REVIEW ARTICLE

Exercise-induced lactylation: A novel mechanism regulating mitochondria-lipid droplet interaction and energy homeostasis

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ABSTRACT

The exercise-induced rise in lactate is traditionally considered a by-product of metabolism, which triggers a metabolism-regulating post-translational modification, lactylation. The dynamic properties of lactylation during physical exercise and how this biological process occurs in mitochondria-lipid droplet interactions are summarized in this review. Based on emerging evidence primarily from non-exercise models, lactylation has been proposed as a potential carrier of metabolic memory. It may facilitate phase separation to enhance communication efficiency, mediate metabolic crosstalk within the muscle-adipose axis, and add a new dimension of regulation in exercise metabolism. However, these functions remain hypothetical in the context of exercise and require validation in physiologically relevant models. These mechanisms include altered perilipin 5 (PLIN5) that facilitates contact between organelles to use fatty acids and lactylation deficiency that has adverse effects on lipid homeostasis. Lactylation is a competing mechanism with acetylation in the control of metabolic reactions. Despite some significant progress, major gaps remain in our understanding of the precise regulatory processes of lactylation, its relationships with other signalling pathways, and whether it can be used therapeutically. This research summarizes the modern results, carefully analyses the existing issues, and proposes the future research directions, which may be used as a source of extensive study in this field.

Keywords: Lactylation, Exercise metabolism, Mitochondria-lipid droplet contact, PLIN5, Post-translational modification, Metabolic memory.

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INTRODUCTION

Once considered the final metabolic end product of anaerobic glycolysis, lactate has recently been recognized as an essential molecule with additional biological functions besides energy generation (Liu et al., 2024b; Zhou et al., 2025). The main aspect of this reconceptualization is the discovery of a new post-translational modification, lactylation, in which lactyl groups derived from lactate react covalently with lysine residues of proteins, thus creating a direct relationship between the metabolic flux and epigenetic as well as proteomic regulation (Chen et al., 2025a). The lactate increase during exercise affects the lactylation of proteins, which in turn regulates key metabolic and signalling pathways, so the lactylation of RNA-binding protein, YTHDF2, in cardiomyocytes enhances physiological cardiac hypertrophy and suppresses ischemia-reperfusion injury (Li et al., 2024; Xu et al., 2024). A 2024 study published in Basic Research in Cardiology implied that exercise training universally decreases cardiac protein lactylation and YTHDF2 levels in order to alleviate ischemia-reperfusion injury through the mechanism (Xu et al., 2024). These findings are consistent with a hypothetical model proposing a spatiotemporal lactylation "*rheostat*": acute exercise-induced lactylation may serve as a protective metabolic remodelling, including improvements in mitochondrial function and insulin sensitivity, whereas chronic dysregulation could result in metabolic disorders. (Chen et al., 2025a; Wang and Zhu, 2025). This conceptual framework, while useful for integrating existing evidence, remains to be experimentally validated, particularly in human exercise models.

Despite these achievements, cognitive bias in lactylation research is substantial: most studies focus on pathological situations, which include cancer and immune regulation, and the investigation of its spatiotemporal processes during physiological processes, for instance, exercise metabolism, is insufficient (Chen et al., 2025c; Zhao et al., 2025b). In addition, the existing findings mainly rely on single models or partial evidence that lacks a detailed analysis of the patterns of regulation of different types and intensities of exercises and individual differences (Skryabin et al., 2023; Wang and Zhu, 2025). The emerging data suggest that lactylation becomes a key factor in the process of regulating the interactions between mitochondria and lipid droplets, which are crucial organelles allowing the body to manage its energy supply at the time of increased demand. But how lactylation acts in interaction with other signalling pathways, like AMPK and mTOR, and how these regulatory networks are organized hierarchically is unclear, which can make results on this topic more difficult to interpret (Gong et al., 2024). Lack of standardized measures of lactylation in skeletal muscle samples of humans has led to conflicting data on the actual prevalence and variability of lactylation during exercise (Mattingly et al., 2024; Wang and Zhu, 2025), which has complicated the issue of whether this variation is physiologically relevant or not.

