Role of histone modifications in gastric cancer (Review)

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Abstract. Histone modification is an important mechanism of epigenetic regulation. New histone modifications play key roles in the regulation of gene expression and in the development and progression of various diseases. In addition to histone modifications, epigenetic regulation includes classic pathways such as DNA methylation, chromatin remodeling complexes and non-coding RNAs, which interact with each other and jointly shape the occurrence and development of gastric cancer (GC). The present study systematically elaborated on the role of histone modification in GC and introduced several main types of histone modification, including acetylation, methylation, citrullination, ubiquitination and lactylation, focusing on histone lactylation modification and exploring its biochemical basis, interaction with other modifications and functions such as metabolic reprogramming, cell proliferation, migration and immune escape, covering non-tumor and other cancer fields. On this basis, the specific application of histone modification (acetylation, methylation and other modifications) in GC is further explained and the effects of histone lactylation on metabolic reprogramming, proliferation, migration and immune escape of GC are analyzed in detail. Finally, the clinical significance of histone lactylation modifications in the diagnosis and prognosis of GC, biomarkers, therapeutic targets and drug resistance mechanisms provides a reference for an in-depth understanding of the role of histone modifications, especially lactylation modifications, in the development of GC and clinical transformation applications.

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Contents

1. Introduction

Gastric cancer (GC) is one of the deadliest cancers worldwide. It is the fifth most common malignancy worldwide and fourth leading cause of cancer-related deaths (1). The incidence rate of GC in men is twice that in women and there has been a notable increase in the number of cases among individuals under 50 years of age. Despite advances in surgery, chemotherapy and targeted therapy, the overall survival rate of patients with advanced GC remains <40%. Therefore, it is imperative to thoroughly investigate its pathogenesis in order to develop novel diagnostic and therapeutic approaches (2).

Research suggests that aberrant epigenetic regulation is closely related to GC and plays a significant role in the course of this illness (3). Post-translational modifications (PTMs) of histones, the core epigenetic mechanism, affect cell function by dynamically regulating DNA and gene transcriptional activity. PTMs are closely related to the emergence of GC resistance and are involved in pathological processes, such as malignant proliferation (4). Ubiquitination, acetylation and the newly discovered lactylation are three histone changes that have gained much interest because of their crucial function in GC (5,6). An imbalance in ubiquitination can impair the stability of critical tumor suppressor genes, which is similar to a 'double-edged switch' in the course of tumorigenesis. This switch has the ability to stimulate and suppress tumor development (7). Histone deacetylases (HDACs) are overexpressed in GC, resulting in chromatin defects and promoting tumor growth. Hence, epigenetic treatment of GC has increasingly focused on HDACs (8). Histone lactylation alterations deserve special consideration in the study of GC. The emergence of a

unique connection between epigenetic regulation and metabolic reprogramming is the cause of this phenomenon. This change has the potential to directly affect histones, which in turn causes the expression of cancer-causing genes. It has the potential to alter the metabolic trait of high glycolysis into tumorigenic epigenetic alterations. Furthermore, there is growing evidence that lactylation plays a role in controlling the tumor immune microenvironment (9).

The present review aimed to systematically examine the role of lactylation in GC and clarify the molecular processes underlying major histone modifications during the initiation, development, migration and multidrug tolerance of GC. Additionally, it examined the therapeutic promise of these alteration pathways in order to improve our knowledge of the epigenetic disruption mechanisms in GC and offer a basis for creating new, targeted treatment techniques.

