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Research Advances on Lactate and Lactylation in Myocardial Ischemia-Reperfusion Injury

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Abstract. Myocardial ischemia-reperfusion (I/R) injury is a critical aspect of numerous cardiovascular diseases occurring when blood flow is restored to ischemic tissue ironically exacerbating damage. Recent research has revealed a novel role for lactate in this process transcending its traditional view as a mere metabolic byproduct. Instead lactate has emerged as an active signaling molecule with significant implications in I/R injury. During ischemia lactate accumulates and exerts profound effects on cardiomyocyte survival and inflammatory responses. This is facilitated through lactate-derived lactylation a newly identified post-translational modification that influences gene expression and cellular metabolism. This dual function of lactate—as both an energy substrate and a regulatory signal—is explored in depth within this review. Furthermore emerging evidence suggests that lactylation-mediated mechanisms play pivotal roles in cardioprotection inflammation regulation and mitochondrial homeostasis. By considering current metabolic and molecular insights this review endeavors to decipher the complex interplay between lactate metabolism and myocardial injury. In doing so it lays the groundwork for innovative therapeutic strategies targeting lactate with the potential to mitigate I/R-induced cardiac damage. By understanding the multifaceted role of lactate in this context we move closer to developing more effective treatments for cardiovascular diseases associated with I/R injury.

Keywords: lactate, lactylation, myocardial ischemia-reperfusion injury, cardiovascular disease

1. Introduction

Myocardial ischemia-reperfusion injury (MIRI) is a serious complication in cardiovascular disorders and significant vascular procedures involving intricate pathogenesis such as energy metabolism dysregulation oxidative stress inflammatory activation and apoptosis [1] . In recent years, lactate and its associated protein lactylation have garnered increasing attention. lactate transcends its traditional role as the end product of glycolysis to emerge as a signaling molecule that regulates cellular processes and modulates inflammatory responses. Lactylation a newly recognized post-translational modification impacts protein structure and function. However its exact mechanisms in cardiovascular disease remain incompletely understood. Existing evidence indicates a substantial increase in lactate accumulation during MIRI and altered lactylation levels show a significant correlation with inflammatory activation and metabolic dysregulation [2]. These observations

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suggest that lactylation may play a pivotal role in the progression of myocardial injury. This review consolidates current research on lactate and lactylation in MIRI aiming to provide a theoretical foundation for enhancing our understanding of the underlying pathological mechanisms. By synthesizing this knowledge we aspire to pave the way for the development of innovative therapeutic interventions targeting MIRI potentially contributing to improved patient outcomes.

2. Physiological functions and metabolic pathways of lactate

2.1. Production and metabolism of lactate

Lactate serves as the key end product of glycolysis its production being intrinsically tied to cellular oxygen levels. In hypoxic conditions cells convert glucose to pyruvate through anaerobic glycolysis which is subsequently reduced to lactate by lactate dehydrogenase (LDH).This process regenerates NAD^+ and helps sustain cellular energy production [3]. Conversely under normoxic conditions lactate is cleared from the circulation and transported into mitochondria through the mitochondrial lactate shuttle mechanism. Here lactate is reconverted to pyruvate by LDH isoenzymes and enters the tricarboxylic acid cycle for ATP generation. Furthermore lactate transported to the liver undergoes gluconeogenesis (the Cori cycle) converting it back to glucose thereby facilitating the recycling of energy substrates [4]. The regulation of lactate production transport and clearance is governed by tissue oxygenation status energy demand and monocarboxylate transporters. This dynamic balance is essential for maintaining cellular energy homeostasis underscoring the crucial role lactate plays in energy metabolism.

2.2. The role of lactate in energy metabolism

Lactate is more than just the final product of glycolysis, it also serves as a vital substrate for cellular energy production and signaling. Under hypoxic conditions lactate maintains ATP synthesis from glycolysis. When oxygen is available lactate is actively metabolized and transported into mitochondria via monocarboxylate transporters (MCTs).Here lactate dehydrogenase (LDH) catalyzes its conversion to pyruvate entering the tricarboxylic acid cycle to produce ATP. Moreover lactate supports metabolic coupling between tissues via the intercellular lactate shuttle enabling lactate exchange to fulfill the energy needs of distant cells [5].

2.3. Regulatory effects of lactate on cellular signaling pathways

Lactate functions beyond being a crucial metabolite in glycolysis, it also acts as a signaling molecule regulating cellular functions. Under hypoxic or stressful conditions lactate inhibits prolyl hydroxylase (PHD) activity stabilizing hypoxia-inducible factor-1α (HIF-1α) and boosting expression of glycolytic enzymes and glucose transporters [6]. Additionally lactate promotes anti-inflammatory responses through GPR81 receptor activation inhibiting the cAMP-PKA signaling pathway and suppressing inflammatory mediator synthesis [7]. Moreover lactate modulates NF-κB signaling and NLRP3 inflammasome assembly and activation influencing oxidative stress apoptosis and inflammatory processes [8].

