Published in final edited form as:

Biochimie. 2016 May ; 124: 74–83. doi:10.1016/j.biochi.2015.10.013.

Nutrient Sensing and Utilization: Getting to the Heart of Metabolic Flexibility

Timothy M. Griffin^{a,b,c,d,*}, Kenneth M. Humphries^{a,b,c,*}, Michael Kinter^{a,b,*}, Hui-Ying Lim^{a,b,d,*}, and Luke I. Szweda^{a,b,c,*}

Timothy M. Griffin: Tim-Griffin@omrf.org; Kenneth M. Humphries: Kenneth-Humphries@omrf.org; Michael Kinter: Mike-Kinter@omrf.org; Hui-Ying Lim: Hui-Ying-Lim@omrf.org; Luke I. Szweda: Luke-Szweda@omrf.org

^aAging and Metabolism Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, 73104, USA

^bDepartment of Geriatric Medicine, Reynolds Oklahoma Center on Aging, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA

^cDepartment of Biochemistry and Molecular Biology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, 73104, USA

^dDepartment of Physiology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, 73104, USA

Abstract

A central feature of obesity-related cardiometabolic diseases is the impaired ability to transition between fatty acid and glucose metabolism. This impairment, referred to as “metabolic inflexibility”, occurs in a number of tissues, including the heart. Although the heart normally prefers to metabolize fatty acids over glucose, the inability to upregulate glucose metabolism under energetically demanding conditions contributes to a pathological state involving energy imbalance, impaired contractility, and post-translational protein modifications. This review discusses pathophysiologic processes that contribute to cardiac metabolic inflexibility and speculates on the potential physiologic origins that lead to the current state of cardiometabolic disease in an obesogenic environment.

Graphical Abstract

Corresponding Author: Timothy M. Griffin, Ph.D., Associate Member, Aging and Metabolism Research Program, Oklahoma Medical Research Foundation, MS 21, 825 NE 13th St, Oklahoma City, OK 73104 USA, Phone: (405) 271-7579; Fax: (405) 271-1437.

*All authors contributed equally to this work.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

Metabolic inflexibility; Obesity; Cardiovascular; Mitochondrial; Peroxisome; ROS

1. Introduction

Organismal metabolism is among the most highly regulated processes in biology. Maintaining metabolic homeostasis is challenging due to the variation in food availability, diet composition, and caloric content of dietary macronutrients (i.e., carbohydrates, fat, and protein). Consequently, precise nutrient sensing and utilization is necessary for coordinating multiple organ systems to regulate metabolic balance. Organisms accomplish this by continuously monitoring and producing neurochemical signals and circulating soluble factors that function across a range of time-scales, tissues, and cell types. A central feature of obesity and age-related chronic diseases, such as diabetes and heart disease, is the impaired regulation of how macronutrients are sensed and metabolized. In particular, aging and obesity are associated with the development of insulin resistance and adipose tissue accumulation [1]. At the cellular level, these changes are associated with an impaired ability to transition between the utilization of different macronutrients (e.g. glucose versus fat) to meet biosynthetic and bioenergetic demands. This impairment is generally referred to as “metabolic inflexibility” and is considered a central pathologic feature of chronic metabolic diseases [2].

The goal of this review is to discuss the physiologic and pathophysiologic mechanisms involved in the regulation of glucose versus fatty acid oxidation. Multiple organ systems, such as the liver, brain, skeletal muscle, pancreas, and adipose tissue, are involved in this process. Here, we focus on the role of the heart as both a target and contributor to the metabolic inflexibility that occurs with aging and obesity. We discuss recent research about how changes in neuroendocrine and redox-sensitive signaling pathways impair macronutrient sensing and oxidation under physiologic and pathophysiologic conditions. We

also discuss the role of reversible post-translation mitochondrial protein modifications and reactive oxygen species (ROS) as intra- and inter-cellular mediators of cardiac function and metabolism. Finally, we review intriguing new findings that suggest that the heart itself is the source of secreted soluble factors--“cardiokines”--that contribute to the overall regulation of whole body metabolism. These findings also highlight cardiac regulatory pathways that are shared between mammals and more evolutionarily distant model organisms, such as drosophila. An improved understanding of the evolutionary origins of how glucose and fatty acid metabolism are regulated may help to develop new dietary and therapeutic strategies to improve cardiovascular function and overall health as we age.

2.1 Metabolic Inflexibility and Cardiac Pathophysiology

Cardiac output is an energetically demanding process, accounting for approximately 10–20% of whole-body metabolic demand during resting conditions [3]. The heart derives energy primarily from the oxidation of fatty acids. Non-hormonal mechanisms ensure that when both glucose and fatty acids are present, the heart preferentially uses fatty acids. This phenomenon, first noted by Randle in 1963, ensures that fatty acid oxidation reduces glucose utilization [4]. It occurs through an elegant series of allosteric inhibitions that became known as the Randle Cycle. The general biochemical outcome of the Randle cycle is to conserve glucose for the brain in the absence of food or to enhance glycogen synthesis in the muscles after feeding [4–7]. While this glucose-sparing phenomenon has a strong role in survival during times of nutrient deprivation, it becomes problematic in today’s world with the epidemic rise in obesity and diabetes, which limit the metabolic flexibility to oxidize glucose during periods of enhanced energetic demands.

Prolonged reliance on fatty acid oxidation that occurs as a result of diets high in fat content results in obesity, diabetes, and cardiac pathologies. For example, mice that exclusively rely on fatty acid oxidation induced by diabetes [8], peroxisome proliferator-activated receptor (PPAR) overexpression [9], or phosphofructokinase-2 (PFK-2) deficiency [10], develop lipotoxicity and cardiac hypertrophy. In the case of diabetes, this metabolic inflexibility contributes to diabetic cardiomyopathy [11]. In fact, paradoxically, starvation also elevates levels of circulating fatty acids that, in turn, increase the utilization of fatty acids relative to glucose for energy production in multiple tissues [12–17]. Thus, the dilemma with such metabolic conditions is that the Randle cycle functions not only as a glucose-sparing phenomenon, but rather a feed forward mechanism to increase cardiac metabolic inflexibility.

Maintaining dynamic glucose utilization in the presence of fatty acids is essential for optimal cardiac function. For example, the heart rapidly oxidizes glucose following β -adrenergic stimulation to supply ATP during increased cardiac output. The dynamic capacity to increase glucose utilization is also necessary for the heart to recover from pathophysiological metabolic stresses, such as ischemia/reperfusion [13]. Thus, understanding the mechanisms by which the heart overrides the Randle cycle may be one approach to developing therapeutic targets to promote metabolic flexibility and thereby minimize cardiomyopathies associated with increased dietary fat, obesity, and diabetes. For such a strategy, it is important to consider the metabolic factors that contribute to the Randle

cycle. The increase of acetyl CoA, citrate, and NADH generated by fatty acid oxidation inhibits the oxidation of glucose at two key regulatory points (Fig. 1). When fatty acids are oxidized, an increase in the Krebs cycle intermediate, citrate, inhibits PFK-1, which is the first committed and rate limiting step in glycolysis [18]. The mitochondrial enzyme pyruvate dehydrogenase (PDH) is also central to regulating the use of glucose relative to fatty acids for energy homeostasis. PDH commits glycolytically-derived pyruvate for ATP production [19–21]. PDH is regulated by various isoforms of pyruvate dehydrogenase kinase (PDK1, 2, 3, 4) and phosphatase (PDP1 and 2), with phosphorylation resulting in enzyme inhibition. Products of fatty acid oxidation (NADH and acetyl-CoA) activate PDKs resulting in PDH phosphorylation and inhibition [19–21]. Thus, when fatty acids are available, the intrinsic capacity to utilize glucose is low. Understanding how the heart normally overrides the Randle cycle provides both opportunities and challenges for restoring cardiac metabolic flexibility.

2.2 Sympathetic Stimulation of Glycolytic Flux: Targeting PKA

The autonomic nervous system, comprised of the sympathetic and parasympathetic systems, is the primary means of regulating cardiac output and coordinating the moment-to-moment changes in contractile demand with commensurate changes in metabolism. The effects of the sympathetic stimulation are mediated by β -adrenergic receptors and the downstream production of cyclic AMP (cAMP) (Fig. 1). The main intracellular target of cAMP is cyclic AMP dependent protein kinase (PKA). Activation of PKA concertedly increases cardiac contractility and metabolism via the phosphorylation of specific protein substrates that enhance Ca^{2+} cycling [22]. Thus, activation of the β -adrenergic pathway is an efficient mechanism of coordinating appropriate metabolic and biomechanical responses to rapid increases in contractile demands and acute stresses.

The primary means of increasing glycolytic flux upon sympathetic stimulation is via the activation of PFK-2, a bifunctional enzyme containing both kinase and phosphatase activities that produces and degrades fructose-2,6-bis-phosphate, respectively [23, 24]. This metabolite is a potent activator of PFK-1, a rate-limiting step of glycolysis. The catalytic activity of PFK-2 is regulated by its phosphorylation state [25]. Phosphorylation of the heart isoform of PFK-2 (PFKFB2) increases its kinase activity and production of fructose-2,6-bis-phosphate. With sympathetic stimulation, PKA mediates the phosphorylation and activation of PFK-2 [23, 26]. Additional metabolic signals, such as insulin and nutrient stress, also activate PFK-2 via Akt and AMPK mediated phosphorylation, respectively [27, 28]. β -adrenergic and insulin stimulation of glycolysis in the cytosol occurs in concert with activation of mitochondrial pyruvate utilization via activation of PDH [29]. The mechanism involves Ca^{2+} activation of PDP1, and dephosphorylation of PDH [30]. In sum, PKA mediated phosphorylation of PFK-2 and increased cytosolic and mitochondrial Ca^{2+} promotes glycolytic flux even in the presence of fatty acids [31].

