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L- and D-Lactate: unveiling their hidden functions in disease and health

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Abstract
Lactate, once considered a mere byproduct of anaerobic metabolism, is now recognized as a critical signaling molecule with diverse roles in physiology and pathology. There are two stereoisomers of lactate: L- and D-lactate. Recent studies have shown that disruptions in these two lactate stereoisomers have distinct effects on health and disease. L-lactate is central to glycolysis and energy transfer through the Cori cycle but also acts as the dominant lactylation isomer induced by glycolysis, influencing metabolism and cell survival. Although less studied, D-lactate is linked to metabolic disorders and plays a role in mitochondrial dysfunction and oxidative stress. This review focuses on both L- and D-lactate and examines their biosynthesis, transport, and expanding roles in physiological and pathological processes, particularly their functions in cancer, immune regulation, inflammation, neurodegeneration and other diseases. Finally, we assess the therapeutic prospects of targeting lactate metabolism, highlighting emerging strategies for intervention in clinical settings. Our review synthesizes the current understanding of L- and D-lactate, offering insights into their potential as targets for therapeutic innovation.

Keywords L-lactate, D-lactate, Lactylation, Epigenetic, Metabolism

Introduction

Lactate, often characterized as a simple metabolic byproduct, is traditionally viewed as a waste product of anaerobic metabolism. During glycolysis, pyruvate is reduced to lactate by the action of the enzyme lactate dehydrogenase (LDH) [1, 2]. This reduction serves to regenerate positive oxidized nicotinamide adenine dinucleotide (NAD^+), allowing glycolysis to proceed in the absence of sufficient oxygen. For decades, lactate was seen primarily as a secondary metabolite, particularly in highly glycolytic tissues such as skeletal muscle, where it accumulates during intense exercise or hypoxia [3–5]. This simplistic view of lactate as an energy byproduct has since evolved, with emerging evidence highlighting its crucial roles in metabolic regulation, signaling, and disease processes.

Recent discoveries have dramatically altered the perception of lactate, establishing it as a vital intermediary in metabolism and an important signaling molecule [6, 7]. Lactate exists in two stereoisomeric forms: L-lactate and D-lactate (Fig. 1). L-lactate, the predominant isomer in human metabolism, is produced by LDH-A, which is highly expressed in glycolytic tissues [8]; it is exported from cells via monocarboxylate transporters (MCTs), such as MCT1 and MCT4, facilitating its distribution throughout various tissues, where it can be utilized by more oxidative cells, including cardiomyocytes and neurons [9, 10]. This mechanism forms part of the "lactate shuttle" model, where lactate acts as a fuel source

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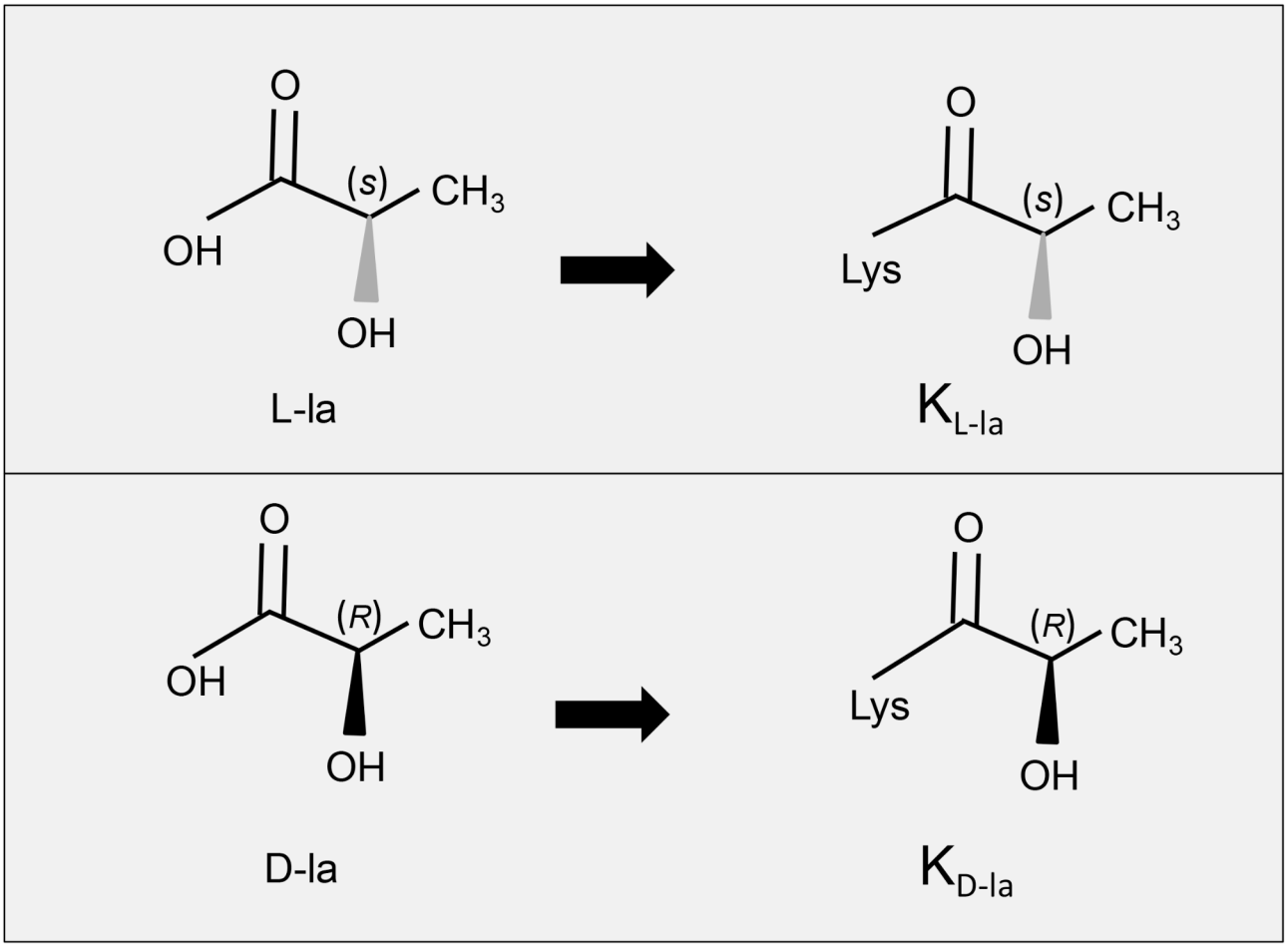

Fig. 1 A schematic diagram illustrating the structure isomers of L- and D-Lactate. L- and D-lactate are two stereoisomers of lactate. In the Fischer projection, the hydroxyl group on the chiral carbon atom of D-lactate is located on the right side while the hydroxyl group of L-lactate is located on the left side, which makes the lactylation modification involved by them also produce similar structural differences, generating Lysine D-lactylation (K_{D-la}) and Lysine L-lactylation (K_{L-la}) separately [15, 16]

transferred between tissues and cells [11, 12]. L-lactate is reconverted to pyruvate and enters the tricarboxylic acid (TCA) cycle, contributing to oxidative phosphorylation and adenosine triphosphoric acid (ATP) production in oxygen-rich environments [13, 14].

In normal cellular metabolism, L-lactate production occurs predominantly through anaerobic glycolysis, a pathway activated under hypoxic conditions when oxygen is scarce. In this context, cells rely on glucose metabolism to produce energy without the need for oxygen; hence, the term 'anaerobic glycolysis.' In contrast, many cancer cells exhibit an altered metabolic phenotype known as 'aerobic glycolysis' or the Warburg effect, in which L-lactate is produced even in the presence of oxygen [5, 17] (Fig. 2). Despite this increased interest in cancer cell metabolism because of the original findings of Warburg [17], it has to be borne in mind that "aerobic glycolysis" is a phenomenon observed in cancer cells in culture [18]. This metabolic reprogramming enables cancer cells to generate both the energy and biosynthetic precursors required for rapid proliferation [19]. Importantly, compared with anaerobic glycolysis, aerobic glycolysis relies on distinct molecular mechanisms [19, 20]; distinguishing between these two metabolic states provides critical insight into the metabolic adaptability of cancer cells and highlights the importance of targeting specific pathways that underpin their metabolic flexibility.

