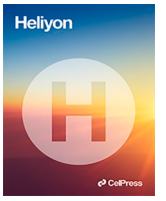
Heliyon 10 (2024) e38426

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Lactate and lysine lactylation of histone regulate transcription in cancer

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ARTICLE INFO

Keywords:
Histone
Post-translational modification
Lactate
Lysine lactylation
Transcription
Cancer

ABSTRACT

Histone lysine modifications were well-established epigenetic markers, with many types identified and extensively studied. The discovery of histone lysine lactylation had revealed a new form of epigenetic modification. The intensification of this modification was associated with glycolysis and elevated intracellular lactate levels, both of which were closely linked to cellular metabolism. Histone lactylation plays a crucial role in multiple cellular homeostasis, including immune regulation and cancer progression, thereby significantly influencing cell fate. Lactylation can modify both histone and non-histone proteins. This paper provided a comprehensive review of the typical epigenetic effects and lactylation on classical transcription-related lysine sites and summarized the known enzymes involved in histone lactylation and delactylation. Additionally, some discoveries of histone lactylation in tumor biology were also discussed, and some prospects for this field were put forward.

1. Introduction

The human genome, which contained about 2 m of linear DNA, must be compacted to fit within the small volume of the cell nucleus. This compaction was achieved by wrapping DNA around histone proteins, forming complex macromolecular structures known as chromatin [1]. Chromatin was then further folded and highly condensed into chromosomes, which helped to minimize their size and maintain their stability. For DNA-dependent processes such as replication, transcription, repair, and recombination to occur, chromosomes must unwind to allow access to the DNA template. However, the organization of chromatin was highly dynamic and variable, constantly transitioning between different states. These dynamic changes increased the accessibility of DNA within chromatin, thereby precisely regulating various cellular activities.

The basic unit of chromatin was the nucleosome, which consisted of a central histone octamer (comprising two each of histones H2A, H2B, H3, and H4) and 147 base pairs of DNA wrapped around it [2]. These histone proteins underwent various (such as methylation, acetylation, phosphorylation, and ubiquitination. These modifications served as epigenetic marks that regulate DNA-templated processes at the molecular level.

Developments in proteomics, driven by high-resolution mass spectrometry and specific antibody-based enrichment techniques, had made the identification of novel histone PTMs more straightforward, leading to the discovery of many new epigenetic marks. Research on tumor metabolism had revealed that various metabolites can modify histones, including through histone lactylation. Histone

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https://doi.org/10.1016/j.heliyon.2024.e38426
Received 26 July 2024; Received in revised form 24 September 2024; Accepted 24 September 2024
Available online 1 October 2024

Abbreviations and acronyms:

LDH	lactate dehydrogenase
PTMs	post-translational modifications
BMDMs	bone marrow-derived macrophages
Arg1	arginase 1
Pan-Kla	pan-lactylation
AD	Alzheimer's disease
BMSCs	bone marrow mesenchymal stem cells
EC	endothelial cell
FMT	the transdifferentiation of fibroblasts into myofibroblasts
ZGA	zygotic genome activation
BLCA	bladder cancer
HCC	hepatocellular carcinoma
DML	demethylzeylasteral
LCSC	liver cancer stem cell
GBM	glioblastoma
TMZ	temozolomide
AML	acute myeloid leukemia
HCC	liver cancer
LUAD	lung adenocarcinoma
PCAF	P300/CBP-associated factor
MCT	monocarboxylate transporter
K183	lactated at lysine 183
DAMP	damage-associated molecular pattern
HMGB1	High mobility group box-1 protein
HAT	histone acetyltransferase
ZZ	zinc-finger
AARS1	alanyl-tRNA synthetase 1
PPi	pyrophosphate
DBD	DNA binding domain
HDACs	Histone deacetylases
Kla	lysine lactylation
Kac	Lysine actylation
EwS	Ewing's sarcoma
HDACi	HDAC inhibitors
Kcr,ε	N-crotonyllysine
K(D-bhb)	-N-D-β-hydroxybutyryllysine
HPTMs	Histone post-translational modifications
TME	tumor microenvironment
UM	uveal melanoma

lactylation, first reported by Zhang et al., in 2019, was a modification formed by adding a lactate group to a lysine residue in the histone tail [3]. Similar to other histone PTMs such as acetylation, methylation, phosphorylation, and ubiquitination, histone lactylation involved specific signaling pathways that regulate its activation, maintenance, and removal. Key components in this process included histone lactylases, which added the lactate group ("writers"); specific protein domains that recognized lactylation marks ("readers"); and histone lysine delactylases, which removed the lactate group ("erasers"). Currently, histone lactylation was recognized as an important new epigenomic modifier with a broad range of biological functions. Significant progress has been made in research on histone lactylation, and this field holds great promise for future discoveries.

In this paper, we systematically reviewed lactic acid metabolism and the histone lysine lactation modification process, and partially summarized the research status of typical histone lactation modification sites and key related enzymes, with a particular focus on the field of oncology. Currently, research on the regulatory functions of lactic acid and non-histone lactation is expanding, whereas progress in understanding histone lactation and its role in epigenetic regulation remains comparatively slow. The evidence that histone lysine lactation shared similar effects and functions (e.g., regulating gene transcription, the cell cycle, and DNA damage repair) with traditional histone post-translational modifications (PTMs) like methylation and acetylation suggested that histone lactation warranted significant attention [4]. Building on existing studies, it was essential not only to further elucidate the physiological and pathological processes influenced by lysine lactation at different histone sites but also to clarify the specific mechanisms and regulatory pathways involved in histone lysine lactation, thereby facilitating its translation into practical applications and advancing its use as a novel approach for disease prevention and treatment. This paper summarized current research and outlined future directions, aiming

to provide a foundation for subsequent investigations into histone lysine lactation.