Elevated sympathetic nervous system tone is predominant in obesity and diabetes [32–34]. While in the short term this may improve metabolic flexibility by increasing glucose oxidation, chronic sympathetic stimulation is pathological and promotes hypertrophy and exacerbates the progression of heart failure [35, 36]. The cause of this increased sympathetic

drive is not completely understood but may be due to factors such as autonomic neuropathy or orthostatic hypotension. Hyperadrenergic signaling, to an extent, is attenuated by desensitization of receptors and this may impact metabolic cardiac metabolism. Indeed, blocking chronic adrenergic stimulation with metoprolol, a beta-blocker, decreases diabetic cardiomyopathy [37, 38]. One effect of this therapeutic may be to promote proper PKA signaling that is disrupted by chronic activation. However, changes to PKA signaling that occur downstream of the receptor upon chronic activation are less understood. We hypothesize that alterations in PKA signaling affect the activation of PFK-2 and impair its ability to overcome the Randle cycle. This may lead to an uncoupling of adrenergic signaling and metabolic flexibility that drives a pathological feed forward mechanism for sustained fatty acid oxidation. PKA itself is a poor therapeutic target because of its ubiquitous expression and tissue specific effects on cellular physiology. However, this limitation may be overcome by targeting cardiac-specific regulators of PKA that facilitate the proper activation of metabolic enzymes and improve the coordination of contractility and metabolism.

Hyperadrenergic signaling also impairs metabolic flexibility by increasing the production of mitochondrial-derived free radicals [39]. This increased oxidative stress may be exacerbated by changes that occur to mitochondria, such as protein hyperacetylation [40], discussed below, and contribute to further bioenergetic defects. This is especially true because changes in the cellular redox balance affect insulin signaling, which further impairs glucose oxidation. The connections between chronic adrenergic signaling and changes in mitochondrial function have not been well explored and may represent an important area for developing therapeutic targets.

2.3 Pyruvate Oxidation: A Metabolic Flexibility Toggle

It is well known that high dietary fat and ensuing obesity are often associated with the inability of the heart to appropriately metabolize glucose resulting in heavy reliance on fatty acids for energy production [13, 15, 41–43]. This metabolic inflexibility has been attributed to deficits in insulin stimulated glucose uptake, given that the heart exhibits indices of suppressed insulin signaling and/or glucose transport with high dietary fat [13, 15, 42, 43]. We recently reported that reductions in the ability of cardiac mitochondria to oxidize glucose-derived pyruvate occur within the first day of feeding mice a high fat diet prior to loss of insulin signaling [41]. A selective increase in pyruvate dehydrogenase kinase 4 (PDK4) content and subsequent phosphorylation and inhibition of pyruvate dehydrogenase (PDH) were found to be responsible [41]. Increases in PDK4 mRNA and/or protein or declines in the active fraction of PDH were previously thought to require high dietary fat durations of weeks [15, 21, 43–46] rather than hours [41]. The rapidity of the response was likely overlooked because PDH activity is often assessed under nonphysiologic conditions and/or analyses are performed after animals have been fasted, a traditional experimental protocol that also provokes elevated PDK4 [41]. We have shown that rapid diet-induced PDK4-dependent loss of PDH activity could not be overcome, even when cardiac mitochondria were exposed to conditions that reflect maximal energetic demand [41]. As such, inhibition of PDH might be expected to exert immediate limitations on energetic

capacity and contractile function of the heart, particularly under conditions of stress, and initiate and exacerbate cardiovascular disease.

Potential consequences of PDK4-dependent inhibition of PDH are the inability to meet energetic demand and the development of pathophysiologic variations in myocardial Ca^{2+} transients and content. Glucose utilization must increase in response to physiologic stimuli to ensure elevated rates of energy production and enhanced contractile function. Ca^{2+} -dependent activation of PDH is an indispensable component of β -adrenergic stimulation, committing pyruvate for ATP production [20, 21, 47]. The inability to overcome enhanced PDK4 expression due to high dietary fat may reduce Ca^{2+} -dependent activation of PDH, thus limiting the energetic capacity of the heart. These events would be predicted to compromise contractile function and promote cardiac hypertrophy. Furthermore, prolonged high dietary fat and obesity induce atherosclerosis that, in turn, increases the frequency of episodes of ischemia/reperfusion that provoke Ca^{2+} overload and myocardial free radical production [13, 48]. The inability to fully activate PDH would further exacerbate Ca^{2+} overload and ischemia/reperfusion damage. In support of this possibility, pharmacologic inhibition of PDKs or knockout of PDK4 has been shown to diminish infarct size or enhance recovery of contractile function upon *in vivo* or *ex vivo* cardiac ischemia/reperfusion [49–52].

Beyond the likelihood of exerting immediate effects on cardiovascular function and the heart's ability to respond to pathophysiologic stress, our recent findings demonstrate that diet-induced increases in PDK4 protein levels and inhibition of PDH initiate and are required for loss in insulin signaling [41]. Evidence indicates that this is likely due to enhanced free radical production. High dietary fat induces heavy reliance on mitochondrial β -oxidation for energy production [13, 15, 41–43]. Mitochondria respiring on fatty acids relative to glucose-derived pyruvate produce greater levels of free radical species [53–55]. Moreover, mice that have catalase targeted to the mitochondria (i.e., mCat mice) show diminished mitochondrial hydrogen peroxide (H_2O_2) production and do not develop insulin resistance with chronic high fat diet [53]. Thus, the effects of high dietary fat on PDK4-mediated inhibition of PDH has both immediate implications for the capacity of the heart to meet increased demand and the long-term cardiovascular health of an organism.

The question that emerges is: Why is the heart designed to respond so rapidly to high dietary fat by increasing PDK4 expression, particularly given the likely consequences on cardiac function? Interestingly, the swift increase in PDK4 protein levels with high dietary fat is reminiscent of that observed with food deprivation (e.g. fasting/starvation [44, 56, 57]) or periodic cessation of food consumption during the day (e.g. diurnal post-absorptive state [58]). All of these nutritional states have in common high levels of circulating fat. When food is scarce, PDK4-dependent inhibition of PDH may represent an evolutionarily advantageous response to preserve limited glucose for use by glycolytic tissues (e.g. brain) [59]. This pro-survival response may be misappropriated in the context of high dietary fat, obesity, and/or diabetes, compromising the normal function of the heart and driving the development of cardiovascular disease.

3.1 Metabolic Pathway Regulation and Nutrient Sensing: Role of Reactive Metabolic Intermediates and Oxygen Species

Since the initial description of the Randle cycle, additional mechanisms have been described for how lipid metabolism affects the balance between fatty acid oxidation and carbohydrate metabolism. The role of reactive molecular species, including reactive metabolic intermediates (e.g. acetyl-CoA and succinyl-CoA) and reactive oxygen species (e.g. H_2O_2), are novel contributors to this control. Whereas the Randle cycle is a coordinated series of allosteric interactions that modulate enzyme activities, these reactive species modulate metabolism by post-translational modifications. An intriguing component of regulating a biochemical activity by this type of post-translational modification is the specificity of the reactions and the means by which the resulting changes are regulated. For acetylation and succinylation, regulation appears based on the balance between the production of the acetyl-CoA and succinyl-CoA and de-acylation mediated by a family of sirtuins. For redox-based modifications, regulation is based on the production of specific reactive species and modulation by the antioxidant enzyme and repair systems (e.g. thioredoxins, glutaredoxins). An open question currently is the site-specificity and functional impact, if any, of specific modifications. In the case of protein acetylation, for example, a large number of modification sites have been identified but the factors that determine the sites of modification and functional impact of each are generally not understood. In the case of protein phosphorylation, by comparison, individual sites of modification have consistently been directly linked to corresponding changes in function. It is possible that a similar direct site-specific link to functional changes does not exist for oxidation and acetylation so that a key factor may be the extent to which the entire protein is decorated with these modifications.

3.2 Regulation via Reversible Mitochondrial Protein Modifications

Recently, the appreciation of protein acetylation and succinylation as new regulatory post-translational modifications has grown [60, 61]. Several proteomics experiments have described an extensive acetylome and succinylome at both the overall protein level and at specific modification sites [62–64]. As a group, these reports list over 4000 acetylation sites in nearly 2000 proteins, including a report of over 2000 acetylation sites in 400 mitochondrial proteins. A similarly large number of succinylation sites have also been reported [65]. Bioinformatics analyses link these modified protein to a number of metabolic pathways. Furthermore, the pattern of acetylation is responsive to both calorie restriction and metabolic flexibility in a manner that is reminiscent of the Randle cycle's adjustment between carbohydrate and lipid utilization [61, 66, 67]. Thus, these protein modifications may play a regulatory role in specific metabolic pathways or be pathological mediators when occurring at elevated levels [68].

Our own research suggests acetylation of mitochondrial proteins is propagating metabolic inflexibility [40]. We have shown that cardiac mitochondria isolated from type 1 diabetic mice have deficiencies in supporting oxidative phosphorylation from pyruvate and glutamate. However, these mitochondria fully retain the capacity for fatty acid supported ATP production. These alterations in substrate selection are accompanied by hyper-acetylation of mitochondrial proteins and increased superoxide production. Mitochondria

locked into a mode that prevents alternate substrate utilization poses a problem for breaking the Randle cycle. This is because increasing glycolysis in the cytoplasm must be coordinated with entry and subsequent oxidation of pyruvate in mitochondria.