D-lactate, though less prevalent, is gaining attention because of its unique roles; it is produced primarily through bacterial fermentation in the gastrointestinal tract and, to a lesser extent, in human cells under specific pathological conditions [21, 22]. The role of D-lactate in human physiology has long been overlooked because of its low concentration compared with that of L-lactate. However, increasing evidence suggests that D-lactate has distinct metabolic and signaling roles, particularly in contexts such as gut dysbiosis, mitochondrial dysfunction, and certain metabolic disorders [22–24]. Conditions

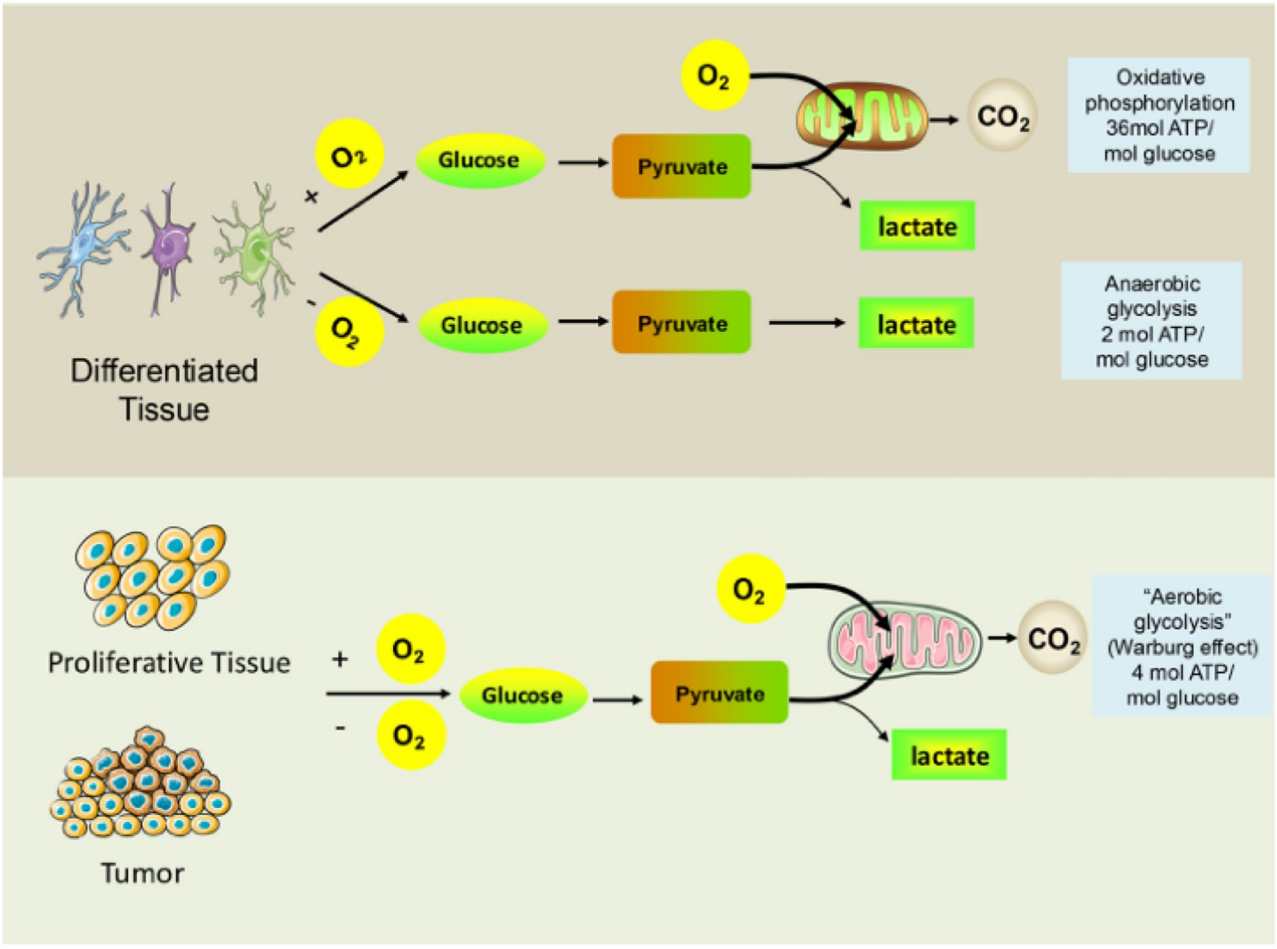

Fig. 2 A schematic diagram illustrating the differences between oxidative phosphorylation, anaerobic glycolysis, and aerobic glycolysis (Warburg effect). In oxygen-rich conditions, differentiated tissues metabolize glucose to pyruvate via glycolysis and fully oxidize it in mitochondria through oxidative phosphorylation. When oxygen is limited, cells shift to lactate production (anaerobic glycolysis), which regenerates NAD^+ for glycolysis but yields less ATP. Cancer cells and proliferative tissues favor glucose conversion to lactate even with oxygen (aerobic glycolysis), though mitochondria remain functional. Proliferating cells also channel ~ 10% of glucose into biosynthetic pathways for macromolecule synthesis [19]

such as short bowel syndrome and disruptions in methylglyoxal metabolism can both lead to the accumulation of D-lactate to toxic levels, resulting in metabolic acidosis and neurological complications [21, 25, 26]. Overall, D-lactate accumulation is typically a consequence of pathological states such as gut disorders and dysbiosis, and its role in normal metabolism is minimal compared with that of L-lactate.

This evolving understanding of the distinct biochemical roles of L- and D-lactate has transformed the reputation of lactate from a mere marker of anaerobic metabolism to a critical regulator of cellular homeostasis, intercellular communication, and immune responses. This paradigm shift highlights the importance of lactate in various pathophysiological settings, including cancer, inflammation, and neurodegenerative diseases, where altered lactate levels and signaling may drive disease progression or present novel therapeutic targets [6, 27, 28]. In this review, we analyze and review the functions of L- and D-lactate and elucidate the mechanisms by which they regulate various pathological and physiological conditions, opening new fields for L- and D-lactate-mediated precision medicine for disease therapy.

Biosynthesis and transport of L- and D-Lactate

Biosynthesis of L- and D-Lactate

L-lactate is the dominant form of lactate in humans and eukaryotes and is catalyzed by LDHA from pyruvate to L-lactate. L-lactate can be further oxidized into pyruvate in the cell and then enter the mitochondria for TCA metabolism. As the dominant isomer in human physiology, L-lactate is produced ubiquitously in most tissues, especially in glycolytic cells such as skeletal muscle and erythrocytes [29, 30]. Additionally, the enzyme LDHA is highly expressed in these tissues, reflecting their reliance on glycolysis for energy production, particularly during periods of oxygen scarcity or high energy demand. Because this process is closely linked to glycolysis,

ensuring that NAD^+ regeneration maintains ATP production during hypoxia or high energy demand [31–33], L-lactate is critical for sustaining metabolic flux under anaerobic conditions [34, 35]. In addition, "aerobic glycolysis" is the major process responsible for L-lactate production, and glutaminolysis is the minor process responsible for L-lactate production in cancer cells [36, 37].

