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REVIEW

Histone Lactylation in Diseases: Regulation by Traditional Chinese Medicine and Therapeutic Implications

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Abstract: Histone lactylation, as a common post-translational modification (PTM), is crucial in diseases. Aberrant histone lactylation has been linked to disease pathogenesis, thus positioning it as a therapeutic target. This review summarizes the bidirectional relationship between histone lactylation and diseases, emphasizing how Traditional Chinese medicine (TCM) regulates lactate levels to restore histone lactylation homeostasis. Mechanistically, TCM modulates histone lactylation through dual regulation of lactyltransferases and lactate metabolism, thereby influencing disease progression in inflammatory, metabolic, and neoplastic disorders. Notably, TCM is characterized by unique advantages of cost-effectiveness, high efficacy, and minimal adverse effects. For diseases with established drug resistance, TCM offers a promising therapeutic alternative in managing drug-resistant illness by regulating histone lactylation. This review is conducive to understanding the relationship between histone lactylation and disease. TCM effectively treats diseases through the regulation of histone lactylation, thereby highlighting its potential for disease treatment application.

Keywords: histone lactylation, disease, Traditional Chinese medicine, mechanism, therapeutic target

Introduction

Histone lactylation, which is a product of glycolysis and is regulated by lactate, has received widespread attention in recent years.[1] As a prevalent post-translational modification (PTM), lactate-induced histone lactylation significantly impacts the etiology and development of diverse diseases, especially cancer. For example, regulating histone lactylation can promote cancer cells' invasion and migration,[2] and can accelerate liver fibrosis progression,[3] and induce the pyroptosis.[4] Interestingly, given the widespread occurrence of histone lactylation across diverse cell types, interventions directed at this process have the potential to exert a broad range of effects.[5] For example, specific interventions to regulate the histone lactylation process could inhibit liver fibrosis.[6] Therefore, as a newly-proposed PTM, histone lactylation not only paves the way for exploring histone lactate's role in diseases but also signals a new approach for disease treatment.

What is known includes the mechanisms of histone lactylation (Figure 1) and its mechanistic role in disease (Figure 2). Lactate derived from abnormal glycolysis (eg, the Warburg effect in cancer) serves as a substrate for lactyltransferases like p300, driving aberrant histone lactylation. Traditional Chinese medicine (TCM) has a long-standing history, featuring unique theories and extensive experience.[7] In recent years, TCM research has explored the effect of natural medicines on histone lactylation and made certain progress. An increasing number of TCMs and their various dosage forms and preparations have shown efficacy in common diseases by regulating histone lactylation. For example, Sal B has demonstrated efficacy by inhibiting lactate dehydrogenase A (LDHA) to reduce lactate production, altering histone lactylation, and exerting therapeutic potential in inflammatory liver diseases.[8]

TCM and its active ingredients possess distinct advantages, including low cost, high efficacy, and minimal side effects.[9,10] For example, preclinical studies have shown that DML exhibits no biotoxic effects in nude mouse tumor xenograft models, highlighting its potential as a safe and effective adjuvant anticancer agent.[11] This attribute is particularly valuable in diseases

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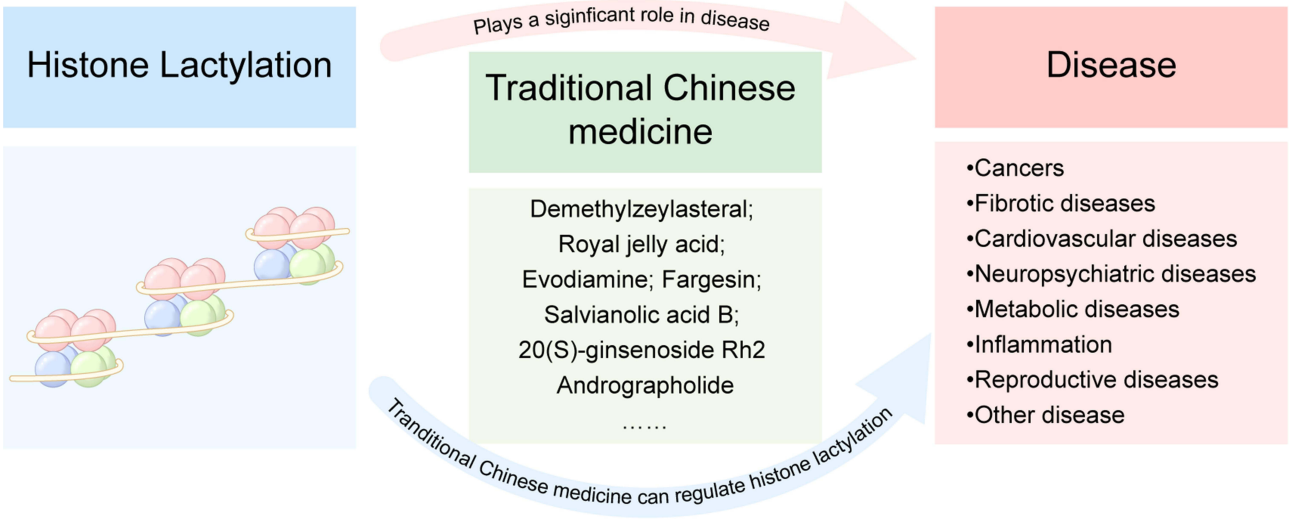
Graphical Abstract



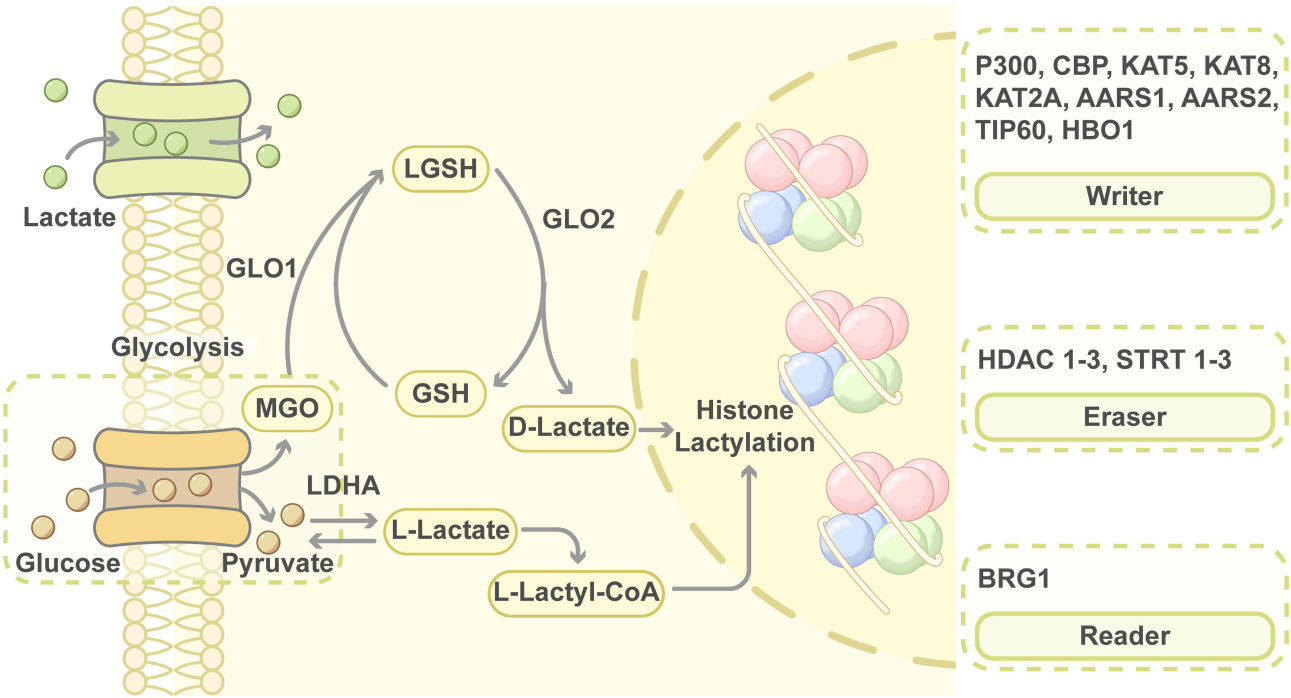


Figure 1 Mechanisms of histone lactylation and regulatory enzymes.
Abbreviations: GLO1, glyoxalase 1; LGSH, lactoylglutathione; GSH, Glutathione; MGO, methylglyoxal.

with established drug resistance, where conventional therapies often fail to achieve durable responses. In advanced prostate cancer (PCa), for instance, most anti-angiogenic and immunotherapeutic strategies yield limited remission, whereas TCM offers a promising alternative.[12,13] Evodiamine inhibits the lactylation of HIF1A histones induced by lactate. Subsequently, it significantly inhibits both the angiogenesis driven by Sema3A and the transcriptional expression of PD-L1, inducing ferroptosis in PCa cells.[14] Thus, TCM presents a novel therapeutic option in drug-resistant malignancies.