While a mitochondrial acetyl transferase has been identified [69], growing evidence suggests that non-enzymatic reactions of acetyl-CoA and succinyl-CoA are responsible for these modifications. Indeed, mitochondria have an optimal micro-environment for these reactions given the alkaline pH and elevated concentration of acetyl-CoA in the matrix [70, 71]. Intriguingly, in our work, we found that chemically inducing acetylation of control heart mitochondria preferentially inhibits pyruvate supported oxidative phosphorylation [40]. This suggests that proteins involved with pyruvate oxidation are particularly sensitive to acetylation, perhaps due to their microenvironment, proximity to acetyl-CoA, abundance, or resistance to deacetylation by the mitochondrial deacetylase, SIRT3. Others have shown that acetylation of the E1 α subunit of pyruvate dehydrogenase alters its phosphorylation, reduces enzyme activity, and suppresses PDH enzymatic activity [72]. Interestingly though, in our experiments we have found that inhibition of pyruvate-supported mitochondrial respiration by acetylation is not due to a decrease in PDH activity. This suggests that yet other aspects of pyruvate oxidation are sensitive to acetylation and impair metabolic flexibility. Removal of mitochondrial protein acetyl or succinyl modifications via activation of mitochondrial sirtuins, such as SIRT3 or SIRT5 respectively, is an additional approach to restore metabolic flexibility under obesogenic and diabetic conditions [70].

3.3 Role of Free Radicals in Nutrient Sensing and Cardiac Function

Another type of reactive species linked to fatty acid oxidation is reactive oxygen species (ROS) [53]. The primary types of ROS generated during fatty acid oxidation are superoxide and H₂O₂. Mitochondria are traditionally seen as the most significant source of ROS in a cell, but new interest is focusing on peroxisomes because of their integral role in lipid metabolism. Peroxisomes are single membrane-bound organelles that generate ROS during very-long-chain fatty acid (vLCFA) metabolism [73] (Fig. 2A). The most common pathway for lipid metabolism is β -oxidation. The chemical reactions of β -oxidation in peroxisomes are functionally identical to those in mitochondria, but they use a different set of enzymes with different substrate preferences. A key part of these differences in peroxisomes is the first step in β -oxidation catalyzed by the enzyme acyl-CoA oxidase. This enzyme transfers the electrons produced to O₂ to generate H₂O₂ while the dehydrogenated fatty acid moves to the next step in the reaction. Several other H₂O₂ generating enzymes are also found in the peroxisome. H₂O₂ has been implicated in impaired insulin signaling [74]. However, the effect of ROS on insulin signaling appears to depend on the type, magnitude, duration, and intracellular location as enhanced ROS has also been shown to increase insulin sensitivity [75].

One reason for variable effects of ROS on redox-sensitive insulin signaling targets is modulation by the cellular antioxidant system. Catalase is an abundant antioxidant enzyme involved in the breakdown of H₂O₂. Catalase is primarily localized to peroxisomes, and in fact, the presence of catalase is used for the detection of peroxisomes in a number of imaging techniques. As mentioned previously, mice that have catalase targeted to the

mitochondria (i.e., mCat mice) show diminished mitochondrial H₂O₂ production and do not develop insulin resistance with chronic high fat diet [53]. These findings implicate excessive H₂O₂ production in metabolic inflexibility. We have shown the mice fed a high fat diet rapidly (within 1 day) increase the expression of catalase in the heart (Fig. 2A), with no similar increase in other tissues such as the liver [54]. Catalase was the only antioxidant enzyme with increased expression; no changes in protein abundance were observed in other antioxidant enzymes (e.g., superoxide dismutases, peroxiredoxins, glutathione peroxidases) or related proteins (e.g., glutathione reductases, thioredoxin, thioredoxin reductase, and glutathione-S-transferases). Catalase was also increased by 1 day of fasting in mice. These findings suggest that both the high fat diet and fasting increased lipid metabolism, resulting in a flux of peroxisomal H₂O₂ production and catalase upregulation. However, the functional impact of the H₂O₂-catalase response to increase fatty acid oxidation is not clear. Changes in heart function occur before hyperglycemia in mouse models of obesity and insulin resistance, consistent with the defect being the declined use of glucose rather than the glucose intolerance per se [76, 77].

Our recent studies in the fruit fly, *Drosophila melanogaster*, suggest that peroxisome-derived ROS may be an evolutionarily conserved redox signal for regulating cardiac physiology. The fly heart is organized as a linear tube comprising non-muscle pericardial cells surrounding contractile cardiomyocytes. We have recently shown that elevated levels of ROS are present in the pericardial cells compared to cardiomyocytes under normal, physiological conditions [78]. Perturbation of pericardial ROS levels causes cardiomyocyte dysfunction, revealing that ROS in pericardial cells act in a paracrine manner to regulate normal cardiac function. We further found that ROS do not diffuse from pericardial cells into the cardiomyocytes to exert their function; rather ROS control the production of downstream signals that act in turn on the cardiomyocytes to regulate their physiology in a paracrine fashion (Fig. 2B). In our further quest to identify the cellular source of ROS in pericardial cells, we have discovered that peroxisomes are more abundant in pericardial cells relative to cardiomyocytes. Conversely, the cardiomyocytes possess more mitochondria than the pericardial cells. We also found that genetic manipulations that disrupt peroxisomal lipid metabolism in pericardial cells are linked to diminished levels of pericardial ROS levels, as well as to impaired neighboring cardiomyocyte function.

Based on these findings, peroxisomes in pericardial cells may serve as lipid sensors by producing differing amounts of ROS that act as paracrine signals from the pericardial cells to modulate cardiomyocyte function. The finding that peroxisome-generated ROS acts in an autocrine and paracrine manner to regulate cardiomyocyte activity advances an emerging area of focus on peroxisomes as central regulators of lipid metabolism and redox signaling [79]. The upregulation in catalase in response to increased lipid metabolism may serve as a feedback mechanism to regulate H₂O₂ levels in the heart while still preserving redox-stimulated contraction. Overall, our studies on peroxisome function in the fly and mammalian hearts suggest that these organelles regulate cardiomyocyte activity by modulating the rate of H₂O₂ production and catalase-dependent consumption. A critical area for future work is to identify the downstream redox-sensitive signaling targets of peroxisomal ROS and how these targets regulate glucose and lipid utilization and ultimately contractile function.

4.1 “Cardiokines”: Heart Communication Branches Out

An emerging theme in the field of energy metabolism is the ability of metabolically active organs to communicate in an autocrine and/or paracrine manner via the release of soluble bioactive factors. The most notable example is adipose tissue, which secretes numerous factors termed adipokines involved in the regulation of substrate utilization and metabolic homeostasis. For example, adipocyte secreted peptides, such as leptin and adiponectin, regulate multiple metabolic processes, including appetite and insulin sensitivity [80]. With the development of obesity, immune cells located within adipose tissue, in particular macrophages, are also a source of numerous cytokines and chemokines [81]. These inflammatory molecules modulate tissue metabolism locally and systemically by triggering cellular inflammation and inducing immune cell activation and migration. In fact, there is growing evidence of an intrinsic relationship between inflammation and metabolism in multiple cell types and disease states [82–84]. Other tissues, such as skeletal muscle, liver, and heart, also secrete factors that modulate metabolism, inflammation, and cellular growth/repair [85]. Indeed, it has been recognized for more than three decades that the heart could serve as an endocrine organ, as first shown by the presence of electron dense-core granules in the atrial cardiomyocytes indicative of a secretory role of these cells [86]. Subsequently, a number of proteins, collectively described as “cardiokines”, were found to be produced by the heart, including the atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), myostatin, growth differentiation factor (GDF)-15, and activin A [87]. While most cardiokines identified act in an autocrine manner to regulate cardiac function and response to stress [85], the natriuretic peptides were recently shown to play an important role in mediating communication between the heart and other target organs to regulate whole-body energy metabolism. Here, we review the rapidly evolving field investigating how adipokines and cardiokines modulate substrate uptake and oxidation, and we discuss how these factors may contribute to the metabolic inflexibility that occurs with aging and obesity.

4.2 Adipokines and an Adipose Tissue–Heart Axis

Adipokines such as leptin and adiponectin are well-documented mediators of glucose and fatty acid metabolism in metabolically active tissues such as skeletal muscle and liver. In the heart, these adipokines also regulate cardiomyocyte metabolism by increasing glucose and fatty acid uptake and oxidation [88]. For example, adiponectin acutely stimulates glucose uptake and oxidation in primary cardiomyocytes *in vitro* within the first hour of treatment [89]. By 24 hours, however, PDH activity becomes inhibited and glucose oxidation declines. This decline occurs together with an increase in fatty acid import and oxidation [89–91]. In contrast, leptin does not alter *in vitro* glucose uptake or metabolism acutely or after 24 hours [92]. Rather, the major metabolic effect of leptin on cardiomyocyte metabolism is to increase the uptake of vLCFA. Leptin treatment also acutely stimulates fatty acid oxidation; however, this effect is lost within 24 hours, resulting in the accumulation of intracellular lipids [92]. In an *in vivo* mouse model of lipotoxic cardiomyopathy, recombinant adenovirus-induced hyperleptinemia rescued the cardiac lipotoxic pathology and was associated with an increase in cardiac AMP-activated protein kinase phosphorylation, suggesting that the net effect of chronic leptin treatment was increased cardiac fatty acid oxidation [93]. Similarly, the protective effects of leptin against lipotoxic cardiomyopathy were also demonstrated by selectively re-expressing the leptin receptor in the

cardiomyocytes of obese leptin receptor mutant db/db mice [94] or by chronic leptin treatment in obese leptin mutant ob/ob mice compared relative to equivalent caloric restriction weight loss [95]. These results, including additional work with adiponectin deficient or transgenic mice, suggest a generally protective role for adiponectin and leptin in cardiac pathophysiology [96].