In contrast, D-lactate production in humans and eukaryotes occurs mostly through non-LDH pathways, mainly the methylglyoxal pathway, in abnormal metabolic states (Fig. 3). The methylglyoxal pathway is a branch of glycolysis that converts glucose to methylglyoxal and then to D-lactate [38]. In addition, D-lactate can also be produced by gut microbes (such as *Lactobacillus*) that breakdown glucose to produce D-lactate, which is absorbed through the gut and into the blood. For example, in short bowel syndrome, increased intestinal permeability and bacterial overgrowth lead to elevated D-lactate levels, which are involved in multiple pathological processes [21, 25]. The human gut microbiota, particularly species of the Firmicutes and Bacteroidetes phyla, are significant producers of D-lactate during carbohydrate fermentation [39]. Additionally, in prokaryotes, D-lactate is the main type of lactate [40]. In addition, the isoform D-LDH is also responsible for the limited production of D-lactate in human tissues, although its physiological role remains less defined than that of L-lactate [41]. These studies revealed that understanding the biosynthesis of D-lactate and its accumulation in pathological states is important for the treatment of diseases.

Overall, L-lactate plays a central role in maintaining metabolic homeostasis under anaerobic conditions [42, 43], whereas the relevance of D-lactate is more pronounced in pathological contexts [44, 45]. Understanding the distinct biosynthetic pathways and roles of these two lactate isomers provides crucial insights into their contributions to both normal physiology and disease states.

Transport of L- and D-Lactate

L- and D-lactate share a common transport system, as suggested by substrate competition studies [46]. The role of lactate in cellular metabolism is highly dependent on its efficient transport across membranes, a process mediated by MCT [47, 48]. MCTs are classified as a specific category of transmembrane transporters with the solute carrier family 16 (SLC16) family [49]. Among the 14 identified MCTs, MCT1-4 (also known as Slc16a1, Slc16a7, Slc16a8, and Slc16a3 respectively) are expressed in different tissues and are involved in catalytic proton coupling and the bidirectional transport of monocarboxylic acid [10]. MCT1 and MCT4 are the primary transporters responsible for lactate uptake and export, respectively [50, 51]. MCT1 is expressed predominantly in tissues with high oxidative capacity, such as cardiac and skeletal muscle, where it facilitates the uptake of

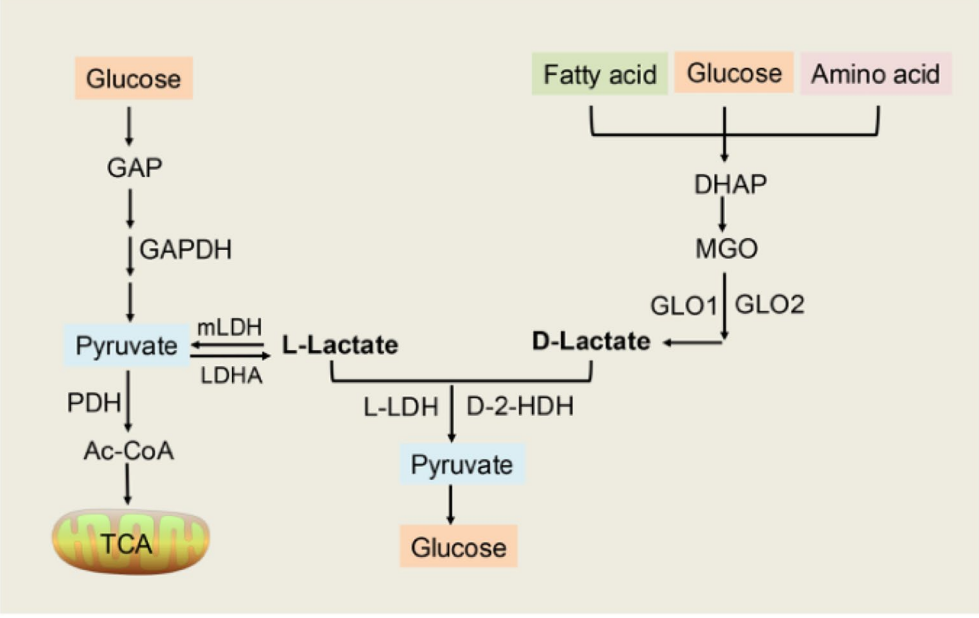

Fig. 3 Schematic diagram of the biosynthesis of L- and D-Lactate in eukaryotic. L-lactate is produced by glycolysis pathway, D-lactate is produced by glyoxalase pathway. In human physiology, L-lactate is the dominant isomer and D-lactate is produced at much lower levels, primarily by gut microbiota during carbohydrate fermentation. In dysbiosis, lactate-producing bacteria are a significant source of L- and D-lactate. Abbreviations: GAP: Glyceraldehyde 3-phosphate; GAPDH: Glyceraldehyde 3-phosphate dehydrogenase; TCA: Tricarboxylic acid cycle; PDH: Pyruvate dehydrogenase; LDHA: Lactate dehydrogenase A; L-LDH: L-lactate dehydrogenase A with M subunit; D-2-HDH: D-2-hydroxy acid dehydrogenase; DHAP: Dihydroxyacetone phosphate; MGO: Methylglyoxal; GLO1: Glyoxalase 1; GLO2: Glyoxalase 2; mLDH: Mitochondrial lactate dehydrogenase

lactate for oxidation and ATP production. In contrast, MCT4 is expressed in glycolytic tissues and plays a key role in exporting lactate to prevent intracellular acidification during anaerobic glycolysis.

In summary, both proton (MCT1-4) and sodium-dependent transporters (Slc5a8 and Slc5a12, also known as sMCT1, sMCT2 respectively) medicated the transport system [7, 52, 53]. These transporters are promiscuous and can act on a variety of substrates, including pyruvate or ketone bodies [7, 52]. Disruptions in lactate transport are implicated in various diseases, such as cancer and cardiovascular diseases [47, 54–56]. In cancer, the overexpression of MCT4 in glycolytic tumor cells contributes to the formation of an acidic microenvironment, promoting tumor growth, immune evasion, and metastasis [47]. Similarly, in conditions such as type 2 diabetes, MCT4 expression is upregulated, and lactate transport homeostasis is disrupted, leading to oxidative stress and inflammatory responses that exacerbate myocardial damage [56].Collectively, these transporters maintain lactate homeostasis, ensuring the use of lactate as both fuel and a signaling molecule and understanding the regulation of MCTs is crucial for developing interventions aimed at restoring lactate homeostasis in disease contexts where lactate dynamics are disrupted. Targeting lactate transport could offer therapeutic potential in treating such conditions.

The expanding roles of L- and D-Lactate in cellular metabolism and energy homeostasis

L-lactate functions as both metabolic fuel and a signaling molecule; it is produced during anaerobic glycolysis and shuttled to oxidative tissues such as the heart and brain, where it is reconverted to pyruvate for entry into the TCA cycle, supporting ATP production [6, 13, 29, 57]. This lactate shuttle is crucial for maintaining energy homeostasis, especially during periods of high metabolic demand, such as exercise or hypoxia [58–60]. Moreover, lactate supports metabolic flexibility, enabling cells to shift between carbohydrate and lipid metabolism depending on oxygen and substrate availability [61, 62]. In addition to its metabolic role, L-lactate modulates key signaling pathways linked to cell growth, survival, and immune responses [63, 64]; it can regulate the cell cycle and proliferation by interacting with the anaphase-promoting complex APC/C [65]. Some proposed mechanisms suggest that the entry of L-lactate into neurons alters the ATP/ADP ratio or affects the cellular redox state [66]. Additionally, L-lactate exerts an immunomodulatory effect by promoting the differentiation of regulatory T cells (Tregs), thereby contributing to immune suppression within the tumor microenvironment [67]. This immunomodulatory function allows lactate to contribute to both tumor progression and immune evasion, highlighting its complexity as both a substrate and a regulatory signaling molecule in health and disease.

