RESEARCH HIGHLIGHT

Lactylation regulates cardiac function

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A new study connects the metabolism of the heart with its underlying function. This connection involves an unusual post-translational modification of the cardiac myosin heavy chain which is catalyzed by the energetic metabolite lactate.

The human heart pumps over 7000 liters of blood per day, while estimates say it generates and consumes up to 30 kg of ATP.[1] However, what connects the function of the heart to the energetic metabolites it generates remains poorly understood. Now, in a new study in *Cell Research*, a new link has been found by identifying and characterizing a unique post-translational modification (PTM) that occurs on the cardiac myosin heavy chain, a major component of the cardiac sarcomere.[2] Of note, this PTM is directly related to the energetic metabolite lactate, thus providing a molecular connection between the fuel the heart consumes and its underlying function.

In their study, Zhang and colleagues began by using a model of systolic heart failure caused by the continuous delivery of angiotensin II (Ang II) through an implanted osmotic minipump. After several weeks, animals given a slow infusion of Ang II develop a decline in overall heart function, often measured by a parameter known as ejection fraction, as well as a compensatory increase in the size of each cardiomyocyte (i.e., cardiac hypertrophy) and evidence of cardiac fibrosis. As such, this pharmacological model mirrors what is often seen in human heart failure. The authors then subjected their control- and Ang II-treated mice to an unbiased proteomic assessment, with a particular emphasis on the level and changes in protein lactylation. Lactate is the end-product of glycolysis, but recent efforts have noted that it can be used to modify specific lysine residues on a wide range of histone and non-histone proteins.[3] In the current study, a little over 3000 proteins were resolved with roughly 160 lactylated proteins detected and some 551 unique lactylation sites identified. The site with the greatest difference between control- and Ang II-treated samples was the lysine at position 1897 of the α-myosin heavy chain (α-MHC K1897). The authors were able to generate an antibody that specifically recognized α-MHC K1897 lactylation and show that in both mouse models and human samples, levels of α-MHC K1897 lactylation decline in heart failure.

The authors next sought to understand how this PTM regulates cardiac physiology. They quickly honed in on how myosin heavy chain lactylation affected the interaction of myosin with another sarcomeric protein, titin. Titin is a giant protein, ~3 MDa in size, that links the Z-discs to the M-lines in the middle of the sarcomere.[4] The current hypothesis is that this protein acts as a large scaffold bound to both myosin and actin, therefore acting as a molecular bridge between the thin and thick filaments.[4] Of note, the authors found that compared to wild-type α-MHC, an α-MHC K1897R mutant unable to undergo lactylation, had greatly attenuated interactions with titin (Fig. 1). To understand the physiological significance of these observations, the authors created an α-MHC K1897R knockin (KI) mouse. These animals had the expected reduction in α-MHC lactylation, reduced α-MHC–titin interactions and evidence of augmented heart failure when given Ang II.

The reversible lactylation on histone and non-histone proteins is generally achieved through the enzymatic activity of other proteins, proteins often termed writers and erasers. In this regard, the authors identified that α-MHC lactylation was catalyzed by the p300 acetyltransferase, the same enzyme previously implicated in generating histone lactylation.[5] In contrast, the reverse reaction was dependent on SIRT1, an NAD-dependent deacylase. However, neither a change in the level or activity of p300 or SIRT1 could explain the decline of α-MHC K1897 lactylation observed in heart failure. The authors then turned to the supply of lactate itself. The authors manipulated cardiac lactate levels through three different and complementary strategies. These include manipulation of lactate dehydrogenase A (LDHA), the key enzyme responsible for the conversion of pyruvate to lactate, direct delivery of sodium lactate to animals or inhibition of monocarboxylate transporter 4 (MCT4), the key lactate transporter found in cardiomyocytes. By using these diverse strategies, the authors were able to observe that augmenting lactate levels in cardiomyocytes improved heart failure, while lowering lactate levels had the opposite effect. These results are consistent with other observations suggesting that failing human hearts consume significantly more lactate than non-failing hearts.[6] However, the authors cleverly used their K1897R KI mouse to show that the improvement seen by augmenting lactate levels was, at least in part, driven by alterations in α-MHC K1897 lactylation.