Thus, how might changes in adipokines, such as leptin and adiponectin, contribute to cardiac metabolic inflexibility? A study by Sweeney and colleagues showed that adipocyte-conditioned medium derived from primary adipocytes of wild-type and streptozotocin-induced diabetic rats induced profound differences in cardiomyocyte metabolism. The conditioned medium from wild-type rats increased cardiomyocyte glucose and fatty acid uptake and oxidation; whereas, the medium from the diabetic rats stimulated non-oxidative glucose metabolism and suppressed fatty acid oxidation [88]. These substantial metabolic differences, however, do not mirror the lipid-centric metabolic inflexibility pattern observed in diabetic hearts (e.g., Fig 1C). A targeted analysis of the changes in adipokine concentrations in the diabetic rat conditioned medium showed significant reductions in adiponectin, leptin, and visfatin, while resistin, tumor necrosis factor alpha, interleukin-6, and free fatty acid concentrations remained unchanged [88]. Except for adiponectin, these altered adipokine concentrations differ from the typical changes observed in the serum of obese, type 2 diabetic patients and animal models in which leptin, visfatin, resistin, tumor necrosis factor alpha (TNF- α), interleukin-6 (IL-6), and free fatty acid levels are increased. As previously discussed, leptin stimulates fatty acid uptake and oxidation, consistent with a metabolically inflexible obese phenotype. Furthermore, resistin treatment impairs basal and insulin-stimulated glucose uptake [97]. However, less is known about the effects of visfatin, TNF- α , and IL-6 on substrate uptake and utilization in cardiomyocytes. Visfatin (i.e., nicotinamide phosphoribosyltransferase) is a rate-limiting enzyme in the NAD⁺ salvage pathway. Transgenic overexpression of visfatin in the mouse heart increased NAD⁺ levels [98], which would be expected stimulate cell respiration by activating key regulatory enzymes (e.g. PDH) as well as NAD⁺-dependent sirtuins. Conversely, TNF- α and IL-6 appear to impair cardiomyocyte metabolism by independently inhibiting PDH and electron transport chain activity [99]. Moreover, TNF- α overexpression in cardiac AC16 cells promotes glucose oxidation by downregulating PDK4 and reducing the expression of peroxisome proliferator-activated receptor coactivator 1 α (*PGC-1 α*), a transcriptional co-activator of mitochondrial biogenesis and lipid metabolism genes [100]. Thus, at this point, it is not clear how adipokines contribute cardiac metabolic inflexibility given these contrasting effects on cardiomyocyte metabolism. The clinical relevance of these adipokines in terms of diagnostic potential or therapeutic efficacy continues to be evaluated due to the challenges of determining their role in specific types and stages of heart disease pathologies [96, 101–105]. In addition, epicardial adipose tissue is a local source of secreted adipokines and other bioactive metabolic factors, which adds to the complexity of relating changes in serum adipokine concentrations to the onset and progression of cardiovascular disease [106].

4.3 Cardiac Natriuretic Peptides and a Heart–Adipose Tissue Axis

Natriuretic peptides (ANP/BNP) are the most studied cardiokines that were originally identified as important factors in blood pressure control through the regulation of

intravascular blood volume and vascular tone [107]. Increased cardiac contractility and distension of atrial and ventricular cardiomyocytes stimulate ANP and BNP production and secretion. However, in addition to increased mechanical strain, numerous other conditions also increase cardiac natriuretic peptide production, including neurohormones, cytokines, growth factors, and hypoxia [108]. Clinically, ventricular hypertrophy, inflammation, and fibrosis are associated with increased BNP production.

Several studies indicate a potential autocrine and paracrine role for natriuretic peptides in regulating heart metabolism. For instance, in cultured primary cardiomyocytes, ANP treatment increased glucose uptake, particularly during hypoxia [109, 110]. These early studies suggest that activation of phospholipase C and calcium-dependent mobilization of glucose transporters to the surface membrane facilitate this enhanced glucose uptake [109, 110]. However, it is not yet clear to what extent ANP stimulates oxidative versus non-oxidative glucose metabolism, whether or not BNP also stimulates glucose uptake, and if natriuretic peptides can override conditions that promote metabolic inflexibility.

Recent work on the leptin receptor mutant *db/db* mouse, which develops obesity and type 2 diabetes, suggests a potential role for these peptides in cardiac and systemic metabolic regulation. Transcript levels of ANP and BNP in the heart were downregulated by >2-fold in *db/db* mice [111]. Treatment with BNP via osmotic pumps reduced bodyweight, fasting insulin levels, HOMA-IR scores, cardiomyocyte death, and cardiac hypertrophy and fibrosis in *db/db* mice [112]. In addition to the potential cardiac-specific effects of BNP treatment, adipocyte hypertrophy was reduced in subcutaneous, perirenal, and epicardial fat, suggesting additional cardiac-independent effects on metabolism. Indeed, there is growing evidence that natriuretic peptides influence the metabolism of other tissues such as fat.

Studies now demonstrate that ANP and BNP bind to natriuretic peptide receptors on human fat cells and can induce adipocyte triglyceride lipolysis through the cGMP–cGMP-dependent protein kinase (PKG) pathway [113, 114]. Working through the same cGMP–PKG pathway, ANP and BNP also trigger p38 mitogen-activated protein kinase (MAPK) signaling to elicit a transcriptional response resulting in elevated expression of PPAR γ coactivator-1 α (PGC-1 α) and uncoupling protein 1 (UCP1) [115]. PGC-1 α is one of the determinants of brown fat development and a key regulator of mitochondrial biogenesis [116], whereas UCP1, through its uncoupling of fuel oxidation from ATP generation, promotes heat generation and energy expenditure. Therefore, by activating PGC-1 α and UCP1 transcription, cardiac-derived natriuretic peptides positively regulate brown adipose tissue formation and promote thermogenesis. Increased natriuretic peptides also promote beige adipocyte development in white adipose tissue [115]. Activation of brown adipose tissue increases the uptake and clearance of plasma triglycerides [117]. Thus, natriuretic peptide induction of brown and beige adipocyte activity may protect against obesity-induced cardiac metabolic inflexibility by increasing the clearance of excess circulating fatty acids and decreasing the lipid “load” on cardiomyocytes under conditions of cardiac stress. However, as cardiac natriuretic peptides also stimulate adipocyte triglyceride lipolysis independent of β -adrenergic signaling [115], the potentially beneficial effects of ANP and BNP must be considered in the broader context of the net release and clearance of circulating lipids, the duration of action, and the physiologic cardiovascular conditions that

stimulate ANP and BNP production. Unraveling these local and systemic effects remains a challenge for future therapeutic applications involving cardiac natriuretic peptides.

4.4 A Cardiac-specific *Mediator* of Cardiokines and Systemic Metabolism?

A recent discovery by Olson and colleagues added a new twist to the cardiac-specific regulation of metabolism and insulin sensitivity. This work focused on the role of the Mediator complex, a multi-subunit assembly of about 30 nuclear proteins that regulate gene transcription by interacting with RNA polymerase II and other coactivators/repressors within the transcriptional pre-initiation complex [118]. Cardiac-specific overexpression of Mediator complex subunit 13 (MED13), one of the four components of the kinase submodule of the Mediator complex that regulates transcriptional activity, ameliorated the development of high-fat diet-induced obesity and insulin resistance in mice [119]. Conversely, cardiac-specific deletion of MED13 exacerbated diet-induced obesity and insulin resistance [119]. MED13 is negatively regulated by a heart-specific microRNA, miR-208a, and pharmacologic inhibition of miR-208a also protects against high-fat diet-induced obesity and insulin resistance [119]. The Olson group went on to show that in *Drosophila*, heart- and striated muscle-specific knockdown of MED13 also promoted obesity [120].

To understand how manipulating cardiac-specific MED13 modulates systemic metabolism, the authors adopted a two-pronged approach. First, using *Drosophila* to conduct an RNAi screen, they identified Wingless (Wg, the *Drosophila* Wnt1) as the cardiac-derived factor that mediates the metabolic effects of MED13 in flies [120]. Second, in mice, they identified white adipose tissue and liver as the principal target tissues that respond to and are likely responsible for cardiac MED13 signaling [121]. Heterotypic parabiosis experiments showed that MED13 overexpression in the heart induced the production of a circulating soluble factor(s) that in turn increased the lipid uptake and oxidation in white adipose tissue and liver [121]. Furthermore, in-depth analysis of heart metabolism showed that cardiac MED13 overexpression stimulated glucose and fatty acid oxidation under fed and fasted states, respectively [121]. The soluble factor(s) mediating these responses are not known. ANP and BNP gene expression were increased in MED13 transgenic mice, although circulating proteins levels only showed an increasing trend [66]. Future work is needed to understand how MED13 increases overall metabolic flux in the heart while promoting metabolic flexibility in the fed-fast transition. Whether or not cardiac MED13 overexpression also promotes metabolic flexibility in the heart under conditions of high dietary fat and obesity remains to be determined. Overall, this research suggests that modulating gene transcription in the heart induces multi-organ changes in metabolism through factors beyond hemodynamic regulation of oxygen delivery.