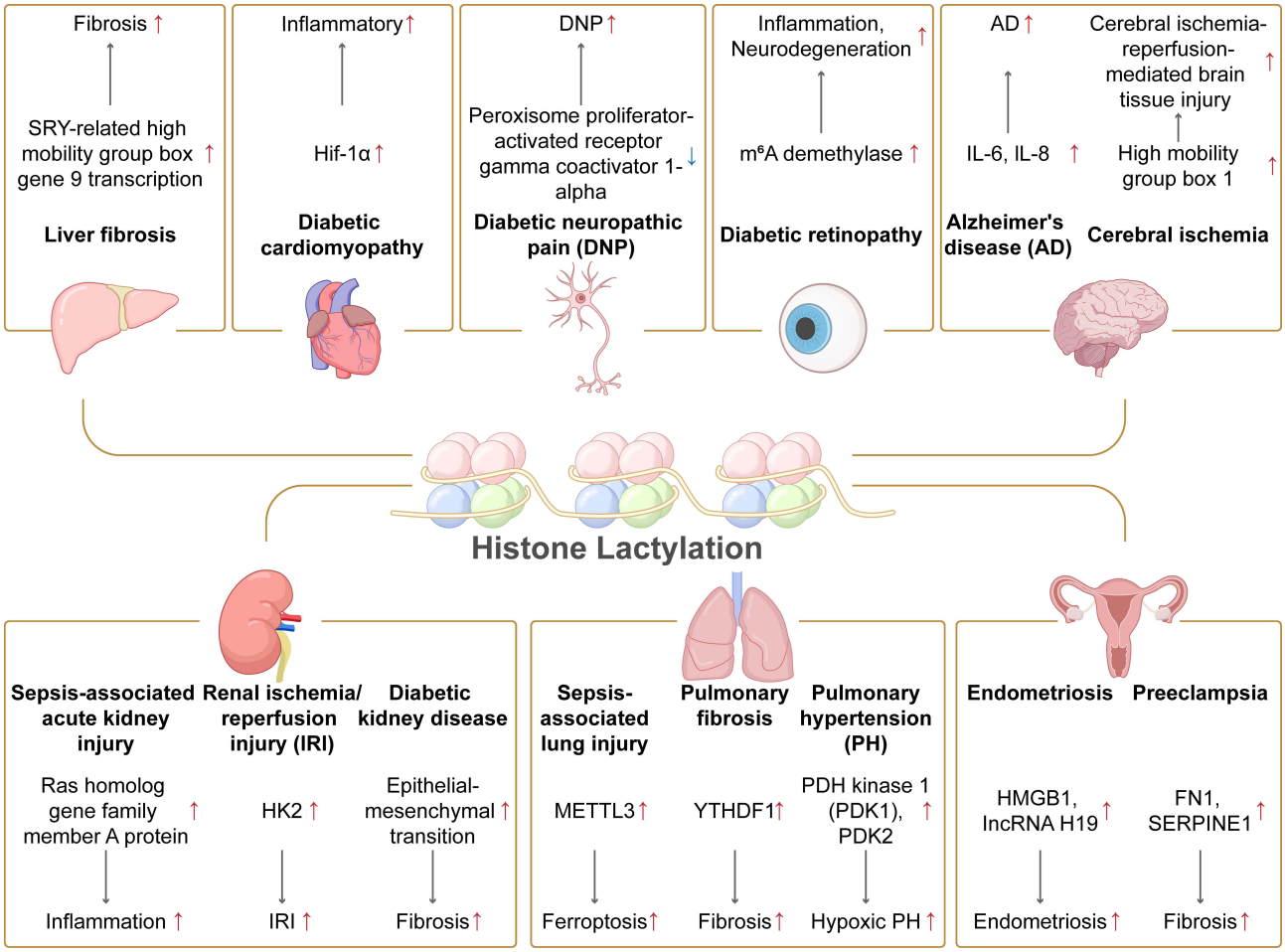


Figure 2 Mechanisms of histone lactylation in selected non-oncological diseases. For example, in liver fibrosis, aberrant histone lactylation leads to the upregulation of SRY-related high mobility group box gene 9 transcription, resulting in fibrosis; in endometriosis, HMGB1 and lncRNA H19 are upregulated, resulting in fibrosis.
Abbreviations: HIF-1α, hypoxia-inducible factor 1-alpha; HK2, hexokinase 2; METTL3, methyltransferase-like 3; HMGB1, high-mobility group box 1, a protein widely distributed in body tissues and organs.

What remains unknown, however, is that no comprehensive review has yet synthesized the mechanistic links between TCM-mediated lactylation modulation and therapeutic outcomes. Clinical translation of TCM-based histone lactylation regulation is hindered by a lack of systematic reviews on preclinical evidence.

This review aims to summarize how histone lactylation relates to diseases and emphasize that the regulation of histone lactylation can treat diseases. We also summarize TCM treatment of common diseases by regulating histone lactylation. These explorations will help develop an effective treatment strategy to provide a useful reference for related research.

Histone Lactylation and Disease

Cancers

Aberrant lactylation has been discovered as a driver of disease pathogenesis, linking metabolic reprogramming to epigenetic dysregulation (Table 1). This section elucidates the mechanisms by which dysregulated histone lactylation fuels tumor progression through enhanced oncogene expression, induction of immune evasion, and acquisition of drug resistance (Figure 3).

In non-small cell lung cancer (NSCLC), histone lactylation promotes cellular senescence and telomerase regulation, which plays a role by regulating the expression of telomerase reverse transcriptase.[49] Another study showed that histone

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Table 1 Histone Residues Modified by Lactylation and Their Known Biological Significance

Histone Residues	Species	Biological Significance	References
H2K108	Human and mice	NR	[15,16]
H2K11	Human and mice	NR	[15,16]
H2K115	Human and mice	NR	[15,16]
H2K116	Human	NR	[15,16]
H2K120	Human	NR	[15,16]
H2K13	Human	NR	[15,16]
H2K15	Human and mice	NR	[15,16]
H2K16	Human and mice	NR	[15,16]
H2K20	Human and mice	NR	[15,16]
H2K23	Human	NR	[15,16]
H2K43	Human	NR	[15,16]
H2K5	Human and mice	NR	[15,16]
H2K85	Human and mice	NR	[15,16]
H3K14	Mice	Drives EMT; promotes ferroptosis in vascular ECs by targeting promoter regions of ferroptosis-related genes (TFRC and SLC40A1) under LPS stimulation	[15–18]
H3K18	Human and mice	Promotes CRC liver metastases; mediates resistance to bevacizumab and cisplatin; upregulates c-Myc in breast cancer cells; drives GBM cell self-renewal; induces liver fibrosis progression; promotes YTHDF1 transcription and neuronal protein 3.1 mRNA m6A methylation; triggers EndMT-induced atherosclerosis; enhances NF-κB signaling in microglia to mediate inflammation and apoptosis; promotes METTL3 transcription and anti-inflammatory effects	[3,15,16,19–31]
H3K23	Human and mice	NR	[15,16]
H3K27	Human and mice	NR	[15,16]
H3K56	Mice	Acts as an epigenetic regulator to promote oncogene expression	[15,16,32]
H3K79	Human	NR	[15,16]
H3K9	Human and mice	Enriched at angiogenic gene promoters to promote transcription; drives myoblast differentiation; activates LUC7L2 transcription; facilitates LAMC2 expression for ESCC invasion; regulates hepatocellular carcinoma stem cell tumorigenicity and progression; correlates with angiogenesis gene activation; promotes microglia M1 polarization and inflammation; enhances HIF-1α transcription	[15,16,33–40]
H4K12	Human and mice	Increases glycolytic activity; enriches at NF-κB signaling gene promoters (Ikbkb, Rela, Relb) to activate transcription; facilitates Hif-1α transcription; specifically suppresses SLFN5 expression in TNBC cells; triggers NLRP3 transcriptional activation	[15,16,41–45]
H4K16	Human	NR	[15,16]
H4K18	Mice	NR	[15]
H4K31	Human and mice	NR	[15,16]

(*Continued*)

Table 1 (Continued).

Histone Residues	Species	Biological Significance	References
H4K5	Human and mice	Links to glycolysis activation via low expression of DNAJC12, a metabolic regulatory protein	[15,16,46]
H4K77	Human	NR	[15,16]
H4K8	Human and mice	Critically regulates astrocyte polarization; induces upregulation of key meiotic genes	[15,16,47,48]
H4K91	Human and mice	NR	[15,16]

Abbreviations: EMT, epithelial-mesenchymal transition; ECs, endothelial cells; CRC, colorectal cancer; GBM, glioblastoma; NF-κB, nuclear factor κB; METTL3, methyltransferase-like 3; ESCC, esophageal squamous cell carcinoma; HIF-1α, hypoxia-inducible factor 1-alpha; SLFN5, Schlafen 5; TNBC, triple-negative breast cancer; DNAJC12, a protein involved in metabolic regulation; NR, not reported.

lactylation-mediated down-regulation of HK-1 and up-regulation of IDH3G gene expressions NSCLC could promote cell proliferation and modulate cellular metabolism.[50] Concerning ocular melanoma, histone lactylation efficiently drives its development. It upregulates YTH N^6-methyladenosine RNA-binding protein 2 (YTHDF2) transcription, then induces the degradation of PER1 and TP53 mRNAs by binding to their N^6-methyladenosine (m^6A) sites, or boosts ALKBH3 through the N^1-methyladenosine demethylation of SP100A.[51,52] Notably, a recent study has elucidated that increased histone lactylation is closely associated with a poorer clinical status in clear cell renal cell carcinoma (ccRCC).[53] By inducing the activation of platelet-derived growth factor receptor β (PDGFRβ) expression, histone lactylation promotes the progression of ccRCC.[54] A study has elucidated that increased histone lactylation promotes hepatocellular carcinoma (HCC) development.[55] Specifically, histone lactylation upregulates endothelial cell-specific molecule 1 expression in HCC, which facilitates cell malignant phenotypes, tumor growth, and metastasis.[56] In addition, in colorectal cancer (CRC), elevated histone lactylation upregulates LINC00152 (a key oncogenic long noncoding RNA (lncRNA)), promoting CRC

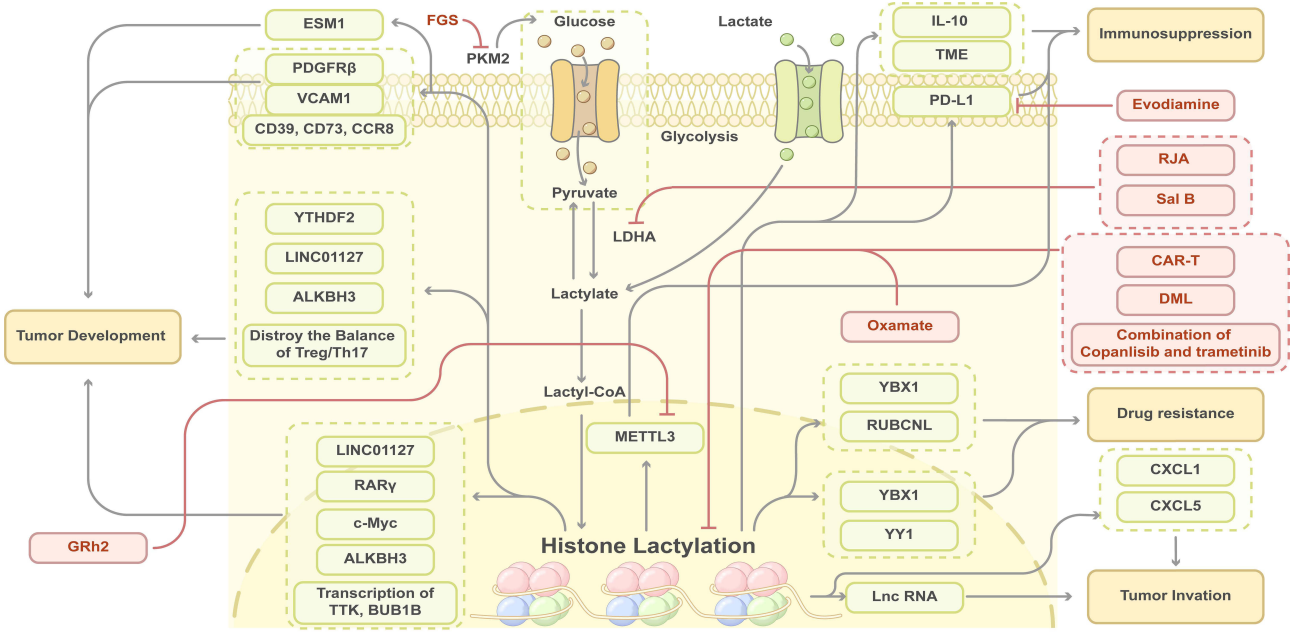

Figure 3 Histone lactylation production and its induction of tumor development, invasion, immunosuppression, and drug resistance are shown. Red text represents inhibitors in the pathway.