2. Lactate and histone lactylation

Lactic acid is an important organic compound found extensively in living organisms, playing a crucial role in metabolic processes and disease development. As a byproduct of anaerobic glycolysis, lactic acid production increased when the demand for oxygen and ATP exceeded the cell's supply, such as during stress responses like exercise and infection [5]. Historically, lactic acid was regarded merely as a metabolic byproduct, but it is now understood to function as an energy source within cells or to be released into neighboring tissues [3,6]. Additionally, the most common lactic acid anion, L-lactate, was mistakenly believed to be produced only under hypoxic conditions in skeletal muscle during contraction. Current research demonstrated that L-lactate was produced even under fully aerobic conditions [7] and can be reversibly converted with pyruvate via a REDOX reaction facilitated by lactate dehydrogenase (LDH). The metabolic transformation of lactic acid and glucose was known as the Cori cycle. In the state of hypoxia, the rate of NAD + formation via the respiratory chain was insufficient to sustain glycolysis. At this stage, pyruvate formed through muscle fermentation was converted to lactic acid by LDH, regenerating NAD+ and allowing glycolysis to proceed. The lactic acid was then converted back into glucose in liver cells through a pathway called gluconeogenesis and released into the bloodstream to supply glucose to the muscles and brain [8] (Fig. 1.). The exchange of lactate within and between cells, known as the lactate shuttle, encompassed lactate transport between the cytoplasm and organelles such as mitochondria and peroxisomes [9,10], as well as between different organs like the heart [11], liver [12], and kidneys [13], and between astrocytes and neurons [14]. Moreover, lactic acid also acts as a signaling molecule involved in various cellular regulatory processes, including immune regulation, anti-inflammatory responses, wound healing, and maintenance of cellular homeostasis.

In recent years, research on the role of lactic acid in the tumor microenvironment has intensified. Glycolysis-dependent metabolic enhancement was a common feature of tumors and rapidly proliferating cells, as lactic acid provided a quick energy source, making it a focal point in the study of energy metabolic reprogramming. Even in the presence of sufficient oxygen, tumor cells preferentially

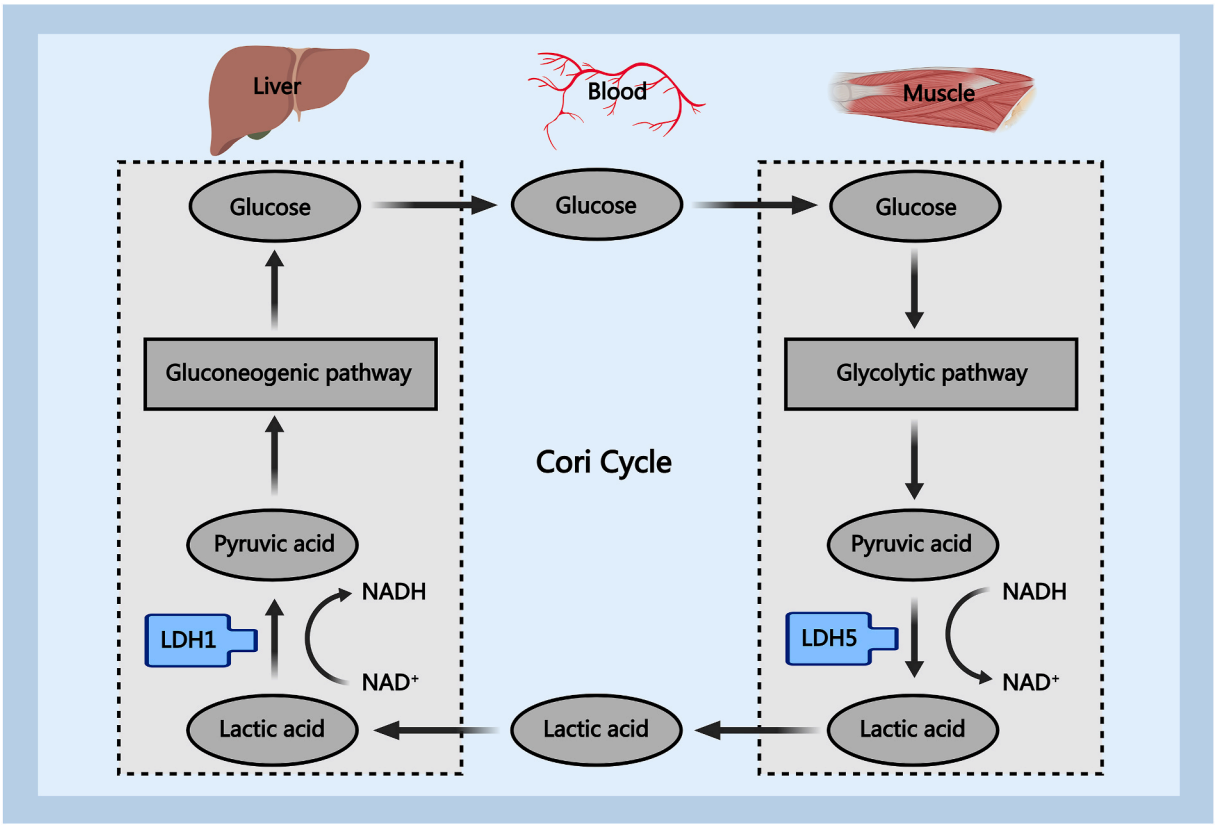

Fig. 1. Diagram of the Cori Cycle. The Cori Cycle illustrated the metabolic transformation of lactic acid and glucose.
During intense exercise, the rate of glycolysis significantly exceeded the rate of NAD + formation via the respiratory chain. During this process, pyruvate produced by glycolysis in muscles was converted into lactic acid by LDH5, regenerating NAD+ and allowing glycolysis to continue. In liver cells, lactic acid was converted back into glucose by LDH1 via the gluconeogenesis pathway, and then released into the bloodstream to meet the glucose demands of muscle and brain tissues, thus facilitating the regeneration of NAD+ and the interconversion of lactic acid and glucose. **LDH: lactate dehydrogenase.**

produced lactic acid via anaerobic glycolysis [15], a characteristic known as the Warburg effect [16]. The role of lactic acid in tumorigenesis and development was highly complex. On one hand, lactic acid can increase the stemness of $CD8^+$ T cells, enhancing anti-tumor immunity independently of its pH-regulating function [17]. On the other hand, lactic acid contributed to shaping a complex and diverse tumor microenvironment by mediating various metabolic interactions, recruiting and modulating immune cells [18], transforming growth factor signaling, and facilitating oncogene activation and tumor suppressor gene loss [19].

