

Lactylation and exercise: A molecular link to disease alleviation (Review)

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Abstract. Regular physical activity improves physical capacity and overall health by enhancing cardiopulmonary function and muscle strength, reducing stress, and improving psychological well-being and quality of life. Despite these known benefits, the molecular mechanisms that underlie these effects remain incompletely understood. Lactylation, a modification wherein lactate molecules form ester bonds with proteins, induces functional changes in these proteins. Evidence indicates that exercise can regulate lactylation, which, in turn, affects intracellular signaling pathways and metabolic processes. This modulation plays a role in promoting health and facilitating disease alleviation. The present review offers an extensive review of the mechanisms through which exercise influences lactylation and discusses the potential clinical applications of lactylation in the prevention and treatment of exercise-related diseases.

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1. Introduction

Exercise provides a broad spectrum of health benefits. Research indicates that engaging in regular physical activity improves

cardiovascular health, strengthens immune function, regulates metabolic processes and lowers the risk of chronic conditions such as diabetes and heart disease (1-5). Additionally, exercise enhances cognitive function, reduces stress and anxiety and promotes psychological well-being (6-9). It plays an essential role in maintaining bone and muscle health by increasing bone density and improving muscle strength (10-13). In summary, exercise serves as a crucial strategy for the prevention and management of numerous diseases, contributing to overall health and helping to slow the aging process (14-16). Despite these known benefits, the specific mechanisms through which exercise contributes to disease prevention and treatment remain incompletely understood.

During physical activity, muscles undergo intense exertion, producing energy that supports the ongoing exercise. In high-intensity activities, muscle cells may not receive enough oxygen, leading to an increase in anaerobic metabolism and lactate production (17-19). Lactate accumulation is a typical physiological response to exercise, commonly associated with muscle fatigue and diminished performance (18,19). Recent studies, however, suggest that lactate is not merely a metabolic byproduct but also plays a key physiological role, particularly in lactylation modifications (20-22). Lactylation refers to the process in which lactate molecules bind to specific protein sites through esterification, subsequently altering the function of the proteins (23-25). These lactylation modifications are crucial in cellular signaling, gene expression and metabolic regulation, influencing cellular adaptability, antioxidant defenses, and stress response mechanisms (26-28).

Studies indicate that exercise can regulate lactylation modifications, which subsequently affect cellular signaling and metabolic processes, thereby promoting overall health and aiding in disease relief. The aim of the present review is to summarize the current evidence on how exercise regulates lactylation modifications and to discuss the potential clinical relevance of these changes to disease prevention and treatment.

2. Lactate and lactylation modification

Lactate is an essential byproduct of metabolism, primarily generated in the cytoplasm, where it plays a fundamental

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role in glycolysis (29-31). When oxygen availability is limited or metabolic demands are heightened, cells convert glucose to pyruvate via glycolysis. In oxygen-deprived conditions, such as ischemia, pyruvate is unable to enter the mitochondria for oxidative phosphorylation, leading to its conversion into lactate. This metabolic process is catalyzed by lactate dehydrogenase (LDH), which transforms pyruvate into lactate and simultaneously facilitates the oxidation of NADH to NAD⁺, ensuring the uninterrupted progression of glycolysis (32-34).

The increase in lactate production is associated not only with the energy requirements of cells but also with the regulation by several critical proteins. Among these, LDH is a key enzyme in the synthesis of lactate (35,36), while other enzymes involved in glycolysis, such as glucose transporters (GLUT), pyruvate kinase M, hexokinase 2, aldolase A and phosphofructokinase, contribute to the regulation of this process (37-40). For instance, tumor cells commonly exhibit higher levels of LDH and increased enzymatic activity, leading to accelerated lactate production (41-43). Moreover, members of the GLUT family, including GLUT1 and GLUT3, facilitate glucose uptake, supplying the essential substrates for glycolysis (44,45). At the same time, lactate accumulation causes a decrease in local pH, which triggers the export of lactate through specific transporters, such as monocarboxylate transporters, thereby preventing excessive accumulation and maintaining the acid-base balance within the cell (46-49). The coordinated action of these proteins ensures proper regulation of lactate synthesis while maintaining cellular integrity and supporting the capacity of the cell to adapt to changes in the environment (Fig. 1).

Lactylation, similar to other post-translational modifications, influences both the activity and structure of polypeptides by adding lactyl groups to the side chains of amino acids. Lysine lactylation (Kla), a modification originating from lactate, was first discovered in 2019. This modification is highly conserved across various species and occurs in different cellular lineages (50-52). When lactate accumulates to a certain level, either intracellularly or extracellularly, it activates the lactylation process within the cell (53-55).

Lactylation is triggered when lactate acts as the primary substrate. Following the conversion of lactate into lactyl-CoA, the lactylation process commences (56,57). Specific acetyltransferases utilize lactyl-CoA as a substrate, transferring the lactyl group to lysine residues in both histone and non-histone proteins. This modification leads to alterations in their molecular structure and regulates their biological activities. The reactions are mediated by 'writers' such as P300/CREB-binding protein (58-60), methyltransferase-like 3 (61-63), lysine Acetyltransferase 2A and others (64-67). By contrast, 'erasers' such as histone deacetylases (HDACs) (68-71), histone demethylases (72) and sirtuins (73-75) remove the lactyl group from lysine residues, preventing the persistent effects of Kla. The coordinated activity of these 'writers' and 'erasers' maintains the equilibrium of protein lactylation, ensuring the stability of this modification within the organism (Fig. 2).

Proteins prone to lactylation modifications include both histones and non-histone proteins (21,76-80). Initially, lactylation was observed in histones, which prompted extensive research into its regulation. For instance, Yue *et al* (81)

revealed that lactylation at histone H3K9 (H3K9la) contributes to temozolomide resistance in glioblastoma via MLH1 intron retention, a mechanism facilitated by LUC7 like 2, pre-mRNA splicing factor. Specifically, H3K9la levels rise in glioblastoma cells after temozolomide treatment. Inhibition of glycolysis pharmacologically reduces H3K9la, thus increasing the sensitivity of the cell to temozolomide. The accumulation of H3K9la within an intronic region of the *MLH1* gene locus causes intron retention, disrupting normal splicing and MLH1 function, which ultimately enhances resistance to temozolomide.

While considerable research has focused on histone proteins, substantial attention has also been directed toward non-histone proteins (82). For example, Tong *et al* (83) found that a diet lacking serine and glycine plays a dual role, both enhancing anti-tumor immunity and facilitating immune evasion through the lactylation of programmed death-ligand 1 (PD-L1). This dietary modification alters the metabolic conditions of the tumor microenvironment, stimulating anti-tumor immune responses and enhancing T cell-mediated tumor suppression. At the same time, it causes tumor cells to increase PD-L1 expression through lactylation, which in turn suppresses T cell-mediated immune responses and contributes to immune evasion. The lactylation of PD-L1 accumulates within tumor cells, leading to changes in its structure and function, thereby amplifying its immunosuppressive effects.

3. Exercise regulates lactylation modifications in the body

Lactate metabolism during physical exercise plays a role in various physiological processes. High-intensity or anaerobic exercise stimulates rapid energy production in muscles through glycolysis, resulting in a substantial accumulation of lactate (29). When lactate production exceeds the clearance capacity of the body, it accumulates in the muscles and bloodstream; however, lactate is not merely a 'waste product'. Instead, it acts as an energy substrate, which can be reused by other tissues in the body, such as the heart, liver and resting or non-working muscles. It participates in oxidative metabolism or is converted into glucose (via the Cori cycle) for subsequent use (84) (Fig. 3). Studies have consistently shown that lactate accumulation promotes lactylation modifications, which play a role in regulating disease progression during exercise.