LACTYLATION AS A KEY MEDIATOR OF MITOCHONDRIA-LIPID DROPLET CROSSTALK IN EXERCISE METABOLISM

Exercise-induced lactate elevation may trigger dynamic lactylation processes that potentially target proteins at mitochondria-lipid droplet interfaces, with PLIN5 and ATAD3A being candidate targets based on preliminary evidence (Chen et al., 2023a; Miner et al., 2023). The general hypothesis underlying this conceptual framework proposes that lactylation could stimulate protein binding affinity and stabilize cellular contacts between organelles, thereby potentially facilitating fatty acid transport from lipid droplets to mitochondria for β-oxidation and optimizing cellular energy metabolism during increased energy demands (Cui and Liu, 2020; Kien et al., 2022). It is important to note that this mechanism has been primarily investigated in vitro and in pathological models; direct evidence from exercise physiology remains limited. In contrast to aberrant lactylation in pathological conditions, which facilitates tumour growth and immunosuppression, physiological lactylation during exercise has been hypothesized to function as a

spatiotemporal rheostat that could dynamically govern lipid metabolism and energy homeostasis at different exercise stages and specific subcellular sites (Chen et al., 2023b; Wang et al., 2024; Ghadyani et al., 2025; Li et al., 2025a). This characterization is primarily theoretical and derives from integrating evidence across diverse experimental systems; its direct applicability to exercise metabolism requires further investigation. If validated, the proposed rheostatic activity of lactylation could ensure synchrony between organelle activity and metabolic needs in response to exercise, potentially positioning lactylation as a core regulatory activity in exercise metabolism. However, this hypothesis currently lacks direct experimental validation and should be interpreted with caution. . This working model is illustrated in Figure 1.

However, the dynamics between these two changes, be they synergetic, antagonistic, or sequential, are controversial, as a number of in vitro studies involving C2C12 myotubes showed different results with regard to their possible contribution to the stability of mitochondria-lipid droplet contact. One study suggested a complex interplay between AMPK-mediated phosphorylation of PLIN5 and its subsequent lactylation, but the precise sequence and functional hierarchy of these modifications remain unclear(Miner et al., 2023; Bovee et al., 2024). It is not yet clear that PLIN5 is functionally redundant or complementary to other members of the perilipin family (such as PLIN2 and PLIN3), and questions of whether or not there would be a specific primary target protein and decisions about the stability of the regulatory network are also raised (Shi et al., 2025). Such uncertainties highlight the need to have more systematic studies and include phosphorylation-lactylation concomitant mass spectrometry and site-specific mutation combination studies to clarify the complex interactions of lactylation with other post-translational modifications in the context of exercise.

