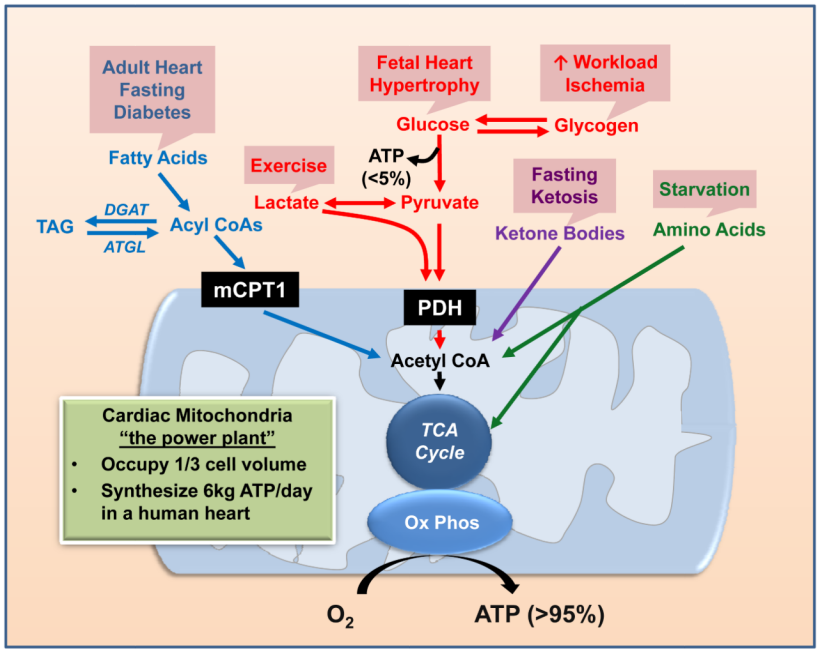

Figure 1. Overview of the Metabolic Network

The energy-yielding substrates (fatty acids, glucose, ketones, and amino acids), via specific catabolic pathways, converge on acetyl CoA production with subsequent entry into the tricarboxylic acid (TCA) cycle. The final step of energy transfer is accomplished through oxidative phosphorylation (OxPhos), supplying greater than 95% of ATP consumed by the heart. The boxes (in pink) above each metabolic pathway indicate the pathological and/or physiological condition in which the specific substrate becomes a predominant contributor to metabolism. TAG, triacylglycerol; DGAT, diacylglycerol acyltransferase; ATGL, adipose triglyceride lipase; mCPT1, muscle form of carnitine palmitoyl transferase; PDH, pyruvate dehydrogenase; TCA, tricarboxcylic acid; O_2, oxygen.