Lactate has been identified as a key metabolite crucial for the body's adaptation to exercise training, playing a role in alleviating anxiety-like disorders. It has been observed that exercise-induced lactate enhances the lactylation of multiple synaptic proteins, among which synaptic vesicle-associated protein 91 (SNAP91) is essential for synaptic function. The lactylation of SNAP91 contributes to synaptic structural formation and neuronal activity within the medial prefrontal cortex, thereby promoting resilience to chronic restraint stress (78). Furthermore, research indicates that exercise can stimulate lactylation modifications in the brain, leading to improvements in both cognitive dysfunction and neuroinflammation in mice. This process involves an increase in lactate accumulation in the brain, which in turn facilitates histone lactylation in microglial cells, influencing their polarization and enhancing the reduction of cognitive dysfunction and neuroinflammation (85).

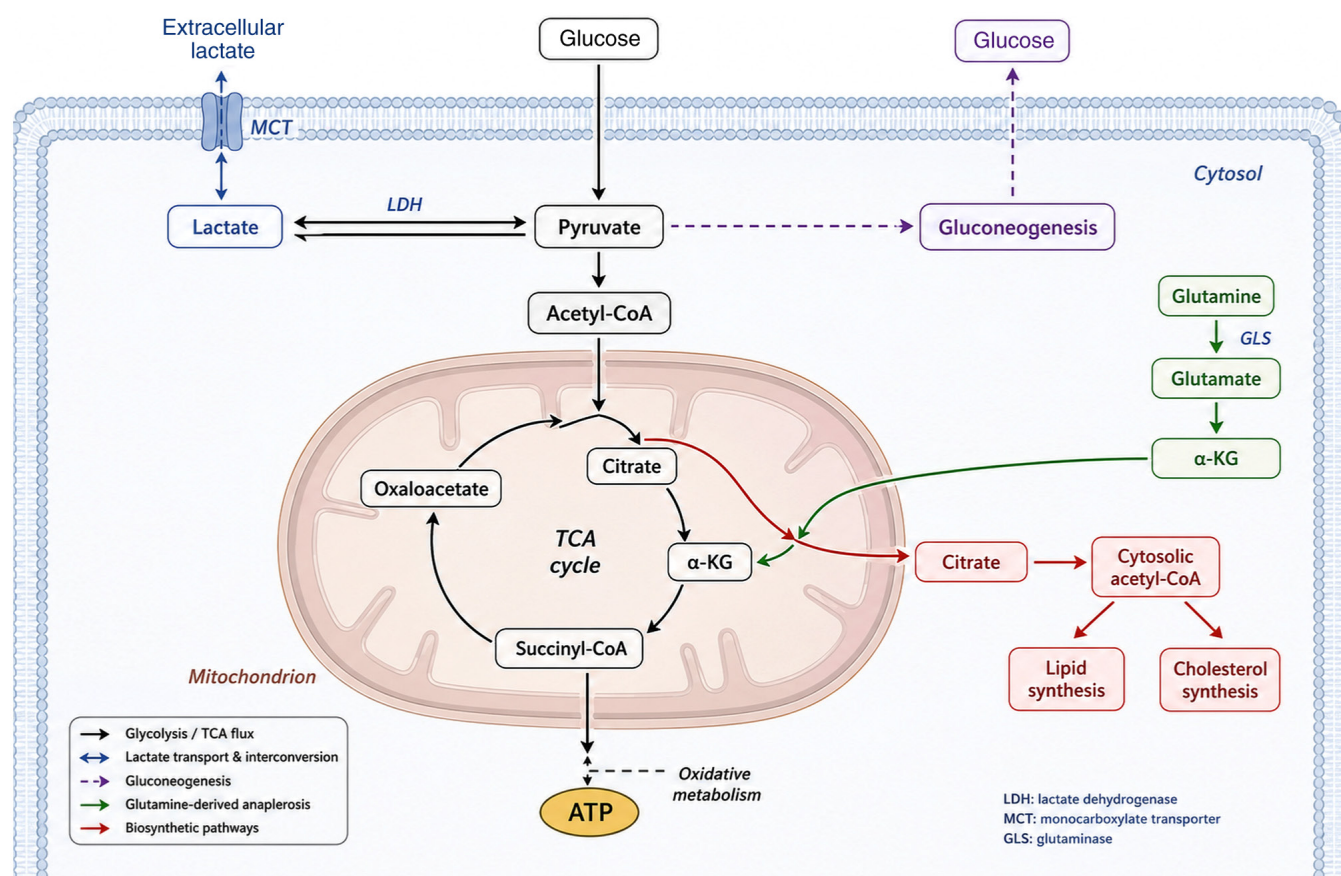


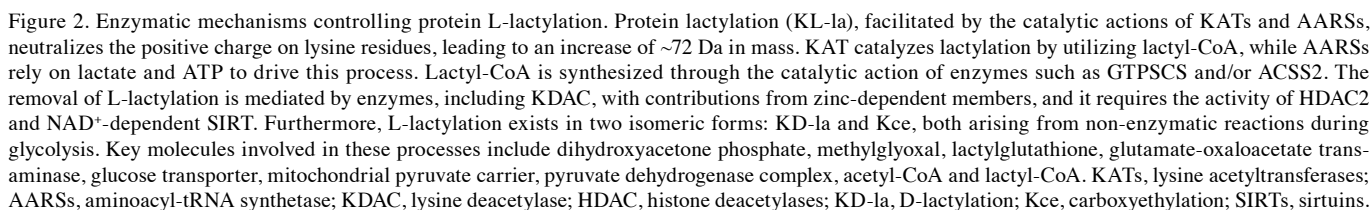
Figure 1. Lactate production and intracellular metabolism involve several key processes. Initially, lactate enters the cytoplasm via the cell membrane through MCT, which originates from external cellular fluids. Lactate can be generated either through glycolysis or by the breakdown of glutamine. Once inside the cell, lactate metabolism follows two primary metabolic pathways. The first pathway converts lactate into pyruvate, which is subsequently transported to mitochondrial compartments for further oxidative processing within the TCA cycle. The second pathway involves converting lactate back into glucose through gluconeogenesis. Proteins involved in these metabolic processes include α -KG, MCT, PDH and components of the TCA cycle. MCT, monocarboxylate transporter; α -KG, α -ketoglutarate; PDH, pyruvate dehydrogenase; TCA, tricarboxylic acid; GLS, glutaminase.

Exercise plays a notable role in regulating lactate accumulation within the brain, which in turn affects lacylation modifications. Additionally, one study reported that acute exercise induced dynamic alterations in histone acetyltransferases and HDACs in the hippocampus of mice (71). This observation suggests that exercise might influence lacylation modifications by adjusting the dynamic balance between 'writers' and 'erasers' involved in lacylation regulation. However, other research has indicated that high-intensity interval training (5 days per week for 6 weeks) in mice leads to an increase in lactate levels and promotes neuroplasticity in the brain due to lactate accumulation, yet no significant changes in the extent of lacylation modifications were observed (86). These findings imply that the impact of lactate on disease progression may not be solely dependent on lacylation modification regulation. Despite these insights, the research by these authors has several limitations. For example, the authors primarily relied on exogenous lactate supplementation to demonstrate the role of lactate, without incorporating an *in vivo* validation step to confirm glycolysis inhibition. Furthermore, the detection of lacylation modifications was based solely on results from a relatively rare antibody brand, potentially leading to false-negative outcomes.