L-lactate, once known primarily as an energy metabolite, is now recognized as a potent signaling molecule through the $G_{i/o}$-protein coupled receptor GPR81 (also known as HCAR1). As an extracellular messenger, L-lactate activates GPR81 via both autocrine and paracrine pathways. In cancer, lactate produced by tumor cells activates GPR81 on the same cells in an autocrine loop and on immune cells, endothelial cells, and adipocytes in the tumor microenvironment through paracrine signaling, facilitating immune evasion and chemoresistance [68–72]. Notably, GPR81 activation by lactate is independent of proton (H^+)- or MCT-mediated import and does not require the conversion of lactate to pyruvate, indicating that L-lactate is its specific ligand [72]. This unique mechanism is supported by studies showing that lactate signaling through GPR81 works synergistically with insulin to lower intracellular cAMP levels and inhibit lipolysis, suggesting a key role in metabolic regulation [73]. In addition to its role in cancer, GPR81 is expressed in neurons, astrocytes, and endothelial cells across the brain, retina, and blood–brain barrier, as well as in adipose and liver tissues, where it influences lipolysis and gluconeogenesis, thus impacting systemic energy balance [74–76]. In summary, the lactate/GPR81 axis supports tumor angiogenesis, immune evasion, and progression, playing a dual role in both tumor biology and metabolic regulation. This pathway presents a compelling target for the development of novel anticancer therapies aimed at disrupting the role of lactate in promoting tumor survival and progression.

Compared with L-lactate, D-lactate plays a distinct role in certain metabolic and pathological contexts. Excessive D-lactate is associated with D-lactic acidosis, which is characterized by metabolic acidosis and neurological symptoms such as confusion and ataxia [21, 24, 25]. While D-lactate production in human tissues is limited, its accumulation in disease states highlights its potential systemic impact. Recent studies suggest that D-lactate contributes to mitochondrial dysfunction and oxidative stress [77–79]. Specifically, elevated D-lactate levels can impair mitochondrial respiration by inhibiting key enzymes in the electron transport chain (ETC), leading to the increased production of reactive oxygen species (ROS) and reduced ATP generation [79, 80]. This mitochondrial disruption is linked to metabolic disorders such as type 2 diabetes and may exacerbate insulin resistance and cellular stress [81]. Although the precise mechanisms remain to be fully elucidated, the role of D-lactate in mitochondrial regulation and redox balance suggests that it plays a significant role in metabolic dysfunction under specific pathological states.

L-and D-Lactate and diseases

Cancer metabolism

L-lactate is central to cancer metabolism, and increasing evidence indicates that increased glucose metabolism and reprogramming toward aerobic glycolysis are hallmarks of cancer cells, meeting their energy needs for continuous proliferation [82]. The production of L-lactate, particularly through the Warburg effect, i.e., when cancer cells preferentially rely on "aerobic glycolysis", even in the presence of oxygen, in cancer cells, increases [83, 84]. This excess lactate contributes to an acidic tumor microenvironment (TME) that facilitates cancer cell invasion, metastasis, and immune evasion by suppressing cytotoxic T cells and natural killer (NK) cells [85–87]. Lactate-driven lactylation has emerged as a critical factor in DNA repair and chemoresistance. For example, the lactylation of Nibrin (NBS1) at K388 is necessary for the formation of the MRE11-Rad50-NBS1 (MRN) complex, which is involved in homologous recombination. Decreasing lactate levels via LDHA reduces NBS1 lactylation, impairing DNA repair and reducing chemoresistance [88]. Additionally, the lactylation of MRE11 at K673 serves as a vital response to DNA damage, further contributing to tumor resistance [89]. Alanyl-tRNA synthetase (AARS1) functions as both a lactate sensor and a lactyltransferase, mediating the lactylation of proteins such as p53, which promotes tumorigenesis [90]. Recent studies have indicated that AARS1, AARS2, and AlaRS in *Escherichia coli* can sense L-lactate accumulation, driving widespread proteome lactylation [91]. Additionally, the lactylation of proteins such as p53, adenylate kinase 2 (AK2), protein kinase R-like ER kinase (PERK) and nucleolin drives tumorigenesis and immune suppression [92–95]. In colorectal cancer, KAT8-catalyzed lactylation promotes protein synthesis via eukaryotic translation elongation factor 1 alpha 2 (eEF1A2), enhancing carcinogenesis [96]. Similarly, in prostate cancer and ocular melanoma, lactylation influences metabolic reprogramming and tumor progression [97, 98]. Additionally, L-lactate-producing lactic acid bacteria present at various body sites can alter tumor metabolism and contribute to therapeutic resistance, suggesting that the modulation of these bacteria could be a novel therapeutic strategy [84]. Collectively, these findings highlight the potential of targeting lactylation as a means to increase the efficacy of immunotherapy in cancer treatment.

D-lactate levels are significantly increased in various cancers, particularly gastrointestinal cancers, where altered gut microbiota increases D-lactate production [99–101]. D-lactate plays a vital role in regulating cancer cell ferroptosis and macrophage activity, although its exact functions in cancer metabolism are still being elucidated. Elevated D-lactate levels contribute to mitochondrial dysfunction, oxidative stress, and metabolic acidosis, highlighting the involvement of D-lactate in the complex metabolic landscape of tumors [44, 102, 103]. In esophageal squamous carcinoma, Lv et al. [104]. demonstrated that cyclin-dependent kinase 7 (CDK7) phosphorylates nuclear Yes-associated protein 1 (YAP) at S127 and S397, increasing its transcriptional activity and upregulating D-lactate dehydrogenase (LDHD) expression. This pathway helps cancer stem cells evade D-lactate-induced ferroptosis and generates pyruvate to meet the energetic demands of their high self-renewal capacity, suggesting a potential metabolic checkpoint for therapeutic targeting in esophageal squamous carcinoma [105]. Moreover, synthetic D-lactate dimers and organometallic redox catalysts have shown promise in inhibiting cancer cell proliferation [106, 107]. D-lactate, similar to the L-lactate, can enhance DNA repair and influence the resistance of cervical carcinoma cells to anticancer drugs through histone deacetylase inhibition and HCAR1 activation [108]. These findings suggest a critical role for D-lactate in cancer metabolism and present opportunities for therapeutic interventions that target lactate dynamics to disrupt tumor progression.

Immune modulation and inflammation

L-lactate plays a pivotal role in modulating immune responses, particularly in the TME, where its accumulation suppresses cytotoxic T cells and NK cells, which are key players in antitumor immunity [84, 109, 110]. Additionally, L-lactate enhances Treg activity, fostering an immunosuppressive environment. In KRAS-mutant tumors, lactate-driven histone lactylation activates the transcription of circATXN7, a circular RNA that interacts with NF-κB, sequestering it in the cytoplasm and promoting immune escape through increased T cell sensitivity to activation-induced cell death [111]. Lactate-driven lactylation of membrane-organizing extension spike protein (MOESIN) in Tregs further supports tumor immunosuppression via TGF-β signaling, and the inhibition of lactate production via LDH inhibitors diminishes this effect [112]. Furthermore, MCT4-driven metabolic reprogramming in cancer-associated fibroblasts (CAFs) represents a targetable vulnerability in breast cancer [109]. Lactate-mediated modifications extend beyond histone lactylation. For example, METTL16 lactylation promotes cuproptosis in gastric cancer, whereas METTL3-induced m6A RNA modifications in colorectal tumors highlight the regulatory role of lactate in immune responses [113, 114]. Raychaudhuri et al.. further reported that H3K18la and H3K9la dynamically regulate $CD8^+$ T cell transcription by influencing promoters and enhancers. Specifically, H3K18la is linked to inflammatory responses and glycolysis during T cell activation, whereas H3K9la is associated with oxidative phosphorylation and fatty acid metabolism in memory T cells,

underscoring the role of lactate in linking metabolism and epigenetics to $CD8^+$ T cell function [115].

