Letter to the Editor

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New mechanisms: From lactate to lactylation to rescue heart failure

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SUMMARY Lactylation of α-myosin heavy chain (α-MHC) has recently been reported to preserve sarcomeric structure and function and attenuate the development of heart failure. Specifically, lactylation enhanced the interaction of α-MHC with the sarcomeric protein Titin, thereby maintaining normal sarcomeric structure and myocardial contractile function. Furthermore, the administration of lactate or inhibition of lactate efflux potentially treats heart failure by restoring lactylation of α-MHC and the interaction of α-MHC with Titin. This finding highlights the significant role of α-MHC lactylation in myocardial diseases and presents a new therapeutic target for the treatment of heart failure.

Keywords α-MHC, lactylation, sarcomeric structure and function, heart failure, Titin

To the Editor,

The heart acts as a pump, facilitating the transportation of blood throughout the human body through the uninterrupted series of contractions and relaxations of its muscular walls (*1*). Heart failure (HF) was charactered by cardiac hypertrophy, fibrosis, abnormal Ca^{2+}-handling. It is reported that sarcomeric proteins Titin plays vital role in regulating the contraction response to cardiac stiffness, as well as a significant therapy target especially in HF with preserved Ejection Fraction (HFpEF) (*2*). In physiological contexts, α-myosin heavy chain's (α-MHC) tail associates with Titin to formulate thick myofilament. A stable structure of thick myofilaments is crucial to maintain the normal structure and contractile function of the heart. However, the key factors that determine the binding between myosin and Titin remain unclear.

In 2019, Professor Zhao firstly demonstrated that lactylation, a type of lactate-mediated protein post-translational modification, plays a significant role in cancer metabolism and immune cells (*3*). Lactylation also has a strong correlation with vascular function, neuroregulation, hypoxia, glycolysis and cell metabolism. While lactate was once considered as a by-product of metabolism, it now has a crucial role as an energy source for the heart. Increasing evidence supports this crucial role in cardiac hypertrophy, injury and HF. Nonetheless, as crucial energy source, there is limited knowledge regarding the physiological and pathological significance of lactate in cardiomyocytes.

A study published in Cell Research by Sun *et al*. has identified the lactylation landscape of heart in mice with HF using lactylation modification-omics (*4*). Their study revealed a significant reduction in lactate concentration in cardiomyocytes during HF. This reduction led to a subsequent decrease in the level of lactylation of α-MHCK1897 and a significant drop in the interaction between α-MHC and Titin, ultimately resulting in HF. Firstly, the authors conducted lactylation modification-omics screening and identified a significant decline in the lactylation level of the α-MHCK1897 site in HF. Subsequently, the α-MHCK1897-specific site modification antibody was developed and confirmed a marked reduction in α-MHCK1897 lactylation levels in both HF patients and mice. Then α-MHCK1897R (a lysine (K) to arginine (R) substitution at position 1897) mutant mice was generated to mimic lactylation inactivation to investigate the effect of α-MHCK1897 in HF. The findings revealed that α-MHCK1897R mutant mice considerably reduced the level of α-MHC

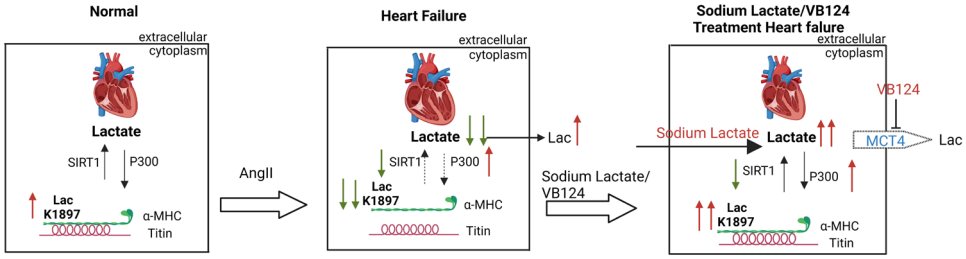

Figure 1. Schematic representation of the proposed mechanistic model of α-MHC lactylation. Under physiological conditions, lactylation of α-MHC preserves its interaction with Titin, maintaining sarcomeric structure and function. However, under pathological stress stimulation, a decrease in lactate concentration in cardiomyocytes leads to a reduction in α-MHC lactylation and α-MHC-Titin interaction, impairing cardiac structure and function. Administering sodium lactate or inhibiting MCT4 in cardiomyocytes can increase lactate concentration, promoting α-MHC lactylation and α-MHC-Titin interaction, which alleviates heart failure.

lactylation, disrupted the interaction between α-MHC and Titin, and worsened HF symptoms. Furthermore, p300 and SIRT1 were identified as acyltransferase and delactylase of α-MHC, respectively. Notably, the primary cause for the reduction of α-MHCK1897 lactylation level is the decrease in lactate concentration in cardiomyocytes, resulted from the excessive efflux and consumption of lactate in cardiomyocytes. Last but not least, sodium lactate (NALA) and VB124, a monocarboxylate transporter 4 (MCT4) inhibitor, were administered to enhance lactate concentration in cardiomyocytes, increase the level of α-MHCK1897 lactylation and significantly alleviate HF (Figure 1).

Lactylation is infrequently observed in HF, giving rise to several intriguing questions. The study conducted various experiments using a mouse model, but disparities in cardiac structure and function exist between mice and humans. The universality and reliability of the results may be limited by subjective evaluations. Therefore, further verification is required to establish the applicability of the research findings to humans. The study indicated that lactylation of α-MHC can preserve the structure and function of sarcomere, thereby decreasing the incidence of HF. Nonetheless, the specific mechanism of lactylation leading to these effects is confined. Though the influence of lactylation on cardiac structure and function were identified, further long-term observations would enable a more nuanced understanding of lactylation's role in heart disease. Although the findings are highly significant for comprehending heart disease, an evaluation of lactate as a possible therapeutic target for clinical application has not yet been conducted. Further research is imperative to assess the practicality and safety of regulating system lactate.

Additionally, there are some studies worth exploring to gain a better understanding of the lactylation mechanism in heart disease. Firstly, researching the roles of lactate and delactate enzymes and their interaction with other modification methods, such as acetylation and methylation (*5,6*). Secondly, the impact of lactylation on the progression of cardiovascular disease, in particular cardiomyocyte injury, myocardial fibrosis and HF, should be investigated. Thirdly, studying the correlation between lactylation and other modifications linked to heart disease and its regulatory mechanism would enhance understanding of the etiology of the disease. Finally, investigating the involvement of lactylation in various tissues and diseases can enhance our comprehension and potential utilisation of this process(*7,8*).

In summary, Sun and his colleagues' study offered a novel approach towards examining the mechanism and treatment of HF. The study uncovered the crucial part of lactylation in regulating myocardial sarcomere structure and functionality, which generating new insights into the pathogenesis of HF. Overall, the lactylation of α-MHCK1897 could be a potentially effective therapeutic target for treating HF, with great translational potential, particularly for patients who have HF and low lactate levels.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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