Broader epigenetic landscape in GC. A number of studies demonstrate that there is a communication system between them known as 'cross-talk' (10-12). DNA methyltransferases (DNMTs, including DNMT1, DNMT3A and DNMT3B) are the enzymes that catalyze DNA methylation, which involves the selective addition of methyl groups (-CH_3) to specific bases in DNA molecules. In GC, it can result in the transcriptional silencing of important tumor suppressor genes, such as CDH1, MLH1, CDH11 and IGFBP7. This is frequently the case in highly methylated local areas of the genome. Low-methylation areas often lead to genomic instability, whereas the clustering of histone modifications or methylation-binding proteins further strengthens gene silencing. The position, composition and stability of nucleosomes are dynamically regulated by chromatin remodeling complexes, including the switching defective/sucrose nonfermenting (SWI/SNF) family, the imitation SWI (ISWI) family, the nucleosome remodeling and deacetylation/Menin-MLL Inhibitor (Mi-2)/chromodomain helicase DNA-binding (CHD) family and the inositol requiring 80 family, which, via ATP hydrolysis, allows transcription factors to approach DNA and regulate transcription, replication, repair, development and genome stability. The SWI/SNF complex consists of components such as AT-rich interaction domain 1A (ARID1A) (13) and the chromatin remodeling factors CHD4 (14) and CHD5 (15), all of which have the potential to cause GC metastasis. Based on their length, non-coding RNAs (ncRNAs) are primarily classified as circular RNAs (circRNAs), PIWI-interacting RNAs (piRNAs), long non-coding RNAs (lncRNAs) and small non-coding RNAs (sncRNAs). Although they do not encode proteins, they are involved in GC angiogenesis, metabolism, immune escape and chemotherapy resistance. CircPOFUT1 (16), circVAPA (17) and other similar compounds increase cisplatin resistance in GC and facilitate cell proliferation, migration and invasion. hsa_circ_0073453 (18) and circ_0136666 (19) influence CD8+ cells, eventually resulting in immune evasion (20).

2. Histone modification

Direct protein modification regulates transcriptional activity by altering the histone structure or charge, which in turn affects chromatin compaction and gene accessibility. It regulates gene 'activation' or 'inactivation' without affecting DNA sequences, making it a fundamental component of epigenetic regulation (21,22).

Histones are fundamental proteins that reside in the nucleus of eukaryotic cells. They make up the core elements of nucleosome subunits, which are made up of an octamer of four core histones (H3, H4, H2A and H2B) surrounded by a 147-base-pair DNA segment (23). Each histone has a unique side chain or tail, which is highly enriched in lysine and arginine residues (24). These changes alter the charge density between histones and DNA, allowing the precise regulation of chromatin transcription (Fig. 1). They are one of the core mechanisms behind the epigenetic changes that regulate gene activation or suppression without altering the underlying DNA sequence. Histone modifications take numerous forms, including methylation, acetylation, ubiquitination and lactylation (25).

Acetylation modification. Histone acetyltransferase (HAT) mediates the chemical process of acetylation. In this procedure, acetyl groups are transferred from an acetyl coenzyme A (acetyl-CoA) molecule to another molecule. This procedure activates the protein function by attaching an acetyl group supplied by acetyl-CoA to the lysine residues of histones. Thus, acetyl-CoA, a crucial intermediate, has a significant influence on acetylation activity. The main HAT families include the MYST proteins, p300/CBP and the Gcn5-related N-acetyltransferase (GNAT) superfamily (26). The GNAT superfamily includes the members Gcn5, PCAF, Elp3, Hpa2 and HAT1 (27), which can interact with particular substrates and play roles in chromatin remodeling and gene transcription. In addition to their HAT activity, p300/CBP proteins act as transcriptional coactivators and interact with other transcription factors to promote gene transcription. Moz, Ybf2/Sas3, Sas2 and Tip60 are examples of MYST proteins (28). Additionally, acetylated lysine residues in proteins have been identified by dual PHD finger (DPF) domain proteins (e.g., MOZ and DPF2), YEATS domain proteins (e.g., MLLT3 and Taf14) and bromodomain proteins (e.g., BRD4 and BRDT) (29). They function as lysine acetylation readers, receiving signals from acetylated lysine residues and binding to specific acetylating complexes. BRD4, which has been found to be a histone acetylation reader and an upcoming anti-cancer treatment target, is one of these that encourages GC progression and metastasis (30). The chemical process of removing acetyl groups from lysine residues, which is opposite to acetylation, is catalyzed by HDACs. HDACs are primary deacetylases that remove acetyl groups (31). The main categories of HDACs are NAD^+- and Zn^{2+}-dependent HDACs (32). By eliminating acetyl groups, the positive charge of histones is restored, which increases the affinity between histones and the negatively charged DNA backbone, resulting in chromatin compaction. As a result, the mixing of transmission factors and RNA polymerase with DNA is prevented, inhibiting gene expression (33). The dysregulation of HDAC activity is closely associated with cancer, fibrotic illnesses, cardiovascular and renal diseases, neurodegenerative diseases and mental disorders.

