Metabolic Remodeling in the Hypertrophic Heart

Fuel for Thought

John C. Chatham, Martin E. Young

When it comes to fuel for energy production, it is commonly accepted that the heart is an omnivore, capable of oxidizing a wide range of carbon substrates, and that this metabolic plasticity is necessary to maintain a high and variable workload in the midst of an ever-changing hormonal and nutritional state. It is also widely appreciated that shifts in substrate utilization in the heart occur in response to chronic metabolic and hemodynamic stresses. What is less clear, however, is whether such chronic metabolic shifts should be considered a cause or consequence in the pathogenesis of contractile dysfunction. In the case of diabetes mellitus, the heart exhibits an increased dependence on fatty acids for oxidative energy production, and this increase in lipid metabolism has been proposed to significantly contribute to the etiology of impaired cardiac function. Similarly, increased rates of fatty acid oxidation immediately after an ischemic event have been implicated in exacerbation of reperfusion injury. However, in both of these pathophysiological settings, compelling data to support a direct causal relationship between contractile abnormalities and metabolic dysregulation remain elusive.

In response to pressure overload–induced cardiac hypertrophy, the heart reverts more toward a fetal-like metabolic profile, indicative of a decrease in fatty acid oxidation (concomitant with an increased reliance on carbohydrates for oxidative energy metabolism). It has been suggested that this substrate shift, which is associated with reactivation of other fetal-like hallmarks (eg, myosin heavy chain isoform switching), contributes to the progression to overt contractile failure. Dietary, pharmacological, and genetic strategies have been used in attempts to provide insight regarding the impact that substrate shifts have on pressure overload–induced remodeling; however, mixed results have been reported. For example, high-fat feeding attenuates hypertension-induced myocardial remodeling and contractile dysfunction in rats. Similar findings have been reported in animal models of heart failure, which are associated with restoration of fatty acid oxidative capacity. Conversely, induction of fatty acid metabolism enzymes through use of peroxisome proliferator-activated receptor-α agonists prevents substrate switching and augments pressure overload–induced contractile dysfunction. On the other hand, both dietary and pharmacological interventions have significant systemic effects, and peroxisome proliferator-activated receptor-α activation influences processes beyond fatty acid oxidation. These experimental shortcomings, in addition to the tight coupling between cardiac work and oxidative metabolism, have made demonstration of a direct causal relationship between shifts in substrate utilization and contractile dysfunction a significant challenge.

In the current issue of Circulation Research, Kolwicz and colleagues used a novel genetic approach designed to establish a more definitive relationship between the metabolic shifts with contractile dysfunction observed in pressure overload–induced hypertrophy. The investigators hypothesized that heart-specific genetic ablation of acetyl-CoA carboxylase 2 (ACC2H−/−), which generates malonyl-CoA (a critical inhibitor of mitochondrial fatty acid uptake), would prevent the characteristic substrate switching during pressure overload–induced hypertrophy, concomitant with the other aspects of remodeling (inclusive of contractile function). Consistent with this hypothesis, using ex vivo assessment of substrate utilization, Kolwicz et al revealed the predicted transverse aortic constriction (TAC)–induced alterations in substrate reliance (ie, decreased fatty acid oxidation and increased glucose oxidation) in wild-type hearts, but these changes were absent in the ACC2H−/− hearts. The lack of substrate switching observed in ACC2H−/− hearts was associated with marked attenuations in TAC-induced hypertrophic growth (cardiomyocyte size, heart weight, and molecular markers [bnp mRNA], fibrosis, and contractile dysfunction). Collectively, these observations are consistent with the concept that perturbations in cardiac metabolism play a causal role in the remodeling of the heart in response to pressure overload.

