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A metabocentric view of cardiac remodeling

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Physiologic and pathologic stressors promote changes in metabolism that are associated with cardiac remodeling. Metabolic alterations in the heart are a summation of responses of several organs and organ systems, which transform the milieu of circulating substrates and stimuli and prompt cardiac adaptation or remodeling. Nevertheless, the mechanisms by which metabolism causes cardiac remodeling remain unclear. Difficulties in delineating metabolic mechanisms of tissue remodeling are in part due to technical issues as well as to the lack of conceptual clarity with regard to causal entailment of metabolic processes. This review discusses some metabolic mechanisms by which stressors such as exercise, pregnancy, and pressure overload promote metabolism-mediated cardiac remodeling. Adopting conceptual frameworks based on relational biology and delineating hierarchies of metabolic causation could lend new insight into how metabolism coordinates cardiac remodeling.

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The mechanisms by which exercise as well as other physiological or pathological stressors regulate cardiac structural and functional remodeling have been difficult to uncover. Such mechanisms, and their causal relationships with each other, are important to identify because they could provide a gateway for developing novel and actionable strategies to deter or delay heart disease. This article tackles a particularly difficult subject—metabolic changes as a cause of cardiac remodeling.

Difficulties in measuring cardiac metabolism *in vivo*

For several reasons, it has been difficult to delineate how changes in metabolism contribute to cardiac remodeling. This issue is particularly difficult to address in the context of exercise, which promotes dynamic and systemic changes in metabolism. For example, some results suggest that adaptation to exercise increases the basal rate of glycolysis [1,2••], whereas others suggest diminished [3] or unchanged [4] glycolytic activity. The reasons for such discrepancies could be due to factors specific to each model system (e.g. exercise intensity, type of exercise, rodent strain), differences in cardiac perfusion protocols (e.g. substrate levels, addition of hormones), or the time of day at which heart metabolism is measured (i.e. circadian influences; [5–7]). Uncertainty in interpretation is compounded by the fact that most experimental approaches to address metabolic changes in the heart require us to extrapolate results from *in vitro* or *ex vivo* studies to the *in vivo* system. Although removal of cardiac myocytes from the heart, or the heart from the body, allows for strict control of experimental variables, these approaches irretrievably destroy the complex interactions and relationships of the original system [8,9]. This issue is particularly germane to the heart, which is an opportunistic omnivore with high metabolic demand that responds to numerous humoral factors and neural inputs, many of which change dynamically during or after pathological or physiological stimuli [10,11].

Although measuring metabolism *in vivo* would overcome many of these obstacles, it is no easy task. Inferences regarding radiolabeled glucose uptake (e.g. 2-[^{18}F]fluoro-2-deoxy-D-glucose) are limited by the fact that measuring glucose uptake does not provide information of its utilization by metabolic pathways. In this regard, nuclear magnetic resonance and radioactive or stable isotope tracing approaches are useful for understanding changes in cardiac metabolism *in vivo* [12]. Particularly attractive are approaches that strive to minimize obfuscation caused by tracer incorporation and that provide information on the activity of numerous metabolic pathways. For example, deep network tracing, which introduces $^{13}C_6$-glucose or other stable tracers via a stress-free, *ad libitum* diet, is capable of revealing the relative activities of numerous anabolic and catabolic pathways simultaneously [13••]. This approach could be used to understand how pathways with lower flux, for example, biosynthetic pathways of glucose metabolism [10], change with exercise adaptation or other stimuli. Importantly, deep network tracing provides information necessary for understanding how metabolic pathway *relationships* change over time or under conditions of stress, which is more useful than knowing how the activity of only one or a few pathways change.

Although deep network tracing may enable deeper understanding of cardiac metabolism *in vivo*, its

widespread use is currently limited by access to the necessary instrumentation and by the expertise required to analyze and interpret the data [14]. In lieu of these measurements, an approach dependent on operationalization can provide understanding of *in vivo* metabolism. Using operationally defined parameters, phenomena that are not directly measurable are inferred by examining strictly defined variables. We used this approach to find that myocardial glycolytic rate decreases during or near the end of an intense bout of exercise [2••]. Required for this analysis was knowledge that: 1) phosphofructokinase 1 (PFK1) is the rate-limiting and committed step of glycolysis [15,16,17•]; 2) 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFK2) phosphorylation (at S483) can promote PFK1 activation [18–20]; 3) glycogenesis occurs when PFK1 is inhibited [21]; and 4) elevated levels of circulating lactate and fatty acids diminish cardiac glucose utilization [22]. In our analysis, exercise acutely altered all of these operationally defined parameters: $PFK2^{S483}$ phosphorylation was lower, glycogen levels increased by fivefold, and circulating levels of competing substrates were higher [2••]. These findings provide logically consistent, convergent evidence that a relatively intense bout of exercise acutely decreases PFK1 activity and glycolytic rate.

