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Insights into metabolic remodeling of the hypertrophic and failing myocardium

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COMMENTARY

The healthy heart demonstrates remarkable metabolic plasticity. Although it utilizes predominantly fatty acids for ATP generation, it also has the capacity to derive energy from glucose, ketones, lactate and particular amino acids.¹ Such fuel flexibility helps to maintain adequate provision of chemical energy to fuel the unrelenting mechanical work of the heart, especially under conditions of increased physiological or pathological stress. A predominant line of thinking has been that, because of this large energy demand, myocardial metabolic derangements are likely to be causative in heart failure. This seems reasonable, as the heart hydrolyzes nearly 50× its mass in ATP each day!¹ It is therefore prudent to assume that decrements in ATP production caused by dysregulation of fat or glucose oxidation would promote deleterious changes in cardiac function and structure.

Numerous studies appear to support the concept that metabolism is altered in the failing heart, with a general consensus that during the course of myocardial remodeling the heart switches from fatty acid preference to glucose use.^{2–4} This switch is associated with decreased levels of high energy phosphate reserves,¹ suggesting that the failing heart is a fuel-deficient organ. Nevertheless, our understanding of how these metabolic changes occur, when they happen, and to what extent they change is unclear. Even the direction of the changes is still being debated. For example, numerous studies have clearly shown that fat oxidation capacity is decreased in rodent models of heart failure¹; yet, the results of clinical studies are variable, showing that fatty acid oxidation in the failing heart is diminished,⁵ augmented,^{6–8} or unchanged.⁹ While the failing or hypertrophied heart may rely more on glucose metabolism,¹ recent studies have shown that actual rates of glycolysis and glucose oxidation may be decreased,¹⁰ due in part to myocardial insulin resistance^{10–13} or decrements in mitochondrial oxidative capacity.¹⁴ Undoubtedly, a better understanding of

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DISCLOSURES

None.

the metabolic changes occurring in the diseased heart would be helpful in developing metabolic therapies to improve pump sustenance and function.

In this issue of *Circulation: Heart Failure*, Lai et al. used molecular profiling strategies to derive broad mechanistic understanding of the metabolic changes that occur in different forms of cardiac hypertrophy in mice.¹⁵ The authors used a broad systems biology approach, employing both unbiased transcriptomic profiling and targeted quantitative metabolic profiling, to understand the metabolic changes associated with compensated cardiac hypertrophy, exercise-induced physiological hypertrophy, and heart failure. Compensated hypertrophy, induced by transverse aortic constriction (TAC), and heart failure, induced by a combination of TAC and a small apical myocardial infarction, resulted in a defined set of >1000 differentially expressed genes. Interestingly, most of these transcriptional changes were in directional concordance despite the marked differences in cardiac structure and function between the two models. Unlike the transcriptional profiles, metabolite changes were sufficient to dichotomize the groups: the compensated hypertrophic heart showed relatively few differences in the abundance of metabolites, whereas the failing heart showed elevated levels of numerous acylcarnitine esters, higher lactate levels, and altered abundance of Krebs cycle intermediates. The authors suggest that such elevations in lactate and acylcarnitine species and lower abundance of many Krebs cycle intermediates is suggestive of a “bottleneck” of carbon flux into mitochondria, which could diminish the capacity of the heart to produce ATP. The modest differences in amino acid abundance in the compensated and decompensated heart could be further suggestive of dysregulation in the balance of myocardial anabolic and catabolic pathways. Taken together, these data suggest a critical and rate-limiting role of mitochondrial oxidative metabolism in cardiac metabolism and provide further evidence for profound dysregulation of mitochondrial metabolism in the failing myocardium.