Skeletal muscles and the skeletal system function as an integrated musculoskeletal unit during exercise. Skeletal muscles generate force through contraction, whereas the skeleton provides support and stability for movement. Regular physical activity can improve skeletal-muscle strength and physical function (12,13) and, through mechanical loading, improve or preserve bone mineral density (10,11). Together, these adaptations support physical performance and overall health.

Recent research indicates that exercise can enhance both skeletal muscle strength and bone density by regulating lacylation modifications in muscles and bones. For instance, the study by Chang *et al* (87), first identified differences in lacylation modifications of skeletal muscle proteins post-exercise, although the authors did not explore the significance of these changes. By contrast, Meng *et al* (88) conducted further research, confirming the mechanism. Their study demonstrated that exercise induces histone lacylation modifications (H3K9la) in skeletal muscles, which regulates the expression of aging-related genes, ultimately preventing skeletal muscle aging.

In addition to histone lacylation, post-exercise lactate accumulation has been shown to stimulate non-histone lacylation modifications. For example, Jia *et al* (89) demonstrated that



Furthermore, preclinical evidence suggests that exercise-associated lactate may promote osteogenesis through lactylation. In an ovariectomized mouse model, Wu *et al* (91) demonstrated that endothelial cell-derived lactate increased H3K18la in bone mesenchymal stem cells and upregulated COL1A2, COMP, ENPP1 and TCF7L2, which promoted osteoblast differentiation; exercise partially rescued the osteoporotic phenotype. Similarly, in treadmill- and tail-suspension mouse models and mechanically stretched bone mesenchymal stem cells, Dai *et al* (92) found that mechanical stress increased

Exercise plays a notable role in reducing body fat and preventing chronic conditions such as cardiovascular diseases. Both aerobic exercise and strength training are particularly effective in promoting fat metabolism, improving

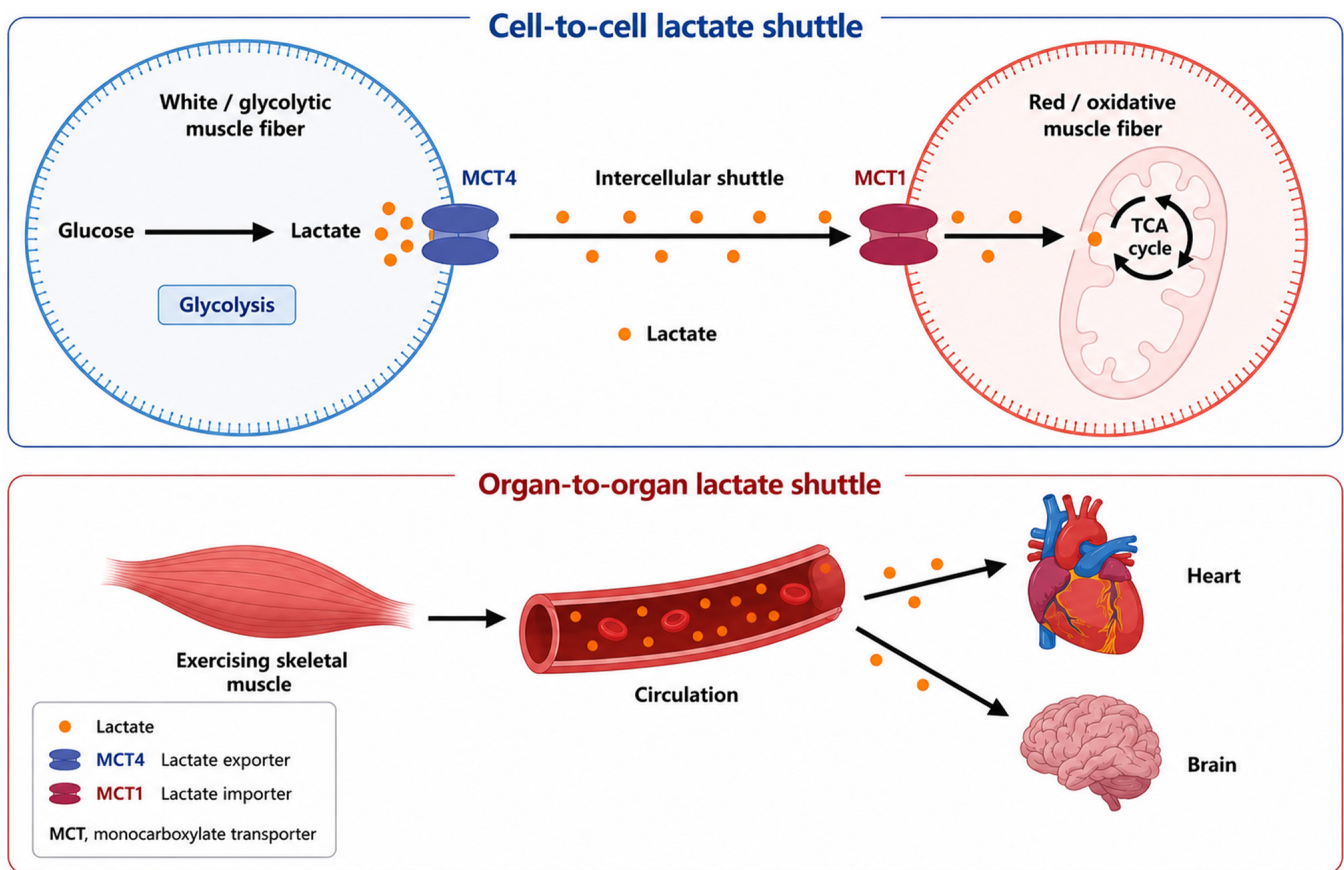


Figure 3. Inter-organ lactate shuttle during physical activity. During physical activity, lactate generated by white/glycolytic muscle fibers is transported between cells to red/oxidative muscle fibers, the heart, and the brain. From there, it is moved into the mitochondria for aerobic oxidation. MCT1, monocarboxylate transporter 1; MCT4, monocarboxylate transporter 4; TCA, tricarboxylic acid cycle.

cardiovascular health, decreasing the risk of coronary heart disease and enhancing overall well-being (95-97). Lactylation modifications have been identified in these processes. In the context of cardiovascular diseases, research indicates that exercise-induced lactylation of endothelial methyl-CpG binding protein 2 (Mecp2) inhibits atherosclerosis via the Ereg/MAPK signaling pathway (98). Additionally, studies have shown that exercise-induced lactylation of Mecp2 in macrophages reduces atherosclerosis by promoting M2 macrophage polarization (99). These findings suggest that exercise may help prevent atherosclerosis by enhancing lactylation modifications. Atherosclerosis serves as an early stage in myocardial ischemia-reperfusion injury. Notably, a study has suggested that exercise can mitigate myocardial ischemia-reperfusion injury by regulating lactylation modifications. From a mechanistic perspective, exercise-induced lactylation of YTHDF2 in cardiomyocytes prevents apoptosis, thus reducing myocardial ischemia-reperfusion injury (100).