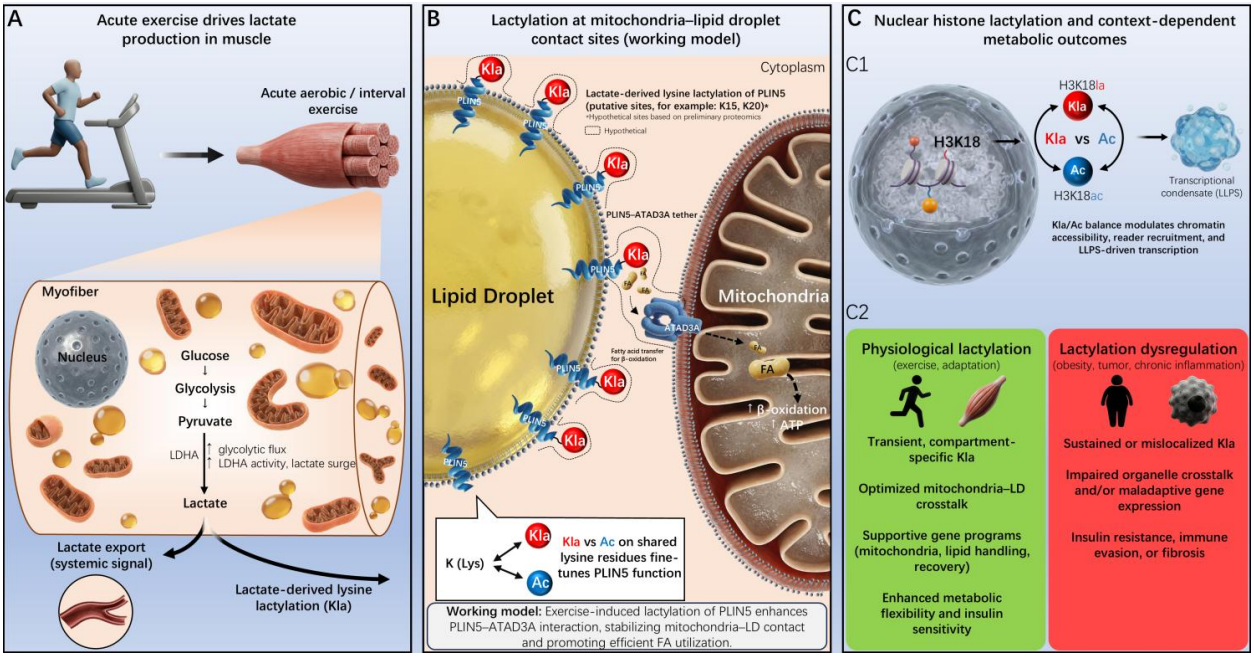

Figure 1. Exercise-induced lactylation coordinates organelle crosstalk and gene programs in skeletal muscle.

LACTYLATION OF PLIN5 PROMOTES MITOCHONDRIA-LIPID DROPLET CONTACT

Lactylation is a novel type of post-translational modification based on the lactate molecule and has emerged as a central controller of protein activity and cellular metabolism, including lipid metabolism and organelle interaction (Lu et al., 2024; Hu et al., 2025). By the operation of lactylation, a major interaction of mitochondria

and lipid droplets (LD) can be mediated by PLIN5, which is a lipid droplet-associated protein that is essential to support the biochemical and mechanical linkage between lipid droplets and mitochondria (Miner et al., 2023; Bezawork-Geleta et al., 2025). The experimental results suggest that lactylation of PLIN5 at specific, though to-be-agreed-upon lysine residues of PLIN5 (such as K15 and K20, as preliminary mass spectrometry analyses show), this augmented binding affinity to the ATAD3A mitochondrial protein is observed(Chen et al., 2022). However, the exact lactylation sites on PLIN5 remain inconsistent across studies, with differences attributed to variations in detection technologies and experimental conditions, making definitive confirmation of this process difficult. Importantly, the PLIN5 lysine lactylation can serve as a rival to acetylation on the same site, thereby specifying its binding with ATAD3A (Hu et al., 2025). This interaction is increased by simulating lactylation through the lysine site-directed alterations (i.e., like lysine to something neutral, like a K to Q) to facilitate the formation of persistent sites of mitochondria-LD contact (Liu et al., 2024a). These contact sites play a vital role in efficient delivery of fatty acids in lipid droplets to the mitochondria to undergo β-oxidation and therefore, increase cellular energy production (Wang et al., 2025a). These contact sites play a vital role in the efficient delivery of fatty acids from lipid droplets to mitochondria for β-oxidation and therefore increase cellular energy production. Thus, lactylation acts as a molecular mediator of organelle communication and increased lipid utilization during increased energy demand such as exercise. The evidence-augmented interaction between the PLIN5 and ATAD3A during lactylation underlines the idea that, along with a metabolic role, lactate is a signalling molecule and changes the important proteins to control intracellular lipid transportation and mitochondrial activity (Mandadzhiev, 2025; Wang and Zhu, 2025). It is this regulatory axis that could stimulate metabolic plasticity and energy homeostasis, clarifying the reason why exercise-triggered lactate production may control the behaviour of mitochondrial lipid droplets to meet the energy needs of the cell (Ahmadi Hekmatikar et al., 2025; Wang and Zhu, 2025).