The research has shown that the mass shift of lysine residues in human MCF-7 cells corresponded to the mass change resulting from the attachment of a lactate group to the ε-amino group of lysine [3]. This conclusion was further confirmed through metabolic labeling using isotope-labeled glucose and lactate. Based on the finding, Zhang et al. introduced the concept of histone lactylation in 2019. Additionally, during the activation of M1 macrophages, lactate-mediated histone lactylation promoted their transformation into late-phase repair macrophages with a more stable phenotype [20]. This transformation occurred because histone lactylation enhanced the transcription of genes related to macrophage repair [3]. This study suggested that, similar to histone acetylation, histone lactylation can directly promote gene transcription. Histone lactylation reflected cellular lactate levels, thereby initiating lactate modifications and linking cellular metabolism with the transcriptome. This connection formed a bridge between epigenetics and metabolic reprogramming. The study of histone lactylation has become a prominent topic in epigenetics, providing crucial insights into the mechanisms of cell regulation and the development of related diseases.

3. Research status of histone lactylation sites

Common post-translational modifications of histones, such as methylation and acetylation, have been shown to alter nucleosome structure, regulate gene silencing and transcriptional activity, and facilitate DNA repair [21,22]. These modifications were also closely linked to cell cycle regulation, particularly during proliferation and differentiation [23,24]. Similarly, histone lactylation has been found to exhibit comparable epigenetic effects and may even possess broader regulatory functions [4]. Unlike the relatively fixed roles of methylation and acetylation in gene silencing and activation, lactylation can exert diverse transcriptional regulatory functions on different genes depending on the environmental context, and may even produce opposite effects on the same gene under different biological conditions. Additionally, changes in chromatin structure tightness and stability due to lactylation can impact chromatin accessibility and interaction with other proteins, mediating signal transduction and functional regulation across various cellular processes [25,26].

The study by Zhang et al. has identified histone lactylation sites, highlighting the non-metabolic role of lactate in physiological and pathological processes as a source of histone lysine lactylation. They identified 26 histone lactylation sites in human HeLa cells and 16 sites in mouse bone marrow-derived macrophages (BMDMs) [3]. This finding suggested that histone lactylation can occur at multiple lysine residues and may have significant implications for gene regulation and disease progression.

3.1. H3K18la

Currently, histone H3K18 is the most extensively studied site for histone lactylation. A comprehensive study on H3K18 lactylation in human and mouse tissues revealed that H3K18la was enriched at active enhancers near genes critical for tissue-specific functions [27]. This suggested that H3K18la is not only a marker for active promoters but also a marker for tissue-specific activity enhancers [27]. The enrichment of H3K18la at several key gene promoters highlighted its significant role in various cellular processes and diseases, including tumor progression, angiogenesis, embryonic development, macrophage polarization, and sepsis.

The Warburg effect, which highlighted the role of increased lactic acid production in promoting tumor growth during glycolysis [15], suggested that lactate-mediated histone lactylation may be a significant epigenetic modification in tumor progression. Yu et al. found that H3K18la accelerated the development of ocular melanoma by promoting the expression of the YTHDF2 gene [28]. Additionally, the enrichment of H3K18la in the promoter region of breast cancer cells up-regulated the expression of the oncogene c-Myc, thereby exerting a pro-tumor effect [29]. In bladder cancer, H3K18la targeted the oncogene LCN2 and promoted tumor progression by enhancing LCN2 expression [30].

In addition to its pro-tumor effects, H3K18la was implicated in the progression of various diseases. For instance, an increase in H3K18la levels induced the expression of the inflammatory factor arginase 1 (Arg1) [3], thereby stimulating the anti-inflammatory function of macrophages in sepsis and aiding in the distinction between septic shock and non-septic shock [31]. H3K18la was also enriched in gene promoters activated in hepatic stellate cells, suggesting its role in hepatic stellate cell activation and pulmonary fibrosis [32]. Elevated levels of H3K18la and total histone lactylation have been observed in highly calcified tissues, indicating that histone lactylation significantly promoted vascular calcification. Consequently, lactate levels in circulating cells could serve as a potential biomarker for predicting pathological calcification [33]. Additionally, H3K18la and pan-lactylation (Pan-Kla) were significantly upregulated in the hippocampus of naturally aged mice and those modeled with Alzheimer's disease (AD), offering new insights into the epigenetic regulation mechanisms of lactylation in brain aging and AD [34].

In addition, H3K18la played a crucial role in body development and cell differentiation. For example, during osteogenesis, histone lactylation and the expression of related osteogenic genes were downregulated in bone marrow mesenchymal stem cells (BMSCs) of osteoporosis patients. In contrast, endothelial cell (EC)-derived lactate triggered H3K18la in BMSCs, stimulating the transcription of osteogenic genes and thereby alleviating osteoporosis [35]. The transcription factor JunB, which regulated osteoblast differentiation and bone formation [36,37], was significantly enriched with H3K18la at its proximal promoter, leading to its activation [38]. This suggested that H3K18la directly participated in the regulation of osteoblast differentiation. Furthermore, scleral hypoxia, a critical factor in myopia, induced glycolysis and increased lactic acid levels. This promoted the transdifferentiation of fibroblasts into

myofibroblasts (FMT) via H3K18la, contributing to myopia development [39]. The recent study had also uncovered a conserved metabolic mechanism in the preimplantation development of mammalian embryos, where H3K18la played a significant role in major zygotic genome activation (ZGA), linking lactate metabolism to epigenetic inheritance in mammalian embryos [40].

Finally, transcriptional activation induced by the enrichment of H3K18la in certain target gene promoters can result in specific effects. For example, in bladder cancer (BLCA), the key transcription factors YBX1 and YY1, driven by H3K18la, promoted cisplatin resistance. This discovery was valuable for further investigating the mechanisms of cisplatin resistance and provided new targets and approaches for overcoming this challenge [41]. Additionally, increased levels of H3K18la had been observed in patients with colorectal cancer who developed resistance to bevacizumab [42]. Inhibiting histone lactylation effectively suppressed the occurrence, progression, and survival of colorectal cancer under hypoxic conditions, thereby enhancing the clinical efficacy of bevacizumab in treating colorectal cancer.

3.2. H3K9la

Although the mechanisms of action and biological functions of H3K9la were less understood compared to other histone modifications such as methylation and acetylation, preliminary findings suggested that H3K9la may play a role in influencing various cellular processes.