Exercise is commonly used for fat loss, primarily by increasing energy expenditure and improving adipose-tissue metabolism (95,96). In a preclinical high-intensity interval-training study, training increased pan-lactylation of proteins in inguinal white adipose tissue. In 3T3-L1 adipocytes, lactate treatment increased fatty acid synthase lactylation, inhibited fatty acid synthase activity, and reduced palmitate and triglyceride synthesis, suggesting that fatty acid synthase lactylation may contribute to high-intensity interval training-associated fat loss (101).

Exercise is widely acknowledged for its effectiveness in preventing disease progression, yet excessive exercise can still have detrimental effects on health, with mechanisms linked to lactylation modifications. For instance, research has shown that excessive exercise leads to an accumulation of lactate in skeletal muscles, which is then transferred to the liver. This causes the lactylation of SH3 domain-containing protein 3 (SORBS3) and triggers liquid-liquid phase separation (LLPS). The LLPS of SORBS3 enhances its interaction with flotillin 1, selectively promoting the sorting of F-box protein 2 into small extracellular vesicles, referred to as 'lactosomes'. These lactosomes induce apoptosis in hepatocytes and activate hepatic stellate cells via the MCL1-BAX/BAK signaling pathway, ultimately contributing to the development of liver fibrosis (102).

To summarize, moderate and appropriate exercise plays a notable role in regulating mood and mental well-being, promoting muscle homeostasis and preventing osteoporosis through the modification of lactylation. Additionally, evidence suggests that such exercise can effectively prevent as well as treat the initiation and progression of myocardial ischemia-reperfusion injury (Table I).

4. Translational potential and clinical challenges of exercise-related lactylation

Clinical trials and meta-analyses support the benefits of exercise for cardiovascular health, depressive symptoms and bone

Table I. Mechanisms of lactylation modulation by exercise.

Effects of exercise on diseases	Target tissues	Exercise form	Lactylation modification sites	Mechanism of action	(Refs.)
Enhance stress resistance	Brain	Treadmill exercise (60 min daily, 14 days)	SNAP91	Exercise promotes lactate levels in the brain and lactylation modifications, with SNAP91 lactylation enhancing synaptic structure formation and neuronal activity in the medial prefrontal cortex.	(78)
Improve cognitive dysfunction and neuroinflammation	Brain	Treadmill exercise (50 min daily, 5 days a week, 8 weeks)	Histone	Exercise promotes the accumulation of lactate in the brain, which then enhances histone lactylation modifications in microglial cells, influencing microglial cell polarization.	(85)
Promote brain neuroplasticity	Brain	High-intensity interval training (5 days a week, 6 weeks)	Not proven	Unclear	(86)
Inhibit skeletal muscle aging	Skeletal muscle	Long-duration treadmill running (3 times a week, 30 min per session, for 2 months)	H3K9la	Exercise promotes histone lactylation and inhibits skeletal muscle aging by regulating age-related pathways.	(88)
Maintain skeletal muscle homeostasis	Skeletal muscle	Acute swimming (20 min daily, 5 days)	Vps34	Post-exercise lactate accumulation promotes Vps34 lactylation, which enhances the binding of Vps34 with Beclin1, ATG14L, and UVRAG, stimulating Vps34 lipid kinase activity and promoting autophagy to maintain skeletal muscle homeostasis.	(89)
Maintain skeletal muscle homeostasis	Skeletal muscle	Treadmill exercise (5 min on days 1 and 2, 40 min on day 3)	mTOR	Post-exercise lactylation of mTOR inhibits mTOR pathway activation and promotes skeletal muscle autophagy.	(90)
Inhibit osteoporosis	Bone	Treadmill exercise (8 min per session, 5 days a week, 8 weeks)	H3K18la	Exercise promotes histone lactylation and inhibits osteoporosis by promoting osteoblast differentiation.	(91)
Inhibit osteoporosis	Bone	Treadmill exercise (20-55 min daily, 5 days a week, 8 weeks)	Unclear	Exercise promotes lactylation modifications after exercise, which may alleviate osteoporosis.	(92)
Inhibit atherosclerosis	Vessels (endothelial cells)	Moderate-intensity treadmill exercise (30-60 min daily, 3-5 days a week, 12 weeks)	Mecp2	Exercise-induced endothelial Mecp2 lactylation inhibits atherosclerosis through the Ereg/MAPK signaling pathway.	(98)
Inhibit atherosclerosis	Vessels (macrophages)	Treadmill exercise (60 min daily, 5 days a week, 8 weeks)	Mecp2	Exercise-induced endothelial Mecp2 lactylation inhibits atherosclerosis by promoting macrophage M2 polarization.	(99)
Inhibit myocardial ischemia-reperfusion injury	Heart	Swimming (twice daily, starting with 10 min per session, for 4 weeks)	YTHDF2	Exercise-induced YTHDF2 lactylation in cardiomyocytes inhibits apoptosis, thereby suppressing myocardial ischemia-reperfusion injury.	(100)

Table I. Continued.

Effects of exercise on diseases	Target tissues	Exercise form	Lactylation modification sites	Mechanism of action	(Refs.)
Reduce fat	Adipose tissue	High-intensity interval training (5 days a week, 8 weeks)	FASN	Lactate produced by high-intensity interval training increases the pan-lactylation level of proteins in inguinal white adipose tissue. Fatty acid synthase lactylation inhibits <i>de novo</i> lipogenesis, inducing fat reduction.	(101)

health (1-3,6,7,10). However, direct human evidence linking exercise to defined protein lactylation events remains limited. In two human skeletal-muscle biopsy studies, neither acute nor chronic resistance training, nor a single bout of endurance exercise, produced a significant increase in global skeletal-muscle protein lactylation (103,104). Therefore, lactylation cannot yet be used to guide exercise prescription or serve as a therapeutic target in clinical practice.

The most immediate translational opportunity is to determine whether site-specific lactylation events can serve as biomarkers of exercise response. Future human studies should use repeated sampling around well-characterized exercise interventions, targeted lactyl-proteomic assays and clinically meaningful outcomes to establish whether a lactylation signature predicts or mediates the benefits of exercise.

Several challenges must be addressed before clinical implementation. Lactylation is dynamic and cell-type specific, and measurements from blood or bulk tissue may not reflect the relevant target cells. Assay specificity, sampling time, exercise dose, diet, medication use and disease stage may also influence the results. In addition, associations between lactate, lactylation and clinical outcomes do not establish causality or justify broad pharmacological manipulation of lactylation.

Overall, current evidence supports lactylation as a promising mechanistic and biomarker framework rather than an established clinical target. Translation will require reproducible, target-specific evidence in humans showing that modulation of a defined lactylation event improves outcomes beyond those achieved by exercise alone.

5. Conclusion and future perspectives

Lactylation modifications have attracted growing interest as a notable post-translational modification mechanism, particularly due to their involvement in exercise-induced disease prevention and treatment. Exercise influences lactate metabolism and lactylation modifications, which play a role in enhancing physical fitness, improving cardiovascular and pulmonary health and promoting mental well-being. Moreover, exercise offers new insights into the molecular mechanisms regulating intracellular metabolism, gene expression, and antioxidant defense. By modulating the activity of various proteins, lactylation modifications affect cellular adaptive responses, contributing to the relief of diseases such as cardiovascular conditions, skeletal muscle aging, osteoporosis and

neurological diseases. Additionally, an expanding body of research indicates that lactate, once considered just a metabolic byproduct, actively participates in complex physiological regulatory processes, providing new perspectives for applying exercise therapy in the treatment of diseases.