The relevance of the research to physiological processes is limited by the experimental models used (Chen et al., 2025a; Dunzhu et al., 2025; Wang and Zhu, 2025). Most studies rely on the overexpression or mutation of PLIN5 in immortalized cell lines, which may not reliably reflect endogenous expression patterns and regulatory networks in primary muscle cells and whole tissues (Chen et al., 2025c). Furthermore, animal models using global LDHA knockouts provide metabolic phenotypes related to lactate deficiency by completely abolishing lactate production—an extreme condition that does not mimic the transient lactate elevations characteristic of human exercise physiology, thereby limiting the generalizability of results to physiological conditions (An et al., 2023; Gao et al., 2025; Li et al., 2025b). The lack of animal models with specific muscle lactylation markers has hindered proper evaluation of lactylation function in exercise metabolism; consequently, in vitro results should be interpreted with caution when extrapolated to in vivo exercise contexts (Ahmadi Hekmatikar et al., 2025; Mandadzhiev, 2025). Furthermore, the exact lysine sites of PLIN5 that are lactylated have also not been consistent across studies (Sun et al., 2022), with differences attributed to differences in detection technologies and experimental environments, which makes it difficult to confirm this process (Gong et al., 2024; Lu et al., 2024; Wu et al., 2025).

EFFECTS OF LACTYLATION DEFICIENCY ON CELLULAR METABOLISM

Lactylation plays a vital role in the maintenance of relationships between mitochondria and lipid droplets and lipid metabolism, which has been shown in the studies of the impact of lactylation deficit (Lin and Ren, 2024; Mao et al., 2024; Zhao et al., 2025a). Down-regulation of lactate dehydrogenase A (LDHA), which plays an important role in lactate production, leads to a significant drop in intracellular levels of lactylation (Hu et al., 2024; Xia et al., 2024; Chen et al., 2025b; Peng and Du, 2025). This weakens the structural integrity of contact points between mitochondria and lipid droplets, which reduces transportation of fatty aci Metabolic diseases included and abnormal accumulation of lipid droplets in cells (Ippolito et al., 2022; Jia et al., 2023;

Mao et al., 2024; Zhao et al., 2025a). Metabolic diseases include lipid dysregulation, specifically the development of insulin resistance, which is typical of metabolic syndrome and type 2 diabetes (Feng et al., 2022; Maschari et al., 2022; Cao et al., 2025; Long et al., 2025). However, studies show that adipocyte-specific deletion of Ldha in obese mice paradoxically increases insulin sensitivity, indicating that the metabolic effects of lactylation modulation are context-dependent and vary by tissue (Feng et al., 2022; Lin et al., 2022). While these data suggest that lactylation contributes to lipid metabolic homeostasis under certain conditions, the divergent outcomes across different models highlight the need for caution in generalizing its role.

Representative experimental models and metabolic outcomes associated with lactylation deficiency are summarized in Table 1. As shown, the metabolic consequences of reduced lactylation vary substantially by model: global LDHA knockout causes systemic metabolic disruption, cellular LDHA knockdown impairs lipid handling and insulin sensitivity, while adipocyte-specific LDHA deletion in obese mice improves insulin sensitivity. These divergent outcomes indicate that the effects of lactylation modulation are highly tissue-specific and context-dependent. Rather than uniformly disrupting cellular homeostasis, lactylation appears to exert distinct metabolic effects depending on the specific tissue manipulated and the completeness of lactylation ablation. This complexity highlights the need for cautious interpretation of lactylation function in metabolic health.

Table 1. Representative models of reduced lactylation and their metabolic consequences.