Considering the fundamental metabolic role of histone lactylation, research indicated that lactate secretion and the levels of histone lactylation induced by lactate can be notably suppressed by the methyltransferase METTL15, particularly affecting H3K9la. This

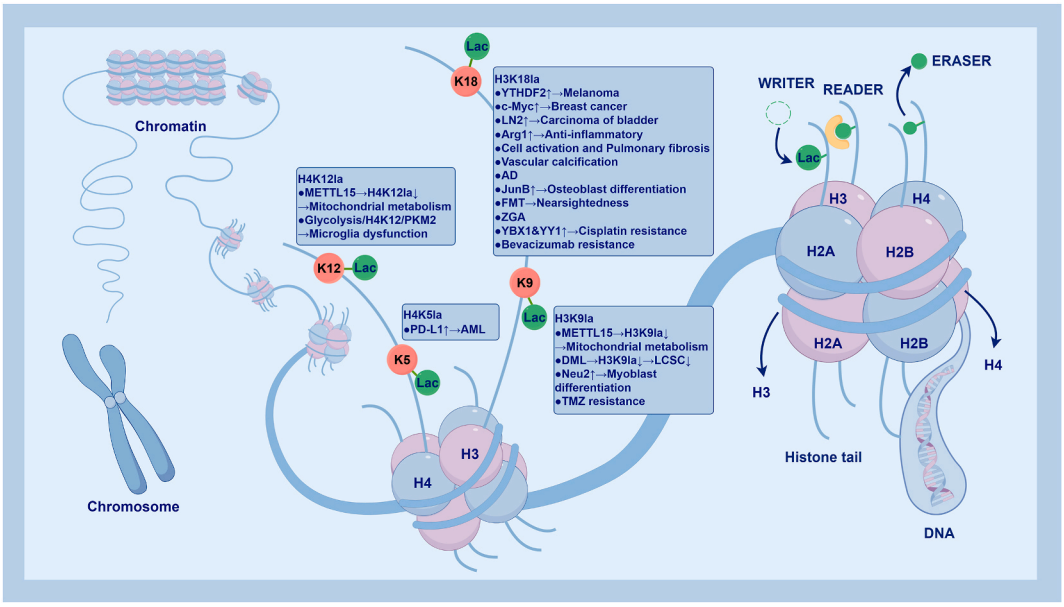

Fig. 2. The schematic diagram illustrating histone lysine lactylation and its associated effects.
The fundamental unit of chromatin, the nucleosome, was composed of a central histone octamer (two each of histones H2A, H2B, H3, and H4) and 147 base pairs of DNA. The lactate group attached to the lysine on the histone tail via a lactate 'writer,' creating a histone lysine lactylation modification that 'readers' can recognize to perform specific functions, which can be reversed by a lactate 'eraser'. Histone lactylation modifications changed the spatial configuration of chromatin, influenced DNA accessibility, and regulated the expression of numerous genes. Based on existing studies, the functions of H3K18la included: accelerating the occurrence of ocular melanoma by promoting the expression of YTHDF2; H3K18la enrichment in the promoter region up-regulated c-Myc and promoted breast cancer; promoting the progression of bladder cancer by enhancing the expression of LCN2; Arg1 expression was induced to stimulate the anti-inflammatory function of macrophages in sepsis; mediating hepatic stellate cell activation and pulmonary fibrosis; promoting vascular calcification; promoting AD; regulating osteoblast differentiation by activation of JunB; promoting FMT and thus myopia; mediating ZGA; driving YBX1 and YY1 to promote cisplatin resistance in BCa; and mediating bevacizumab treatment resistance in patients with colorectal cancer. Studies on H3K9la included: the inhibition of H3K9la by METTL15 to establish a study model of mitochondrial metabolism and histone lactation; DML inhibited H3K9la and thus inhibited LCSC tumorigenesis; activating Neu2 to facilitate myoblast differentiation; and mediating the emergence of TMZ resistance in GBM cells. H4K5la induced PD-L1 transcriptional activation, promoting the progression of AML. METTL15 inhibited H4K12la in a manner similar to its inhibition of H3K9la. The positive feedback loop involving glycolysis, H4K12la, and PKM2 can exacerbate microglial dysfunction in patients with AD.
YTHDF2: YTH domain-containing protein 2; c-Myc: c-Myelocytomatosis; LCN2: Neutrophil gelatinase-associated lipocalin; Arg1: Arginase-1; AD: Alzheimer's disease; JunB: Transcription factor JunB; FMT: Fibroblasts transdifferentiate into myofibroblasts; ZGA: Major zygotic genome activation; YBX1: Y-box-binding protein 1; YY1: Zinc finger transcription factor YY1; BCa: Carcinoma of bladder; METTL15: 12S rRNA N4-methylcytidine (m4C) methyltransferase; DML: Demethylzeylasteral; LCSC: Liver cancer stem cell; Neu2: Vasopressin-neurophysin 2-copeptin; GBM: Glioblastoma; TMZ: Temozolomide; PD-L1: Programmed cell death 1 ligand 1; AML: Acute myeloid leukemia; PKM2: Pyruvate kinase isozyme type M2.

observation offered a promising model for investigating the interplay between mitochondrial metabolism and histone lactylation [43].

In tumor progression, similar to H3K18la, H3K9la has recently been implicated in promoting hepatocellular carcinoma (HCC) progression. A triterpenoid anti-tumor compound, demethylzeylasteral (DML), has been shown to inhibit liver cancer stem cell (LCSC) tumorigenesis by disrupting the lactylation of metabolic stress-related histones [44].

In the regulation of cell differentiation, inhibiting lactic acid intake or production can decrease lactic acid levels and impair myoblast differentiation. Specifically, during myoblast differentiation, lactic acid preferentially increased H3K9la levels and accumulated in the promoter region of Neu2. This underscored the essential role of H3K9la in Neu2-mediated myoblast differentiation [45].

Additionally, lactylation had been found to be upregulated in relapsed glioblastoma (GBM) tissues and temozolomide (TMZ)-resistant cells, particularly at H3K9. Mechanistically, H3K9la induced TMZ resistance in GBM cells by promoting Luc7L2-mediated retention of MLH1 intron 7 [46]. Targeting H3K9la could potentially offer a novel approach to overcoming TMZ resistance and enhancing its clinical therapeutic efficacy.

3.3. H4K5la & H4K12la

Research into the epigenetic effects of specific histone lactylation sites was still emerging. Apart from the H3K18 and H3K9 sites discussed earlier, other potential histone lysine lactylation sites had been identified to regulate specific genes and signaling pathways, influencing disease progression.