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3. Mechanisms underlying myocardial ischemia–reperfusion injury

3.1. Oxidative stress and mitochondrial dysfunction

Figure 1 illustrates the pathogenesis of myocardial ischemia reperfusion injury. During I/R oxygen reintroduction triggers a rapid ROS surge exceeding antioxidant system capacities leading to oxidative stress. This excessive ROS not only directly damages lipids proteins and nucleic acids but also disrupts redox homeostasis serving as a key mediator of reperfusion injury.

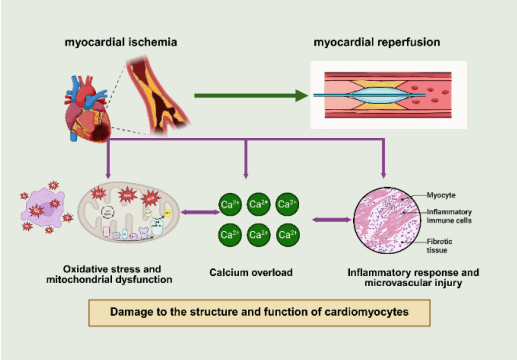

Figure 1. Diagram of the pathogenesis of myocardial ischemia reperfusion injury

Mitochondria are the primary sites of ROS generation during early reperfusion, with complexes I and III of the mitochondrial electron transport chain (ETC) identified as major contributors. Under ischemic conditions myocardial cells accumulate high succinate levels due to impaired oxygen supply. Upon reperfusion succinate is rapidly oxidized driving electron flow through complex II and back to complex I initiating reverse electron transport (RET) and superoxide anion production. This mechanism is considered the main cause of the "ROS burst" observed early during reperfusion. The excessive ROS damage ETC complexes inhibiting their function and decreasing ATP synthesis thereby exacerbating myocardial metabolic dysfunction.

In addition to ETC inhibition, ROS-induced mitochondrial membrane damage contributes to the abnormal opening of the mitochondrial permeability transition pore (mPTP). Sustained mPTP opening results in loss of mitochondrial membrane potential ion imbalance and mitochondrial swelling leading to outer membrane rupture and cytochrome c release into the cytosol. Cytochrome c activation triggers the caspase-dependent apoptotic pathway initiating programmed cell death in cardiomyocytes [9]. Studies show that inhibiting mPTP opening or targeting Cyclophilin D (CypD) a key mPTP regulator significantly reduces reperfusion-induced mitochondrial damage and apoptosis. These findings emphasize the crucial role of mPTP in oxidative stress-induced mitochondrial dysfunction.

Furthermore, ROS also inflict damage to mitochondrial DNA (mtDNA), leading to base oxidation, strand breaks, and other structural damage. mtDNA's proximity to the electron transport chain and lack of histone protection make it highly susceptible to oxidative stress. mtDNA damage impairs respiratory chain subunit synthesis and assembly reducing electron transport efficiency. Additionally cytosolic mtDNA functions as a damage-associated molecular pattern (DAMP) activating the cGAS-STING pathway and innate immune responses [10]. This cascade amplifies apoptotic and inflammatory signaling, further contributing to myocardial injury.

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3.2. Calcium overload

During myocardial ischemia–reperfusion (I/R) acidosis correction activates the sodium-hydrogen exchanger (Na^+-H^+ exchanger) causing a rapid intracellular Na^+ accumulation. This disrupts the ion concentration gradient activating the sodium-calcium exchanger (NCX) resulting in a substantial Ca^{2+} influx into the cytoplasm. The elevated intracellular Ca^{2+} concentration triggers a cascade of pathological events ultimately leading to cellular injury and death.

The influx of excess calcium ions into mitochondria through the mitochondrial calcium uniporter (MCU) can have detrimental effects on mitochondrial function. While calcium is essential for normal mitochondrial function an overload of calcium can lead to the premature opening of the mitochondrial permeability transition pore (mPTP) causing a loss of mitochondrial membrane potential and disrupting ATP synthesis. This disruption exacerbates myocardial injury. Additionally an excess of calcium in mitochondria results in an increase in reactive oxygen species (ROS) production which damages mitochondrial membranes and creates a cycle of dysfunction. Strategies such as inhibiting MCU activity or delaying the premature opening of mPTP have shown promise in reducing calcium overload and mitigating mitochondrial dysfunction [11]. Additionally, modulating the activity of the Na^+-Ca^{2+} exchanger has also emerged as a potential therapeutic approach to prevent calcium overload and lessen myocardial damage. These interventions underscore the importance of maintaining calcium homeostasis to mitigate reperfusion-induced myocardial injury and suggest promising avenues for therapeutic research and development.