In inflammatory diseases, lactate-induced histone lactylation in macrophages contributes to lung fibrosis by promoting the expression of profibrotic mediators [116–118]. In conditions such as IBD and rheumatoid arthritis, the B cell adapter for PI3K (BCAP) suppresses glycogen synthase kinase 3 beta (GSK3β) and FOXO1, influencing lactate production, histone modifications, and macrophage polarization [119]. Lactate also induces SMCT2 expression in $CD4^+$ T cells, driving lactate uptake and increasing IL-17 production via PKM2/STAT3 signaling, suggesting that targeting SMCT2 could help alleviate chronic inflammatory disorders [120]. While D-lactate is less prevalent, it contributes to proinflammatory responses, particularly gut dysbiosis and increased intestinal permeability [121, 122]. Elevated D-lactate levels activate macrophages, triggering TNF-α and IL-6 production and driving systemic inflammation [123, 124]. Cortney et al.. reported that D-lactate elevation and IL-10 in prosthetic joint infections play a role in the immune response, whereas gut-derived D-lactate supports Kupffer cells in pathogen clearance [125, 126]. Furthermore, D-lactate modulates macrophage polarization, shifting from an anti-inflammatory M2 phenotype to a proinflammatory M1 phenotype, as observed in hepatocellular carcinoma [125, 126]. In IBD, elevated D-lactate is correlated with disease severity and systemic inflammation, suggesting that D-lactate is a potential biomarker for IBD management [127, 128]. Collectively, these findings underscore the dual roles of L- and D-lactate in immune modulation and inflammation, with L-lactate primarily promoting immunosuppression in cancer and D-lactate driving proinflammatory responses. Future research into their crosstalk could reveal novel therapeutic targets for immune and inflammatory diseases.

Neurodegenerative diseases

In the brain, L-lactate is produced by neurons and astrocytes and serves as an auxiliary energy source for neurons [66]. Recent findings indicate that low-density lipoprotein receptor-related protein 1 (LRP1) regulates the lactylation of ADP-ribosylation factor 1 (ARF1), influencing astrocyte–neuron mitochondrial translocation, a mechanism that may protect against ischemic organ damage and highlights the role of LRP1 in astrocytic mitochondrial transport [129]. In early Alzheimer's disease (AD), excessive glycolysis leads to intracellular lactate accumulation, triggering excessive histone lactylation, amplifying glycolysis-related gene expression, and creating a feedback loop that exacerbates glucose metabolism in microglia [130]. Additionally, L-lactate stabilizes NDRG family member 2 (NDRG2), inhibiting TNFα expression and promoting neuroprotection postischemia [31]. Impaired oxidative phosphorylation in AD further accelerates disease progression via the isocitrate dehydrogenase 3 noncatalytic subunit beta (IDH3β)-lactate-paired box 6 (PAX6) feedback loop [131]. Lactylation also supports neural development, where lactylation enhances the expression of genes vital for neural crest cell differentiation [132]. These findings underscore the complex role of L-lactate in maintaining microglial and neuronal homeostasis, with implications for neurodegenerative disease progression.

Although less explored in neurodegeneration, D-lactate is associated with D-lactic acidosis, a condition observed in patients with malabsorption syndromes such as short bowel syndrome [44, 133, 134]. Excess D-lactate entering the bloodstream leads to neurological symptoms, including encephalopathy [134, 135]. The differential metabolism of methylglyoxal and D-lactate in cancer and AD cells may help explain the "eternal youth" of cancer cells and the "premature death" of AD neurons [26]. Most neurodegenerative diseases attributed to D-lactate result from life-threatening D-lactic acidosis, a rare complication occurring primarily in patients with malabsorption due to surgically altered gastrointestinal tract anatomy, such as in short bowel syndrome or following bariatric surgery. D-lactic acidosis is characterized by the rapid development of neurological symptoms [44, 103]. While most neurodegenerative effects of D-lactate are linked to D-lactic acidosis in patients with gastrointestinal surgeries, its connection to neurological disorders suggests a potential role for D-lactate as a biomarker for neurodegenerative conditions, warranting further investigation.

Other diseases

The involvement of L-lactate in cardiovascular disease is gaining recognition [55, 136]. For example, the reduced lactylation of α-MHC-k1897 contributes to heart failure [137]. In vascular health, nuclear receptor subfamily 4 group A member 3 (NR4A3)-mediated histone lactylation has emerged as a novel metabolome–epigenome signaling cascade implicated in arterial calcification [138]. Additionally, L-lactate is crucial in early development. Using the FiLa lactate probe, researchers observed lactate enrichment in the nuclei of two-cell embryos an determined that it was critical for preimplantation development; the inhibition of lactate production halted blastocyst formation, underscoring the role of lactate in embryogenesis [139]. In infectious disease, the upregulation of the expression of protein S6 kinase 2 (S6K2), which is linked to lactylation, enhances susceptibility to white spot syndrome virus in shrimp, indicating the role of lactylation in the pathogen response [140]. The lactylation of Yin Yang-1 (YY1) in microglia also promotes retinal neovascularization, identifying the lactate/p300/

YY1/FGF2 axis as a potential retinopathy therapy target [141].

In angiogenesis, L-lactate promotes blood vessel formation in multiple contexts. Physical exercise stimulates VEGFA expression and cerebral angiogenesis via GPR81 in brain endothelial cells [70]. This angiogenic effect extends to wound healing, where macrophage-derived VEGF facilitates new vessel formation, involving both aerobic and anaerobic glycolysis in hypoxic, damaged cells, as well as immune-cell activation and proliferation [70, 142]. In tumors, L-lactate activates endothelial cells and induces angiogenesis through HIF-dependent and HIF-independent pathways, which rely on MCT1-mediated lactate import and prolyl hydroxylate (PHD) inhibition [143, 144]. Recently, a distinct HIF-independent mechanism in which accumulated lactate during hypoxia binds to NDRG3, preventing its degradation and further promoting angiogenesis, was identified [145]. Together, these findings underscore the potential of L-lactate as a therapeutic target in cardiovascular and developmental disorders.

D-lactate, produced by gut bacteria, has been implicated in cardiovascular disease, as its translocation into systemic circulation may impact cardiovascular health, suggesting that gut barrier-targeted therapies may prevent cardiovascular events [146]. Elevated D-lactate levels aid in the diagnosis of acute appendicitis, with the potential to differentiate types of appendicitis in pediatric patients [147]. In cystic fibrosis, D-lactate is correlated with clinical severity and pancreatic insufficiency, as measured by the Shwachman–Kulczycki score [148]. Elevated D-lactate levels have also been observed in type 1 and type 2 diabetes, where gut dysbiosis and increased, intestinal permeability may contribute to systemic D-lactate elevation [149–151]. This correlation with diabetic complications, possibly through elevated methylglyoxal levels, suggests that D-lactate could serve as a diagnostic marker; however, further studies are needed to clarify its role in various conditions.