Abbreviations: GRh2, 20(S)-ginsenoside Rh2; ESM1, endothelial cell-specific molecule 1; PDGFRβ, platelet-derived growth factor receptor β; CCR8, C-C Chemokine Receptor 8; YTHDF2, YTH N6-methyladenosine RNA-binding protein 2; Treg, Regulatory T; RARγ, Retinoic Acid Receptor gamma; TTK, TTK protein kinase; BUB1B, BUB1 mitotic checkpoint serine/threonine kinase B; FGS, Fargesin; LDHA, lactate dehydrogenase A; TME, tumor microenvironment; PD-L1, programmed cell death-ligand 1; lncRNA, long noncoding RNA; Sal B, Salvianolic acid B; CAR-T, Chimeric antigen receptor-T; DML, Demethylzeylasteral; RJA, Royal jelly acid.

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cell invasion and migration.[2] Another finding is that increased histone H3 lysine 18 lactylation (H3K18la) levels are achieved through the activation of the Hippo pathway by G protein-coupled receptor 37, which results in the up-regulation of CXCL1 and CXCL5 and promotes CRC liver metastases.[26] Furthermore, histone lactylation also enhances the stability of Kcnk6 in a YTHDF2-dependent manner and inhibits Retinoic Acid Receptor gamma (RARγ) expression in macrophages through activation of TRAF6-IL-6-STAT3 signaling to promote colorectal carcinogenesis.[57,58] Elevated levels of H3K18la in CRC patients activated RUBCNL transcription in CRC, promoting resistance to bevacizumab.[25] In the context of colon cancer, histone lactylation promotes the methyltransferase-like 3 (METTL3) expression in Tumor-infiltrating myeloid cells (TIMs) to potently induce the immunosuppressive functions through the lactylation-METTL3-JAK1-STAT3 regulatory axis.[59] Additionally, histone lactylation promotes the malignant biological behavior by facilitating ubiquitin-specific peptidase 39 expression to target PI3K/AKT/HIF-1α signal pathway in endometrial carcinoma (EC).[60] Potassium Two Pore Domain Channel Subfamily K Member 1 was significantly up-regulated in human breast cancer, which can promote H3K18 lactylation in breast cancer cells via LDHA.[61] H3K18la enrichment can upregulate c-Myc (oncogenic transcription factor) expression in breast cancer cells, thereby enhancing breast cancer progression.[30] In pancreatic ductal adenocarcinoma (PDAC), histone lactylation potentially involves developing an immunosuppressive tumor microenvironment (TME) in liver metastasis (LMT), which shows enhanced immune evasion and weakened immune responses.[62] Histone lactylation also activates TTK protein kinase (TTK) and BUB1 mitotic checkpoint serine/threonine kinase B (BUB1B) transcription in pancreatic ductal adenocarcinoma cells for the first time, and TTK and BUB1B transcription drives the cell cycle and accelerates tumorigenesis.[63] Glucose transporter 3 (GLUT3) heightened the glycolysis process and augmented lactic acid generation in gastric cancer (GC) through modulating LDHA, which promoted lactylation in GC cells, and thus led to the promotion of the occurrence and progression of GC.[64] Another example is that the promotion of GC progression and metastasis by H3K18 lactylation-mediated vascular cell adhesion molecule 1 expression occurs via the AKT-mTOR-CXCL1 axis.[22] Intracellular lactate enhanced CD39, CD73 and C-C Chemokine Receptor 8 (CCR8) expressions through H3K18la, which perturbs the Treg/Th17 balance, and drives NF-κB-related LINC01127 expression, consequently promoting the self-renewal of glioblastoma (GBM) cells.[27,29] Besides, histone lactylation heightens the immunosuppressive function of macrophages in GBM by enhancing the expression of interleukin-10 (IL-10).[65] In acute myeloid leukemia (AML), histone lactylation serves as a promoting factor for programmed cell death-ligand 1 (PD-L1) expression, thereby leading to the induction of immunosuppression.[66] Although histone lactylation has been shown to facilitate the migration of ovarian cancer cells, the precise functions it plays in epithelial ovarian cancer (EOC) remain unclear.[67] H3K18la activates key transcription factors YBX1 and YY1 in patients with bladder cancer (BCa), leading to cisplatin resistance in BCa.[24]

Additionally, in the context of cancer, a instance of crosstalk between histone lactylation and other PTMs is exemplified by pyruvate dehydrogenase complex component X acetylation and its subsequent effect on H3K56la. Pyruvate dehydrogenase complex component X is acetylated at Lys488 by p300, a modification that impairs its binding to dihydrolipoyl transacetylase, thereby hindering pyruvate dehydrogenase complex assembly.[32] Pyruvate dehydrogenase complex inactivation triggered by acetylation promotes aerobic glycolysis, resulting in elevated intracellular lactate levels.[32] These increased lactate concentrations induce H3K56 lactylation, which in turn accelerates tumor progression.[32] These observations demonstrate that histone lactylation can potentially generating synergistic effects with other post-translational modifications and modulate the disease process.[32]

Fibrotic Diseases

Histone lactylation is indispensable in the activation of hepatic stellate cells (HSCs).[6] It has been found that the blockade of histone lactylation can alleviate liver fibrosis.[68] H3K18 lactylation functioned as a crucial inducer in the progression of liver fibrosis by enhancing SRY-related high mobility group box gene 9 transcription. This implies that the attenuation of histone lactylation could potentially serve as a novel therapeutic strategy for alleviating liver fibrosis.[3] In pulmonary fibrosis, histone lactylation induced by lactate has been shown to enhance the profibrotic phenotype in macrophages, potentially through increasing the expression of pro-fibrotic mediators.[69,70] Additionally, hyper-H3K18la has been shown to promote the transcription of YTHDF1 (m^6A readers) and mediate the m^6A methylation of neuronal protein 3.1 mRNA, which is regarded as a factor contributing to the progression of arsenite-related idiopathic pulmonary fibrosis.[23]

Cardiovascular Diseases

NR4A3-mediated histone lactylation represents a novel metabolome-epigenome signaling cascade mechanism.[71] It has been shown to be involved in the pathogenesis of medial arterial calcification (MAC).[71] Moreover, overexpression of histone lactylation exacerbates Ang II–induced hypertrophy in neonatal mouse cardiomyocytes, and this is associated with the promotion of cardiac hypertrophy. Conversely, the inhibition of histone lactylation attenuates the development of cardiac hypertrophy.[72] In diabetic cardiomyopathy (DCM), lactylation of macrophages potentiates the inflammatory response induced by palmitic acid by facilitating the transcription of hypoxia-inducible factor 1-alpha (HIF-1α), which in turn exacerbates myocardial damage.[41] Moreover, H3K18 lactylation is enriched in the hexokinase 2 (HK2) promoter to facilitate renal ischemia/reperfusion injury (IRI) via increasing HK2 levels.[73] In pulmonary hypertension (PH), the lactic acid pool, whose increase is mediated by PDH kinase 1 (PDK1) and PDK2, promotes the proliferation of pulmonary artery smooth muscle cells (PASMCs). This occurs through upregulating histone lactylation, and ultimately leads to the initiation of hypoxic PH.[74] Additionally, both in vitro and in vivo studies, as well as investigations in atherosclerotic patients' arteries, have demonstrated that lipid peroxidation can result in EndMT-induced atherosclerosis (AS) by augmenting lactate-dependent H3K18la.[20]

Neuropsychiatric Diseases

Growing evidence suggests that histone lactylation is strongly associated with Alzheimer's disease (AD), the most widespread type of neurodegenerative disorder.[28,43] In senescent microglia, a glycolysis/H4K12la/PKM2 positive feedback loop is discovered, which plays a pivotal role in exacerbating microglial activation and dysfunction in AD.[43] Further research has indicated that amplified H3K18la in microglia directly boosts the NF-κB signaling pathway by augmenting its binding to the promoter of Rela (p65) and NFκB1 (p50). Subsequently, the H3K18la/NFκB axis upregulates the senescence-associated secretory phenotype constituents IL-6 and IL-8.[28] In cerebral ischemia, the cerebrovascular disease of the highest incidence, increased histone lactylation is found to enhance HMGB1 (high-mobility group box 1, a protein widely distributed in body tissues and organs) in OGD/R-treated N2a cells.[4] This leads to cellular pyroptosis and exacerbates cerebral ischemia-reperfusion (CI/R)-mediated brain tissue injury.[4] Lactate dehydrogenase promotes the development of diabetic neuropathic pain (DNP), which implies that lactate may play a role in increasing histone lactylation and down-regulating peroxisome proliferator-activated receptor gamma coactivator 1-alpha expression in the prefrontal cortex of mice.[75] However, the precise mechanisms through which histone lactylation promote DNP development remain to be elucidated by future research.