Current findings also indicate that the effects of lactylation are context dependent. In exercise models, lactylation has been associated with potentially beneficial adaptations in skeletal muscle, bone and cardiovascular tissues, whereas studies of osteoarthritis suggest that specific lactylation events may contribute to disease progression. These observations highlight the importance of defining the relevant tissue, target protein and exercise context before drawing therapeutic conclusions.

Future studies should identify site-specific and cell-specific lactylation events that change reproducibly in response to well-characterized exercise interventions. Standardized sampling windows, targeted lactyl-proteomic assays and clinically meaningful outcomes will be needed to determine whether these events mediate exercise benefits or can serve as biomarkers of response. Rigorous human studies are also required to establish causality, safety and clinical value before lactylation can be considered a therapeutic target.

In conclusion, lactylation provides a useful molecular framework for investigating how exercise-related lactate signaling may influence disease-relevant pathways. Its clinical application will require robust human evidence demonstrating target specificity, causality and added value beyond established exercise interventions.

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LW conceptualized the review, provided project management and supervision, and wrote, reviewed and edited the

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Ethics approval and consent to participate

Not applicable.

Patient consent to participate

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

- Molloy CD, Long L, Mordi IR, Bridges C, Sagar VA, Davies EJ, Coats AJS, Dalal H, Rees K, Singh SJ and Taylor RS: Exercise-based cardiac rehabilitation for adults with heart failure-2023 Cochrane systematic review and meta-analysis. *Eur J Heart Fail* 25: 2263-2273, 2023.
- Dibben GO, Faulkner J, Oldridge N, Rees K, Thompson DR, Zwisler AD and Taylor RS: Exercise-based cardiac rehabilitation for coronary heart disease: A meta-analysis. *Eur Heart J* 44: 452-469, 2023.
- Isath A, Koziol KJ, Martinez MW, Garber CE, Martinez MN, Emery MS, Baggish AL, Naidu SS, Lavie CJ, Arena R and Krittanawong C: Exercise and cardiovascular health: A state-of-the-art review. *Prog Cardiovasc Dis* 79: 44-52, 2023.
- Hashimoto Y, Takahashi F, Okamura T, Hamaguchi M and Fukui M: Diet, exercise, and pharmacotherapy for sarcopenia in people with diabetes. *Metabolism* 144: 155585, 2023.
- Martínez-Vizcaíno V, Sanabria-Martínez G, Fernández-Rodríguez R, Cavello-Redondo I, Pascual-Morena C, Álvarez-Bueno C and Martínez-Hortelano JA: Exercise during pregnancy for preventing gestational diabetes mellitus and hypertensive disorders: An umbrella review of randomised controlled trials and an updated meta-analysis. *BJOG* 130: 264-275, 2023.
- Heissel A, Heinen D, Brokmeier LL, Skarabis N, Kangas M, Vancampfort D, Stubbs B, Firth J, Ward PB, Rosenbaum S, *et al*: Exercise as medicine for depressive symptoms? A systematic review and meta-analysis with meta-regression. *Br J Sports Med* 57: 1049-1057, 2023.
- Noetel M, Sanders T, Gallardo-Gómez D, Taylor P, Del Pozo Cruz B, van den Hoek D, Smith JJ, Mahoney J, Spathis J, Moresi M, *et al*: Effect of exercise for depression: Systematic review and network meta-analysis of randomised controlled trials. *BMJ* 384: e075847, 2024.
- Zhu F, Zhu X, Bi X, Kuang D, Liu B, Zhou J, Yang Y and Ren Y: Comparative effectiveness of various physical exercise interventions on executive functions and related symptoms in children and adolescents with attention deficit hyperactivity disorder: A systematic review and network meta-analysis. *Front Public Health* 11: 1133727, 2023.
- Padilha C, Souza R, Grossl FS, Gauer APM, de Sá CA and Rodrigues-Junior SA: Physical exercise and its effects on people with Parkinson's disease: Umbrella review. *PLoS One* 18: e0293826, 2023.
- Mohebbi R, Shojaa M, Kohl M, von Stengel S, Jakob F, Kersch-Schindl K, Lange U, Peters S, Thomasius F, Uder M and Kemmler W: Exercise training and bone mineral density in postmenopausal women: An updated systematic review and meta-analysis of intervention studies with emphasis on potential moderators. *Osteoporos Int* 34: 1145-1178, 2023.
- Zhao Z, Du Y, Yan K, Zhang L and Guo Q: Exercise and osteoimmunology in bone remodeling. *FASEB J* 38: e23554, 2024.
- McLeod JC, Currier BS, Lowisz CV and Phillips SM: The influence of resistance exercise training prescription variables on skeletal muscle mass, strength, and physical function in healthy adults: An umbrella review. *J Sport Health Sci* 13: 47-60, 2024.
- Mølmen KS, Almquist NW and Skattebo Ø: Effects of exercise training on mitochondrial and capillary growth in human skeletal muscle: A systematic review and meta-regression. *Sports Med* 55: 115-144, 2025.
- Boa Sorte Silva NC, Barha CK, Erickson KI, Kramer AF and Liu-Ambrose T: Physical exercise, cognition, and brain health in aging. *Trends Neurosci* 47: 402-417, 2024.
- Lu X, Chen Y, Shi Y, Shi Y, Su X, Chen P, Wu D and Shi H: Exercise and exerkines: Mechanisms and roles in anti-aging and disease prevention. *Exp Gerontol* 200: 112685, 2025.
- Subramanian V, Tucker WJ, Peters AE, Upadhyay B, Kitzman DW and Pandey A: Cardiovascular aging and exercise: Implications for heart failure prevention and management. *Circ Res* 137: 205-230, 2025.
- Lee S, Choi Y, Jeong E, Park J, Kim J, Tanaka M and Choi J: Physiological significance of elevated levels of lactate by exercise training in the brain and body. *J Biosci Bioeng* 135: 167-175, 2023.
- Brooks GA, Osmond AD, Arevalo JA, Duong JJ, Curl CC, Moreno-Santillan DD and Leija RG: Lactate as a myokine and exerkine: Drivers and signals of physiology and metabolism. *J Appl Physiol* (1985) 134: 529-548, 2023.
- Ahmadi Hekmatikar AH, Zolfaghari G, Basereh A, Awang Daud DM and Khoramipour K: Context matters: Divergent roles of exercise-induced and tumor-derived lactate in cancer. *Biomolecules* 15: 1010, 2025.
- Chen J, Huang Z, Chen Y, Tian H, Chai P, Shen Y, Yao Y, Xu S, Ge S and Jia R: Lactate and lactylation in cancer. *Signal Transduct Target Ther* 10: 38, 2025.
- Hu Y, He Z, Li Z, Wang Y, Wu N, Sun H, Zhou Z, Hu Q and Cong X: Lactylation: The novel histone modification influence on gene expression, protein function, and disease. *Clin Epigenetics* 16: 72, 2024.
- Yu X, Yang J, Xu J, Pan H, Wang W, Yu X and Shi S: Histone lactylation: From tumor lactate metabolism to epigenetic regulation. *Int J Biol Sci* 20: 1833-1854, 2024.
- Wang J, Wang Z, Wang Q, Li X and Guo Y: Ubiquitous protein lactylation in health and diseases. *Cell Mol Biol Lett* 29: 23, 2024.
- Lu Z, Zheng X, Shi M, Yin Y, Liang Y, Zou Z, Ding C, He Y, Zhou Y and Li X: Lactylation: The emerging frontier in post-translational modification. *Front Genet* 15: 1423213, 2024.
- Liao Z, Chen B, Yang T, Zhang W and Mei Z: Lactylation modification in cardio-cerebral diseases: A state-of-the-art review. *Ageing Res Rev* 104: 102631, 2025.
- Zhu W, Guo S, Sun J, Zhao Y and Liu C: Lactate and lactylation in cardiovascular diseases: Current progress and future perspectives. *Metabolism* 158: 155957, 2024.
- Zhu Y, Liu W, Luo Z, Xiao F and Sun B: New insights into the roles of lactylation in cancer. *Front Pharmacol* 15: 1412672, 2024.
- Xu B, Liu Y, Li N and Geng Q: Lactate and lactylation in macrophage metabolic reprogramming: Current progress and outstanding issues. *Front Immunol* 15: 1395786, 2024.
- Li X, Yang Y, Zhang B, Lin X, Fu X, An Y, Zou Y, Wang JX, Wang Z and Yu T: Lactate metabolism in human health and disease. *Signal Transduct Target Ther* 7: 305, 2022.
- Chen L, Huang L, Gu Y, Cang W, Sun P and Xiang Y: Lactate-lactylation hands between metabolic reprogramming and immunosuppression. *Int J Mol Sci* 23: 11943, 2022.
- Ouyang J, Wang H and Huang J: The role of lactate in cardiovascular diseases. *Cell Commun Signal* 21: 317, 2023.
- Certo M, Llibre A, Lee W and Mauro C: Understanding lactate sensing and signalling. *Trends Endocrinol Metab* 33: 722-735, 2022.
- Zhang Y, Zhai Z, Duan J, Wang X, Zhong J, Wu L, Li A, Cao M, Wu Y, Shi H, *et al*: Lactate: The mediator of metabolism and immunosuppression. *Front Endocrinol (Lausanne)* 13: 901495, 2022.
- Li R, Yang Y, Wang H, Zhang T, Duan F, Wu K, Yang S, Xu K, Jiang X and Sun X: Lactate and lactylation in the brain: Current progress and perspectives. *Cell Mol Neurobiol* 43: 2541-2555, 2023.
- Sharma D, Singh M and Rani R: Role of LDH in tumor glycolysis: Regulation of LDHA by small molecules for cancer therapeutics. *Semin Cancer Biol* 87: 184-195, 2022.
- Tan C, Li L, Han J, Xu K and Liu X: A new strategy for osteoarthritis therapy: Inhibition of glycolysis. *Front Pharmacol* 13: 1057229, 2022.
- Yang L, Li S, Yu L, Leng J and Li N: Targeting glycolysis: Exploring a new frontier in glioblastoma therapy. *Front Immunol* 15: 1522392, 2025.