Summary, it is worth noting that the regulation of diseases by L- and D-lactate exists within a complex network of interplay and mutual influence in diseases (Fig. 4). The impact of L- and D-lactate on inflammation

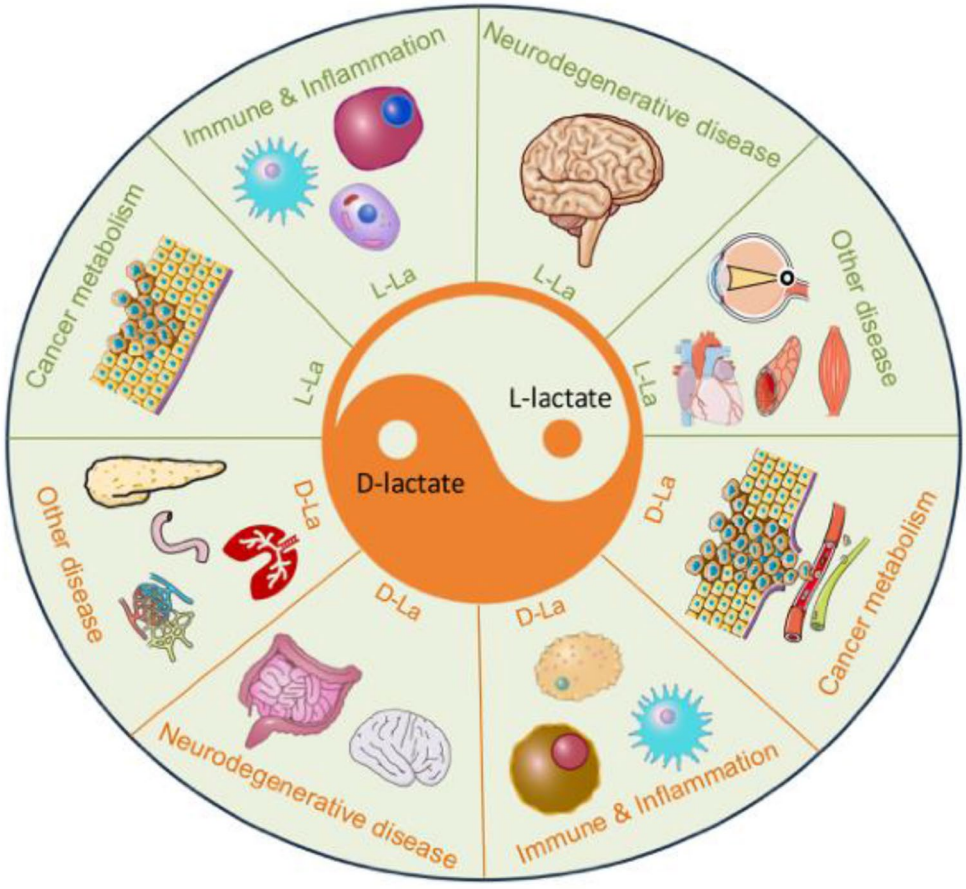

Fig. 4 Schematic diagram of L- and D-lactate in various diseases. Both L-lactate and D-lactate are involved in cancer metabolism, immune and inflammation, neurodegenerative disease, muscle function, retina disease and other diseases

could serve as a driving factor for the tumorigenesis. In addition, inflammation driven by L- and D-lactate, often linked to infectious diseases. Within this intricate network, L- and D-lactate emerges as a critical regulator, influencing intracellular signaling, gene expression, intercellular communication, and immune responses, thereby shaping disease progression. The diverse effects of L- and D-lactate underscore the need for a holistic perspective in disease research and treatment. Understanding its mechanisms across various diseases could enable the development of precise, targeted therapies with improved efficacy and fewer side effects.

Lactate shuttle hypothesis

Intracellular and intercellular shuttle of lactate

Targeting pathological lactate levels, regulating lactate transport, and modulating disease-related lactate levels offers promising therapeutic strategies for different lactate-related diseases in the future. One prominent approach for targeting lactate metabolism involves the inhibition of MCTs, which regulate lactate transport across cell membranes. The "lactate shuttle" hypothesis highlights the pivotal role of lactate in the transport of substrates for oxidation and gluconeogenesis, as well as in cellular signaling pathways [5]. Brooks initially proposed that lactate shuttling can take two forms: intracellular and intercellular [5]. Intracellular shuttling primarily occurs between the cell membrane and mitochondria [152]. When lactate is transported in cells, there are a variety of mechanisms, with the lactate/H^+ cotransporter-mediated shuttle facilitating the transmembrane movement of both L- and D-lactate. In particular, MCTs are recognized as key mediators of L-lactate transport [153]. Although the H^+ cotransport mechanism of D-lactate resembles that of L-lactate, the specific proteins mediating D-lactate transport remain unidentified. In addition to H^+ cotransport, D-lactate transport within cells involves both D-lactate/pyruvate and D-lactate/malate reverse transporters. The D-lactate/pyruvate transporter shuttles D-lactate from the cytoplasm to the mitochondrial membrane while moving pyruvate in the reverse direction. The D-lactate/malate transporter, potentially localized within the inner mitochondrial membrane, transfers D-pyruvate (generated after mitochondrial D-LDH oxidation) into the mitochondria and exports malate to the cytoplasm [8, 77]. The intracellular lactate shuttle hypothesis challenges traditional perspectives by revising the concept of lactate oxidation as an inherent cellular function. Furthermore, L-lactate production during exercise serves as an adaptive cellular response, with lactate acting as a signaling molecule that underpins the enhancement of lactate oxidation capacity through training [154].

Intercellular L-lactate shuttling mainly occurs between cells that depend on glycolysis and those engaged in oxidative respiration, such as glycolytic and oxidative muscle fibers, skeletal and cardiac muscles, astrocytes and neurons [155, 156]. According to Brooks et al.., lactate is produced and accumulates rapidly in muscle cells at the beginning of exercise. Subsequently, part of this lactate is transported to neighboring tissues, where it is internalized and oxidized by adjacent cells, while the remainder enters the bloodstream and is transported to organs such as the heart, liver, and kidneys, where it serves as a substrate for oxidative energy production and gluconeogenesis [3]. In coculture systems of cardiomyocytes and fibroblasts, lactate production in fibroblasts increases, with MCT1 translocating to the myocardial membrane to facilitate lactate uptake [157]. Similarly, in the brain, lactate produced by astrocytes is taken up by neurons, contributing to energy metabolism via conversion to pyruvate and acetyl-CoA, which also plays a role in regulating fatty acid synthesis [158]. Impaired lactate shuttling from glial cells to neurons disrupts brain metabolism, leading to neurodegeneration akin to that observed in AD [159]. This shuttling mechanism is also present in the kidney, where lactate is produced by proximal tubule cells and consumed by distal tubule cells [160]. Recently, lactate shuttling within the TME has emerged as a novel area of interest in cancer biology. Lactate not only meets the energy requirements of stromal cells but also regulates their function through its role as a signaling molecule, with activated stromal cells subsequently supporting tumor progression [161]. In summary, lactate shuttling underscores the multifaceted roles of lactate in energy metabolism and signal transduction, offering new therapeutic insights into the functions of lactate in both health and disease.

Histone lactylation

Histone lactylation and enzymes

The discovery of histone lactylation by Zhao's and Galligan's team both supported the role of lactate in gene regulation [16, 57, 162]. They reported that both $K_{L\text{-}la}$ and $K_{D\text{-}la}$ are predominantly modified on histones and that $K_{L\text{-}la}$ is the primary lactylation isomer on histones [57]. As a newly identified type of posttranslational modification, histone lactylation links lactate metabolism to transcriptional control and which also directly links the metabolic and epigenetic roles of lactate. Also, recent findings have revealed the enzymatic processes underlying this newly identified histone modification driven by L- or D-lactate, identifying key regulatory factors and their role in gene regulation and expression [104, 163, 164] (Fig. 5). Among these factors, p300 was the first protein identified with a "writer" function for histone lactylation. In HEK293T cells, p300 overexpression led to a slight increase in histone Kla levels, whereas p300 silencing in HCT116 and HEK293T cells resulted in a reduction in Kla, confirming