Metabolic Diseases

Diabetic retinopathy (DR), chronic kidney disease (CKD), gestational diabetes mellitus (GDM), and diabetic kidney disease (DKD) are among the metabolic diseases that have been the subject of extensive research.[18,42,76,77] In DR, an elevation in the level of the protein related to fat mass and obesity, which is an m^6A demethylase, was detected under diabetic conditions.[77] Lactate-mediated histone lactylation acts as the driving force behind this increase. It leads to the regulation of CDK2 mRNA stability in a way that depends on m^6A-YTHDF2.[77] This in turn promotes angiogenesis, initiates diabetic microvascular leakage, and brings about retinal inflammation and neurodegeneration in the context of DR.[77] Moreover, in CKD, the glycolytic enzyme 6-Phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3) drives kidney inflammation and fibrosis through enhancing histone lactylation, particularly H4K12la, which was enriched at the promoter of nuclear factor κB (NF-κB) signaling genes and activated their transcription, such as Ikbkb, Rela, and Relb.[42] In GDM, a pioneering study on histone lactylation has shown that the histone lactylation modification landscape in GDM and identified CACNA2D1 as a crucial gene with differential histone lactylation modification, which promotes cell vitality and proliferation in GDM.[76] Significantly, H3K14la drives epithelial-mesenchymal transition (EMT), which is widely recognized as a critical contributor to DKD, and eventually facilitates renal fibrosis that significantly contributes to the progression of DKD into end-stage renal disease.[18]

Inflammation

Porphyromonas gingivalis msRNA P.G_45033 enhances glycolysis and histone lactylation in macrophages, which further leads to the induction of amyloid-β production and therefore contributes to exacerbating the development of both periodontitis and AD.[78] Concerning sepsis-associated acute kidney injury (SA-AKI), H3K18la activates the expression of Ras homolog gene family member A (RhoA) protein by enriching at the promoter belonging to RhoA and mediates the inflammation occurring downstream and causes apoptosis, contributing to renal damage.[21] Moreover, lactate promotes METTL3 transcription and thus m^6A-modification on acyl-CoA synthetase long chain family member 4 in sepsis-associated lung injury by augmenting the p300-mediated H3K18la process taking place at the promoter area of METTL3, ultimately inducing mitochondria-dependent iron death.[19] Conversely, the inhibition of METTL3 has been demonstrated to suppress lactate-induced ferroptosis and alleviate lung injury.[19]

Reproductive Diseases

Lactate-induced histone lactylation in endometriosis affects the progression of endometriosis by upregulating the expression of HMGB1, which promotes endometriosis progression.[79] Moreover, the elevated expression levels of lncRNA H19 in endometriosis patients contribute to abnormal glucose metabolism and increased histone lactylation levels in vivo, thereby enhancing cell proliferation and migration and facilitating the progression of endometriosis.[80] Nevertheless, the precise mechanism through which lncRNA H19 increases levels of aerobic glycolysis and histone lactylation in endometriosis remains to be elucidated. Under preeclampsia, the blood flow of the uteroplacental is reduced, leading to placental hypoxia.[81] Hypoxia-induced lactate triggers the expression of the fibrosis-related genes FN1 and SERPINE1 by histone lactylation, which promotes placental fibrosis.[81]

Other Disease

Other than the previously described situations, histone lactylation is involved in pathological neovascularization and myopia.[33,82] In pathological neovascularisation, a feedback loop between H3K9 lactylation (H3K9la) and histone deacetylase 2 (HDAC2) has been identified as a key regulatory mechanism driving VEGF-induced angiogenesis.[33] Nevertheless, the overexpression of HDAC2 has been observed to diminish H3K9la and consequently inhibit angiogenesis.[33] Additionally, scleral glycolysis facilitates fibroblast-to-myofibroblast transdifferentiation by lactate-induced histone lactylation, thereby enhancing the response to myopia induction.[82] These research studies underscore that histone lactylation is essential to disease survival, development, invasion and metastasis (Table 2).

Targeted Histone Lactylation in Disease Therapy

Targets Related to H3K18

Histone lactylation alterations in disease hold significant therapeutic potential. Specifically, the role of histone lactylation in disease therapy involves targeting different modification sites (eg, H3K18, H3K56, H4K5, H4K8) to regulate aberrant epigenetic programs (Figure 4).

Chu et al found that H3K18la was significantly increased in the septic shock patients. Notably, the H3K18la levels were higher in patients with septic shock than in those with non-septic shock according to severity.[31] This suggests that H3K18la might be an indicator of the severity level of sepsis. Additionally, the anti-inflammatory effects mediated by H3K18la, such as IL-10 overexpression, might have a significant part to play in the function of macrophages in suppressing inflammation and also in the arginase-1 (Arg1) expression during sepsis.[31] These findings suggest that H3K18la may be involved in the regulation of inflammatory cytokine expression in sepsis, and that it can enhance the overexpression of Arg1, which in turn triggers the anti-inflammatory function of macrophages.[31] These observations give prominence to the possibility that H3K18 could be an innovative target for tackling sepsis. Circular RNA is a lncRNA, which has been reported to govern the onset and progression of multiple human diseases. circXRN2 prevents large tumor suppressor kinase 1 from SPOP-mediated degradation by binding to the Speckle-type POZ degron and then activates the Hippo signaling pathway in human BCa to suppress tumor progression driven by H3K18 lactylation.[84] Moreover, in Zebrafish, metformin reduces H3K18la to decrease production of reactive oxygen species, thereby mutes neutrophil response to both caudal fin injury and otic vesicle inflammation.[85] In

Table 2 Summary of Studies Concerning Histone Lactylation in Different Diseases

Disease Type	Disease	Species	Tissue/Cell	Lactylation Sites	Regulation	Effects	Reference
Cancer	NSCLC	Mice	NSCLC cells	H4K8, H4K16	Lactate source: endogenous lactate derived from 2-DG, and exogenous lactate by treating with sodium lactate writer: NR	Promote cellular senescence and telomerase regulation	[49]
		Human	NSCLC cells	Histone	Lactate source: exogenous lactate by treating with lactate solution writer: NR	Promote cell proliferation and modulate cellular metabolism	[50]
	Ocular melanoma	Human	Ocular melanoma cells	H3K18	Lactate source: endogenous lactate derived from increased glycolysis, glucose and rotenone, and exogenous lactate by treating with sodium lactate writer: EP300	Promote tumorigenesis	[52]
		Human	Ocular melanoma cells	H3K18	Lactate source: endogenous lactate derived from 2-DG and oxamate writer: NR	Potentiate tumor progression and diminish promyelocytic leukemia protein nuclear condensates	[51]
	ccRCC	Human	Cancer-associated fibroblasts	Histone	NR	An increased lactylation score correlated with poorer clinical status	[53]
		Human	Human RCC cell lines	H3K18	Lactate source: endogenous lactate derived from 2-DG and oxamate writer: NR	Drive ccRCC Progression	[54]
	HCC	Human	HCC cells	Histone	NR	Promote HCC development	[55]
		Mice	HCC cells	H3K9, H3K56	Lactate source: endogenous lactate derived from 2-DG writer: NR	Facilitate cell malignant phenotypes, tumor growth, and metastasis	[56]

(*Continued*)

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Table 2 (Continued).

Disease Type	Disease	Species	Tissue/Cell	Lactylation Sites	Regulation	Effects	Reference
	CRC	Human	Colonic epithelial cells	H4K8	Lactate source: exogenous lactate by treating with lactate solution writer: NR	Promotes cancer cells invasion and migration	[2]
		Mice and human	CRC cells	H3K18	Lactate source: endogenous lactate derived from 2-DG and oxamate writer: NR	Promote CRC liver metastases	[26]
		Mice	Bone marrow-derived macrophages cells	H3K18	Lactate source: endogenous lactate derived from oxamate, and exogenous lactate by treating with lactate solution writer: NR	Promote inflammation-associated carcinogenesis	[57]
		Mice and human	Macrophages	H3K18	Lactate source: endogenous lactate derived from 2-DG and exogenous lactate from tumor cells writer: NR	Promote colorectal tumorigenesis	[58]
		Mice	CRC cells	H3K18	Lactate source: endogenous lactate treated with siRNA for EP300 and EP300 inhibitor, A-485 writer: NR	Promote resistance to bevacizumab treatment	[25]
	Colon cancer	Mice and human	TIMs	H3K18	Lactate source: endogenous lactate derived from increased rotenone writer: NR	Induce the immunosuppressive functions of TIMs	[59]
	EC	Mice and human	EC cells	Histone	Lactate source: endogenous lactate derived from 2-DG and oxamate writer: NR	Promoting the malignant biological behavior of EC cells	[60]
	Breast cancer	Mice	Breast cancer cells	Pan histone, H3K18	NR	Promote proliferation and metastasis of breast cancer cells	[61]
		Human	Human breast cancer cell lines	H3K18	Lactate source: exogenous lactate by treating with lactate solution writer: NR	Enhance breast cancer progression	[30]
	PDAC	Mice	Tumor cells	H4K12	NR	Implication for shaping immuno-suppressive TME during LMT	[62]
		Mice and human	PDAC cells	H3K18	Lactate source: endogenous lactate derived from increased glycolysis writer: P300 eraser: HDAC2	Drive the cell cycle and accelerate tumorigenesis	[63]
	GC	Mice	GC cells	H3 histone	Lactate source: endogenous lactate derived from GLUT3 knockdown writer: NR	Promote the occurrence and progression of GC	[64]
		Human	GC cells	H3K18	Lactate source: exogenous lactate by treating with lactate solution writer: NR	Promote GC progression and metastasis	[22]

	GBM	Mice	Macrophages and T cells	H3K18	Lactate source: endogenous lactate derived from sodium oxamate and 2-DG, and exogenous lactate by treating with lactate solution and sodium lactate writer: NR	Induce immunosup-pressive TME formation	[27]
		Human	GBM cells	H3K18	Lactate source: endogenous lactate derived from glucose, and exogenous lactate by treating with lactate solution writer: NR	Promote the self-renewal of GBM cells	[29]
		Mice and human	Macrophages	Histone	Lactate source: endogenous lactate derived from 2-DG and GNE-140 writer: NR	Promote the immunosuppressive activity of monocyte-derived macrophages in GBM	[65]
	AML	Human	AML cells	H4K5	Lactate source: endogenous lactate derived from 2-DG, and exogenous lactate by treating with lactate solution writer: NR	Drive immunosuppression	[66]
	EOC	Human	Ovarian cancer cells	H3K18	Lactate source: endogenous lactate derived from oxamate, and exogenous lactate by treating with lactate solution writer: NR	Promote the migration of ovarian cancer cells	[67]
	BCa	Mice	Cisplatin-resistant BCa cell lines	H3K18	Lactate source: endogenous lactate derived from 2-DG and oxamate, and exogenous lactate by treating with sodium lactate writer: NR	Promote cisplatin resistance	[24]
Fibrotic diseases	Liver fibrosis	Mice	HSCs	H3K18	Lactate source: endogenous lactate derived from oxamate and DCA, and exogenous lactate by treating with lactate solution writer: NR	Hepatic stellate cell activation and liver fibrosis	[6]
		Mice and human	LX-2 cells	H3K18	Lactate source: endogenous lactate derived from rotenone, 2-DG and glucose, and exogenous lactate by treating with lactate solution writer: NR	Enhance hepatic stellate cell activation and liver fibrosis	[68]
		Mice	HSCs	H3K18	Lactate source: endogenous lactate derived from LDHA knockout writer: NR	Accelerate liver fibrosis progression	[3]
	Pulmonary fibrosis	Mice	RAW264.7 cells	Histone	Lactate source: endogenous lactate derived from increased glycolysis writer: NR	Increase the expression of pro-fibrotic mediators	[70]
		Mice	Macrophages	Histone	Lactate source: exogenous lactate by treating with lactate solution writer: P300	Boost the profibrotic phenotype	[83]
	Idiopathic pulmonary fibrosis	Mice	Alveolar epithelial cells and myofibroblasts	H3K18	Lactate source: exogenous lactate by treating with $NaAsO_2$ and lactate solution writer: NR	Promote the progression of arsenite-related idiopathic pulmonary fibrosis	[23]

(*Continued*)

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Table 2 (Continued).