5.1 Summary and Perspectives

Fueling the heart is a highly regulated process involving multiple levels of control, from substrate availability to the post-translational modification of mitochondrial proteins. Understanding the conditions that override specific regulatory mechanisms, such as the allosteric inhibition characteristic of the Randle Cycle, is critical for restoring metabolic flexibility that is lost with the development of diabetic cardiomyopathy and aging. Paradoxically, the ability to override the Randle Cycle and rapidly diminish glucose

utilization potentially conferred an evolutionary advantage during periods when food was scarce. Organisms experience changes in food availability and macronutrient composition in response to seasonal and environmental changes. The ability to partition limited fuel among different organ systems to support a hierarchy of functions critical for life, such as glucose sparing for the brain and nervous system, may have conferred a significant evolutionary advantage for survival. Similar to a high fat meal, starvation elicits an increase in circulating fatty acids, elevated expression of PDK4, and inhibition of PDH ensuring that heart and skeletal muscle preferentially consume available fat for energy production. This pro-survival response preserves limited glucose for use by glycolytic tissues such as the brain to maintain cognitive function. In its absence, organisms would be at increased risk for severe hypoglycemia and death if glucose were rapidly consumed by cardiac and skeletal muscle during periods of fasting. However, this evolutionary advantage may be afforded at the expense of the heart's energetic capacity and ability to respond to stress.

We propose that regular changes in the ability to utilize glucose, dependent on dietary composition, time of day, and the concentrations of circulating bioactive factors such as adipokines or cardiokines, will create periods during which the heart's response to physiologic and pathophysiological stress is compromised. Thus, an evolutionarily conserved response to periodic starvation likely has profound implications for human health in the modern world of chronic excess calories and fat-rich foods. We believe that such a perspective, particularly in light of our rapidly progressing discoveries of new metabolic regulatory mechanisms, may improve our understanding of how mitochondrial, cellular, and systems-level metabolic regulatory mechanisms are coordinated to control glucose and fatty acid utilization. This need is great considering the prevalence of cardiovascular disease and metabolic syndrome in obese and elderly individuals, a population that has increased rapidly in recent years.

Acknowledgments

We would like to thank our colleagues, Drs. Holly Van Remmen, Scott Plafker, and Ann Louise Olson, as well as the members of our labs, for many insightful discussions on the topics discussed in this review. This work was supported by the National Institute of General Medical Sciences (P20GM103441 to TMG; P20GM104934 to KMH; P20GM103636 to HYL), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (R03AR066828 to TMG), and the National Institute on Aging (R01AG049058 to TMG) of the National Institutes of Health. Support also from the American Heart Association (14GRNT20510031 to KMH and 13SDG14680005 to HYL). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the American Heart Association.

References

1. Riera CE, Dillin A. Tipping the metabolic scales towards increased longevity in mammals. *Nat Cell Biol.* 2015; 17:196–203. [PubMed: 25720959]
2. Muoio DM. Metabolic inflexibility: when mitochondrial indecision leads to metabolic gridlock. *Cell.* 2014; 159:1253–1262. [PubMed: 25480291]
3. Duncker DJ, Bache RJ. Regulation of coronary blood flow during exercise. *Physiological reviews.* 2008; 88:1009–1086. [PubMed: 18626066]
4. Randle PJ, Garland PB, Hales CN, Newsholme EA. The glucose fatty-acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. *Lancet.* 1963; 1:785–789. [PubMed: 13990765]

5. Depre C, Vanoverschelde JL, Taegtmeyer H. Glucose for the heart. *Circulation*. 1999; 99:578–588. [PubMed: 9927407]
6. Hue L, Taegtmeyer H. The Randle cycle revisited: a new head for an old hat. *American journal of physiology Endocrinology and metabolism*. 2009; 297:E578–591. [PubMed: 19531645]
7. Randle PJ. Regulatory interactions between lipids and carbohydrates: the glucose fatty acid cycle after 35 years. *Diabetes/metabolism reviews*. 1998; 14:263–283. [PubMed: 10095997]
8. Stanley WC, Lopaschuk GD, McCormack JG. Regulation of energy substrate metabolism in the diabetic heart. *Cardiovascular research*. 1997; 34:25–33. [PubMed: 9217869]
9. Finck BN, Lehman JJ, Leone TC, Welch MJ, Bennett MJ, Kovacs A, Han X, Gross RW, Kozak R, Lopaschuk GD, Kelly DP. The cardiac phenotype induced by PPARalpha overexpression mimics that caused by diabetes mellitus. *The Journal of clinical investigation*. 2002; 109:121–130. [PubMed: 11781357]
10. Donthi RV, Ye G, Wu C, McClain DA, Lange AJ, Epstein PN. Cardiac expression of kinase-deficient 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase inhibits glycolysis, promotes hypertrophy, impairs myocyte function, and reduces insulin sensitivity. *The Journal of biological chemistry*. 2004; 279:48085–48090. [PubMed: 15331593]
11. Boudina S, Abel ED. Diabetic cardiomyopathy revisited. *Circulation*. 2007; 115:3213–3223. [PubMed: 17592090]
12. Harmancey R, Wilson CR, Wright NR, Taegtmeyer H. Western diet changes cardiac acyl-CoA composition in obese rats: a potential role for hepatic lipogenesis. *Journal of lipid research*. 2010; 51:1380–1393. [PubMed: 20093477]
13. Lopaschuk GD, Ussher JR, Folmes CD, Jaswal JS, Stanley WC. Myocardial fatty acid metabolism in health and disease. *Physiological reviews*. 2010; 90:207–258. [PubMed: 20086077]
14. Taegtmeyer H, Wilson CR, Razeghi P, Sharma S. Metabolic energetics and genetics in the heart. *Annals of the New York Academy of Sciences*. 2005; 1047:208–218. [PubMed: 16093498]
15. Wilson CR, Tran MK, Salazar KL, Young ME, Taegtmeyer H. Western diet, but not high fat diet, causes derangements of fatty acid metabolism and contractile dysfunction in the heart of Wistar rats. *The Biochemical journal*. 2007; 406:457–467. [PubMed: 17550347]
16. Holness MJ, Sugden MC. Glucose utilization in heart, diaphragm and skeletal muscle during the fed-to-starved transition. *The Biochemical journal*. 1990; 270:245–249. [PubMed: 2396984]
17. Spriet LL, Tunstall RJ, Watt MJ, Mehan KA, Hargreaves M, Cameron-Smith D. Pyruvate dehydrogenase activation and kinase expression in human skeletal muscle during fasting. *Journal of applied physiology*. 2004; 96:2082–2087. [PubMed: 14966024]
18. Mor I, Cheung EC, Vousden KH. Control of glycolysis through regulation of PFK1: old friends and recent additions. *Cold Spring Harb Symp Quant Biol*. 2011; 76:211–216. [PubMed: 22096029]
19. Bowker-Kinley MM, Davis WI, Wu P, Harris RA, Popov KM. Evidence for existence of tissue-specific regulation of the mammalian pyruvate dehydrogenase complex. *The Biochemical journal*. 1998; 329(Pt 1):191–196. [PubMed: 9405293]
20. Rardin MJ, Wiley SE, Naviaux RK, Murphy AN, Dixon JE. Monitoring phosphorylation of the pyruvate dehydrogenase complex. *Analytical biochemistry*. 2009; 389:157–164. [PubMed: 19341700]
21. Sugden MC, Holness MJ. Mechanisms underlying regulation of the expression and activities of the mammalian pyruvate dehydrogenase kinases. *Archives of physiology and biochemistry*. 2006; 112:139–149. [PubMed: 17132539]
22. Bers DM. Cardiac excitation-contraction coupling. *Nature*. 2002; 415:198–205. [PubMed: 11805843]
23. Rider MH, van Damme J, Vertommen D, Michel A, Vandekerckhove J, Hue L. Evidence for new phosphorylation sites for protein kinase C and cyclic AMP-dependent protein kinase in bovine heart 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase. *FEBS letters*. 1992; 310:139–142. [PubMed: 1327869]
24. Hue L, Rider MH. Role of fructose 2,6-bisphosphate in the control of glycolysis in mammalian tissues. *The Biochemical journal*. 1987; 245:313–324. [PubMed: 2822019]