Metabolic dysregulation as a direct link to the development of cardiac dysfunction has gained increased acceptance over the last several decades, a concept that is strengthened further in the study by Kolwicz et al. However, despite the development of more refined techniques for measuring substrate utilization, as well as increasingly sophisticated genetic approaches for manipulating key regulatory enzymes, establishment of the molecular underpinnings by which shifts in cardiac metabolism causally influence remodeling remains elusive. A classic perspective has centered on energetics, based on the relatively simple viewpoint that metabolic dysregulation leads to impaired energy transfer that results in
impared contractile function.\textsuperscript{13} Given that fatty acids act as a primary source of ATP for the contracting adult heart, multiple laboratories have speculated that diminished fatty acid oxidative capacity negatively impacts cardiac function through energy starvation. Consistent with this idea, Kolwicz et al\textsuperscript{12} highlighted a modest decrease in the phosphocreatineto-ATP ratio in wild-type but not ACC2H\textsuperscript{−/−} hearts after TAC. Although it is tempting to link the development of metabolic inflexibility to impaired bioenergetics, the decline in the phosphocreatine-ATP ratio appears to be caused by an impaired creatine kinase flux and a decrease in total tissue creatine content, at least in overt heart failure.\textsuperscript{14} Clearly, an impaired energetic reserve has important implications in the failing heart; however, a strong case linking dysregulation in substrate utilization and decreased phosphocreatine/ATP remains lacking.

What is becoming increasingly apparent is that metabolic intermediates in both glucose and lipid metabolism can have potent effects on cardiomyocyte function and that the changes in these so-called metabolic signals are more likely to contribute to pathophysiological changes associated with metabolic inflexibility than subtle changes in energetics. For example, it is well established that other pathways of glucose metabolism, such as the pentose phosphate pathway, diacylglycerol pathay, and hexosamine biosynthesis pathway, although not consuming the majority of glucose entering the cell, can significantly affect cellular function. The hexosamine biosynthesis pathway has long been described as a nutrient-sensing pathway, and although its role in mediating metabolic signaling in the heart remains relatively understudied, it has garnered increasing interest because it plays a key role in regulating the modification of Ser/Thr residues of numerous nuclear and cytoplasmic proteins by the O-linked attachment of a single monosaccharide, N-acetyl-D-glucosamine, more commonly known as O-GlcNAc.\textsuperscript{15–17} In the context of the heart, increases in O-GlcNAc levels have been implicated in mediating the adverse effects of diabetes, and acute activation of O-GlcNAc levels has also been shown to be cardioprotective.\textsuperscript{18–20} With regard to cardiac hypertrophy, a number of studies have demonstrated that pressure overload–induced hypertrophy appears to increase flux through the hexosamine biosynthesis pathway (consistent with increased glucose utilization), and furthermore, that cardiac-specific genetic ablation of O-GlcNAc transferase, which catalyzes O-GlcNAc synthesis, prevents TAC-induced hypertrophy.\textsuperscript{21,22} Interestingly, it has also been reported recently that O-GlcNAc synthesis is required for activation of the transcriptional reprogramming that occurs at the onset and progression of cardiac hypertrophy.\textsuperscript{23}

In addition, augmentation of glucose metabolism by increasing GLUT1 expression in the heart was found to attenuate TAC-induced remodeling; however, the impact of increased GLUT1 on the hexosamine biosynthesis pathway or other accessory pathways of glucose metabolism is not known.\textsuperscript{24} Indeed, it is perhaps something of a paradox that augmenting glucose use with GLUT1 overexpression and increasing fatty acid use in the ACC2H\textsuperscript{−/−} model both attenuated the response to TAC. This perhaps reinforces the notion that other metabolic signaling pathways may be of importance. These might include lipid metabolism pathways. Decreased fatty acid oxidation capacity, in the face of sustained or elevated fatty acid availability, would be predicted to facilitate the channeling of fatty acyl groups into nonoxidative pathways.\textsuperscript{4,25} Many of these pathways, including diacylglycerol and phospholipid biosynthesis, play critical roles in cellular signaling. Furthermore, comparable to the glucose-derived posttranslational modification discussed above (ie, O-GlcNAcylation), direct palmitoylation of several proteins critical to cardiomyocyte function has been demonstrated.\textsuperscript{26}

In summary, through the use of a novel mouse model of augmented fatty acid oxidation (ie, ACC2H\textsuperscript{−/−}), Kolwicz et al\textsuperscript{12} have established a causal relationship between pressure overload–induced alterations in cardiac metabolism and remodeling. These exciting findings open the door to several unanswered questions, particularly in relation to the mechanisms by which shifts in metabolism act in a signaling manner to facilitate remodeling of the myocardium in response to stresses (Figure). Undoubtedly, the findings fuel the concept that modulation of metabolism in a targeted fashion is potentially a viable therapeutic strategy in the treatment of hypertrophic cardiomyopathy.

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