Disease Type	Disease	Species	Tissue/Cell	Lactylation Sites	Regulation	Effects	Reference
Cardiovascular diseases	MAC	Mice and human	Vascular smooth muscle cells	H3K18	Lactate source: exogenous lactate by treating with sodium lactate writer: NR	Promote vascular calcification	[71]
	Pathological cardiac hypertrophy	Mice	Cardiomyocytes	H3K18	Lactate source: endogenous lactate derived from glucose, 2-DG, oxamate and GNE-140 and exogenous lactate by treating with lactate solution writer: NR	Promote cardiac hypertrophy	[72]
	DCM	Mice	Macrophages	H4K12	Lactate source: exogenous lactate by treating with lactate solution writer: NR	Exacerbate myocardial damage	[41]
	IRI	Mice	Human proximal tubular cell line HK-2	H3K18	Lactate source: endogenous lactate derived from increased glycolysis writer: NR	Lead to renal IRI	[73]
	PH	Mice	PASMC	H3K18, H4K5	Lactate source: endogenous lactate derived from oxamate, and exogenous lactate by treating with lactate solution writer: NR	Promote PASMC proliferation	[74]
	AS	Mice and human	Human coronary artery endothelial cells, mouse aortic endothelial cells	H3K18	Lactate source: endogenous lactate derived from oxidized low-density lipoprotein, 2-DG, oxamate, and siLDHA-treated human coronary artery endothelial cells, and exogenous lactate by treating with lactate solution writer: NR	Lead to EndMT-induced AS	[20]
Neuropsychiatric diseases	AD	Mice and human	Microglia	H4K12	Lactate source: endogenous lactate derived from shikonin and compound 3K, and exogenous lactate by treating with lactate solution writer: NR	Exacerbate microglial activation and dysfunction in AD	[43]
		Mice	Senescent microglia	H3K18	Lactate source: exogenous lactate by treating with lactate solution Writer: NR	Promote brain aging and AD pathological phenotypes	[28]
	CI/R	Mice	N2a cells	H3K18	Lactate source: endogenous lactate derived from OGD/R writer: NR	Induce the pyroptosis	[4]
	DNP	Mice	Brain prefrontal cortex tissues	Histone	Lactate source: endogenous lactate derived from oxamate writer: NR	Promote the development of DNP	[75]

Metabolic diseases	DR	Human	Human umbilical vein endothelial cells	H3K18	Lactate source: exogenous lactate by treating with lactate solution writer: NR	Facilitate angiogenesis, trigger diabetic microvascular leakage, and induce retinal inflammation and neurodegeneration	[77]
	CKD	Mice	Kidney cortex	H4K12	Lactate source: endogenous lactate derived from PFKFB3 writer: NR	Promote kidney inflammation and fibrosis	[42]
	GDM	Human	Placental tissues	H3K18	NR	Promote cell vitality and proliferation in GDM	[76]
	DKD	Mice	Kidney tissues or cells	H3K14	Lactate source: endogenous lactate derived from oxamate writer: NR	Facilitate EMT	[18]
Inflammation	Periodontitis	Human	Macrophages	Histone	Lactate source: endogenous lactate derived from 2-DG writer: NR	Exacerbate the development of both periodontitis and AD	[78]
	SA-AKI	Mice	Renal tubular epithelial cells	H3K18	Lactate source: endogenous lactate derived from 2-DG, glucose transporter GLUT1 inhibitor, BAY-876 and oxamic acid sodium writer: NR	Promote renal dysfunction in SA-AKI	[21]
	Sepsis-associated lung injury	Mice	Alveolar epithelial cells	H3K18	Lactate source: endogenous lactate derived from knocking down p300 and exogenous lactate by treating with lactate solution writer: NR	Promote ferroptosis	[19]
Reproductive diseases	Endometriosis	Human	Endometrial stromal cells	H3K18	Lactate source: exogenous lactate by treating with lactate solution writer: NR	Promote the progression of endometriosis	[79]
		Human	Human endometrial stromal cells	H3K18	Lactate source: endogenous lactate derived from 2-DG and exogenous lactate by treating with sodium lactate writer: NR	Promote the progression of endometriosis	[80]
	Preeclampsia	Human	HTR-8/ SVneo and TEV-1 cell	H3K18	Lactate source: endogenous lactate by treating with hypoxia and oxamate, and exogenous lactate by treating with sodium lactate writer: NR	Promoting placental fibrosis	[81]
Other disease	Pathological neovascularization	Mice and human	Human retinal microvascular endothelial cell	H3K9	Lactate source: endogenous lactate derived from increased glycolysis writer: NR	Promote angiogenesis	[33]
	Myopia	Human, mice and guinea pigs	Scleral and HSFs	H3K18	Lactate source: endogenous lactate derived from 2-DG and GNE-140 writer: NR	Promote myopia	[82]

Abbreviations: NSCLC, Non-small cell lung cancer; 2-DG, 2-deoxy-D-glucose; ccRCC, Clear cell renal cell carcinoma; HCC, Hepatocellular carcinoma; CRC, Colorectal cancer; EP300, E1A binding protein p300; TIMs, Tumor-infiltrating myeloid cells; EC, Endometrial carcinoma; PDAC, Pancreatic ductal adenocarcinoma; HDAC2, histone deacetylase 2; GC, Gastric cancer; GBM, Glioblastoma; TME, tumor microenvironment; AML, Acute myeloid leukemia; EOC, Epithelial ovarian cancer; BCa, Bladder cancer; DCA, dichloroacetate; HSCs, Hepatic stellate cells; LDHA, lactate dehydrogenase A; MAC, Medial arterial calcification; DCM, Diabetic cardiomyopathy; IRI, Renal ischemia/reperfusion injury; PH, Pulmonary hypertension; PASMC, Pulmonary artery smooth muscle cell; AS, Atherosclerosis; AD, Alzheimer's disease; CI/R, Cerebral ischemia-reperfusion; OGD/R, Oxy-gen-glucose deprivation/reoxygenation; DNP, Diabetic neuropathic pain; DR, Diabetic retinopathy; CKD, Chronic kidney disease; PFKFB3, 6-Phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; GDM, Gestational diabetes mellitus; DKD, Diabetic kidney disease; EMT, Epithelial-mesenchymal transition; SA-AKI, Sepsis-associated acute kidney injury; HSFs, human scleral fibro-blasts; GNE-140, lactate dehydrogenase inhibitor; NR, not reported.

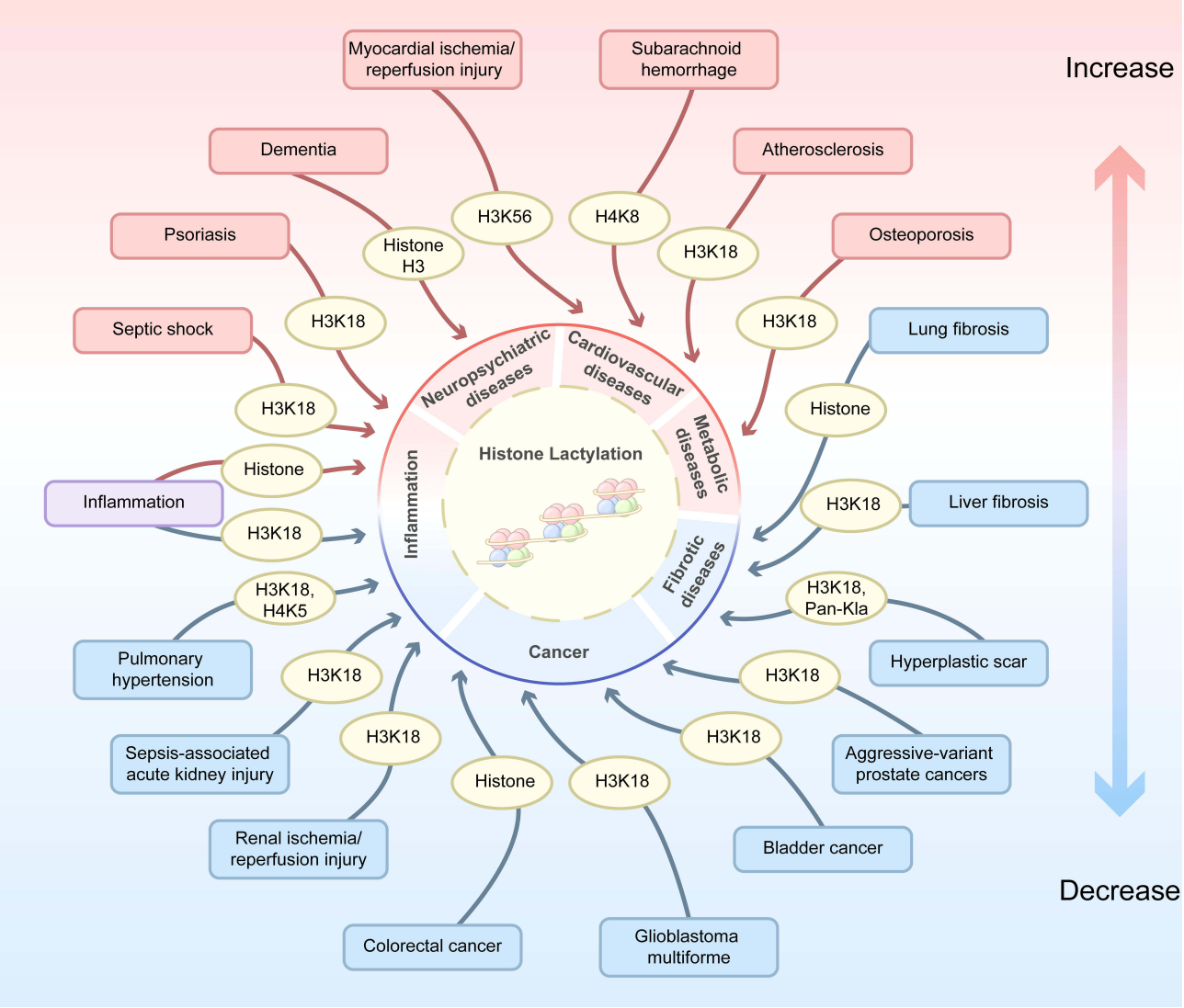

Figure 4 The role of histone lactylation in disease therapy via modulating at different sites. The purple section indicates that histone lactylation can be therapeutic in inflammation by modulating different sites.