3.3. Inflammatory response and microvascular injury

During MIRI, the release of inflammatory mediators leads to the infiltration of neutrophils monocytes and macrophages exacerbating oxidative stress and cellular damage. This activation of endothelial cells results in increased expression of adhesion molecules and enhanced vascular permeability which further aggravates tissue edema and microcirculatory dysfunction. Additionally complement activation and inflammasome formation contribute to cell death through apoptosis and necrosis. Microvascular injury is characterized by capillary obstruction endothelial barrier dysfunction and the no-reflow phenomenon all of which hinder proper myocardial reperfusion. Emerging research indicates that targeting inflammatory pathways and protecting endothelial cells could be promising strategies for improving outcomes following ischemia-reperfusion events [12].

4. The role of lactate in myocardial ischemia–reperfusion injury

4.1. Effects of lactate on myocardial cell survival

Lactate influences cardiomyocyte survival in myocardial ischemia-reperfusion injury (MIRI) through metabolic reprogramming and oxidative stress pathways. During ischemia, enhanced glycolysis increases lactate accumulation in cardiomyocytes. This lactate serves as an alternative oxidative substrate, transported into mitochondria via MCT1 and oxidized to pyruvate by LDH, sustaining tricarboxylic acid cycle function and ATP generation. During reperfusion, elevated lactate concentrations inhibit apoptosis through GPR81 activation, suppressing the cAMP-PKA pathway and reducing mPTP opening [13]. However, excessive lactate exacerbates metabolic acidosis, inhibiting Na^+/H^+ exchange to induce calcium overload, calpain activation, and cardiomyocyte necrosis [14]. Lactylation regulates monocytes/macrophages' anti-inflammatory and pro-angiogenic

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activities by modulating histone modifications that promote reparative gene transcription. Histone lactylation significantly enhances cardiac function post-myocardial infarction [15].

4.2. Regulation of myocardial cell function by lactate

Lactate modulates cardiomyocyte electrophysiology and contractility through ion channel and contractile protein regulation. Hu et al. [16] identified through multi-omics analyses that glycolysis correlates with arrhythmia, whereas lactate contributes to valvular atrial fibrillation. Histone lactylation enhances cardiomyocyte viability by activating mitophagy to eliminate damaged mitochondria [17]. Metabolically, lactate shuttles between cardiomyocytes and endothelial cells through the intercellular lactate shuttle, maintaining NAD^+/NADH equilibrium and improving electron transport chain efficiency. Lactate-mediated modification of α-myosin heavy chain (α-MHC) enhances titin binding, preserving sarcomere integrity and contractility to attenuate heart failure progression [18].

4.3. Lactate-cardiovascular function relationship

Lactate's cardiovascular role extends beyond energy metabolism to include systemic cardiovascular modulation. Recent studies demonstrate that lactate improves cardiac output and peripheral perfusion in porcine ischemic cardiogenic shock models by increasing stroke volume, enhancing contractility, and optimizing ventriculo-arterial coupling without altering heart rate or blood pressure [19]. As a recognized signaling molecule during cardiac ischemia-reperfusion, lactate modulates myocardial metabolism and inflammatory responses to influence cardiovascular function [20]. Thus, lactate functions not only as an energy metabolite but as a cardiovascular regulator demonstrating therapeutic potential.

5. Prospects of lactate and lactylation in the treatment of Myocardial Ischemia–Reperfusion Injury (MIRI)

5.1. Advances in pharmacological modulation of lactate metabolism

Lactate dehydrogenase (LDH), a pivotal enzyme in lactate metabolism, catalyzes the reversible conversion between pyruvate and lactate. Its aberrant activity is closely linked to the dysregulation of myocardial energy metabolism during myocardial ischemia–reperfusion injury (MIRI). In recent years, significant progress has been achieved in the development of LDH inhibitors, which have emerged as promising candidates for regulating cardiac energy metabolism and alleviating cellular injury. A growing body of evidence demonstrates that various natural compounds and synthetic small molecules—such as polyphenols and pyrazole derivatives—can act as LDH inhibitors, effectively reducing lactate accumulation, restoring the myocardial energy balance, and thereby conferring cardioprotective effects [21].