The fusion of –omics strategies, such as that employed by Lai et al., has a remarkable potential for increasing our understanding of how metabolic changes integrate and contribute to cardiovascular disease. Illustrative of this power is the finding that many metabolic changes in the hypertrophic heart are not reflected in the transcriptional profile. With the exception of fatty acid oxidation, which was inhibited in mitochondria isolated from the failing heart and showed harmonious changes in both the myocardial transcriptome and metabolome, there were few changes in the expression of genes related with mitochondrial function. This is a surprising finding given the numerous published studies showing reduced expression of electron transport chain proteins in the hypertrophied or failing heart.¹ Such a result also raises many questions: (1) How do so many changes in metabolism occur without remarkable changes in the transcriptional metabolic machinery?; (2) Are different forms of hypertrophy caused, at some level, by the metabolic changes, or are the metabolic changes simply reflective of altered cardiac structure and function?; and (3) What do changes in each metabolic pathway tell us about cardiac growth and remodeling?

Post-translational regulation could be one explanation for some of the changes in metabolism that occur in the hypertrophied heart. This idea is most robustly supported by data showing remarkable changes in acylcarnitine and organic acid abundance in the hearts

of mice subjected to voluntary wheel running despite differential expression of only *six* genes compared with hearts of sedentary mice. Although this form of metabolic remodeling does not appear to require changes in gene expression, in the failing heart, both the transcriptomic and metabolomic data were congruent with the measured decrease in mitochondrial fat oxidation. Hence, these findings not only demonstrate converse changes in metabolism between physiological and pathological forms of hypertrophy, but they also suggest mechanistic differences by which the same metabolic pathway is regulated. It appears that, in the failing heart, a “bottleneck” phenomenon occurs where mitochondrial carbon influx from fat and glucose catabolism is deficient, which is at least partially due to down-regulation of the fatty acid oxidation machinery. In the physiologically hypertrophied heart, however, these metabolic pathways are enhanced—the carbon “valves” for fat and glucose catabolism are effectively open—yet this does not require transcriptional changes. Thus, pathological hypertrophy appears to be associated more with transcriptional metabolic changes, while the exercised heart maintains fuel flexibility by regulating metabolism at the post-translational level. It would be of high interest and importance to identify the metabolic proteins and specific post-translational modifications involved in the regulation of myocardial metabolism, which may promote “beneficial” forms of cardiac hypertrophy.¹⁶ Potential candidates include acetylated,¹⁷ nitros(yl)ated,¹⁸ or succinylated¹⁹ metabolic proteins, which could elicit changes in myocardial metabolism and elude structural and functional changes.

The current study provides evidence for dysregulation of other critical metabolic pathways as well. Modest changes in several amino acids in hypertrophied and failing hearts were associated with changes in the expression of genes involved in the degradation of proline, alanine, tryptophan, and branched-chain amino acids (BCAAs). Because amino acids are critical for anabolic processes underlying myocyte growth, it is important to understand how changes in particular amino acid subfamilies contribute to cardiac remodeling. Other metabolomic studies show changes in amino acid abundance in the pressure-overloaded and failing mouse heart as well,¹¹ yet it remains to be determined how such changes regulate the remodeling process. Increases in BCAAs, for example, are suggested to be causative in the development of systemic insulin resistance²⁰; however, in the cardiomyopathic heart, this hypothesis has not been tested. It is possible that changes in amino acid uptake or intracellular catabolism could regulate nodal cell signaling pathways involved in the hypertrophic response (e.g., mTOR).¹⁶ Further work is required to shed light on the role of amino acid metabolism in heart failure.

Overall, the findings by Lai et al. pave the way for future mechanistic studies on the role of specific metabolic transcriptional programs and post-translational modifications in heart disease. The work also underscores high discordance in the literature pertaining to metabolic changes in the hypertrophied and failing heart. Are disagreements in glucose and fatty acid metabolic changes in the failing heart due to species- or model-specific differences? For example, Lai et al. used female mice, whereas most other studies have predominantly used male mice. Are discrepant findings in lipid metabolism,^{11, 15} for example, due to such gender differences or are they due to dissimilar procedural protocols? These are important questions that must be addressed to further clarify the role of metabolism in heart failure.

Without doubt, the work by Lai et al. is a first step toward opening productive dialogue on these issues, while at the same time illustrating the potential of multi-systems approaches for unveiling new insights on the role of metabolism in cardiac remodeling.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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