Various post-translational modifications such as ubiquitination, phosphorylation, glycosylation, and palmitoylation had been reported to regulate PD-L1 expression [47]. Notably, the tumor-derived metabolite lactate also influenced PD-L1 expression [48,49], suggesting a potential link between histone lactylation and PD-L1 regulation. One study demonstrated that lactic acid accumulation promoted the nuclear translocation of E3BP and H4K5la, leading to transcriptional activation of PD-L1. This revealed the involvement of the STAT5-lactate-PD-L1 signaling network in acute myeloid leukemia (AML) progression [50], indicating E3BP and H4K5la as potential metabolic targets in tumor progression. Furthermore, PD-1/PD-L1-based immunotherapy may represent a novel treatment strategy for AML characterized by STAT5-induced vigorous glycolysis and lactic acid accumulation. Additionally, methyltransferase METTL15 had shown significant inhibition of H4K12la alongside H3K9la [19], highlighting ongoing research opportunities in metabolic regulation of histone lactylation. Recent research also indicated elevated histone H4K12la levels in microglia near Aβ plaques in AD. Mechanistically, a glycolysis/H4K12la/PKM2 positive feedback loop exacerbated microglial dysfunction in AD patients, suggesting that disrupting this loop through histone lactylation may offer a potential treatment approach for AD [51] (Fig. 2.).

4. Histone lactylation 'writers' and 'erasers': histone lactase and de-lactase

4.1. Writer

4.1.1. CBP/p300

Histone acetyltransferase (p300) had been identified as an enzyme that potentially promotes histone lactylation [3,52]. Due to their sequence homology and functional overlap, the histone acetyltransferases CBP and p300 were often studied together and referred to as the CBP/p300 complex [53]. Initially, CBP/p300 were recognized for their acetylation catalytic activity. For instance, CBP/p300-mediated acetylation of H3K56 was a critical histone modification that links chromatin assembly with DNA synthesis, cell proliferation, and cancer [54].

In recent years, CBP/p300 has emerged as a significant driver of tumorigenesis. Although earlier studies suggested that the loss of CBP/p300 could promote tumorigenesis, more recent findings indicated that CBP/p300 was often overexpressed in cancer cells, including drug-resistant variants, where it activated oncogene transcription and induced cancer cell proliferation, metastasis, immune escape, and drug resistance [53].

A recent study on lung adenocarcinoma (LUAD) found that the CBP/p300 inhibitor SGC-CBP30 reduced the expression of UPP1, H3K27ac, and H3K9ac. SGC-CBP30 simultaneously inhibited cell proliferation and induced apoptosis, effects that could be reversed by UPP1 overexpression both in vitro and in vivo [55]. This suggested that CBP/p300 not only promoted the acetylation of multiple histone sites but also regulated non-histone acetylation. For instance, CBP/p300-related factor PCAF-mediated acetylation of LDHB K82 significantly reduced LDHB activity, impaird hepatic lactate clearance, and led to lactate accumulation [56]. This underscored the broad and site-nonspecific role of CBP/p300 in acetylation of both histone and non-histone proteins. This suggested that CBP/p300 may also exhibit similar characteristics in its protein lactation activity, including a diversity of modification sites and protein types.

Recent studies had discovered that CBP/p300 exhibited lactate catalytic activity and played a role in epigenetic regulation. The transfection of p300 siRNA into cells resulted in decreased histone lactation and acetylation levels [57], providing direct evidence of p300's histone lactate transferase function. Lactic acid was transported into cells via monocarboxylate transporter 1 (MCT1), which upregulated CBP/p300-mediated histone lactation, thereby activating the TLR4/NF-κB signaling pathway and ultimately causing breast inflammation [58]. Similarly, CBP/p300's lactation-promoting effect extended to non-histone proteins, such as the transcription factor YY1, which had been shown to be lactated at lysine 183 (K183) and regulated by p300. Highly lactated YY1 directly enhanced FGF2 transcription and promoted angiogenesis. Furthermore, overexpression of p300 increased YY1 lactation and enhanced angiogenesis in vitro [59]. During multimicrobial sepsis, macrophages uptook extracellular lactic acid via monocarboxylate transporters (MCTs), promoting the lactation of the damage-associated molecular pattern (DAMP) molecule HMGB1 through a CBP/p300-dependent mechanism [60,61]. Lactated HMGB1 was released from macrophages via exosomal secretion, thereby

increasing endothelial cell permeability [62]. Overall, CBP/p300 was currently regarded as a broad-acting lactate transferase, capable of promoting histone and non-histone lactation. There was no evidence of site specificity, and its effects were mediated through epigenetic regulation of specific gene transcriptional activation or direct regulation of molecular activity.

The exact mechanism of CBP/p300 as a histone lactation modification enzyme remained unclear. However, by examining its role as an acetylase, we may uncover the specific processes and mechanisms by which CBP/p300 catalyzed histone lactation. The intrinsic histone acetyltransferase (HAT) activity of the CBP/p300 protein originated from its HAT domain, primarily inducing the acetylation of histones H3 and H4 [63,64]. The catalytic core of the CBP/p300 protein comprised four parts: the bromine domain, HAT domain, cysteine/histidine-rich region (including PHD and RING), and the zinc-finger (ZZ) domain. The bromine, HAT, and PHD domains formed a single unit, linked by the RING and ZZ domains [65–67]. The acetylation of H3 and H4 lysine [66,68,69] necessitated the binding of H3 and H4 lysine. The ZZ domain recognized the H3 tail and promoted acetylation at the H3K27 and H3K18 sites [66]. The HAT activity of acetyltransferase involved transferring the acetyl group from acetyl-CoA to the N-terminal lysine ε-amino group of histone proteins. In a similar process, L-lactic acid was converted to L-lactate coenzyme A [70], with p300 transferring lactate Kylase A produced by lactate to the lysine residues on the histone tail [3].

4.1.2. AARS1

Historically, acyltransferases such as p300 had been regarded as the primary catalytic enzymes mediating the lactylation of substrate proteins. In this catalytic process, p300 transferred the lactate group from the donor molecule Lactyl-CoA to the lysine residue of the substrate protein [3,70]. However, the mechanism by which lactate was converted into Lactyl-CoA in mammalian cells remained poorly understood. Given that the concentration of Acetyl-CoA in tumor cells was over 1000 times higher than that of Lactyl-CoA [70], it suggested that the primary function of p300 remained the catalysis of acetylation, with its lactate transferase activity potentially inhibited. This raised the question of whether p300 functioned as a true lactate transferase.