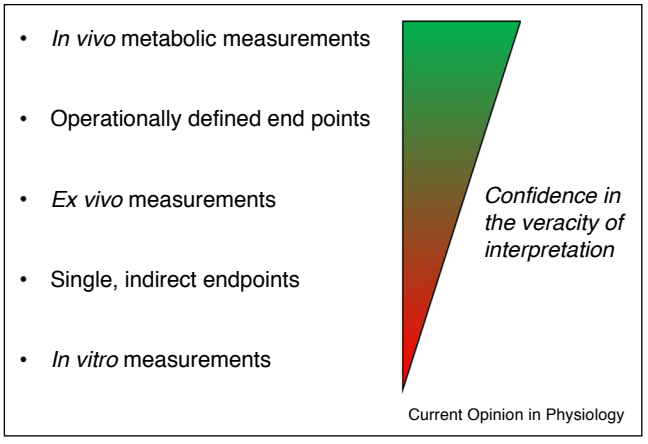
Difficulties extrapolating *ex vivo* metabolic measurements to the *in vivo* system

Ex vivo cardiac approaches are useful for assessing metabolism in a tightly controlled system. Data are commonly interpreted assuming that the conditions in the perfusion system are similar to that *in vivo*. However, recent studies indicate that *ex vivo* perfusion systems promote regions of anoxia in the heart by disrupting the vasoregulatory network [23•]. Moreover, saline-based perfusion solutions have lower oxygen carrying capacity compared with red blood cell perfusion solutions [24] or solutions containing artificial oxygen carriers [25]. In addition, perfusion solutions often fail to recapitulate the substrate spectrum normally available to the heart *in vivo*, which could bias results. Thus, *ex vivo* analysis of metabolism may not be capable of recapitulating the metabolic state *in vivo*. Nevertheless, the perfused heart approach has been remarkably successful for quantifying the activity of particular pathways, especially glucose oxidation, fatty acid oxidation, and glycolysis. It is useful for understanding the metabolic inclinations of the isolated organ, especially in the context of gene deletion or overexpression. Although slight differences in perfusion protocols can confer disparate results, combining *in vivo* endpoints from tissue samples or from operationally defined parameters with *ex vivo* metabolic measurements increases confidence in interpretation. For example, recent studies of cardiac growth in the context of pregnancy show diminished glucose oxidation in the maternal heart *ex vivo*, which was complemented by findings of upregulated pyruvate dehydrogenase kinase 4 and higher levels of circulating competing substrates (e.g. fatty acids) [26••]. Together, the complementary measurements, along with harmonious reports in the literature [10], provide strong evidence that the maternal heart diminishes its reliance on glucose oxidation. In contrast, single endpoint measurements (e.g. immunoblots of metabolic enzymes) or inductive reasoning from the *in vitro* setting (e.g. isolated cardiomyocytes) provides the least confidence to interpretations of the *in vivo* scenario (Figure 1), at least in the context of intermediary metabolism.