38. Lee YB, Min JK, Kim JG, Cap KC, Islam R, Hossain AJ, Dogsom O, Hamza A, Mahmud S, Choi DR, *et al*: Multiple functions of pyruvate kinase M2 in various cell types. *J Cell Physiol* 237: 128-148, 2022.
39. İlhan M: Non-metabolic functions of pyruvate kinase M2: PKM2 in tumorigenesis and therapy resistance. *Neoplasma* 69: 747-754, 2022.
40. Kooshki L, Mahdavi P, Fakhri S, Akkol EK and Khan H: Targeting lactate metabolism and glycolytic pathways in the tumor microenvironment by natural products: A promising strategy in combating cancer. *Biofactors* 48: 359-383, 2022.
41. Claps G, Faouzi S, Quidville V, Chehade F, Shen S, Vagner S and Robert C: The multiple roles of LDH in cancer. *Nat Rev Clin Oncol* 19: 749-762, 2022.
42. Tufail M, Jiang CH and Li N: Altered metabolism in cancer: Insights into energy pathways and therapeutic targets. *Mol Cancer* 23: 203, 2024.
43. Miholjic TBS, Halse H, Bonvalet M, Bigorgne A, Rouanne M, Dercle L, Shankar V and Marabelle A: Rationale for LDH-targeted cancer immunotherapy. *Eur J Cancer* 181: 166-178, 2023.
44. Franczak MA, Krol O, Harasim G, Jedrzejewska A, Zaffaroni N, Granchi C, Minutolo F, Avani A, Giovannetti E, Smolenski RT and Peters GJ: Metabolic effects of new glucose transporter (GLUT-1) and lactate dehydrogenase-A (LDH-A) inhibitors against chemoresistant malignant mesothelioma. *Int J Mol Sci* 24: 7771, 2023.
45. Chen Z, Vaeth M, Eckstein M, Delgobo M, Ramos G, Frantz S, Hofmann U and Gladow N: Characterization of the effect of the GLUT-1 inhibitor BAY-876 on T cells and macrophages. *Eur J Pharmacol* 945: 175552, 2023.
46. Wang N, Jiang X, Zhang S, Zhu A, Yuan Y, Xu H, Lei J and Yan C: Structural basis of human monocarboxylate transporter 1 inhibition by anti-cancer drug candidates. *Cell* 184: 370-383. e13, 2021.
47. Singh M, Afonso J, Sharma D, Gupta R, Kumar V, Rani R, Baltazar F and Kumar V: Targeting monocarboxylate transporters (MCTs) in cancer: How close are we to the clinics? *Semin Cancer Biol* 90: 1-14, 2023.
48. Kobayashi M, Narumi K, Furugen A and Iseki K: Transport function, regulation, and biology of human monocarboxylate transporter 1 (hMCT1) and 4 (hMCT4). *Pharmacol Ther* 226: 107862, 2021.
49. Babl N, Decking SM, Voll F, Althammer M, Sala-Hojman A, Ferretti R, Korf C, Schmidl C, Schmidleithner L, Nerb B, *et al*: MCT4 blockade increases the efficacy of immune checkpoint blockade. *J Immunother Cancer* 11: e007349, 2023.
50. Zhang D, Tang Z, Huang H, Zhou G, Cui C, Weng Y, Liu W, Kim S, Lee S, Perez-Neut M, *et al*: Metabolic regulation of gene expression by histone lactylation. *Nature* 574: 575-580, 2019.
51. Izzo LT and Wellen KE: Histone lactylation links metabolism and gene regulation. *Nature* 574: 492-493, 2019.
52. Notarangelo G and Haigis MC: Sweet temptation: From sugar metabolism to gene regulation. *Immunity* 51: 980-981, 2019.
53. Xiong J, He J, Zhu J, Pan J, Liao W, Ye H, Wang H, Song Y, Du Y, Cui B, *et al*: Lactylation-driven METTL3-mediated RNA m⁶A modification promotes immunosuppression of tumor-infiltrating myeloid cells. *Mol Cell* 82: 1660-1677.e10, 2022.
54. Wang J, Yang P, Yu T, Gao M, Liu D, Zhang J, Lu C, Chen X, Zhang X and Liu Y: Lactylation of PKM2 suppresses inflammatory metabolic adaptation in pro-inflammatory macrophages. *Int J Biol Sci* 18: 6210-6225, 2022.
55. Mao Y, Zhang J, Zhou Q, He X, Zheng Z, Wei Y, Zhou K, Lin Y, Yu H, Zhang H, *et al*: Hypoxia induces mitochondrial protein lactylation to limit oxidative phosphorylation. *Cell Res* 34: 13-30, 2024.
56. Li F, Si W, Xia L, Yin D, Wei T, Tao M, Cui X, Yang J, Hong T and Wei R: Positive feedback regulation between glycolysis and histone lactylation drives oncogenesis in pancreatic ductal adenocarcinoma. *Mol Cancer* 23: 90, 2024.
57. Yang Z, Yan C, Ma J, Peng P, Ren X, Cai S, Shen X, Wu Y, Zhang S, Wang X, *et al*: Lactylome analysis suggests lactylation-dependent mechanisms of metabolic adaptation in hepatocellular carcinoma. *Nat Metab* 5: 61-79, 2023.
58. Xu Y, Ma X, Ni W, Zheng L, Lin Z, Lai Y, Yang N, Dai Z, Yao T, Chen Z, *et al*: PKM2-driven lactate overproduction triggers endothelial-to-mesenchymal transition in ischemic flap via mediating TWIST1 lactylation. *Adv Sci (Weinh)* 11: e2406184, 2024.
59. Yang K, Fan M, Wang X, Xu J, Wang Y, Tu F, Gill PS, Ha T, Liu L, Williams DL and Li C: Lactate promotes macrophage HMGB1 lactylation, acetylation, and exosomal release in polymicrobial sepsis. *Cell Death Differ* 29: 133-146, 2022.