25. Rider MH, Bertrand L, Vertommen D, Michels PA, Rousseau GG, Hue L. 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase: head-to-head with a bifunctional enzyme that controls glycolysis. *The Biochemical journal*. 2004; 381:561–579. [PubMed: 15170386]
26. Kitamura K, Kangawa K, Matsuo H, Uyeda K. Phosphorylation of myocardial fructose-6-phosphate,2-kinase: fructose-2,6-bisphosphatase by cAMP-dependent protein kinase and protein kinase C. Activation by phosphorylation and amino acid sequences of the phosphorylation sites. *The Journal of biological chemistry*. 1988; 263:16796–16801. [PubMed: 2846551]
27. Marsin AS, Bertrand L, Rider MH, Deprez J, Beauloye C, Vincent MF, Van den Berghe G, Carling D, Hue L. Phosphorylation and activation of heart PFK-2 by AMPK has a role in the stimulation of glycolysis during ischaemia. *Curr Biol*. 2000; 10:1247–1255. [PubMed: 11069105]
28. Mouton V, Toussaint L, Vertommen D, Gueuning MA, Maisin L, Havaux X, Sanchez-Canedo C, Bertrand L, Dequiedt F, Hemmings BA, Hue L, Rider MH. Heart 6-phosphofructo-2-kinase activation by insulin requires PKB (protein kinase B), but not SGK3 (serum- and glucocorticoid-induced protein kinase 3). *The Biochemical journal*. 2010; 431:267–275. [PubMed: 20687898]
29. McCormack JG, Denton RM. The activation of pyruvate dehydrogenase in the perfused rat heart by adrenaline and other inotropic agents. *The Biochemical journal*. 1981; 194:639–643. [PubMed: 7306008]
30. Denton RM, Randle PJ, Martin BR. Stimulation by calcium ions of pyruvate dehydrogenase phosphate phosphatase. *The Biochemical journal*. 1972; 128:161–163. [PubMed: 4343661]
31. Depre C, Ponchaut S, Deprez J, Maisin L, Hue L. Cyclic AMP suppresses the inhibition of glycolysis by alternative oxidizable substrates in the heart. *The Journal of clinical investigation*. 1998; 101:390–397. [PubMed: 9435311]
32. Alvarez GE, Beske SD, Ballard TP, Davy KP. Sympathetic neural activation in visceral obesity. *Circulation*. 2002; 106:2533–2536. [PubMed: 12427647]
33. Balcioglu AS, Muderrisoglu H. Diabetes and cardiac autonomic neuropathy: Clinical manifestations, cardiovascular consequences, diagnosis and treatment. *World J Diabetes*. 2015; 6:80–91. [PubMed: 25685280]
34. Grassi G, Dell'Oro R, Facchini A, Quarti Trevano F, Bolla GB, Mancia G. Effect of central and peripheral body fat distribution on sympathetic and baroreflex function in obese normotensives. *J Hypertens*. 2004; 22:2363–2369. [PubMed: 15614031]
35. Francis GS. Pathophysiology of chronic heart failure. *Am J Med*. 2001; 110(Suppl 7A):37S–46S. [PubMed: 11334774]
36. Triposkiadis F, Karayannis G, Giamouzis G, Skoularigis J, Louridas G, Butler J. The sympathetic nervous system in heart failure physiology, pathophysiology, and clinical implications. *Journal of the American College of Cardiology*. 2009; 54:1747–1762. [PubMed: 19874988]
37. Sharma V, Dhillon P, Wambolt R, Parsons H, Brownsey R, Allard MF, McNeill JH. Metoprolol improves cardiac function and modulates cardiac metabolism in the streptozotocin-diabetic rat. *Am J Physiol Heart Circ Physiol*. 2008; 294:H1609–1620. [PubMed: 18203848]
38. Sharma V, McNeill JH. Parallel effects of beta-adrenoceptor blockade on cardiac function and fatty acid oxidation in the diabetic heart: Confronting the maze. *World J Cardiol*. 2011; 3:281–302. [PubMed: 21949571]
39. Andersson DC, Fauconnier J, Yamada T, Lacampagne A, Zhang SJ, Katz A, Westerblad H. Mitochondrial production of reactive oxygen species contributes to the beta-adrenergic stimulation of mouse cardiomyocytes. *J Physiol*. 2011; 589:1791–1801. [PubMed: 21486840]
40. Vadvalkar SS, Baily CN, Matsuzaki S, West M, Tesiram YA, Humphries KM. Metabolic inflexibility and protein lysine acetylation in heart mitochondria of a chronic model of type 1 diabetes. *The Biochemical journal*. 2013; 449:253–261. [PubMed: 23030792]
41. Crewe C, Kinter M, Szweda LI. Rapid inhibition of pyruvate dehydrogenase: an initiating event in high dietary fat-induced loss of metabolic flexibility in the heart. *PloS one*. 2013; 8:e77280. [PubMed: 24116221]
42. Park SY, Cho YR, Kim HJ, Higashimori T, Danton C, Lee MK, Dey A, Rothermel B, Kim YB, Kalinowski A, Russell KS, Kim JK. Unraveling the temporal pattern of diet-induced insulin resistance in individual organs and cardiac dysfunction in C57BL/6 mice. *Diabetes*. 2005; 54:3530–3540. [PubMed: 16306372]

43. Wright JJ, Kim J, Buchanan J, Boudina S, Sena S, Bakirtzi K, Ilkun O, Theobald HA, Cooksey RC, Kandror KV, Abel ED. Mechanisms for increased myocardial fatty acid utilization following short-term high-fat feeding. *Cardiovascular research*. 2009; 82:351–360. [PubMed: 19147655]
44. Holness MJ, Smith ND, Bulmer K, Hopkins T, Gibbons GF, Sugden MC. Evaluation of the role of peroxisome-proliferator-activated receptor alpha in the regulation of cardiac pyruvate dehydrogenase kinase 4 protein expression in response to starvation, high-fat feeding and hyperthyroidism. *The Biochemical journal*. 2002; 364:687–694. [PubMed: 12049632]
45. Orfali KA, Fryer LG, Holness MJ, Sugden MC. Long-term regulation of pyruvate dehydrogenase kinase by high-fat feeding. Experiments in vivo and in cultured cardiomyocytes. *FEBS letters*. 1993; 336:501–505. [PubMed: 8282119]
46. Zhang L, Mori J, Wagg C, Lopaschuk GD. Activating cardiac E2F1 induces up-regulation of pyruvate dehydrogenase kinase 4 in mice on a short term of high fat feeding. *FEBS letters*. 2012; 586:996–1003. [PubMed: 22569253]
47. Patel MS, Korotchikina LG. Regulation of the pyruvate dehydrogenase complex. *Biochem Soc Trans*. 2006; 34:217–222. [PubMed: 16545080]
48. Bayeva M, Sawicki KT, Ardehali H. Taking diabetes to heart--deregulation of myocardial lipid metabolism in diabetic cardiomyopathy. *J Am Heart Assoc*. 2013; 2:e000433. [PubMed: 24275630]
49. Lewandowski ED, White LT. Pyruvate dehydrogenase influences postischemic heart function. *Circulation*. 1995; 91:2071–2079. [PubMed: 7895366]
50. Liu B, Clanachan AS, Schulz R, Lopaschuk GD. Cardiac efficiency is improved after ischemia by altering both the source and fate of protons. *Circulation research*. 1996; 79:940–948. [PubMed: 8888686]
51. Liu Q, Docherty JC, Rendell JC, Clanachan AS, Lopaschuk GD. High levels of fatty acids delay the recovery of intracellular pH and cardiac efficiency in post-ischemic hearts by inhibiting glucose oxidation. *Journal of the American College of Cardiology*. 2002; 39:718–725. [PubMed: 11849874]
52. Ussher JR, Wang W, Gandhi M, Keung W, Samokhvalov V, Oka T, Wagg CS, Jaswal JS, Harris RA, Clanachan AS, Dyck JR, Lopaschuk GD. Stimulation of glucose oxidation protects against acute myocardial infarction and reperfusion injury. *Cardiovascular research*. 2012; 94:359–369. [PubMed: 22436846]
53. Anderson EJ, Lustig ME, Boyle KE, Woodlief TL, Kane DA, Lin CT, Price JW 3rd, Kang L, Rabinovitch PS, Szeto HH, Houmard JA, Cortright RN, Wasserman DH, Neuffer PD. Mitochondrial H₂O₂ emission and cellular redox state link excess fat intake to insulin resistance in both rodents and humans. *The Journal of clinical investigation*. 2009; 119:573–581. [PubMed: 19188683]
54. Rindler PM, Plafker SM, Szweda LI, Kinter M. High dietary fat selectively increases catalase expression within cardiac mitochondria. *The Journal of biological chemistry*. 2013; 288:1979–1990. [PubMed: 23204527]
55. Seifert EL, Estey C, Xuan JY, Harper ME. Electron transport chain-dependent and -independent mechanisms of mitochondrial H₂O₂ emission during long-chain fatty acid oxidation. *The Journal of biological chemistry*. 2010; 285:5748–5758. [PubMed: 20032466]
56. Jeoung NH, Harris RA. Pyruvate dehydrogenase kinase-4 deficiency lowers blood glucose and improves glucose tolerance in diet-induced obese mice. *American journal of physiology Endocrinology and metabolism*. 2008; 295:E46–54. [PubMed: 18430968]
57. Wu PF, Peters JM, Harris RA. Adaptive increase in pyruvate dehydrogenase kinase 4 during starvation is mediated by peroxisome proliferator-activated receptor alpha. *Biochemical and biophysical research communications*. 2001; 287:391–396. [PubMed: 11554740]
58. Stavinoha MA, Rayspellicy JW, Hart-Sailors ML, Mersmann HJ, Bray MS, Young ME. Diurnal variations in the responsiveness of cardiac and skeletal muscle to fatty acids. *American journal of physiology Endocrinology and metabolism*. 2004; 287:E878–887. [PubMed: 15292029]
59. Jeoung NH, Wu P, Joshi MA, Jaskiewicz J, Bock CB, Depaoli-Roach AA, Harris RA. Role of pyruvate dehydrogenase kinase isoenzyme 4 (PDHK4) in glucose homeostasis during starvation. *The Biochemical journal*. 2006; 397:417–425. [PubMed: 16606348]