Together, these findings suggest that a coupling exists between the heart's energy consumption (i.e., lactate) and cardiac performance (i.e., myosin-regulated sarcomeric function). While originally only lysine acetylation was described, there are now over 20 different types of lysine acylations that have been described including formylation, propionylation, succinylation, malonylation, and the lactylation modification studied here.[3] Each represents a different chemical remnant of a metabolic process, and as such, future studies will be needed to understand whether these other novel PTMs also occur on myosin, or perhaps other sarcomeric proteins. It is also interesting to think whether the insights of Zhang and colleagues can be leveraged for novel therapeutics. For many years, manipulation of myosin's activity was felt to be undruggable. However, recent high throughput

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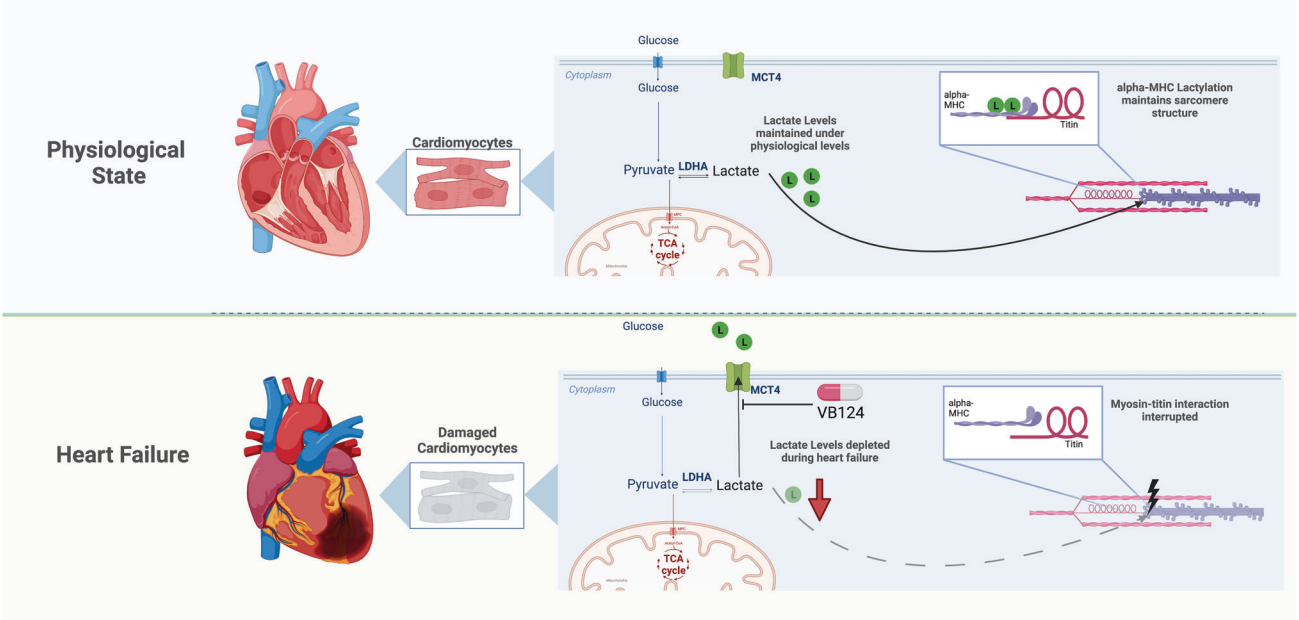

Fig. 1 Schematic diagram showing a mechanistic model of α-MHC lactylation in the heart. Lactylation, a novel PTM, occurs on a specific lysine residue of the α-MHC. This PTM alters the interaction of myosin with titin, thereby modulating cardiac contractility. Levels of lactate are reduced in the failing heart, perhaps due to elevated consumption of this metabolite. The generation of lactate is catalyzed by the enzyme LDHA, while efflux of this metabolite occurs through the transporter MCT4. The small molecule VB124 can inhibit the export of lactate from cells, thereby increasing intracellular levels of this metabolite and potentially aiding the failing heart.

strategies have identified small molecules that increase actin-activated myosin ATPase (e.g., omecamtiv and danicamtiv) or conversely molecules that decrease the myosin ATPase rate (e.g., mavacamten).[7] These molecules are being explored for the treatment of systolic heart failure or hypertrophic cardiomyopathy, respectively. Initial studies have suggested that these types of approaches might be sucessful,[8,9] with mavacamten receiving recent FDA approval, albeit with a boxed warning. Whether or not other aspects of myosin biology can be successfully drugged awaits further study. The authors suggest that manipulating intracellular cardiac lactate levels might be beneficial. The beneficial effects of inhibiting MCT4 with the compound VB124 seen by Zhang and colleagues are consistent with the observations of others suggesting that this compound could beneficially modulate cardiac hypertrophy and failure.[10] Certainly, other approaches targeting the writers and erasers are also possible therapeutic angles. We are often warned that 'we are, what we eat', and this new study suggests that in our hearts, there indeed may be a molecular basis for this old adage.

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ADDITIONAL INFORMATION

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