SA-AKI, by decreasing H3K18la levels, inflammation is reduced and kidney injury is alleviated, thus promoting the enhancement of renal function after SA-AKI.[21] Conversely, increased H3K18la levels were observed to boost activation of the NF-κB pathway, accompanied by aggravated kidney injury in SA-AKI.[21] Another study demonstrated that renal IRI can be alleviated by suppressing H3K18la in renal IRI mice.[73] In the context of liver fibrosis, the specific deletion of HK2 within HSCs has been demonstrated to attenuate H3K18la in these cells and subsequently suppress the progression of liver fibrosis.[6] Interestingly, lactate can elevate the activities of CD39, CD73 and CCR8 genes promotors via inducing histone H3K18 lactylation.[27] Researchers found that decreasing histone H3K18 lactylation may play a key role in altered immunosuppressive TME and promoted immune activation, and inhibition of H3K18 lactylation leads to inhibited lactate production and downregulated the activities of CD39, CD73 and CCR8 gene promotors.[27] The targeted inhibition of H3K18la was shown to effectively restore cisplatin sensitivity in cisplatin-resistant epithelial cells, suggesting that H3K18la might serve as a novel target for the treatment of cisplatin resistance in patients with BCa.[24] In osteoporosis, H3K18la can fuel bone mesenchymal stem cell differentiation into osteoblasts, and thus control bone blood-vessel formation and attenuate osteoporosis.[86] Adiponectin (ADIPOQ) is decreased in the skin tissues of psoriasis patients and holds diagnostic value for this disease.[87] Notably, down-regulation of H3K18la levels inhibits ADIPOQ transcription, thereby reducing ADIPOQ levels, while

inducing H3K18la enhances ADIPOQ protein levels.[87] Treatment using lactate dehydrogenase inhibitor drugs, such as oxamate, reduces H3K18la and H4K5la by decreasing lactate production by HIF-1α targets associated with cell proliferation.[74] This treatment also improves the abnormal proliferation of PASMCs and the condition of vascular remodeling in rats with hypoxic PH.[74] Moreover, copanlisib in tandem with trametinib exhibits a potent effect in suppressing H3K18la and enhancing phagocytosis within activated tumor-associated macrophages, which consequently leads to the eradication of murine PTEN/p53-deficient aggressive-variant prostate cancers (AVPC).[88] Additionally, studies have explored the restorative function of histone lactylation within macrophages. Findings indicate that histone lactylation binds not only to the vicinity of the promoters of anti-inflammatory genes but also to those of TCA cycle genes.[89] This binding facilitates the shift of macrophages from an inflammatory phenotype to a reparative one, prevents sustained tissue damage due to inflammation and preserves cellular homeostasis.[89] For example, inhibiting monocarboxylate transporter 4 (MCT4) exerts its influence by elevating H3K18la, which in turn initiates the local repair function within macrophages.[89] Compared with those in normal skin fibroblasts, the levels of Pan-lysine lactylation (Pan-Kla) and H3K18la are elevated in hypertrophic scar fibroblasts (HSFs).[90] Inhibition of histone lactylation by downregulating snai2 promotes the transcription activity of phosphatase and tensin homologue (PTEN), causing the improvement of autophagy and the inhibition of collagen deposition and cell viability of HSFs.[90]

Other Targets

More recently, researchers have found that lung inflammation and fibrosis, which are induced by $PM_{2.5}$ (airborne fine particulate matter), can be aggravated by inducing glycolysis.[70] This process probably promotes histone lactylation, thereby enhancing the manifestation of pro-fibrotic genes in macrophages. In contrast, if glycolysis is inhibited, histone lactylation can be diminished, and the $PM_{2.5}$-induced lung inflammation and fibrosis can be alleviated.[70] Li et al carried out research examining a combined therapeutic approach with a histone lactylation inhibitor together with macroautophagy/autophagy and bevacizumab treatment in a pre-clinical model derived from bevacizumab-resistant patients. Their findings demonstrated that inhibition of histone lactylation enhances antitumor effects of bevacizumab in CRC.[25] In addition, lactate levels gradually increase during exercise to elevate histone H3 lactylation in microglia, which contributes to improving cognitive dysfunction and neuroinflammation in mice.[91] According to a recent study, during reperfusion following myocardial ischemia, heat shock protein A12A (HSPA12A) expression was reduced, and simultaneously, aerobic glycolytic flux was attenuated in cardiomyocytes.[92] Furthermore, HSPA12A was indispensable for ensuring cardiomyocyte survival during hypoxia/reoxygenation challenges.[92] Moreover, the protective actions of HSPA12A were realized by maintaining the homeostasis of aerobic glycolysis, which was related to H3 lactylation.[92] Besides, the bromodomain-containing protein 4 (BRD4) has been observed to mitigate A1 polarization of astrocytes through H4K8la after subarachnoid hemorrhage (SAH).[47] In turn, knocking down BRD4 is reduces the level of H4K8la, subsequently leading to the exacerbation of A1 polarization in astrocytes.[47] Furthermore, macrophage phenotypes can be generally categorized into two distinct phenotypes. The M1 macrophages release large quantities of pro-inflammatory cytokines, including TNFα and IL1β, and M2 macrophages are mainly driven by IL-4 and IL-13, secrete anti-inflammatory cytokines, have a strong ability to clear apoptotic cells and generate collagen and other proteins for tissue repair.[93] In inflammation, mitochondrial fragmentation promotes an M2 phenotype via histone lactylation, leading to inflammation resolution responses.[93] Similarly, the B-cell adapter for PI3K regulates the shift from an inflammatory state to a reparative macrophage-dominated state by enhancing the process of histone lactylation.[94] Therefore, within the domain of disease treatment, histone lactylation has emerged as a promising target, holding substantial potential for the development of innovative therapeutic strategies.

Current therapeutic strategies for histone lactylation primarily focus on glycolytic inhibitors such as 2-deoxyglucose (2-DG), BAY-876, and LDHA-targeting agents (eg, GNE-140, oxamate), inhibiting key enzymes, or promoting oxidative phosphorylation (eg, metformin, DCA), direct inhibition of lactyltransferases (eg, p300 inhibitors like GNE-140) and indirect modulation via HDAC inhibitors, which disrupt lactate-driven histone modifications (Table 3). However, TCM offers a complementary approach by leveraging its natural compounds to modulate the histone lactylation.

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Table 3 The Regulation of Histone Lactylation in Diseases Therapy

Disease	Intervention	Species	Lactylation Sites	Result	Reference
Septic shock	NR	Human	H3K18	Stimulate the anti-inflammatory function of macrophages in sepsis	[31]
BCa	CircXRN2	Human	H3K18	Suppressed tumor progression	[84]
Inflammation	Metformin	Zebrafish	H3K18	Reduce the inflammatory response	[85]
SA-AKI	Glucose transporter GLUT1 inhibitor, BAY-876	Mice	H3K18	Mitigation of kidney injury and renal function improvement	[21]
IRI	AST-120	Mice	H3K18	Alleviate renal IRI	[73]
Liver fibrosis	Lactylation inhibitors (oxamate and DCA); class I HDAC inhibitors	Mice	H3K18	Inhibit liver fibrosis	[6]
GBM	Oxamate and CAR-T	Mice	H3K18	Enhance the efficacy of CAR-T therapy against GBM	[27]
BCa	Knockdown of YY1 or YBX1, glycolysis inhibitors	Mice	H3K18	Restore cisplatin sensitivity in cisplatin-resistant epithelial cells	[24]
Osteoporosis	Lactate solution	Mice	H3K18	Attenuate osteoporosis	[86]
Psoriasis	Lactate solution	Human	H3K18	Enhance ADIPOQ protein levels	[87]
PH	Oxamate	Mice	H3K18, H4K5	Ameliorate PASMC proliferation and vascular remodeling	[74]
AVPC	Combination of copanlisib and trametinib	Mice	H3K18	Eradicate murine PTEN/p53-deficient AVPC	[88]
AS	Knockout MCT4	Mice	H3K18	Decrease atherosclerotic plaque	[89]
Hyperplastic scar	Silencing of LDHA	Human	Pan-Kla, H3K18	Improve autophagy and inhibit collagen deposition and cell viability of HSFs	[90]
Lung fibrosis	GNE-140	Mice	Histone	Alleviate lung inflammation and fibrosis	[70]
CRC	Bevacizumab, chloroquine, oxamate	Mice	Histone	Reduce the growth of CRC tumors	[25]
Dementia	Exercise training or lactate injection	Mice	Histone H3	Improve cognitive dysfunction and neuroinflammation	[91]
Myocardial ischemia/reperfusion injury	Oxamate	Mice	H3K56	Attenuate myocardial IRI	[92]
SAH	Lactate, 2-DG	Mice	H4K8	Mitigate A1 polarization of astrocytes	[47]
Inflammation	Lactylation inhibitors (sodium oxamate)	Mice	Histone	Promote inflammation resolution responses in macrophages	[93]
Inflammation	Exogenous sodium lactate treatment	Mice	Histone	Promote reparative macrophage transition	[94]

Abbreviations: BCa, Bladder cancer; ADIPOQ, Adiponectin; SA-AKI, sepsis-associated acute kidney injury; IRI, Renal ischemia/reperfusion injury; AST-120, an oral carbonaceous adsorbent; DCA, dichloroacetate; HDAC, histone deacetylase; GBM, Glioblastoma multiforme; CAR-T, Chimeric antigen receptor-T; PH, pulmonary hypertension; PASMC, pulmonary artery smooth muscle cell; AVPC, aggressive-variant prostate cancers; AS, atherosclerosis; MCT4, monocarboxylate transporter 4; LDHA, lactate dehydrogenase A; Pan-Kla, Pan-lysine lactylation; HSFs, hyperplastic scar fibroblasts; GNE-140, lactate dehydrogenase inhibitor; CRC, colorectal cancer; SAH, subarachnoid hemorrhage; NR, not reported.

TCM Regulates Histone Lactylation for the Treatment of Common Diseases

Building on current therapeutic strategies targeting histone lactylation, TCM distinguishes itself with safe therapeutic action and fewer adverse effects. TCM effectively intervenes in the management of common diseases by means of regulating histone lactylation (Figure 5). This section synthesizes mechanistic insights into how TCM monomers and compounds regulate histone lactylation (Table 4).