60. Gao J, Liu R, Huang K, Li Z, Sheng X, Chakraborty K, Han C, Zhang D, Becker L and Zhao Y: Dynamic investigation of hypoxia-induced L-lactylation. *Proc Natl Acad Sci USA* 122: e2404899122, 2025.
61. Wu D, Spencer CB, Ortogo L, Zhang H and Miao C: Histone lactylation-regulated METTL3 promotes ferroptosis via m6A-modification on ACSL4 in sepsis-associated lung injury. *Redox Biol* 74: 103194, 2024.
62. Li D, Liu Z, Zhu M, Yu W, Mao W, Mao D, Wang F and Wan Y: Histone lactylation regulates early embryonic development through m6A methyltransferase METTL3 in goats. *Int J Biol Macromol* 309: 142858, 2025.
63. Cheng S, Chen L, Ying J, Wang Y, Jiang W, Zhang Q, Zhang H, Wang J, Wang C, Wu H, *et al*: 20(S)-ginsenoside Rh2 ameliorates ATRA resistance in APL by modulating lactylation-driven METTL3. *J Ginseng Res* 48: 298-309, 2024.
64. Zhu R, Ye X, Lu X, Xiao L, Yuan M, Zhao H, Guo D, Meng Y, Han H, Luo S, *et al*: ACS2 acts as a lactyl-CoA synthetase and couples KAT2A to function as a lactyltransferase for histone lactylation and tumor immune evasion. *Cell Metab* 37: 361-376. e7, 2025.
65. Zheng B, Pan Y, Qian F, Liu D, Ye D, Yu B, Zhong S, Zheng W, Wang X, Zhou B, *et al*: High sugar induced RCC2 lactylation drives breast cancer tumorigenicity through upregulating MAD2L1. *Adv Sci (Weinh)* 12: e2415530, 2025.
66. Huang J, Wang X, Li N, Fan W, Li X, Zhou Q, Liu J, Li W, Zhang Z, Liu X, *et al*: YY1 lactylation aggravates autoimmune uveitis by enhancing microglial functions via inflammatory genes. *Adv Sci (Weinh)* 11: e2308031, 2024.
67. Wu H, Huang H and Zhao Y: Interplay between metabolic reprogramming and post-translational modifications: From glycolysis to lactylation. *Front Immunol* 14: 1211221, 2023.
68. Moreno-Yruela C, Bæk M, Monda F and Olsen CA: Chiral post-translational modification to lysine ε-amino groups. *Acc Chem Res* 55: 1456-1466, 2022.
69. Moreno-Yruela C, Zhang D, Wei W, Bæk M, Liu W, Gao J, Danková D, Nielsen AL, Bolding JE, Yang L, *et al*: Class I histone deacetylases (HDAC1-3) are histone lysine deacetylases. *Sci Adv* 8: eabi6696, 2022.
70. Fan Z, Liu Z, Zhang N, Wei W, Cheng K, Sun H and Hao Q: Identification of SIRT3 as an eraser of H4K16la. *iScience* 26: 107757, 2023.
71. Qian P, Wang S, Zhang T and Wu J: Transcriptional expression of histone acetyltransferases and deacetylases during the recovery of acute exercise in mouse hippocampus. *J Mol Neurosci* 74: 34, 2024.
72. Duan X, Xing Z, Qiao L, Qin S, Zhao X, Gong Y and Li X: The role of histone post-translational modifications in cancer and cancer immunity: Functions, mechanisms and therapeutic implications. *Front Immunol* 15: 1495221, 2024.
73. Wang M and Lin H: Understanding the function of mammalian sirtuins and protein lysine acylation. *Annu Rev Biochem* 90: 245-285, 2021.
74. Hong W, Zeng X, Wang H, Tan X, Tian Y, Hu H, Ashrafzadeh M, Sethi G, Huang H and Duan C: PGC-1α loss promotes mitochondrial protein lactylation in acetaminophen-induced liver injury via the LDHB-lactate axis. *Pharmacol Res* 205: 107228, 2024.
75. Jin J, Bai L, Wang D, Ding W, Cao Z, Yan P, Li Y, Xi L, Wang Y, Zheng X, *et al*: SIRT3-dependent delactylation of cyclin E2 prevents hepatocellular carcinoma growth. *EMBO Rep* 24: e56052, 2023.
76. Gao R, Li Y, Xu Z, Zhang F, Xu J, Hu Y, Yin J, Yang K, Sun L, Wang Q, *et al*: Mitochondrial pyruvate carrier 1 regulates fatty acid synthase lactylation and mediates treatment of nonalcoholic fatty liver disease. *Hepatology* 78: 1800-1815, 2023.
77. Wang X, Fan W, Li N, Ma Y, Yao M, Wang G, He S, Li W, Tan J, Lu Q and Hou S: YY1 lactylation in microglia promotes angiogenesis through transcription activation-mediated upregulation of FGF2. *Genome Biol* 24: 87, 2023.
78. Yan L, Wang Y, Hu H, Yang D, Wang W, Luo Z, Wang Y, Yang F, So KF and Zhang L: Physical exercise mediates cortical synaptic protein lactylation to improve stress resilience. *Cell Metab* 36: 2104-2117.e4, 2024.
79. Qiao J, Tan Y, Liu H, Yang B, Zhang Q, Liu Q, Sun W, Li Z, Wang Q, Feng W, *et al*: Histone H3K18 and ezrin lactylation promote renal dysfunction in sepsis-associated acute kidney injury. *Adv Sci (Weinh)* 11: e2307216, 2024.
80. Jing F, Zhang J, Zhang H and Li T: Unlocking the multifaceted molecular functions and diverse disease implications of lactylation. *Biol Rev Camb Philos Soc* 100: 172-189, 2025.