Recent research indicated that alanyl-tRNA synthetase 1 (AARS1) acted as a lactate transferase, employing lactic acid and ATP to directly catalyze protein lactylation [71]. Due to AARS1's role in catalyzing the attachment of L-alanine to tRNA, and the structural resemblance between L-lactic acid and L-alanine, it was proposed that AARS1 can also bind L-lactic acid, utilizing it as a donor for lactylation modification. The study further confirmed that AARS1 can directly lactylate histone H3K18 using lactic acid and ATP. The process primarily involved two steps: 1) the production of active lactate-AMP and pyrophosphate (PPi) from lactic acid and ATP; 2) the transfer of the lactate group from lactate-AMP to the lysine residue of the substrate [71].

Another study on AARS1 reported its use as an intracellular lactate sensor that directly bonded to lactate and catalyzed global lysine

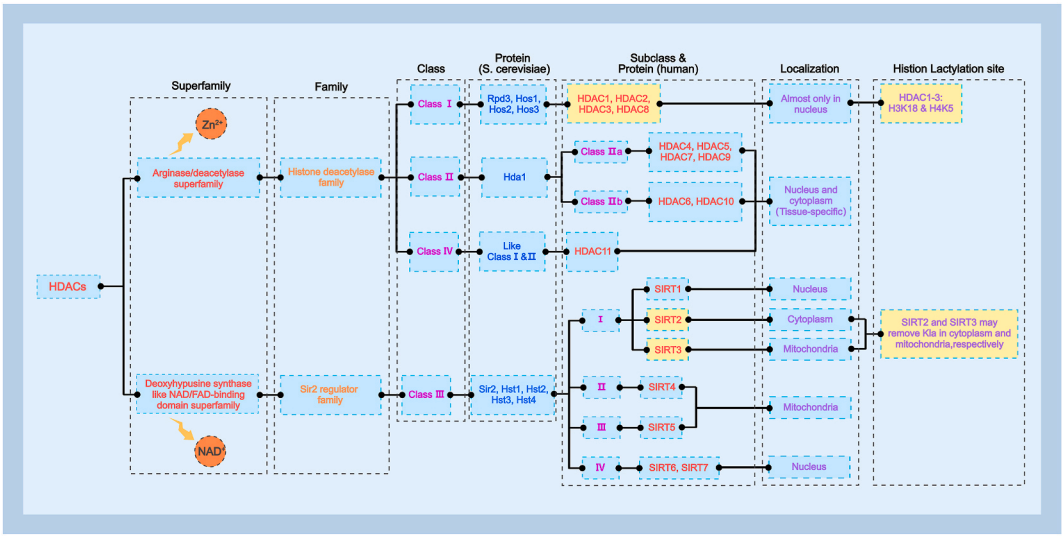

Fig. 3. Classification map of HDACs and sirtuins.
The 18 human HDAC enzymes were classified into the Zn^{2+}-dependent arginase/deacetylase superfamily and the NAD^{+}-dependent deoxyhypusine synthase-like NAD/FAD-binding domain superfamily based on their dependence on metal ions or substrates for their deacetylase function. These were further categorized into the histone deacetylase family and the Sir2 regulator family. Based on yeast protein analogues, HDACs were divided into four classes. Class I RPD3-like proteins, including HDAC1, HDAC2, HDAC3, and HDAC8, were characterized by universal expression and primarily nuclear localization. Class II HDA1 proteins, including HDAC4, HDAC5, HDAC6, HDAC7, HDAC9, and HDAC10, exhibited tissue-specific expression patterns and were localized in both the nucleus and cytoplasm. This class of HDACs was further subdivided into two subcategories: IIa, including HDAC4, HDAC5, HDAC7, and HDAC9, and IIb, comprising HDAC6 and HDAC10. Class III sirtuin proteins included SIRT1, SIRT2, SIRT3, SIRT4, SIRT5, SIRT6, and SIRT7. SIRT1 and SIRT2 were located in both the nucleus and cytoplasm, while SIRT3, SIRT4, and SIRT5 were found in mitochondria. SIRT6 and SIRT7 were predominantly localized in the nucleus. Class IV contained HDAC11, predominantly found in the nucleus and cytoplasm. Recent studies indicated that HDAC1-3 can remove H3K18la and H4K5la, while SIRT2 and SIRT3 may function as lysine de-lactylation enzymes in the cytoplasm and mitochondria, respectively, based on their subcellular localization.

lactylation, which was an ancient and conserved function. AARS1 mediated site-specific lactylation of p53 at K120 and K139 within its DNA binding domain (DBD), thereby hindering its liquid-liquid phase separation, DNA binding, and transcriptional activation, ultimately promoting tumor development [72].

AARS1 might function as a genuine lactate transferase, catalyzing histone lactylation and revealing the diversity of histone lactylation enzymes. It was possible that many unknown molecules also function as site-specific histone lactylation enzymes. Additionally, AARS1 offered a novel target and concept for tumor therapy, emphasizing the significance of lactic acid modification in tumorigenesis and development.

4.2. Eraser

4.2.1. HDACs & Sirtulin

Some histone deacetylases discovered to date also exhibited delactating effects. Histone deacetylases (HDACs) were enzymes that catalyzed the removal of acetyl groups from lysine residues in both histone and non-histone proteins [73]. In humans, there were 18 HDAC enzymes classified into four classes: Class I RPD3-like proteins include HDAC1, HDAC2, HDAC3, and HDAC8, which were characterized by ubiquitous expression and predominantly nuclear localization [73]. Class II HDA1 proteins, including HDAC4, HDAC5, HDAC6, HDAC7, HDAC9, and HDAC10, exhibited tissue-specific expression patterns and were localized in both the nucleus and cytoplasm [74]. Beyond regulating histone-mediated gene expression, this class of HDACs also modulated the activity of various intracellular components via post-translational modifications. These enzymes were further subdivided into two categories: IIa (HDAC4, HDAC5, HDAC7, HDAC9) and IIb (HDAC6, HDAC10) [75]. Class III sirtuin proteins included SIRT1, SIRT2, SIRT3, SIRT4, SIRT5, SIRT6, and SIRT7. SIRT1 and SIRT2 were localized in the nucleus and cytoplasm, while SIRT3, SIRT4, and SIRT5 were present in the mitochondria. SIRT6 and SIRT7 were primarily found in the nucleus [76]. Class IV comprised HDAC11 [74,77,78], which was primarily localized in the nucleus and cytoplasm [79] (Fig. 3.).