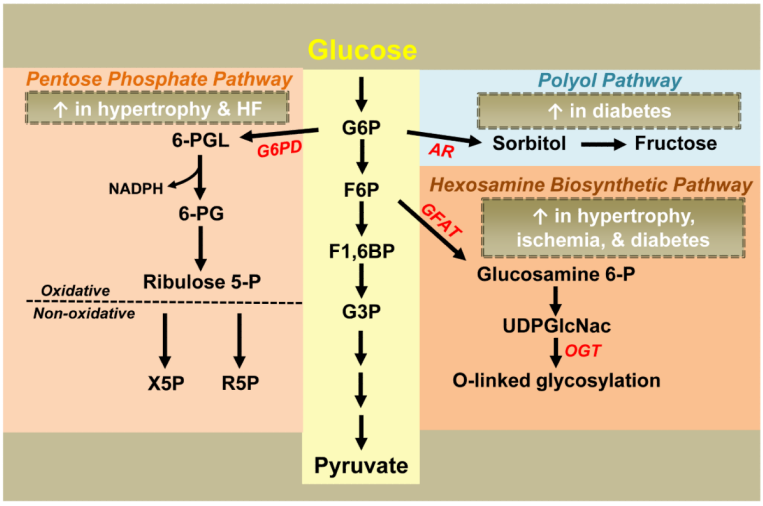

Figure 2. Accessory Pathways of Glucose Metabolism

Multiple accessary pathways of glucose metabolism result in the production of metabolites that do not directly contribute to energy supply but are of important biological function. Evidence has suggested that these pathways are altered in the hypertrophied, failing, ischemic, and/or diabetic heart as indicated. *Glycolysis*: G6P, glucose 6-phosphate; F6P, fructose 6-phosphate; F1,6BP, fructose 1,6-biphosphate; G3P, glyceraldehyde 3-phosphate. *Pentose Phosphate Pathway (PPP)*: G6PD, glucose 6-phosphate dehydrogenase; 6-PGL, 6-phosphoglucono-δ-lactone; NADPH, nicotinamide adenine dinucleotide phosphate; 6-PG, 6-phosphogluconate; Ribulose 5-P, ribulose 5-phosphate; X5P, xylulose 5-phosphate, R5P, ribose 5-phosphate. *Polyol Pathway*: AR, aldose reductase. *Hexosamine Biosynthetic Pathway (HBP)*: GFAT, glutamine fructose 6-phosphate amidotransferase; Glucosamine 6-P, glucosamine 6-phosphate; UDPGlcNAc, uridine diphosphate-N-acetylglucosamine; OGT, O-linked β-N-acetylglucosamine transferase.

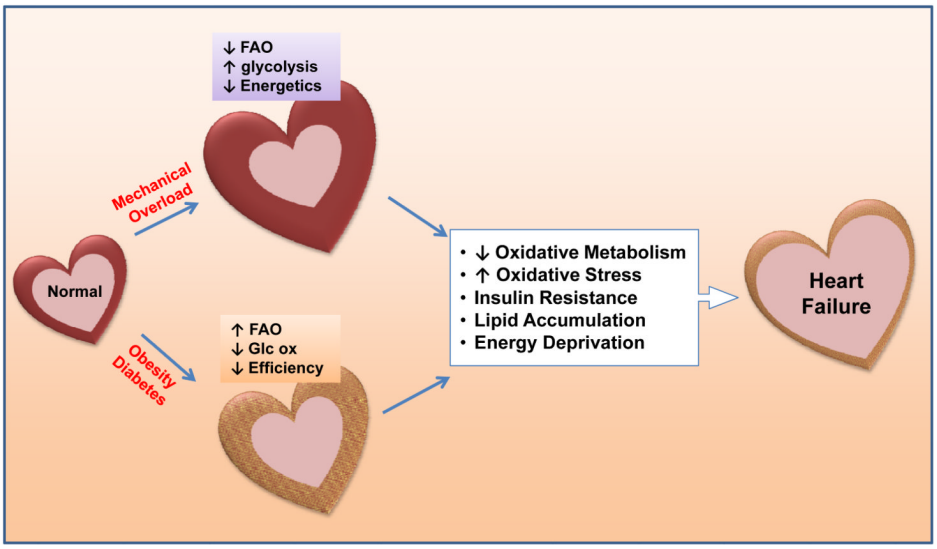

Figure 3. Metabolic Remodeling and the Development of Heart Failure

Pathological hypertrophy in response to mechanical overload, e.g. hypertension, valvular disease or post-MI, is accompanied by metabolic remodeling characterized by decreases in fatty acid oxidation (FAO) and increases in glycolysis. This fetal-like metabolic profile decreases the capacity for ATP synthesis, consistent with the "energy starvation" model. In contrast, the elevated supply of substrates in the heart of obese and/or diabetic individuals leads to an upregulation of FAO with a concomitant decrease in glucose oxidation (Glc ox). This lipid overload condition impairs cardiac efficiency. Regardless of the precipitating factor, the persistent metabolic derangements elicit commonalities of decreased oxidative metabolism, increased oxidative stress, insulin resistance, lipid accumulation, and energy deprivation, all contributing to the progression of heart failure.