Methylation modification. Histone methylation, which was first discovered in the 1960s, is a reversible process in all living organisms. It involves alkylation reactions in which

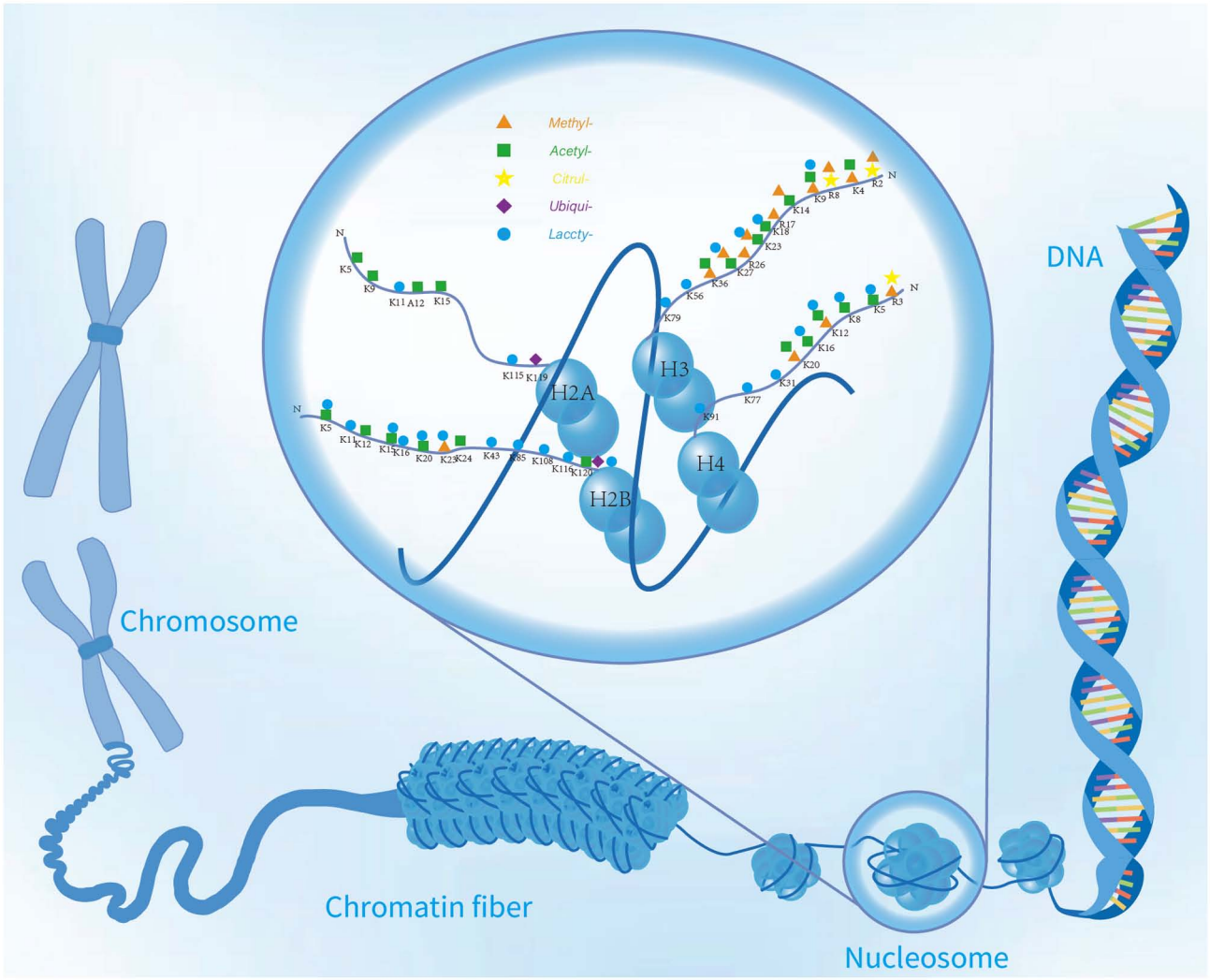

Figure 1. Distribution of multi-type modifications of histone in different residual base sites and structure in chromatin. The various types of histone modification and its distribution in the chromatin structure from the advanced structure of chromosomes to nucleosome, chromatin fiber and DNA double helix structure. The figure marks the modification types of some different histones, including methylation, acetylation, citrullination, ubiquitination and lactylation and the specific distribution of these modifications in different amino acid residue bases of histone H2A, H2B, H3 and H4 (such as K14, K27, K36, etc.), which reflects the effect of histone modification on the structure and function of chromatin in epigenetic regulation.

methyl groups replace hydrogen atoms (34). Histone methyltransferases (HMTs) and histone demethylases (HDMs) work together to maintain histone methylation balance. Using the cofactor S-5'-adenosyl-L-methionine as a methyl donor, histone methylation is catalyzed by HMTs. Methylation of a lysine or arginine residue at a particular site on the tail of histones (primarily H3 and H4) is a part of this process (35). Arginine methylation can occur as symmetric mono-methylated (ME), symmetric di-methylated (ME2S), or asymmetric di-methylated (ME2A), whereas histone lysine residues can be methylated at the ε-amino group as mono-methylated (Me), di-methylated (Me2), or tri-methylated (Me3) (36). The effects of methylation are what make its function so complicated. These results demonstrate site-specific and degree-specific methylation. Some of the histone methylation sites are H3K4, H3K9, H3K27, H3K36, H3K79 and H4K20. The arginine methylation sites include H3R2, H3R8, H3R17, H3R26 and H4R3. Methylation is controlled by HMTs. There are three families of enzymes: N-methyltransferases, lysine-acting Dot1-like proteins and SE domain-containing