Model / manipulation	Tissue / system	Change in lactate / lactylation	Mitochondria–LD contact / lipid phenotype	Metabolic outcomes	References
Global LDHA knockout (whole-body KO)	Whole organism (multiple tissues)	Near-complete loss of lactate production; broad reduction of protein lactylation	Not specifically reported; global disturbance of lipid and energy metabolism is implied	Systemic metabolic phenotypes associated with lactylation deficiency; considered an extreme model that does not mimic transient exercise-induced lactate elevation in humans	(Yang et al., 2021; Li et al., 2025b)
LDHA knockdown in cultured cells	In vitro cellular models (for instance, immortalized cell lines)	↓ intracellular lactate production; ↓ global protein lactylation	Disruption of mitochondria–lipid droplet (LD) contact sites; impaired fatty acid trafficking; abnormal lipid droplet accumulation	Cellular lipid dysregulation linked to insulin resistance–like disturbances, highlighting the role of lactylation in maintaining lipid metabolic homeostasis and insulin sensitivity	(Nian et al., 2022; Yao and Li, 2023; Dong et al., 2024)
Adipocyte-specific LDHA deletion in obese mice	Adipose tissue (adipocyte-specific KO; obese models)	↓ adipocyte lactate production and protein lactylation; reduced lactate signalling to the microenvironment	Not directly reported; alterations in adipose lipid handling and inflammatory milieu are implicated	Paradoxical improvement of systemic insulin sensitivity and reduced adipose macrophage inflammation, illustrating that reduced lactylation can have beneficial effects in specific tissue and metabolic contexts	(Feng et al., 2022; Galle et al., 2022; Lin et al., 2022)

Note: This table summarizes experimental contexts in which lactylation is reduced or impaired and highlights that the metabolic consequences are highly tissue- and context-dependent.

COMPETITIVE REGULATORY MECHANISMS BETWEEN LACTYLATION AND ACETYLATION

Lactylation and acetylation are both lysine-based post-translational modifications that may compete for the same lysine sites (for instance, histone H3 lysine 18, H3K18), based primarily on evidence from non-exercise models (Wang et al., 2022; Xin et al., 2022; Xie et al., 2025; Xu et al., 2025b). Whether this competitive relationship operates similarly during exercise remains to be determined. In addition, lactylation of specific lysine residues has been proposed to facilitate biomolecular condensate formation through liquid-liquid phase separation of metabolic signalling proteins and transcriptional regulators, potentially enhancing signal transduction and transcriptional activation (Dai et al., 2025; Ma et al., 2025; Wang et al., 2025b). The relevance of phase separation to exercise-induced lactylation requires further investigation. The process contributes to the formation of transcriptional machinery and chromatin remodelling complexes at target gene loci, which increase gene expression responses to metabolic stress, including exercise (Dai et al., 2025; Ma et al., 2025; Wang et al., 2025b).

Current research on this competitive interaction is subject to important limitations that affect the reliability of prevailing conclusions (Nitsch et al., 2021; Bao et al., 2025; Xie et al., 2025; Xu et al., 2025b). Most evidence supporting the lactylation-acetylation competition derives from in vitro experiments or static cell models, which may not reflect the dynamic metabolic changes and complex environment of in vivo exercise conditions (Xin et al., 2022; Bao et al., 2025; Xu et al., 2025a). Whether competitive priority between lactylation and acetylation exists during exercise, and how exercise intensity and duration might affect it, remains unknown. Additionally, whether other lysine-targeted modifications (for example, succinylation and malonylation) interfere under exercise-induced metabolic stress has not been investigated (Nitsch et al., 2021; Yao et al., 2024; Ma et al., 2025). Analytical methods currently lack sufficient resolution to reliably distinguish sequential or simultaneous changes in lactylation and acetylation at shared sites (Artiukhov et al., 2021; Ma et al., 2025). Mass spectrometry, despite being considered the gold standard, often shows insufficient sensitivity to detect transient and low-abundance lactylation events induced by acute exercise. Furthermore, commercial lactylation antibodies may cross-react with acetylation, potentially leading to inaccurate quantification (Artiukhov et al., 2021; Yao et al., 2024; Ma et al., 2025). These technical limitations should be considered when interpreting the current evidence base.

The above-mentioned technical issues have contributed to inconsistent findings across research groups. Some reported predominance of lactylation under exercise stress conditions (Wang et al., 2022; Merkuri et al., 2024; Bao et al., 2025; Hou et al., 2025), while others found no obvious competition (Xin et al., 2022; Xie et al., 2025; Xu et al., 2025b, 2025a). These discrepancies highlight that the existence and nature of lactylation-acetylation competition during exercise remain unresolved. Standardized detection protocols and more physiologically relevant models are needed to clarify whether this competitive relationship is consistently present under exercise conditions.