81. Yue Q, Wang Z, Shen Y, Lan Y, Zhong X, Luo X, Yang T, Zhang M, Zuo B, Zeng T, *et al*: Histone H3K9 lactylation confers temozolomide resistance in glioblastoma via LUC7L2-mediated MLH1 intron retention. *Adv Sci (Weinh)* 11: e2309290, 2024.
82. Fan M, Yang K, Wang X, Chen L, Gill PS, Ha T, Liu L, Lewis NH, Williams DL and Li C: Lactate promotes endothelial-to-mesenchymal transition via Snail1 lactylation after myocardial infarction. *Sci Adv* 9: eadc9465, 2023.
83. Tong H, Jiang Z, Song L, Tan K, Yin X, He C, Huang J, Li X, Jing X, Yun H, *et al*: Dual impacts of serine/glycine-free diet in enhancing antitumor immunity and promoting evasion via PD-L1 lactylation. *Cell Metab* 36: 2493-2510.e9, 2024.
84. Bartoloni B, Mannelli M, Gamberi T and Fiaschi T: The multiple roles of lactate in the skeletal muscle. *Cells* 13: 1177, 2024.
85. Han H, Zhao Y, Du J, Wang S, Yang X, Li W, Song J, Zhang S, Zhang Z, Tan Y, *et al*: Exercise improves cognitive dysfunction and neuroinflammation in mice through Histone H3 lactylation in microglia. *Immun Ageing* 20: 63, 2023.
86. Lei Z, Mozaffaritarab S, Kawamura T, Koike A, Kolonics A, Kéringer J, Pinho RA, Sun J, Shangguan R and Radák Z: The effects of long-term lactate and high-intensity interval training (HIIT) on brain neuroplasticity of aged mice. *Heliyon* 10: e24421, 2024.
87. Chang J, Wu W, Qian P, Lu Z, He X, Wang F and Zhang T: Multi-omics study on the effect of moderate-intensity exercise on protein lactylation in mouse muscle tissue. *Front Cell Dev Biol* 12: 1472338, 2025.
88. Meng F, He J, Zhang X, Lyu W, Wei R, Wang S, Du Z, Wang H, Bi J, Hua X, *et al*: Histone lactylation antagonizes senescence and skeletal muscle aging by modulating aging-related pathways. *Adv Sci (Weinh)* 12: e2412747, 2025.
89. Jia M, Yue X, Sun W, Zhou Q, Chang C, Gong W, Feng J, Li X, Zhan R, Mo K, *et al*: ULK1-mediated metabolic reprogramming regulates Vps34 lipid kinase activity by its lactylation. *Sci Adv* 9: eadg4993, 2023.
90. Li Y, Xue L, Wang F, Wang Y, Sun Y, Niu Z, Liu S, Yan Y, Shen S, Zhang K, *et al*: Lactylation of mTOR enhances autophagy in skeletal muscle during exercise. *Cell Chem Biol* 32: 1367-1380.e5, 2025.
91. Wu J, Hu M, Jiang H, Ma J, Xie C, Zhang Z, Zhou X, Zhao J, Tao Z, Meng Y, *et al*: Endothelial cell-derived lactate triggers bone mesenchymal stem cell histone lactylation to attenuate osteoporosis. *Adv Sci (Weinh)* 10: e2301300, 2023.
92. Dai S, Chen Z, Liu X, Dong J, Zhang Z, Yang Z, Huang M, Cai L, Xiao X and Zhu X: Exercise-mediated mechanical stress promotes osteogenic differentiation of BMSCs through upregulation of lactylation via the IER3/LDHB axis. *FASEB J* 39: e70537, 2025.
93. Lan W, Chen X, Yu H, Ruan J, Kang J, Nie X, Cao Y, Tang S and Ding C: UGDH lactylation aggravates osteoarthritis by suppressing glycosaminoglycan synthesis and orchestrating nucleocytoplasmic transport to activate MAPK signaling. *Adv Sci (Weinh)* 12: e2413709, 2025.
94. Xia J, Qiao Z, Hao X and Zhang Y: LDHA-induced histone lactylation mediates the development of osteoarthritis through regulating the transcription activity of TP11 gene. *Autoimmunity* 57: 2384889, 2024.
95. Waters DL, Aguirre L, Gurney B, Sinacore DR, Fowler K, Gregori G, Armamento-Villareal R, Qualls C and Villareal DT: Effect of aerobic or resistance exercise, or both, on intermuscular and visceral fat and physical and metabolic function in older adults with obesity while dieting. *J Gerontol A Biol Sci Med Sci* 77: 131-139, 2022.
96. Eglseer D, Traxler M, Embacher S, Reiter L, Schoufour JD, Weijs PJM, Voortman T, Boirie Y, Cruz-Jentoft A and Bauer S; SO-NUTS consortium: Nutrition and exercise interventions to improve body composition for persons with overweight or obesity near retirement age: A systematic review and network meta-analysis of randomized controlled trials. *Adv Nutr* 14: 516-358, 2023.
97. Paluch AE, Boyer WR, Franklin BA, Laddu D, Lobelo F, Lee DC, McDermott MM, Swift DL, Webel AR, Lane A, *et al*: Resistance exercise training in individuals with and without cardiovascular disease: 2023 update: A scientific statement from the American heart association. *Circulation* 149: e217-e231, 2024.
98. Wang Y, Chen L, Zhang M, Li X, Yang X, Huang T, Ban Y, Li Y, Li Q, Zheng Y, *et al*: Exercise-induced endothelial Mecp2 lactylation suppresses atherosclerosis via the Ereg/MAPK signalling pathway. *Atherosclerosis* 375: 45-58, 2023.
99. Chen L, Zhang M, Yang X, Wang Y, Huang T, Li X, Ban Y, Li Q, Yang Q, Zhang Y, *et al*: Methyl-CpG-binding 2 K271 lactylation-mediated M2 macrophage polarization inhibits atherosclerosis. *Theranostics* 14: 4256-4277, 2024.
100. Xu GE, Yu P, Hu Y, Wan W, Shen K, Cui X, Wang J, Wang T, Cui C, Chatterjee E, *et al*: Exercise training decreases lactylation and prevents myocardial ischemia-reperfusion injury by inhibiting YTHDF2. *Basic Res Cardiol* 119: 651-671, 2024.
101. Chen X, Huang W, Zhang J, Li Y, Xing Z, Guo L, Jiang H and Zhang J: High-intensity interval training induces lactylation of fatty acid synthase to inhibit lipid synthesis. *BMC Biol* 21: 196, 2023.
102. Liu Y, Zhou R, Guo Y, Hu B, Xie L, An Y, Wen J, Liu Z, Zhou M, Kuang W, *et al*: Muscle-derived small extracellular vesicles induce liver fibrosis during overtraining. *Cell Metab* 37: 824-841.e8, 2025.
103. Mattingly ML, Rupple BA, Sexton CL, Godwin JS, McIntosh MC, Smith MA, Plotkin DL, Michel JM, Anglin DA, Kontos NJ, *et al*: Resistance training in humans and mechanical overload in rodents do not elevate muscle protein lactylation. *Front Physiol* 14: 1281702, 2023.
104. Mattingly ML, Anglin DA, Rupple BA, Scarpelli MC, Bergamasco JG, Godwin JS, Mobley CB, Frugé AD, Libardi CA and Roberts MD: Acute and chronic resistance training, acute endurance exercise, nor physiologically plausible lactate in vitro affect skeletal muscle lactylation. *Int J Mol Sci* 25: 12216, 2024.



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