enzymes. These enzymes act on both free and non-histone proteins. Thus, the functions of these proteins are triggered (37). These enzymes are involved in various biological processes, including transcription factor recruitment, binding and chromosome packing. They also control RNA processing/editing, DNA binding and initiation/elongation and are involved in several other connected procedures (38). Additionally, HMTs govern genomic alterations that contribute to cancer development. Indeed, previous studies have shown that they are essential for the development and formation of tumors, while also aiding in preserving stem cell populations in tumors. HMTs are subject to rigorous regulations governing essential cellular activities under typical conditions (39).

HDMs are involved in the process of using specific enzymatic catalysts to eliminate methyl groups from lysine or arginine residues on histone tails (37). The two main enzyme categories in this catalytic process include flavin-dependent amine oxidases, which are the enzyme family to which the first class of HDMs (such as LSD1) belongs and the JmjC domain family, which are the enzyme family to which the

second class of HDMs belongs and which catalyzes ferrous ion oxidation and employs ketoglutarate as a cofactor to demethylate histone lysine residues. Other proteins involved in histone demethylation were also found in the histone lysine demethylase (KDMs) cohort (40) within the KDM1 to KDM9 subfamilies (41,42). HDMs have a dynamic effect on chromatin regions rather than altering the DNA sequences. In addition to preserving genome integrity and stability, they play essential regulatory roles in embryonic development, genetic control, cellular reprogramming and other biological processes. They play an important role in cancer because they are closely linked to disease pathogenesis; this includes boosting mutation rates, changing the copy number of gene segments, enriching transcription factors and remethylating genes that control cell fate. Targeting particular HDMs has opened up an intriguing new area in cancer treatment (Fig. 2) (39).