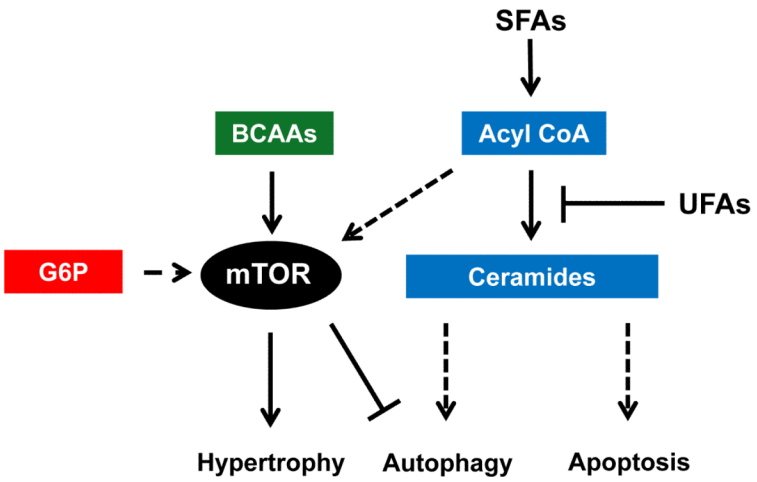

Figure 4. Metabolic Modulation of Growth and Survival Pathways

Interactions of lipids (blue), amino acids (green), and glucose (red) metabolism with pathways of hypertrophy, autophagy, and apoptosis as represented in the literature from various cell culture and animal models. SFAs, saturated fatty acids; UFAs, unsaturated fatty acids; BCAAs, branched chain amino acids; G6P, glucose 6-phosphate; mTOR, Mammalian Target of Rapamycin.

Table 1

Regulators of Substrate Metabolism

Known factors of transcription, protein modification, and allosteric regulators involved in the stimulation or inhibition of metabolic pathways. Numbers indicate relevant references for review. HIF1α, hypoxia-inducible factor 1-alpha, PPARγ, peroxisome proliferator-activated receptor gamma; AMPK, AMP-activated protein kinase; F1,6BP, fructose 1,6-biphosphate; Pi, inorganic phosphate; NAD^+, nicotinamide adenine dinucleotide; NADH, nicotinamide adenine dinucleotide, reduced; G6P, glucose 6-phosphate; FOXO1, forkhead box protein O1; PDK4, pyruvate dehydrogenase kinase 4; PCG-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; ERRα, estrogen-related receptor alpha; MCD, malonyl CoA decarboxylase; ACC2, acetyl CoA carboxylase 2; PP2Cm, protein phosphatase 2Cm; BCKDK, branched chain ketoacid dehydrogenase kinase.

Pathway	Stimulation	Inhibition
Glycolysis	HIF1α[15] PPARγ[209] AMPK[210] Insulin[211] Epinephrine[212] AMP, ADP, Pi[213] NAD^+ [213] F1,6BP[213]	ATP[213] NADH[213] G6P[213] citrate[214]
Glucose oxidation	Insulin[215] Epinephrine[212] NAD^+[213] Calcium[216]	PPARα[209] FOXO1[217] PDK4[16] Fatty Acids[214] Acetyl CoA, NADH, ATP[213]
Fatty acid oxidation	PPAR/PGC-1α/ERR[12-14,209] FOXO1[217] AMPK[210] MCD[218] Adiponectin[219,220] Fatty Acids[221]	ACC2[222] Malonyl-CoA[223] Glucose[214] Lactate[11] Ketone bodies[10]
BCAA catabolism	PP2Cm[17,18] Glucagon[224]	BCKDK[225] NADH, CoA esters[213]
Ketone body oxidation	acetoacetate[213]	

Table 2
Metabolic Therapies Used in the Treatment of Heart Failure

Italics indicate therapies with reported adverse effects. mCPT1, muscle form of carnitine palmitoyl transferase 1; PDK, pyruvate dehydrogenase kinase; MCD, malonyl CoA decarboxylase; PPAR, peroxisome proliferator-activated receptor; PDE, phosphodiesterase; AMPK, AMP-activated protein kinase; MitoQ, mitochondrial-targeted antioxidant; MitoTEMPO, Mitochondria-targeted antioxidant with superoxide and alkyl radical scavenging properties; EUK-8, superoxide dismutase and catalase mimetic; SS peptide, Szeto-Schiller peptide; PUFAs, polyunsaturated fatty acids.

Substrate Preference:
mCPT1 Inhibitors
Partial β-oxidation inhibitors
PDK Inhibitors
MCD inhibitors
Nicotinic Acid Derivatives
PPAR Agonists
Insulin Sensitivity:
Glucagon Like Peptides (GLP-1)
Metformin
Thiazolidinediones
Mitochondrial Function:
PDE inhibitors
AMPK Activators
MitoQ
MitoTEMPO
EUK-8
SS peptides
Dietary Modulation:
PUFAs
Vitamin E