Evidence that metabolism is a cause of cardiac remodeling

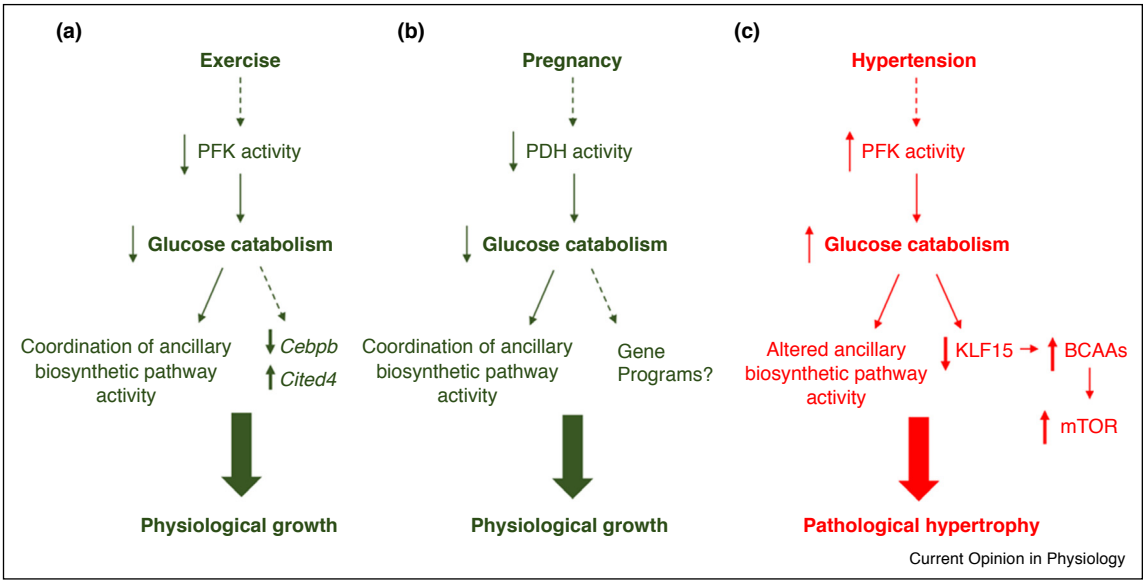
Metabolic pathways provide the cell useable energy (ATP) as well as biosynthetic precursors for nucleotides, phospholipids, and amino acids. Moreover, metabolism coordinates cell signaling, redox state, and transcriptional responses [10,12]. Given the importance of metabolism to each of these factors, it is not surprising that changes in glucose utilization are commonly found to be sufficient causes of cardiac remodeling [10,11]. As reviewed previously [10,11], exercise-induced metabolic periodicity appears important for physiological cardiac growth. Considering the ability of PFK to regulate ancillary biosynthetic pathway activity [17•,27•], the decrease in PFK activity and glycolysis in the heart during exercise [2••] would likely change biosynthetic pathway activity, leading to changes in the synthesis of cellular building blocks. Moreover, low PFK activity is sufficient to regulate the cardiac growth program [e.g. *Cebpb*, *Cited4* [28,29]] [2••], suggesting that decreases in glycolytic rate occurring during exercise may be a formal cause of remodeling (Figure 2a). Pregnancy-induced cardiac growth follows a similar paradigm: decreases in glucose oxidation could augment ancillary biosynthetic pathway activity to initiate cardiac growth programs [26••] (Figure 2b).

Figure 1



Relative confidence in the veracity of metabolic measurements. Generalized schematic of different types of metabolic measurements and the veracity of conclusions derived therefrom.

Figure 2



Working models of the role of glucose metabolism in physiological and pathological cardiac remodeling. Exercise and pregnancy decrease glucose catabolism, which appears critical for physiologic growth. Exercise decreases phosphofructokinase (PFK) activity and glucose catabolism acutely. This coordinates ancillary biosynthetic pathway activity and activates the exercise gene program, that is, it decreases expression of *Cebpb* and increases expression of *Cited4*. Pregnancy-induced changes in progesterone increase Pdk4, which decreases PDH activity and glucose catabolism to promote cardiac growth. The gene programs triggered by this metabolic change remain unclear. Under conditions of pressure overload, as occurs in hypertension, PFK activity is augmented, which would alter ancillary biosynthetic pathway activity. High glucose utilization also appears to diminish Kruppel-like factor (KLF) 15, which suppresses the expression of BCAA catabolic enzymes. This increases BCAA levels in the heart, which activates mTOR and promotes cell hypertrophy.

Nevertheless, the fine mechanistic details remain unclear — *How* do metabolic changes during exercise and pregnancy regulate the transcriptional programs that promote cardiac growth?

Changes in metabolism also appear to cause pathological remodeling. For example, that high levels of PFK activity are sufficient to cause a deleterious form of remodeling are supported by the facts that nearly all PFK allosteric activators increase in the pressure-overloaded, hypertrophic heart [30] and that constitutively high PFK activity is sufficient to promote mild dilated cardiomyopathy [2••]. The formal mechanism was recently found to be due to the capacity of glucose metabolism to regulate KLF15 transcription, branched chain amino acid (BCAA) abundance, and mTOR activity [31••] (Figure 2c).