60. Beltrao P, Albanese V, Kenner LR, Swaney DL, Burlingame A, Villen J, Lim WA, Fraser JS, Frydman J, Krogan NJ. Systematic functional prioritization of protein posttranslational modifications. *Cell*. 2012; 150:413–425. [PubMed: 22817900]
61. Still AJ, Floyd BJ, Hebert AS, Bingman CA, Carson JJ, Gunderson DR, Dolan BK, Grimsrud PA, Dittenhafer-Reed KE, Stapleton DS, Keller MP, Westphall MS, Denu JM, Attie AD, Coon JJ, Pagliarini DJ. Quantification of mitochondrial acetylation dynamics highlights prominent sites of metabolic regulation. *The Journal of biological chemistry*. 2013; 288:26209–26219. [PubMed: 23864654]
62. Choudhary C, Kumar C, Gnad F, Nielsen ML, Rehman M, Walther TC, Olsen JV, Mann M. Lysine acetylation targets protein complexes and co-regulates major cellular functions. *Science*. 2009; 325:834–840. [PubMed: 19608861]
63. Guan KL, Xiong Y. Regulation of intermediary metabolism by protein acetylation. *Trends Biochem Sci*. 2011; 36:108–116. [PubMed: 20934340]
64. Xiong Y, Guan KL. Mechanistic insights into the regulation of metabolic enzymes by acetylation. *J Cell Biol*. 2012; 198:155–164. [PubMed: 22826120]
65. Rardin MJ, He W, Nishida Y, Newman JC, Carrico C, Danielson SR, Guo A, Gut P, Sahu AK, Li B, Uppala R, Fitch M, Riiff T, Zhu L, Zhou J, Mulhern D, Stevens RD, Ilkayeva OR, Newgard CB, Jacobson MP, Hellerstein M, Goetzman ES, Gibson BW, Verdin E. SIRT5 regulates the mitochondrial lysine succinylome and metabolic networks. *Cell Metab*. 2013; 18:920–933. [PubMed: 24315375]
66. Hebert AS, Dittenhafer-Reed KE, Yu W, Bailey DJ, Selen ES, Boersma MD, Carson JJ, Tonelli M, Balloon AJ, Higbee AJ, Westphall MS, Pagliarini DJ, Prolla TA, Assadi-Porter F, Roy S, Denu JM, Coon JJ. Calorie restriction and SIRT3 trigger global reprogramming of the mitochondrial protein acetylome. *Mol Cell*. 2013; 49:186–199. [PubMed: 23201123]
67. Hirschey MD, Shimazu T, Jing E, Grueter CA, Collins AM, Aouizerat B, Stancakova A, Goetzman E, Lam MM, Schwer B, Stevens RD, Muehlbauer MJ, Kakar S, Bass NM, Kuusisto J, Laakso M, Alt FW, Newgard CB, Farese RV Jr, Kahn CR, Verdin E. SIRT3 deficiency and mitochondrial protein hyperacetylation accelerate the development of the metabolic syndrome. *Mol Cell*. 2011; 44:177–190. [PubMed: 21856199]
68. Choudhary C, Weinert BT, Nishida Y, Verdin E, Mann M. The growing landscape of lysine acetylation links metabolism and cell signalling. *Nat Rev Mol Cell Biol*. 2014; 15:536–550. [PubMed: 25053359]
69. Scott I, Webster BR, Li JH, Sack MN. Identification of a molecular component of the mitochondrial acetyltransferase programme: a novel role for GCN5L1. *The Biochemical journal*. 2012; 443:655–661. [PubMed: 22309213]
70. Wagner GR, Hirschey MD. Nonenzymatic protein acylation as a carbon stress regulated by sirtuin deacylases. *Mol Cell*. 2014; 54:5–16. [PubMed: 24725594]
71. Wagner GR, Payne RM. Widespread and enzyme-independent Nepsilon-acetylation and Nepsilon-succinylation of proteins in the chemical conditions of the mitochondrial matrix. *The Journal of biological chemistry*. 2013; 288:29036–29045. [PubMed: 23946487]
72. Jing E, O'Neill BT, Rardin MJ, Kleinriders A, Ilkayeva OR, Ussar S, Bain JR, Lee KY, Verdin EM, Newgard CB, Gibson BW, Kahn CR. Sirt3 regulates metabolic flexibility of skeletal muscle through reversible enzymatic deacetylation. *Diabetes*. 2013; 62:3404–3417. [PubMed: 23835326]
73. Weller S, Gould SJ, Valle D. Peroxisome biogenesis disorders. *Annu Rev Genomics Hum Genet*. 2003; 4:165–211. [PubMed: 14527301]
74. Houstis N, Rosen ED, Lander ES. Reactive oxygen species have a causal role in multiple forms of insulin resistance. *Nature*. 2006; 440:944–948. [PubMed: 16612386]
75. Loh K, Deng H, Fukushima A, Cai X, Boivin B, Galic S, Bruce C, Shields BJ, Skiba B, Ooms LM, Stepto N, Wu B, Mitchell CA, Tonks NK, Watt MJ, Febbraio MA, Crack PJ, Andrikopoulos S, Tiganis T. Reactive oxygen species enhance insulin sensitivity. *Cell Metab*. 2009; 10:260–272. [PubMed: 19808019]
76. Buchanan J, Mazumder PK, Hu P, Chakrabarti G, Roberts MW, Yun UJ, Cooksey RC, Litwin SE, Abel ED. Reduced cardiac efficiency and altered substrate metabolism precedes the onset of

hyperglycemia and contractile dysfunction in two mouse models of insulin resistance and obesity. *Endocrinology*. 2005; 146:5341–5349. [PubMed: 16141388]

77. Zhang L, Jaswal JS, Ussher JR, Sankaralingam S, Wagg C, Zaugg M, Lopaschuk GD. Cardiac insulin-resistance and decreased mitochondrial energy production precede the development of systolic heart failure after pressure-overload hypertrophy. *Circ Heart Fail*. 2013; 6:1039–1048. [PubMed: 23861485]
78. Lim HY, Wang W, Chen J, Ocorr K, Bodmer R. ROS regulate cardiac function via a distinct paracrine mechanism. *Cell Rep*. 2014; 7:35–44. [PubMed: 24656823]
79. Lodhi IJ, Semenkovich CF. Peroxisomes: a nexus for lipid metabolism and cellular signaling. *Cell Metab*. 2014; 19:380–392. [PubMed: 24508507]
80. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. *Nat Rev Immunol*. 2011; 11:85–97. [PubMed: 21252989]
81. Brestoff JR, Artis D. Immune regulation of metabolic homeostasis in health and disease. *Cell*. 2015; 161:146–160. [PubMed: 25815992]
82. McGettrick AF, O'Neill LA. How metabolism generates signals during innate immunity and inflammation. *The Journal of biological chemistry*. 2013; 288:22893–22898. [PubMed: 23798679]
83. O'Neill LA, Hardie DG. Metabolism of inflammation limited by AMPK and pseudo-starvation. *Nature*. 2013; 493:346–355. [PubMed: 23325217]
84. Palsson-McDermott EM, O'Neill LA. The Warburg effect then and now: from cancer to inflammatory diseases. *Bioessays*. 2013; 35:965–973. [PubMed: 24115022]
85. Baskin KK, Winders BR, Olson EN. Muscle as a “mediator” of systemic metabolism. *Cell Metab*. 2015; 21:237–248. [PubMed: 25651178]
86. de Bold AJ. Atrial natriuretic factor: a hormone produced by the heart. *Science*. 1985; 230:767–770. [PubMed: 2932797]
87. Shimano M, Ouchi N, Walsh K. Cardiokines: recent progress in elucidating the cardiac secretome. *Circulation*. 2012; 126:e327–332. [PubMed: 23169257]
88. Palanivel R, Vu V, Park M, Fang X, Sweeney G. Differential impact of adipokines derived from primary adipocytes of wild-type versus streptozotocin-induced diabetic rats on glucose and fatty acid metabolism in cardiomyocytes. *J Endocrinol*. 2008; 199:389–397. [PubMed: 18787059]
89. Palanivel R, Fang X, Park M, Eguchi M, Pallan S, De Girolamo S, Liu Y, Wang Y, Xu A, Sweeney G. Globular and full-length forms of adiponectin mediate specific changes in glucose and fatty acid uptake and metabolism in cardiomyocytes. *Cardiovascular research*. 2007; 75:148–157. [PubMed: 17499232]
90. Onay-Besikci A, Altarejos JY, Lopaschuk GD. gAd-globular head domain of adiponectin increases fatty acid oxidation in newborn rabbit hearts. *The Journal of biological chemistry*. 2004; 279:44320–44326. [PubMed: 15269215]
91. Palanivel R, Ganguly R, Turdi S, Xu A, Sweeney G. Adiponectin stimulates Rho-mediated actin cytoskeleton remodeling and glucose uptake via APPL1 in primary cardiomyocytes. *Metabolism*. 2014; 63:1363–1373. [PubMed: 25108566]
92. Palanivel R, Eguchi M, Shuralyova I, Coe I, Sweeney G. Distinct effects of short- and long-term leptin treatment on glucose and fatty acid uptake and metabolism in HL-1 cardiomyocytes. *Metabolism*. 2006; 55:1067–1075. [PubMed: 16839843]
93. Lee Y, Naseem RH, Duplomb L, Park BH, Garry DJ, Richardson JA, Schaffer JE, Unger RH. Hyperleptinemia prevents lipotoxic cardiomyopathy in acyl CoA synthase transgenic mice. *Proc Natl Acad Sci U S A*. 2004; 101:13624–13629. [PubMed: 15347805]
94. Hall ME, Maready MW, Hall JE, Stec DE. Rescue of cardiac leptin receptors in db/db mice prevents myocardial triglyceride accumulation. *American journal of physiology Endocrinology and metabolism*. 2014; 307:E316–325. [PubMed: 24939734]
95. Rame JE, Barouch LA, Sack MN, Lynn EG, Abu-Asab M, Tsokos M, Kern SJ, Barb JJ, Munson PJ, Halushka MK, Miller KL, Fox-Talbot K, Zhang J, Hare JM, Solomon MA, Danner RL. Caloric restriction in leptin deficiency does not correct myocardial steatosis: failure to normalize PPAR{alpha}/PGC1{alpha} and thermogenic glycerolipid/fatty acid cycling. *Physiol Genomics*. 2011; 43:726–738. [PubMed: 21427359]