Demethylzeylasteral (DML), obtained from *Tripterygium wilfordii* Hook.f., was initially recorded in the Supplement to the Compendium of Materia Medica with the functions of clearing away heat and toxins from the body, expelling wind, and dredging the sinews and collaterals.[11,109,110] It has been demonstrated to induce cell apoptosis in many cancers, such as GC, CRC, non-small-cell lung cancer, PCa.[111–114] Pan et al investigated that DML treatment disrupts glycolysis/gluconeogenesis metabolic networks in liver cancer stem cells (LCSCs), leading to a dose-dependent reduction in intracellular lactate levels.[11] This reduction in lactate levels correlates with suppressed histone lactylation, particularly at H3K9 and H3K56 sites, which are positively associated with oncogenic markers (CD133, BCL2) and the glycolytic enzyme LDHA.[11] DML also induces cell cycle arrest at the S phase by decreasing CDK2, Cyclin D1, and Cyclin E1 expression. These actions collectively impair LCSC proliferation and metastatic potential while enhancing apoptotic signaling.[11]

Royal jelly acid (RJA), as a prominent unsaturated fatty acid with antioxidant, anticancer, antiaging, neurotropic, and anti-inflammatory effects, stems from the natural product royal jelly.[115] Xu et al demonstrated that RJA disrupts glycolysis/gluconeogenesis pathways, as evidenced by the concentration-dependent decrease in key glycolytic enzymes LDHA and LDHB.[95] This metabolic perturbation diminishes intracellular lactate accumulation, thereby inhibiting lactate-mediated H3K9la and H3K14la and producing potent antitumor activity.[95]

Evodiamine is a quinazolinocarboline alkaloid isolated from the fruit of *Tetradium ruticarpum* (A.Juss). T.G.Hartley, a TCM frequently employed to expel cold, alleviate pain, boost Yang, and arrest diarrhea.[116,117] It has treatment functions for

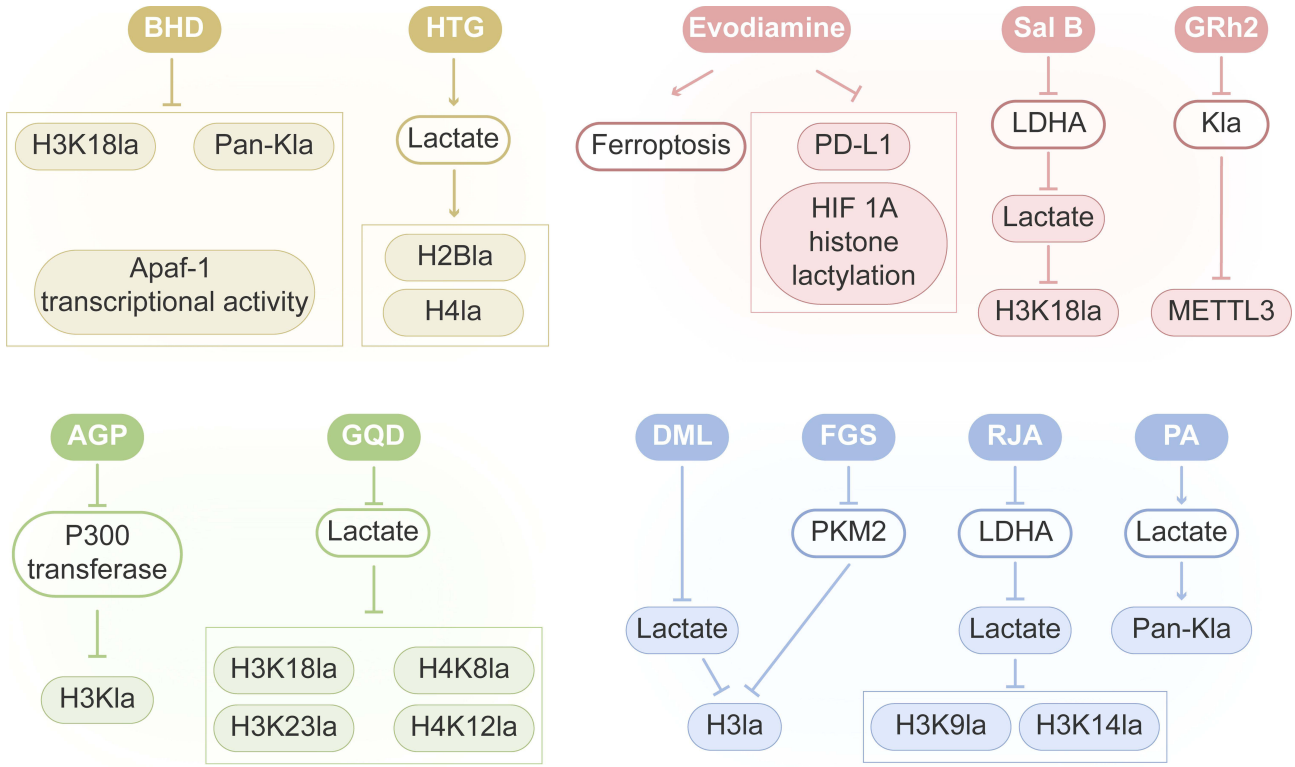

Figure 5 TCM-modulated histone lactylation pathways in disease processes.

Abbreviations: PD-L1, programmed cell death-ligand 1; METTL3, methyltransferase-like 3; LDHA, lactate dehydrogenase A; DML, Demethylzeylasteral; RJA, Royal jelly acid; FGS, Fargesin; Sal B, Salvianolic acid B; GRh2, 20(S)-ginsenoside Rh2; AGP, Andrographolide; PA, Proanthocyanidins; GQD, Gegen Qinlian Decoction; BHD, Buyang Hwanwu Decoction; HTG, Huazhuo Tiaozhi granule.

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Table 4 TCM with the Effect of Disease Treatment via Regulating Histone Lactylation

TCM	Primary Source	Drug Targets	Function	Species	Treatment of Disease	Research Status	Reference
DML	*Tripterygium wilfordii* Hook F	H3 histone	Suppressed the tumorigenicity induced	Mice	HCC	Pre-clinical	[11]
RJA	Natural compound royal jelly	H3K9 and H3K14	Inhibited HCC development	Mice	HCC	Pre-clinical	[95]
Evodiamine	*Evodia rutaecarpa* Bentham	HIF1A histone	Induce ferroptosis in PCa cells	Mice	PCa	Pre-clinical	[14,96]
FGS	Magnolia plants	PKM2 and H3 histone	NSCLC growth inhibition	Mice	NSCLC	Pre-clinical	[97,98]
Sal B	*Salvia miltiorrhiza* Bunge	LDHA and H3K18	Treat liver injury	Mice	Liver injury	Pre-clinical	[8]
GRh2	Ginseng	METTL3	Ameliorate ATRA-resistance	Mice	APL	Pre-clinical	[99,100]
AGP	*Andrographis paniculata* (Burm. F).	P300 lactylation-modified transferase	Alleviate calcification	Mice	CAVD	Pre-clinical	[101]
PA	Grape seed oligomeric proanthocyanidins	The osteogenic differentiation genes of PDLSCs	Recovere osteogenesis of inflamed PDLSCs	Mice	Periodontitis	Pre-clinical	[102,103]
GQD	Radix Puerariae (15 g), Radix Scutellariae (9 g), Coptis chinensis Franch (9 g), and Radix Glycyrrhizae (6 g)	H3K18, H3K23, H4K18, H4K12	Inhibit inflammation response and oxidative stress	Mice	UC	Pre-clinical	[104,105]
BHD	Radix Astra-gali, Radix Angelicae Sinensis, Radix Paeoniae Rubra, Rhizoma Ligustici Chuanxiong, Semen Persicae, Flos Carthami, and Pheretima at a ratio of 120:6:5:3:3:3:3 (dry weight)	Histone 3	Restrain the progression of IS	Mice	IS	Pre-clinical	[106–108]
HTG	*Rhizoma atractylodes macrocephalae* Baizhu (12 g), *fructus aurantii immaturus* Zhishi (6 g), *nelumbinis folium* Heye (10 g), *crataegi fructus* Shanzha (12 g), *salvia miltiorrhiza* Danshen (15 g), *dioscoreae spon-giosae rhizoma* Bixie (10 g), and *Polygonum cuspida-tum* Huzhang (15 g)	Histone H2B and histone H4	Ameliorate hyperlipidaemia	Mice and human	Dyslipidaemia	Clinical trial	[9]

Abbreviations: DML, demethylzeylasteral; TwHF, Tripterygium wilfordii Hook F; HCC, Hepatocellular carcinoma; RJA, royal jelly acid; PCa, Prostate cancer; FGS, Fargesin; NSCLC, Non-small cell lung cancer; Sal B, Salvianolic acid B; LDHA, lactate dehydrogenase A; GRh2, 20(S)-ginsenoside Rh2; APL, Acute promyelocytic leukemia; AGP, andrographolide; CAVD, calcific aortic valve disease; PA, Proanthocyanidins; PDLSCs, Periodontal ligament stem cell; GQD, Gegen Qinlian decoction; UC, Ulcerative colitis; BHD, Buyang Huanwu Decoction; IS, ischemic stroke; HTG, Huazhuo Tiaozhi granule; NR, not reported.

diarrhea and headaches, and displays the capacity to suppress numerous forms of cancer.[116] In DU145 cells, lactate treatment (10 mM, 72 h) promoted H3K18la modification at the HIF1A promoter, an effect abrogated by evodiamine (10 μM, 48 h).[14] Moreover, evodiamine reversed lactate-induced upregulation of HIF1α, GPX4, and PD-L1. Xenograft models further showed that 20 mg/kg evodiamine suppressed nuclear H3K18la levels, reduced the Ki-67 proliferation index, and inhibited angiogenesis.[14] By inducing ferroptosis and disrupting HIF1A histone lactylation mediated angiogenesis, evodiamine demonstrates potential as a therapeutic agent for PCa.[14]

Fargesin (FGS), a neolignan substance extracted from *Magnolia fargesii* (Finet & Gagnep). W.C.Cheng, is utilized in medicine because it exerts remarkable effects on skeleton disease, pulmonary injury, colorectal carcinoma, AS, neurological disease, and more.[118] Guo et al demonstrated that FGS inhibits aerobic glycolysis in A549 cells by targeting PKM2, suppresses H3 histone lactylation, significantly reduces cellular lactate production, and downregulates key glycolytic enzymes, including LDHA, LDHB, PKM. These effects eventually lead to NSCLC growth inhibition.[97] FGS emerges as a viable candidate for NSCLC therapy, whereas inhibitors specifically targeting PKM2 may offer enhanced treatment efficacy in clinical settings.[97]