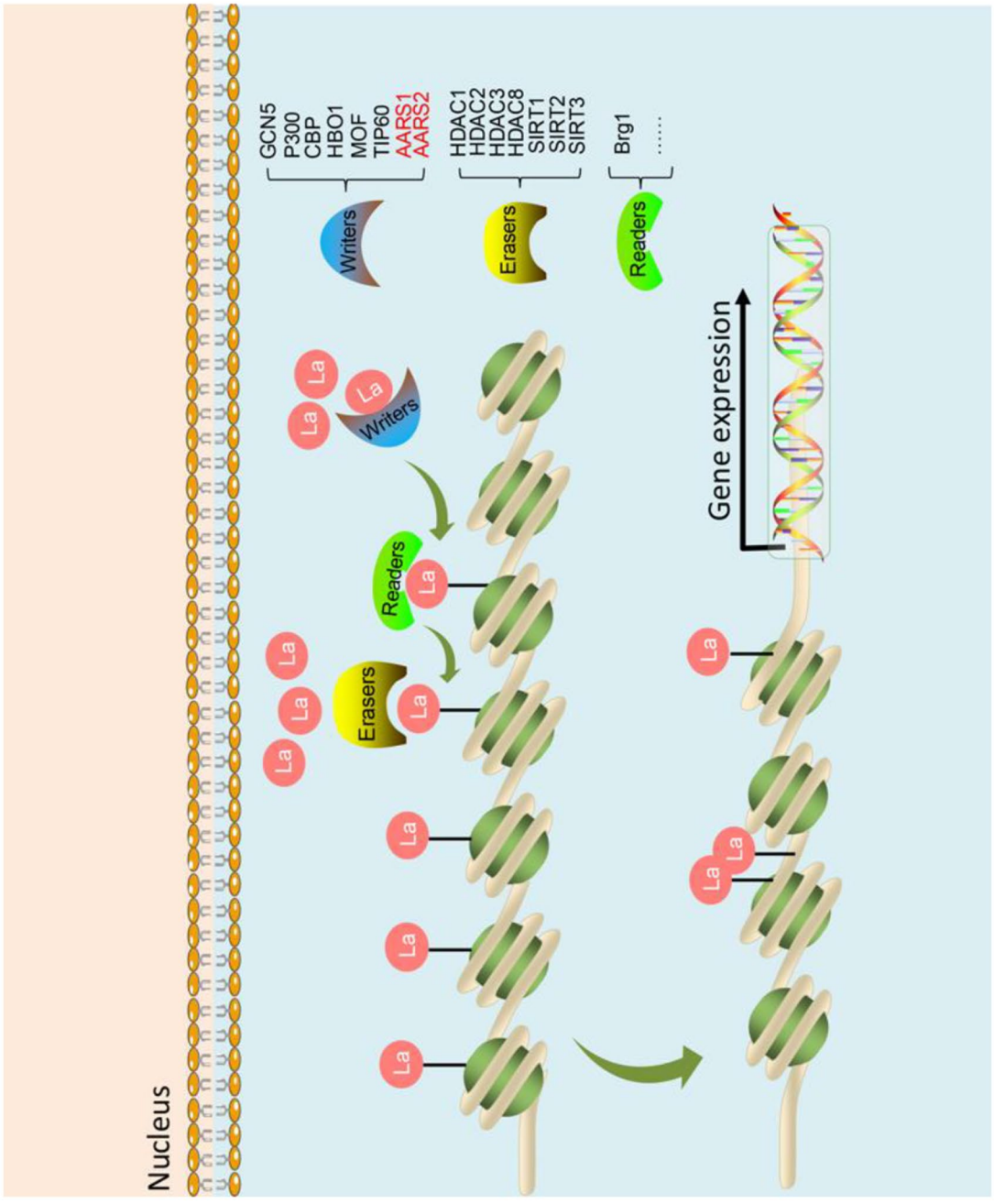

Fig. 5 Schematic diagram of how the enzymes involved in histone lactylation regulate histone lactylation and gene expression. The red AARS1 and AARS2 in writers means they were reported to catalyze the lactylation of nuclear proteins, if they can serve as "writers" of histone lactylation remains uncertain

that p300 is a potential Kla writer [16]. Similarly, in a study of myocardial infarction, lysine acetyltransferase 2 A (or GCN5) was shown to catalyze histone H3K18 lactylation [165], and both p300 and GCN5 were shown to be members of the HAT family. Additionally, HBO1, a newly identified lysine acetyltransferase, has been found to regulate histone Kla both in vitro and intracellularly, with a preference for catalyzing H3K9la [166]. Recent studies have identified AARS1/2 as conserved intracellular sensors of L-lactate that are capable of catalyzing the lactylation of nuclear proteins, thereby acting as lactyltransferases that modulate pathways such as the cGAS, P53, and YAP pathways, which influence tumor progression and immune responses. However, whether AARS1/2 also serve as "writers" of histone lactylation remains uncertain, necessitating further research to validate and elucidate this process [90, 167, 168].

In addition to "writers", HDAC1-3, HDAC8 and SIRT1-3 act as "erasers" of histone lactylation. Christian A. Olsen's group was the first to systematically explore the role of class I histone deacetylases (HDAC1-3) as histone lysine delactylases, demonstrating their ability to reverse lactylation [169]. HDAC3 was found to regulate lactylation at multiple sites, including H4K5. Compared with other sirtuins, Sirtuin 3 (SIRT3) shows particularly strong erasure activity at the H4K16la site [170]. Although few studies have identified "readers" of histone lactylation, Hu et al.. reported that Brg1 (or Smarca4) binds to H3K18la. Proteomic analysis revealed that Brg1 was enriched at pluripotency and epithelial junction gene promoters during iPSC reprogramming, making it the first recognized histone lactylation reader. Further research is needed to fully characterize the potential readers involved in this process, and more studies need to focus on histone lactylation driven by D- or L-lactate [171]. More studies are needed to identify potential readers of histone lactylation. Modulating the 'writers' and 'erasers' of histone lactylation represents a promising therapeutic approach, with emerging strategies offering potential for clinical applications targeting lactate metabolism.

Conclusions and perspectives

Future research on D-and L-Lactate

Once considered mere metabolic byproducts, L- and D-lactate are now considered important regulators of cellular homeostasis, immune function, cancer, and neurodegenerative diseases. While the roles of L-lactate in energy metabolism and immune regulation have been established, the influence of L-lactate on brain function, cardiovascular health, and immune responses warrants further investigation [172, 173]. As the understanding of L-lactate functions deepens, it becomes equally important to explore the unique and potentially tissue-specific roles of D-lactate.

D-lactate, which is primarily produced by lactic acid bacteria, plays a significant role in diseases associated with gut microbiota imbalances. For example, the accumulation of D-lactate has been linked to pathological processes along the gut–liver axis, suggesting its potential as a therapeutic target. Modulating D-lactate activity in this axis could provide novel treatment strategies. Additionally, recent studies have shown that D-lactate can influence immune function by regulating M2 macrophages and reshaping the immunosuppressive TME in hepatocellular carcinoma [123], highlighting the need to investigate its specific roles in cancer and TME modulation. The impact of D-lactate also extends to mitochondrial dysfunction, oxidative stress, and metabolic diseases such as type 2 diabetes and neurodegenerative disorders. Further research into these areas could uncover new insights into the broader physiological roles of D-lactate. Additionally, lactate-related regulatory enzymes, such as lactyl-CoA synthetases, and their substrates (both L- and D-lactate) remain understudied [13, 29].

Interestingly, lactylation may not be the only modification with stereoisomeric forms. For example, β-hydroxybutyrylation could theoretically occur as D- and L-isomers generated from their respective CoA precursors [174]. This possibility raises questions about the distinct regulatory roles of D-lactyl-CoA and L-lactyl-CoA. Understanding how these enzymes orchestrate histone L- and D-lactylation in physiological contexts will be essential for elucidating the regulatory potential of lactate. Future research on these mechanisms may reveal broader physiological impacts of lactate, advancing therapeutic possibilities across diverse disease contexts.

Crosstalk between lactylation and other modifications

Emerging evidence has revealed distinct L-lactate and D-lactate modifications at specific protein sites, although it remains uncertain whether both can cooccur at the same or different sites within a single protein. Additionally, the functional interplay between these two modifications, whether synergistic or antagonistic, remains unexplored. Investigating this crosstalk could provide critical insights into the regulatory role of lactylation in disease mechanisms, particularly in cancer, the immune response, and inflammation. Future studies may pave the way for novel therapies that target these modifications to address diseases with dysregulated lactate signaling.