Note that the classification of different categories and the "class" in protein structure classification were not the same concepts. All HDACs belonged to the α and β protein classes, yet different types of HDACs aroused through single nucleotide polymorphisms or alternative splicing. Protein isomers produced by alternative splicing of the same transcript had different biological activities and were called isoforms (i.e., several different forms of the same HDAC protein). These isoforms shared the same genetic origin. HDACs 1–11, however, were each derived from different genes. Despite their functional relatedness, they were not subtypes of each other [73].

A comparison of the structures of various class I and class II HDACs, along with HDAC homologs from different species, to human classical HDACs revealed significant homology. This homology indicated a conserved set of active site residues and a common mechanism for metal-dependent hydrolysis of acetylated substrates [73]. Histone deacetylases (HDAC1-11, belonging to classes I, II, and IV) required Zn^{2+} [80], in contrast to sirtuins (SIRT1-7, Class III HDACs) which required NAD + as a co-substrate [81] for the deacetylation of acetyllysine residues on protein substrates. This process resulted in the formation of nicotinamide, a deacetylation product, and the metabolite 2′-O-acetyl-ADP-ribose [73].

HDACs were essential for chromatin remodeling and gene expression regulation via specific epigenetic processes [82], whereas the deacetylation of non-histone proteins governed various cellular processes. As with many crucial cellular enzymes, HDACs are subject to various regulatory mechanisms, such as protein-protein interactions and post-translational modifications [83]. Aberrant HDAC activity was implicated in numerous human diseases. Several studies indicated that HDACs were involved in tumor development and progression by means of dysregulated mutations and abnormal gene expression [74,77,78]. Class I HDACs, for example, showed high expression in Ewing's sarcoma (EwS), and patients with increased levels of these HDACs had lower overall survival rates [84]. Therefore, regulating HDACs could be an effective strategy for cancer treatment. Currently, a broad spectrum of HDAC inhibitors (HDACi), characterized by diverse chemical structures and target specificities, had been developed and tested in various malignancies. For example, in vivo and in vitro experimental models from several melanoma studies, along with subsequent clinical trial results, had demonstrated that HDACi can significantly enhance patient response and extend survival [85–89].

Histone lysine acetylation was a highly reversible process, with lysine residues being acetylated by histone/lysine acetyltransferases (HATs/KATs). Histone acetylation was a dynamic process, with histone deacetylation enzymes complementing histone acetyltransferases. This acetylation was regulated by a delicate balance between the reversible activities of these two enzyme families [75]. Similarly, histone lactylation, an important epigenetic modification, may also display dynamic and reversible characteristics, regulated by corresponding delactylation enzymes. Certain HDAC isoenzymes demonstrated preferential enzymatic activity for non-acetyl lysine acylation. For instance, SIRT5 was a potent lysine demalonylase, desuccinylase, and deglutarylase but not a deacetylase [90–93]. In contrast, HDAC8, HDAC11, SIRT2, and SIRT6 exhibited strong long-chain acyl modification activity [94–97]. Besides their deacetylase activity, HDAC1-3 can also remove ε-N-crotonyllysine (Kcr) and ε-N-D-β-hydroxybutyryllysine [K(D-bhb)] PTMs [98,99]. Therefore, lysine deacylase enzymes could potentially catalyze the removal of histone lactylation modifications. Zhao et al. found that class I HDAC1-3 significantly reduced the overall levels of Kac and Kla in histone proteins, as well as the L-lactylation levels of H3K18 and H4K5 [100]. This indicated that HDAC1-3 function as potent lysine de-lactases in vitro, with HDAC1 and HDAC3 showing site-specific activity for histone de-lactylation processes. Additionally, the study discovered that SIRT2 and SIRT3 can remove lactylation modifications from purified histones, potentially due to the subcellular localization of various HDACs. SIRT2 and SIRT3 potentially served as lysine delactylation enzymes in the cytoplasm and mitochondria, respectively, unlike HDAC1-3, which were absent from these compartments [100].

Currently, research on histone delactylation remained in its preliminary stages. Histone delactylation identified thus far was site-specific, implying the diversity of histone delactylation, and suggesting the presence of other unknown delactylation enzymes in cells. Meanwhile, the mechanism of histone delactylation remained unclear, and this represented only the initial step in studying the

elements involved in the histone delactylation process.

In summary, CBP/p300 has a well-established role in promoting histone lysine lactation modification, although no site-specific function has been identified, making it a widely recognized and commonly studied histone lactate enzyme. AARS1 was a newly identified enzyme that catalyzed H3K18 lactation and also mediated the lactation modification of non-histone proteins, such as p53. HDAC1-3 have been shown to be effective lysine de-lactating enzymes in vitro. HDAC1 and HDAC3 can reduce the lactation levels of H3K18 and H4K5, respectively, demonstrating site-specific activity. Additionally, SIRT2 and SIRT3 demonstrated lysine de-lactating activity in the cytoplasm and mitochondria, depending on their subcellular localization. Currently, there remained a gap in the research on histone lactation-related enzymes. Identifying an effective and highly specific enzyme could help clarify the precise mechanisms underlying histone lactation modification and provide a novel target for targeted disease therapy.

5. Histone lactylation and tumors

Histone post-translational modifications (HPTMs) had been definitively shown to play roles in gene activation and silencing in numerous diseases, particularly cancer. The latest identified HPTM, histone lactylation, was also pivotal in tumor development. Warburg's findings linked lactic acid metabolism to the development and progression of malignant tumors [16]. The accumulation of lactic acid in the tumor microenvironment (TME) represented a key tumor phenotype that had garnered significant attention, and elevated lactate levels can induce histone lactylation [101]. Increased lactate levels in the tumor microenvironment were accompanied by a surge in Arg1 expression, which was associated with primary tumors in multiple systems and served as a marker of M2 macrophages [102,103]. Research by Zhang et al. pinpointed numerous precise histone Kla sites in human HeLa cells and mouse BMDMs [3]. These findings suggested that many cells in the TME, including stromal cells, tumor parenchymal cells, and immune cells, were regulated by lactate-induced histone lactylation. Yu et al. found that H3K18la accelerated the occurrence of ocular melanoma by promoting the expression of YTHDF2, an N6-methyladenosine interpretation protein [28]. This was the first identification of the tumor-promoting effect of histone lactylation and confirmed its involvement in cancer development. Subsequent studies had also demonstrated that histone lactylation played an effective role in promoting the occurrence of breast cancer [29], bladder cancer [30], colorectal cancer [42], and liver cancer [44]. Notably, Lucia et al. found that H3K18la induced by increased lactic acid inhibited the progression of uveal melanoma (UM) [104]. Additionally, Liu J et al. observed that during breast cancer treatment with catalpol, lactate levels increased significantly, inducing cell apoptosis [105]. This suggested that the role of histone lactylation in tumorigenesis and development was multifaceted, potentially producing diverse effects on various cancer types, different genes, and distinct biological processes. However, the molecular mechanisms underlying this phenomenon remained unclear.