CONCLUSIONS AND PERSPECTIVES

This review summarizes previous research exploring a potential role for exercise-induced lactylation in metabolic regulation and organelle communication. Lactylation has been associated with changes in mitochondrial function, lipid metabolism, and gene expression across diverse models, and may compete with other lysine acylations, such as acetylation, at shared sites, though this competition remains to be confirmed in exercise contexts. We propose a hypothetical model in which the lactylation of essential proteins, such as PLIN5, could enhance interactions between mitochondria and lipid droplets by modulating protein-protein interactions (for example, with ATAD3A), thereby potentially promoting fatty acid utilization during exercise.

In this proposed framework, loss or dysregulation of lactylation might impair organelle communication and disrupt lipid homeostasis, potentially contributing to insulin resistance in a tissue- and context-specific manner, rather than as a global, unidirectional process. The competitive cross-talk between lactylation and acetylation, if confirmed during exercise, could function as a regulatory switch for protein function and gene expression in response to metabolic stress. Within this model, lactylation is conceptualized as a spatiotemporal rheostat for exercise metabolism, potentially adapting to changes in exercise intensity and the spatial positioning of metabolic organelles as a proposed mechanism for energy balance regulation. Even though recent research has found lactylation as an additional process of organelle communication in exercise metabolism, gaps in understanding and controversy still exist.

More sensitive and specific detection methods are required to provide support and confirm the precise spatiotemporal details of lactylation at different exercise intensities and durations, particularly in human skeletal muscle (Meng et al., 2025). Secondly, the cross-regulation of lactylation and other signalling pathways (such as AMPK and mTOR) and post-translational modifications also needs to be analysed carefully in order to clarify the hierarchical structure of the regulatory network, that is, whether the AMPK-mediated phosphorylation and lactylation of PLIN5 are synergistic or sequential (Hagihara et al., 2021). As existing experimental models (global LDHA deletion, immortalized cell lines) have limitations, tissue-specific and conditional models of these modifications are needed to accurately assess the physiological role of lactylation.

The potential clinical relevance of lactylation for exercise interventions and metabolic disease treatment remains a subject of future inquiry, given current technical and conceptual limitations. A fundamental unanswered question is whether lactylation is a cause of metabolic adaptation or merely a consequence of exercise-induced metabolic stress (Zhang et al., 2024). Exogenous manipulation of lactylation levels, whether through lactate supplementation or potential inhibitors, risks disrupting endogenous metabolic balance and producing unanticipated outcomes. Furthermore, targeting PLIN5 lactylation therapeutically faces specific limitations, including the difficulty of separating lactylation from competing modifications such as acetylation to avoid off-target effects, which currently limits clinical feasibility (Shang et al., 2022).

The therapeutic application of lactylation-related mechanisms would require substantial advances in selective regulation and safety verification. Accordingly, near-term clinical translation should be regarded as a long-term perspective rather than an immediate possibility. Future studies should prioritize developing more sensitive and specific detection tools, establishing physiologically relevant models, and systematically exploring regulatory mechanisms. These foundational advances are needed to determine whether lactylation holds physiological significance in exercise metabolism and, if so, whether it may eventually have relevance for metabolic disease research.

AUTHOR CONTRIBUTIONS

All authors meet the criteria for authorship in accordance with established ethical guidelines. J. Z.: Conceptualization, Investigation, Data Curation, Writing – Original Draft, Validation, Formal Analysis, Methodology. Z. M.: Formal Analysis, Methodology, Validation, Investigation. J. L.: Supervision, Project Administration, Funding Acquisition, Conceptualization, Writing – Review & Editing. All authors have critically reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

AI USE DISCLOSURE

In accordance with current publishing ethics and transparency recommendations, artificial intelligence (AI) tools were used solely to assist with translation and language editing, with the aim of improving clarity and readability. No AI tools were used in the generation of scientific content, including the study design, data collection, analysis, interpretation of results, or the formulation of conclusions. The authors retain full responsibility for the content of the manuscript and confirm its originality, integrity, and accuracy.

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