Histone lactylation has recently been identified as a significant epigenetic marker that is regulated by glycolysis and primarily manifests as K-lactylation [57]. This finding suggests possible crosstalk with other histone modifications, such as phosphorylation and acetylation, creating an interconnected network that responds

to cellular metabolic states. As shown in Fig. 2, differentiated tissues rely on oxidative phosphorylation and anaerobic glycolysis, whereas tumor cells exhibit aerobic glycolysis (the Warburg effect), leading to increased lactate production. This metabolic shift not only fuels energy demand but also provides substrates such as ATP and lactate for phosphorylation and lactylation, respectively. These metabolites can influence chromatin structure through cooperative or competitive interactions between modifications, directly impacting gene expression. Investigating these interactions may clarify how metabolic changes shape the epigenome in various contexts, particularly in cancer, where metabolism and epigenetic regulation are tightly linked. Such studies could reveal novel therapeutic targets that address metabolic and epigenetic dysregulation in tumors and other diseases.

Moreover, many types of acylation, including lactylation, share common enzymatic pathways and are recognized by overlapping 'readers' that facilitate downstream effects. For example, SIRT2 acts as an 'eraser' by removing multiple acyl marks from both histone and nonhistone proteins [175–179], and several metabolic enzymes implicated in disease pathogenesis are known to modulate more than one modification [180]. Histone acetyl transferase (HATs) family, which catalyzes the transfer of the acetyl group from acetyl-CoA to histones, including P300/CBP, MOF, GCN5 and TIP60 are also reported catalyzes the transfer of lactate groups from lactate-CoA to histones in different disease and disease states [16, 88, 165, 181, 182]. Therefore, understanding the dynamic interactions among various lactylation modifications and their crosstalk with other acylation modifications, particularly their competition for regulatory enzymes, may be crucial for fully elucidating disease mechanisms. This knowledge could pave the way for therapeutic strategies that specifically target these acylation pathways, offering new possibilities for precision medicine.

Therapeutic targets of L- and D-Lactate

Key enzymes and transporters involved in lactate homeostasis, such as glycolytic enzymes, MCTs, LDH and mitochondrial pyruvate carriers, have emerged as promising therapeutic targets [6]. Future lactylation-targeted therapeutic approaches will likely focus on developing specific inhibitors and activators that precisely modulate the activity of lactylation-related enzymes, thereby influencing disease progression. Notably, MCT expression is clinically associated with cancer metastasis and poor prognosis [47, 183, 184], highlighting the need to clarify the roles of MCT1 and MCT4 in cancer cell survival and drug resistance. A variety of MCT inhibitors, including cyanoacetic acid, coumarin, flavone, and indole derivatives, have been explored [185], yet only a few have advanced to clinical trials due to challenges with side effects and potential off-target effects. For example, AZD3965, an MCT1 inhibitor that entered phase 1 trials in 2013 under Cancer Research UK's Centre for Drug Development, was generally well tolerated, although common side effects included nausea and fatigue, with dose-limiting cardiac toxicity observed at 20 mg [186].

While MCT4 inhibitors are less developed, recent advancements are encouraging. AZD0095, a selective MCT4 inhibitor, has demonstrated antitumor effects in mouse models when combined with VEGFR inhibitors [187]. However, its efficacy in clinical settings remains to be established, underscoring the need for further trials. Exploring the therapeutic potential of targeting lactate metabolism could significantly advance cancer treatment, particularly by addressing challenges related to drug resistance and metastasis. As research progresses, metabolic modulation may emerge as a critical strategy for innovative cancer therapies.

In addition to MCTs, LDH inhibition represents a promising avenue for anticancer strategies. LDH, composed of various isozymes formed by A and B subunits, includes a recently discovered isozyme, LDH-X, in mature human testes and sperm [188]. Despite extensive research, developing LDH inhibitors with drug-like properties remains challenging. Many inhibitors, such as 2-amino-5-aryl-pyrazine and 3,6-disubstituted dihydropyrones, show potential, yet high LDH abundance and increased expression in tumors indicate that effective inhibition may require high doses, limiting therapeutic viability [189]. To enhance efficacy, combining LDH inhibitors with compounds that target gene expression may offer a solution. Unlike enzyme inhibitors, which often impact both LDH-A and LDH-B, expression inhibitors can selectively target LDH-A through distinct gene regulatory mechanisms. This dual approach, which addresses both LDH expression and activity, could improve outcomes in LDH-targeted therapies. Research into these combined mechanisms may reveal new therapeutic pathways for cancer and other diseases.

In conclusion, as research into D- and L-lactate has progressed, it has become increasingly clear that these molecules play pivotal roles beyond simple metabolism, acting as regulators of cellular homeostasis, immune function, and gene expression. This review highlights the distinct and complementary functions of D- and L-lactate across physiological and pathological landscapes, revealing their potential as dynamic modulators within diverse biological systems. To fully elucidate the breadth of the biological effects of lactate, future studies must integrate lactate metabolism into the broader context of metabolic and signaling networks, recognizing it as a fundamental component of cellular regulation. The advancement of sophisticated analytical and computational methods will

be key in unraveling the complexities of these stereoisomers, enabling the discovery of novel therapeutic targets, particularly for diseases such as cancer, metabolic syndromes, and neurodegenerative disorders. Furthermore, understanding the nuanced role of lactylation and its interplay with other acyl modifications is important for opening entirely new avenues in both basic research and translational science.

Abbreviations

LDH	Lactate dehydrogenase
NAD	Nicotinamide adenine dinucleotide
MCT	Monocarboxylate transporter
TCA	Tricarboxylic acid cycle
ATP	Adenosine triphosphate
LDHA	Lactate dehydrogenase A
LDHB	Lactate dehydrogenase B
GAP	Glyceraldehyde 3-phosphate
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase
PDH	Pyruvate dehydrogenase
L-LDH	L-lactate dehydrogenase A with M subunit
D-2-HDH	D-2-hydroxy acid dehydrogenase
DHAP	Dihydroxyacetone phosphate
MGO	Methylglyoxal
GLO1	Glyoxalase 1
GLO2	Glyoxalase 2
mLDH	Mitochondrial lactate dehydrogenase
ADP	Adenosine diphosphate
HCA1	Hydroxycarboxylic acid receptor 1
Treg	Regulatory T cell
ETC	Electron transport chain
ROS	Reactive oxygen species
NK	Natural killer cells
AARS	Alanyl-tRNA synthetase
PERK	R-like ER kinase
TME	Tumor microenvironment
AK2	adenylate kinase 2
eEFiA2	Eukaryotic translation elongation factor 1 alpha 2
CDK7	cyclin-dependent kinase 7
YAP	Yes-associated protein 1
LDHD	D-lactate dehydrogenase D
MOESIN	Membrane-organizing extension spike protein
IBD	Inflammatory Bowel Disease
UC	Ulcerative colitis
CD	Crohn's disease
AD	Alzheimer's disease
DM	Type 2 diabetes mellitus
CAF	Cancer-associated fibroblasts
METTL	Methyltransferase
BCAP	B cell adapter for PI3K
GSK3β	Glycogen synthase kinase 3 beta
FOXO1	Forkhead box1
PHD	Prolyl hydroxylate
TNF	α-Tumor Necrosis Factorα
ARF1	ADP-ribosylation factor 1
IDH3β	Isocitrate dehydrogenase 3 noncatalytic subunit beta
PAX6	Paired box 6
S6K2	Protein S6 kinase 2
VEGF	Vascular endothelial growth factor
HIF	Hypoxia inducible factor
HAT	Histone acetyl transferase
GCN5	Lysine acetyltransferase 2 A
HDAC	Class I histone deacetylases
SIRT	Sirtuin
SMARCA4	SWI/SNF Related, matrix associated, actin dependent regulator of chromatin, subfamily A, member 4

Author contributions

J.L. and P.M. wrote the main manuscript and original draft and Z.L. and J.X. edited the manuscript. All authors reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

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