The aforementioned studies suggested that metabolic switches represented promising targets for tumor therapy, emphasizing the need to focus on the core metabolite lactate in the TME and its mediated histone lactylation modification. This introduced a new strategy for tumor therapy through metabolic reprogramming and epigenetics, enhancing the TME by modulating histone lactylation, thereby influencing cancer cell plasticity.

6. Discussion

With the ongoing advancement of metabolomics and epigenomics, numerous epigenetic modifications had been discovered, revealing the mechanisms and influencing factors of biological processes such as metabolism, development, and disease through the exploration of their interactions. Previously regarded as metabolic waste, lactic acid has been identified as a crucial energy source and signaling molecule, with its production and utilization conditions well-defined. Epigenetic modifications derived from lactic acid demonstrated a more potent effect than traditional modifications like methylation and acetylation in some biological processes. A prime example was the strong influence of lactylation on the formation of the tumor microenvironment. The Warburg effect, a key metabolic feature of tumors, prioritized glycolysis, resulting in the accumulation of lactic acid, a crucial glycolysis product, in large quantities within the tumor microenvironment, thereby inducing lactylation. This process established a logical connection between lactate modification and the regulation of cancer progression. Similar to traditional epigenetic modifications, lactylation can modify histones, alter chromatin spatial conformation, affect DNA accessibility, directly regulate gene transcription activation, and bridge metabolic reprogramming with epigenetic inheritance [106].

The identification of 26 histone Kla sites in human HeLa cells and 16 sites in mouse BMDMs by Zhang et al. [3] had significantly advanced our understanding of the molecular mechanisms underlying histone lactylation. Identifying the Kla substrate and its exact sites will help elucidate the molecular mechanisms and influencing factors of the specific biological processes regulated by Kla, providing new insights into biological growth and development, disease onset and progression, and potential treatments. At present, studies on site-specific histone lactylation remained in their infancy, and H3K18, the most extensively investigated site, was recognized as both a marker of active promoters and tissue-specific active enhancers [27]. H3K18la regulated the transcriptional activation of numerous critical genes, influencing disease development, tissue growth, cell differentiation, and drug resistance. Moreover, H3K9, H4K5, and H4K12 had also been recognized as significant histone lactylation sites exhibiting similar epigenetic effects. Histone lactylation may exhibit variable regulatory effects in different biological contexts, and the discovery of numerous lactylation sites enhanced the complexity of these effects, indicating promising prospects for the study of histone lactylation, metabolic reprogramming, and epigenetic inheritance.

As with traditional epigenetic modifications, histone lactylation was expected to have "readers," "writers," and "erasers" to facilitate the dynamic balance of epigenetic regulation. Currently, studies on lactylation "writers" based on lysine acetylation modification had identified histone acetyltransferase p300 as a potential enzyme promoting histone lactylation [3,52]. As research

progressed, a new histone lactylase, AARS1, had also been identified [71,72]. HDACs were currently regarded as "erasers" of histone lactylation [99], though the mechanism of histone delactylation remained unclear. Moreover, there was still a lack of studies on lactylation "readers." Numerous studies suggested that there were likely multiple "writers," "readers," and "erasers" that functioned in both site-specific and non-specific manners during histone lactylation, indicating that this field required further exploration.

At present, studies on histone lactylation were in their nascent phase, with a primary emphasis on how lactylation influenced the behavior of tumor cells in the tumor microenvironment. However, there was a lack of in-depth studies on the mechanisms of site-specific modifications and the clinical effects induced by histone lactylation. Thus, it was urgently needed to provide a comprehensive description of the specific mechanisms of histone lactylation and its connection with metabolic reprogramming and cell fate. Interestingly, histone lactylation and histone acetylation, beyond their functional similarities, shared the same enzyme system. This led us to investigate whether a correlation existed and to identify the signals regulating this process, which were among the urgent questions in the field. In addition, the epigenetic effects of different histone lactylation sites across various biological models needed further exploration and summarization. Finally, identifying the "writers," "readers," and "erasers" involved in histone lactylation was essential to elucidate the processes of its occurrence and removal. In conclusion, histone lactylation, as a novel epigenetic modification, presented significant research potential and merited further investigation. Regarding the study of mechanisms, research will uncover the fundamental process of histone lactylation modification, its link to the interplay between epigenetic regulation and metabolic reprogramming, and its role in shaping the TME to influence immune responses and anti-tumor activity. In practical applications, histone lactylation could be leveraged to modulate disease progression and physiological processes, facilitating the development of site-specific drugs, novel therapeutic strategies, and clinical translation.

Funding

This research was supported by funding as followed:

1. The 1.3.5 Project for Disciplines of Excellence (Grant ZYJC21015 to Y.C.)
2. The National Natural Science Foundation of China (No.31771549 to Y.C.)
3. The Natural Science Foundation of Sichuan Province (Grant 2024NSFSC0746 to Y.C.)
4. The Natural Science Foundation of Sichuan Province (Grant 2024NSFSC1947 to W.Z.)

CRediT authorship contribution statement

Yunhao Yang: Writing – review & editing, Writing – original draft, Conceptualization. **Nanzhi Luo:** Writing – original draft. **Zhipeng Gong:** Investigation. **Wenjing Zhou:** Investigation. **Yin Ku:** Investigation. **Yaohui Chen:** Writing – review & editing, Conceptualization.

Declaration of competing interest

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

Acknowledgements

Figs. 1 and 3 were created with medpeer.cn.
Fig. 2 was created with figdraw.com.
No data was used for the research described in the article.

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