Changes in fatty acid and ketone body utilization also have marked effects on pathological remodeling [reviewed in Ref. [10]]. For example, deletion of acetyl CoA carboxylase 2 augments fatty acid oxidation and lowers glucose oxidation in the heart and prevents pressure overload-induced pathological remodeling [32], while deletion of fatty acid oxidation enzymes appears to cause cardiomyopathy [33]. Moreover, overexpression of the fatty acid oxidation enzyme, medium-chain acyl coenzyme A dehydrogenase, promotes physiological cardiac growth and prevents pathological remodeling [34]. Similarly, enhancing ketone body utilization by overexpressing D-β-hydroxybutyrate dehydrogenase [35] or by delivering ketone bodies *in vivo* [36] ameliorates pathological remodeling and cardiac dysfunction, and decreasing ketone body oxidation by deleting enzymes important for their utilization worsens cardiac function and remodeling [37]. It remains unclear how concomitant metabolic changes that occur during altered fatty acid or ketone utilization, for example, changes in glucose utilization and anabolic pathway activity, affect cardiac remodeling.

Metabolism may also regulate cardiac health and responses to stress via metabolite signaling. For example, endogenous metabolites of glycolysis (e.g. glucose-6-phosphate) and of the pentose phosphate pathway (5-aminoimidazole-4-carboxamide ribonucleotide; AICAR) as well as changes in adenine nucleotide pools can activate prohypertrophic kinases such as mTOR and AMPK [reviewed in Ref. 11]. Circulating fatty acids also cause cardiac growth, presumably by activating signaling pathways [38,39]. Given that numerous metabolites have cognate GPCRs [40], it is likely that circulating metabolites change the signaling and transcriptional landscapes of the heart.

How might we obtain deeper understanding?

There are several conceptual hurdles to overcome to understand metabolic causation clearly. One philosophical issue is that causation comes in several flavors and layers. For example, there are ultimate causes, proximate causes, sufficient causes, necessary causes, and the construct of classical (Aristotelean) causation, which harbors four additional types of cause (i.e. efficient, material, formal, and final causes). Moreover, that biological organisms are not machines and that the relationships between biological processes have their own emergent properties add additional wrinkles of causal complexity. The relational nature of the metabolic network involves mutually dependent components and interdependent pathways [8,41], which give rise to properties that emerge from the web of metabolic interactions. The composite effect appears to depend not upon the individual components of metabolism, but on the structural and flux configurations of the web, contemporaneous with signaling events and functional states. Overall, these multifaceted dependencies present a paradox for understanding the extent to which changes in metabolism trigger healthy adaptations or promote structural and functional decline.

Perhaps one way to think through the problem would be first to acknowledge our (over)reliance on reductionism and our poor understanding of the relational nature of metabolic pathways. We are steeped in reductionist thought patterns and approaches, which have been invaluable for understanding the fundamentals of biological constituents. Yet, they fall short for understanding the relational biology implicit in and controlled by metabolism. In particular, reductionism fails to provide useful information about the emergent properties ascribed to particular metabolic flux configurations. Such properties arise when interactions of the metabolic ensemble yield properties beyond that explained by the sum of the parts. A clearer picture of pathway relationships, perhaps via application of deep network tracing [13••], appears important for understanding how the metabolic system works as a whole and changes upon conditions of stress. Once we have that information, we may be able to address more fully how metabolism causes cardiac remodeling. Constructs that integrate network biology with reductionism and causal states should prove useful for obtaining deeper insights into how metabolic changes cause tissue remodeling (Figure 3), and could help lay the foundation for future research agendas.

Conflict of interest statement

Nothing declared.

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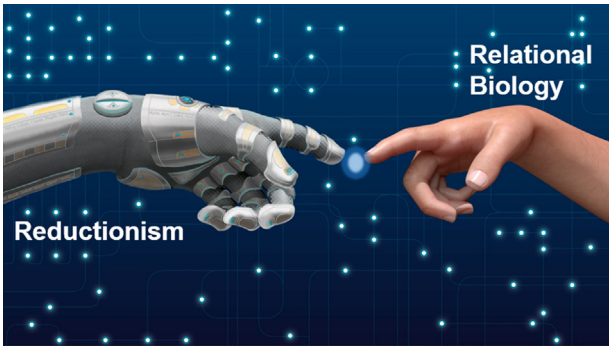
Figure 3



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Conceptual imagery of the creation of new metabolic understanding. Reductionism views organisms as machines, which has an upper limit for understanding biology. Relational biology attempts to capture the relationships between processes and can reveal emergent properties. The integration of these approaches holds promise for developing new understanding of how changes in metabolism regulate tissue structure and function. Illustration by Ben Smith.

The author acknowledges artwork by Ben Smith (https://www.bensmithillustration.com/).

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