Salvianolic acid B (Sal B), obtained from *Salvia miltiorrhiza* Bunge, is a plant highly regarded in TCM.[8] Previous research indicates that Sal B serves as a key element in specific formulas for treating inflammation, and is an effective substance for protecting the liver from damage and fibrosis.[119,120] Mechanistically, Sal B reduces endogenous lactate production by downregulating LDHA, thereby decreasing H3K18la modification levels and inhibiting the NLRP3/caspase-1/IL-1β inflammatory pathway in M1 macrophages.[8] In vitro studies in RAW264.7 cells reveal that Sal B suppresses both inflammation and aerobic glycolysis, with LDHA overexpression abrogating these effects—evidence that LDHA inhibition is central to its mechanism. Sal B demonstrates therapeutic potential in inflammatory liver diseases.[8]

20(S)-ginsenoside Rh2 (GRh2), which is a naturally-occurring compound extracted from the *Panax ginseng* C.A. Mey., has been reported to hold potential in treating leukemia.[121] Cheng et al showed that the levels of histone lactylation and METTL3 expression were significantly elevated in acute promyelocytic leukemia (APL) cells resistant to ATRA.[99] GRh2 increases histone acetylation while suppressing lactylation, phenocopying the effects of lactylation-specific inhibitors.[99] Additionally, GRh2 mitigates ATRA resistance by downregulating histone lactylation levels, and directly inhibiting METTL3 expression in a concentration-dependent manner.[99] This leads to restored ATRA sensitivity, enhanced differentiation therapy efficacy, and promoted apoptosis in ATRA-resistant leukemia stem cells, thus demonstrating its therapeutic potential for APL.[99]

Andrographolide (AGP) is the active ingredient extracted from the Chinese medicine *Andrographis paniculata* (Burm.f). Wall. ex Nees major.[101] It has traditional functions of "clearing heat and detoxification", manifesting efficacy in preventing the occurrence and hindering the progression of heart valve calcification disorder.[117,122] Moreover, the results show that AGP suppresses lactate modifications by interfering with p300 and regulating the glycolytic pathway, leading to inhibiting H3K1la and H3K9la, thereby reducing Runx2 expression and inhibiting calcification in calcific aortic valve disease (CAVD).[101] This mechanistic framework underscores AGP's potential as a therapeutic agent for calcific disorders.[101]

Proanthocyanidins (PA) from *Vitis vinifera* L. exist in the blossoms, nuts, fruits, bark, and seeds of diverse plant species and have the characteristics of anti-inflammation and bone formation facilitation.[123–126] As a beneficial element, it is commonly employed in Chinese herbal formulas to alleviate inflammation.[127] In Periodontitis, the impaired osteogenesis of periodontal ligament stem cells (PDLSCs) under inflammatory conditions was related to reduced lysine lactylation and the inhibition of its restoration.[102] PA can increase lactate production, restore the lactylation amounts of PDLSCs, and thus enable the recovery of osteogenic processes of inflamed PDLSCs through the Wnt/β-catenin signaling pathway.[102]

Gegen Qinlian Decoction (GQD), which is a classic TCM formula, has been extensively applied in the treatment of gastrointestinal disorders.[128] GQD treatment can effectively reduce the levels of H3K18la, H3K23la, H4K8la and H4K12la in ulcerative colitis (UC) and regulate the macrophage polarization, inflammation, oxidative stress, and thus suppress UC progression.[104] But the mechanistic insights into how histone lactylation modulates UC pathogenesis were not explored.

Buyang Hwanwu Decoction (BHD) has the functions of treating stroke, vascular dementia and coronary artery disease.[129] Song et al demonstrated that BHD could inhibit the Pan-Kla and H3K18la protein levels and the apaf-1 transcriptional activity, and thus inhibiting glycolysis and apoptosis in order to restrain the progression of ischemic stroke (IS).[106] However, the precise mechanisms through which histone lactylation modulate IS remain to be elucidated.

Huazhuo Tiaozhi granule (HTG), being a herbal formulation, is commonly employed in clinical settings for lipid-lowering effects.[9] In dyslipidemic rats, 8-week HTG treatment significantly reduced serum total cholesterol and low-density lipoprotein cholesterol, decreased body weight and liver index, and improved hepatic lipid accumulation histopathology.[9] Clinically, HTG lowered plasma total cholesterol and low-density lipoprotein cholesterol in dyslipidemia patients without affecting aspartate transaminase, alanine transaminase, urea nitrogen, or creatinine levels.[9] Mechanistically, HTG elevates hepatic lactate to induce protein lactylation, enriching RNA processing and metabolic pathways.[9] In FFA-stimulated hepatocytes, HTG upregulates H2B/H4 histone lactylation, while suppressing miR-155-5p expression for lipid-lowering efficacy.[9] These findings highlight HTG's potential in targeting histone lactylation for dyslipidemia.[9]

Conclusion

In summary, histone lactylation plays a crucial role in various diseases because it is linked to numerous pathological processes, like cancers, fibrotic diseases, cardiovascular diseases, neuropsychiatric diseases, metabolic diseases, inflammation, reproductive diseases, and so on. In addition, alteration of histone lactylation also contributes to the improvement of the disease. Therefore, histone lactylation emerges as a promising target in disease treatment, given its significant role in both disease development and the corresponding therapeutic strategies. Nevertheless, investigations regarding disease treatment via the modulation of histone lactylation remain in the initial stage. Currently, there is a lack of research on testing the clinical applications of drugs in this context. To promote the evolution of more precisely focused histone lactylation modulators and enable their application in clinical settings, further exploration of the concrete molecular mechanisms underlying histone lactylation is imperative. Moreover, a multitude of potential targets involved in the regulation of histone lactylation also influence other posttranslational modifications, thereby posing challenges to the formulation of specific therapeutic strategies. Therefore, to facilitate their translation into clinical practice, future investigations need to explore the concrete molecular mechanisms by which histone lactylation is regulated—especially in metabolic contexts dominated by glycolysis and lactate accumulation.

The continuous progression and innovative application of TCM play an increasingly important role in the domain of disease treatment. This study summarises that TCM has regulatory effects on histone lactylation in the management of diseases. However, our understanding of the specific active constituents and precise mechanisms underlying Chinese herbal medicine remains incomplete, primarily due to the scarcity of pre-clinical and clinical studies systematically evaluating their biological effects and molecular targets. Despite the multitude of challenges persisting in the utilization of TCM for disease treatment, we believe that, with the continuous advancement of science and technology, TCM will significantly contribute to the further evolution of histone lactylation-based therapeutic modalities. In particular, future research could focus on further exploring the molecular mechanisms of histone lactylation modulated by TCM and deepen the investigation into active components of TCM to elucidate their chemical compositions and regulatory targets. This may promote the development of more effective and targeted TCM-based therapies for disease management.

Abbreviations

2-DG, 2-deoxy-D-glucose; AD, Alzheimer's disease; ADIPOQ, Adiponectin; AGP, Andrographolide; AML, Acute myeloid leukemia; APL, Acute promyelocytic leukemia; Arg1, Arginase-1; AS, Atherosclerosis; AVPC, Aggressive-variant prostate cancers; BCa, Bladder cancer; BHD, Buyang Hwanwu Decoction; BRD4, Bromodomain-containing protein 4; BUB1B, BUB1 mitotic checkpoint serine/threonine kinase B; CAR-T, Chimeric antigen receptor-T; CAVD, Calcific aortic valve disease; CCR8, C-C Chemokine Receptor 8; ccRCC, Clear cell renal cell carcinoma; CI/R, Cerebral ischemia-reperfusion; CKD, Chronic kidney disease; CRC, Colorectal cancer; DCA, Dichloroacetate; DCM, Diabetic cardiomyopathy; DKD, Diabetic kidney disease; DML, Demethylzeylasteral; DNP, Diabetic neuropathic pain; DR, Diabetic retinopathy; EC, Endometrial carcinoma; EMT, Epithelial-mesenchymal transition; EOC, Epithelial ovarian

cancer; EP300, E1A binding protein p300; ESCC, esophageal squamous cell carcinoma; FGS, Fargesin; GBM, Glioblastoma; GC, Gastric cancer; GDM, Gestational diabetes mellitus; GLO1, glyoxalase 1; GLUT3, Glucose transporter 3; GQD, Gegen Qinlian Decoction; GRh2, 20(S)-ginsenoside Rh2; H3K18la, Histone H3 lysine 18 lactylation; GSH, Glutathione; H3K9la, H3K9 lactylation; HCC, Hepatocellular carcinoma; HDAC2, Histone deacetylase 2; HIF-1α, Hypoxia-inducible factor 1-alpha; HK2, Hexokinase 2; HMGB1, High mobility group box 1, a protein widely distributed in body tissues and organs; HSCs, Hepatic stellate cells; HSFs, Hypertrophic scar fibroblasts; HSPA12A, Heat shock protein A12A; HTG, Huazhuo Tiaozhi granule; IL-10, Interleukin-10; IRI, Renal ischemia/reperfusion injury; IS, Ischemic stroke; LCSCs, liver cancer stem cells; LDHA, Lactate dehydrogenase A; LGSH, lactoylglutathione; LMT, Liver metastasis; lncRNA, Long noncoding RNA; m^6A, N6-methyladenosine; MAC, Medial arterial calcification; MCT4, Monocarboxylate transporter 4; METTL3, Methyltransferase-like 3; MGO, methylglyoxal; NF-κB, Nuclear factor κB; NSCLC, Non-small cell lung cancer; OGD/R, Oxy-gen-glucose; deprivation/reoxygenation; PA, Proanthocyanidins; Pan-Kla, Pan-lysine lactylation; PASMCs, Pulmonary artery smooth muscle cells; PCa, Prostate cancer; PDAC, Pancreatic ductal adenocarcinoma; PDGFRβ, Platelet-derived growth factor receptor β; PDK1, PDH kinase 1; PD-L1, Programmed cell death-ligand 1; PDLSCs, Periodontal ligament stem cells; PFKFB3, 6-Phosphofructo-2-kinase/fructose-2, 6-biphosphatase 3; PH, Pulmonary hypertension; PTEN, Phosphatase and tensin homologue; PTM, Post-translational modification; RARγ, Retinoic Acid Receptor gamma; RhoA, Ras homolog gene family member A; RJA, Royal jelly acid; SA-AKI, Sepsis-associated acute kidney injury; SAH, Subarachnoid hemorrhage; Sal B, Salvianolic acid B; TCM, Traditional Chinese medicine; TIMs, Tumor-infiltrating myeloid cells; TME, Tumor microenvironment; TNBC, triple-negative breast cancer; Treg, Regulatory T; TTK, TTK protein kinase; UC, Ulcerative colitis; SLFN5, Schlafen 5; YTHDF2, YTH N6-methyladenosine RNA-binding protein 2.

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Disclosure

The authors report no conflicts of interest in this work.

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