In addition to LDH inhibition, the G-protein–coupled lactate receptor GPR81 has attracted increasing attention as a novel therapeutic target. GPR81 is expressed in cardiomyocytes and vascular endothelial cells, where its activation by lactate modulates inflammatory and apoptotic pathways. In the context of MIRI, excessive activation of GPR81 promotes inflammation and cell death, whereas receptor antagonists have been shown to mitigate reperfusion-induced myocardial injury [22]. Beyond enzymatic and receptor-level interventions, strategies targeting lactate

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transporters and key metabolic enzymes may further help restore myocardial metabolic homeostasis and reduce metabolic stress–induced damage [23].

Overall, both LDH inhibitors and GPR81 antagonists constitute central components of lactate metabolism–based therapeutic strategies. Future research should prioritize the optimization of their selectivity, bioavailability, and safety profiles to enable precise and effective modulation of lactate metabolism in clinical settings.

5.2. Therapeutic strategies targeting protein lactylation

A newly discovered post-translational modification called lactylation is proving to be essential in controlling gene expression and cellular function in heart cells providing a promising target for improving outcomes in myocardial ischemia-reperfusion injury (MIRI). Researchers are now concentrating on developing small-molecule agents that can manipulate lactylation levels which could potentially restore healthy function in heart cells and lessen damage. For example altering histone lactylation like H3K9la can impact DNA repair inflammation and chromatin accessibility ultimately reducing harm to the heart muscle. This avenue of research holds great promise for developing new interventions to protect heart health [2].

Furthermore, gene-editing technologies have shown promise in regulating lactylation by controlling the expression of important metabolic enzymes. Epigenetic tools like the CRISPR/Cas9 system can target genes responsible for lactylation such as LDHA to decrease harmful levels and aid in the healing of heart muscles. This approach offers a precise and effective method for managing lactylation-related issues in cardiomyocytes [24,25].

A novel approach to treating myocardial ischemia-reperfusion injury involves combining enzymatic inhibitors lactate receptor antagonists small-molecule modulators and gene-editing techniques. This comprehensive therapeutic paradigm aims to synergistically regulate lactate metabolism and lactylation ultimately improving treatment outcomes and facilitating myocardial recovery. By targeting multiple pathways simultaneously this strategy holds promise for enhancing efficacy in managing ischemic heart conditions [26].

Focusing on lactylation as a therapeutic approach in MIRI is a promising frontier. The future research should delve into understanding the molecular mechanisms of lactylation and improving the effectiveness of small-molecule and gene-editing treatments for clinical use. There is much potential for advancements in this field.

5.3. Clinical translation and future research directions

Lactate and lactylation-related biomarkers hold great promise for the diagnosis and prognosis of MIRI. Plasma lactate concentration is strongly correlated with the severity of ischemic injury and patient outcomes, while alterations in protein lactylation reflect dynamic shifts in cellular metabolism and epigenetic states, serving as potential indicators for early diagnosis and therapeutic monitoring [27]. Although preliminary studies have investigated the efficacy of lactate metabolism–targeted agents in cardiovascular diseases, clinical translation remains constrained by limited validation of their safety and efficacy [21].

Future research should prioritize understanding the molecular mechanisms involved in lactate metabolism and lactylation during instances of inflammation apoptosis and energy regulation following myocardial ischemia-reperfusion injury (MIRI).Additionally there is a need to explore the potential synergistic effects of combining LDH inhibitors GPR81 antagonists and lactylation modulators in treatment strategies. Furthermore the development of personalized medicine

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approaches that consider the genetic and metabolic profiles of patients is crucial for improving treatment precision and safety in the management of MIRI.

In conclusion targeting lactate metabolism and protein lactylation shows potential for treating myocardial ischemia-reperfusion injury (MIRI).Despite current challenges in translating research to clinical practice advancements in understanding mechanisms and developing multi-target drugs offer hope for personalized treatment strategies that can enhance patient outcomes in the future.

6. Conclusion

The role of lactate and lactylation in myocardial ischemia-reperfusion injury is being increasingly acknowledged for its significant biological significance. Recent research has shown that lactate not only acts as a crucial metabolic intermediary but also plays a key role in regulating various cellular metabolic processes and signaling pathways. The impact of lactate on cardiomyocyte survival and function suggests that it may have a major influence on the progression of cardiovascular diseases. This new perspective provides a fresh understanding of myocardial ischemia-reperfusion injury highlighting the dual nature of lactate in cardiac pathophysiology. While some studies point towards potential benefits of lactate in protecting the heart there is inconsistency in interpretations among different research findings. Some studies suggest that high concentrations of lactate may be harmful while others emphasize its role in promoting metabolic adaptation and protection. This controversy underscores the complex and context-dependent nature of lactate in both healthy and pathological conditions. As such future research should focus on unraveling the specific mechanisms and therapeutic potential of lactate and lactylation in managing myocardial ischemia-reperfusion injury (MIRI).

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