96. Park M, Sweeney G. Direct effects of adipokines on the heart: focus on adiponectin. *Heart Fail Rev.* 2013; 18:631–644. [PubMed: 22893246]
97. Graveleau C, Zaha VG, Mohajer A, Banerjee RR, Dudley-Rucker N, Steppan CM, Rajala MW, Scherer PE, Ahima RS, Lazar MA, Abel ED. Mouse and human resistins impair glucose transport in primary mouse cardiomyocytes, and oligomerization is required for this biological action. *The Journal of biological chemistry.* 2005; 280:31679–31685. [PubMed: 15983036]
98. Hsu CP, Oka S, Shao D, Hariharan N, Sadoshima J. Nicotinamide phosphoribosyltransferase regulates cell survival through NAD⁺ synthesis in cardiac myocytes. *Circulation research.* 2009; 105:481–491. [PubMed: 19661458]
99. Zell R, Geck P, Werdan K, Boekstegers P. TNF-alpha and IL-1 alpha inhibit both pyruvate dehydrogenase activity and mitochondrial function in cardiomyocytes: evidence for primary impairment of mitochondrial function. *Mol Cell Biochem.* 1997; 177:61–67. [PubMed: 9450646]
100. Palomer X, Alvarez-Guardia D, Rodriguez-Calvo R, Coll T, Laguna JC, Davidson MM, Chan TO, Feldman AM, Vazquez-Carrera M. TNF-alpha reduces PGC-1alpha expression through NF-kappaB and p38 MAPK leading to increased glucose oxidation in a human cardiac cell model. *Cardiovascular research.* 2009; 81:703–712. [PubMed: 19038972]
101. Nakamura K, Fuster JJ, Walsh K. Adipokines: a link between obesity and cardiovascular disease. *J Cardiol.* 2014; 63:250–259. [PubMed: 24355497]
102. Parker-Duffen JL, Walsh K. Cardiometabolic effects of adiponectin. *Best Pract Res Clin Endocrinol Metab.* 2014; 28:81–91. [PubMed: 24417948]
103. Smith CC, Yellon DM. Adipocytokines, cardiovascular pathophysiology and myocardial protection. *Pharmacol Ther.* 2011; 129:206–219. [PubMed: 20920528]
104. Sweeney G. Cardiovascular effects of leptin. *Nat Rev Cardiol.* 2010; 7:22–29. [PubMed: 19949425]
105. Turer AT, Hill JA, Elmquist JK, Scherer PE. Adipose tissue biology and cardiomyopathy: translational implications. *Circulation research.* 2012; 111:1565–1577. [PubMed: 23223931]
106. Iacobellis G, Bianco AC. Epicardial adipose tissue: emerging physiological, pathophysiological and clinical features. *Trends Endocrinol Metab.* 2011; 22:450–457. [PubMed: 21852149]
107. de Bold AJ. Thirty years of research on atrial natriuretic factor: historical background and emerging concepts. *Can J Physiol Pharmacol.* 2011; 89:527–531. [PubMed: 21671768]
108. Clerico A, Giannoni A, Vittorini S, Passino C. Thirty years of the heart as an endocrine organ: physiological role and clinical utility of cardiac natriuretic hormones. *Am J Physiol Heart Circ Physiol.* 2011; 301:H12–20. [PubMed: 21551272]
109. Kudoh A, Katagai H, Takazawa T. Atrial natriuretic peptide increases glucose uptake during hypoxia in cardiomyocytes. *J Cardiovasc Pharmacol.* 2002; 40:601–610. [PubMed: 12352323]
110. Sosa V, Carbo R, Guarner V. Participation of glucose transporters on atrial natriuretic peptide-induced glucose uptake by adult and neonatal cardiomyocytes under oxygenation and hypoxia. *Eur J Pharmacol.* 2007; 568:83–88. [PubMed: 17537429]
111. Gutkowska J, Broderick TL, Bogdan D, Wang D, Lavoie JM, Jankowski M. Downregulation of oxytocin and natriuretic peptides in diabetes: possible implications in cardiomyopathy. *J Physiol.* 2009; 587:4725–4736. [PubMed: 19675071]
112. Plante E, Menaouar A, Danalache BA, Broderick TL, Jankowski M, Gutkowska J. Treatment with brain natriuretic peptide prevents the development of cardiac dysfunction in obese diabetic db/db mice. *Diabetologia.* 2014; 57:1257–1267. [PubMed: 24595856]
113. Dessi-Fulgheri P, Sarzani R, Rappelli A. Role of the natriuretic peptide system in lipogenesis/lipolysis. *Nutr Metab Cardiovasc Dis.* 2003; 13:244–249. [PubMed: 14650358]
114. Sengenès C, Berlan M, De Glisezinski I, Lafontan M, Galitzky J. Natriuretic peptides: a new lipolytic pathway in human adipocytes. *Faseb J.* 2000; 14:1345–1351. [PubMed: 10877827]
115. Bordicchia M, Liu D, Amri EZ, Ailhaud G, Dessi-Fulgheri P, Zhang C, Takahashi N, Sarzani R, Collins S. Cardiac natriuretic peptides act via p38 MAPK to induce the brown fat thermogenic program in mouse and human adipocytes. *The Journal of clinical investigation.* 2012; 122:1022–1036. [PubMed: 22307324]
116. Seale P, Lazar MA. Brown fat in humans: turning up the heat on obesity. *Diabetes.* 2009; 58:1482–1484. [PubMed: 19564460]

117. Bartelt A, Bruns OT, Reimer R, Hohenberg H, Ittrich H, Peldschus K, Kaul MG, Tromsdorf UI, Weller H, Waurisch C, Eychmuller A, Gordts PL, Rinninger F, Bruegelmann K, Freund B, Nielsen P, Merkel M, Heeren J. Brown adipose tissue activity controls triglyceride clearance. *Nat Med.* 2011; 17:200–205. [PubMed: 21258337]
118. Poss ZC, Ebmeier CC, Taatjes DJ. The Mediator complex and transcription regulation. *Crit Rev Biochem Mol Biol.* 2013; 48:575–608. [PubMed: 24088064]
119. Grueter CE, van Rooij E, Johnson BA, DeLeon SM, Sutherland LB, Qi X, Gautron L, Elmquist JK, Bassel-Duby R, Olson EN. A cardiac microRNA governs systemic energy homeostasis by regulation of MED13. *Cell.* 2012; 149:671–683. [PubMed: 22541436]
120. Lee JH, Bassel-Duby R, Olson EN. Heart- and muscle-derived signaling system dependent on MED13 and Wingless controls obesity in *Drosophila*. *Proc Natl Acad Sci U S A.* 2014; 111:9491–9496. [PubMed: 24979807]
121. Baskin KK, Grueter CE, Kusminski CM, Holland WL, Bookout AL, Satapati S, Kong YM, Burgess SC, Malloy CR, Scherer PE, Newgard CB, Bassel-Duby R, Olson EN. MED13-dependent signaling from the heart confers leanness by enhancing metabolism in adipose tissue and liver. *EMBO Mol Med.* 2014; 6:1610–1621. [PubMed: 25422356]

Highlights

- Adaptive cardiac glucose sparing is maladaptive with obesity and caloric excess
- Lipids impair glucose use via cytosolic and mitochondrial enzymatic switches
- Lipid oxidation induces post-translational modifications that alter cardiac function
- Cardiokines are emerging factors linking heart function and systemic metabolism

Figure 1. Physiologic and pathophysiologic metabolic regulation in the heart

(*Left*) Under glucose sparing conditions, fatty acid oxidation excludes glucose oxidation through allosteric regulation of the key glycolytic enzymes phosphofructokinase-1 (PFK-1) and pyruvate dehydrogenase (PDH) (i.e., the Randle Cycle). Critical regulatory metabolites are colored according to their enzyme targets for feedback inhibition (blue for PDH; orange for PFK-1). (*Center*) Epinephrine and norepinephrine coordinate the rapid utilization of glucose in the presence of fatty acids through β -adrenergic receptor dependent production of cyclic AMP (cAMP) and activation of cyclic AMP dependent protein kinase (PKA). PKA stimulates glucose oxidation by activating PFK-1 (via PFK-2) and PDH (via pyruvate dehydrogenase phosphatase, PDP) (green=activation). (*Right*) Metabolic inflexibility is associated with elevated circulating lipids and an inability to oxidize substantial glucose even in the presence of epinephrine. Glucose utilization is impaired due to a reduction in PFK-2 content, overexpression of pyruvate dehydrogenase kinase 4 (PDK4), and mitochondrial protein acetylation (red=inactivation). Under these conditions, glucose sparing is unnecessary due to elevated blood glucose levels.

Figure 2. Peroxisomal lipid metabolism as a cellular nutrient sensor and mediator of cardiac function

A. Very-long-chain fatty acids (vLCFA) are preferentially oxidized in peroxisomes, which generate medium chain acyl CoAs for further oxidation in mitochondria. High fat diets as well as fasting-induced lipolysis rapidly increase cardiac catalase levels, presumably to preserve physiologic redox signaling. Sustained lipid metabolism elevates the production of reactive Acyl-CoA metabolic intermediates (e.g., acetyl-CoA and succinyl-CoA) and accumulation of post-translational modifications (PTM), notably protein lysine acetylation. Sustained lipid metabolism also elevates ROS production and is associated with impaired insulin signaling and glucose utilization through unknown mechanisms. B. Heart contractile function in *Drosophila melanogaster* relies on pericardial cell ROS production. Genetic manipulation of antioxidant levels in pericardial cells, but not cardiomyocytes, induce cardiac dysfunction, indicating that pericardial ROS indirectly regulates cardiomyocyte contractility in a paracrine manner. Pericardial cells are abundant in peroxisomes, suggesting a central role for lipid-mediated peroxisomal ROS signaling, or possibly even the generation of β -oxidation intermediates, in cardiomyocyte paracrine signaling.