Lactylation modification. In the 1920s, Otto Warburg discovered that tumor tissue uses considerably more glucose than healthy tissue. The Warburg effect is a counterintuitive observation in that tumor cells continue to produce lactate from glucose, even in an oxygen-rich environment (13). Lactate was previously thought to be both an energy source and a metabolic byproduct of the Warburg effect (43,44). The important functions of lactate in the body have been discovered in an increasing number of studies over the past few years. It is now appreciated beyond a superficial metabolic byproduct role. Professor Yingming Zhao at the University of Chicago initially demonstrated the existence of histone lysine lactylation (Kla) in 2019 and proved that it was a novel epigenetic change (45). Through specific receptors, lactate can activate downstream signaling pathways and serve as a substrate to support Kla activity. Understanding how Kla functions may offer insights into tumor treatment because it has a unique impact on tumor growth (46). Kla is a covalent modification in which the lactate moiety (-CO-CH_3OH) is linked to lysine residues on proteins via an amide bond. It consists of three stereochemically distinct isomers that are structurally similar: L-lactylation (KL-La), D-lactylation (KD-La) and N-ε-(carboxyethyl)-lysine (Kce). At present, 9,275 Kla locations have been identified, of which 9,256 are non-histones (47). Most Kla is present on the lysines of H2A, H2B, H3 and H4, especially H3K18 (48). Using liquid chromatography-mass spectrometry to analyze animal cells, Varner *et al* (49) found that the levels of lactoyl-CoA were 20-350 times lower than those of other key lactoyl-CoA compounds. Kla's dynamic equilibrium uses lactoyl-CoA as its substrate and is jointly controlled by lactyltransferase and delactylase enzymes, resulting in covalent bonding under certain enzymatic or non-enzymatic conditions (50). The source of lactoyl-CoA production may be glycolysis, lactate buildup, or metabolic bypasses that use coenzyme A. P300/CBP was the first possible lactyltransferase discovered (45,51); however, indirect participation cannot be excluded. Lactyltransferases, including alanine tRNA synthetase (AARS1) (52), KAT2A, HBO1 (53), KAT8 (54), GNAT13, YiaC and CobB (55,56), have been reported to increase in recent years. Known deacetylases include Class I histone deacetylases (HDAC1-3) (56) and SIRT1-3 (57). Research suggests that repair genes, pluripotency genes, transcription factors (58), pro-inflammatory factors (59), m6A-associated regulatory proteins (60), fibrosis-related genes and essential signaling pathway proteins are the downstream target genes of H3K18la-mediated transcriptional activation (61). Additionally, H3K18la and H4K5la may function together to regulate PD-L1 expression (Fig. 3) (62).

Other modifications. Histone modifications vary and include histone ubiquitination and citrullination, as well as the previously mentioned changes. Citrullination of histones is a unique modification procedure, which converts positively charged or methylated arginine residues into neutral citrulline residues. The interaction between proteins as well as between proteins and nucleic acids is impacted by this shift (63). Enzymes, such as peptide arginine deaminase (PAD), which transforms arginine residues into citrulline residues, play a major role in this process. When arginine is highly alkaline, positively charged side chains are hydrolyzed and neutral urea is produced (64). This alteration affects the fundamental processes of cells in a significant way, such as via apoptosis, differentiation and immune response. The fact that this change can directly stimulate the growth and spread of cancer is even more significant (65,66). PAD can worsen rheumatoid arthritis in the pathological state by causing autoantibodies and setting off the body's inflammatory reaction (67,68). Studies have demonstrated that PAD can be used as both a therapeutic target and a diagnostic indicator. Non-small cell lung cancer, GC, hepatitis B virus-related hepatocellular carcinoma and various malignant blood tumors are all associated diseases (69). PAD inhibitors can also be used in cancer therapy; PAD4 inhibitors are particularly noteworthy because they can stop tumor metastasis in patients with cancer and prevent accompanying thrombosis (70,71). The ATP-dependent process of ubiquitination links ubiquitin molecules to substrate proteins, with cell survival, proliferation and differentiation all being affected by this process (72). Ubiquitination can be categorized into four types: Mono-, poly-, homogeneous and heterogeneous polyubiquitination. E1-Ub, E2-Ub and E3-Ub ligases are three enzymes that mediate ubiquitination, which is a histone modification (73). Ubiquitinated proteins can be removed by deubiquitination enzymes (DUBs), which reverse the ubiquitination process. Early research has demonstrated that several DUBs, including USP4 (UNP), USP6 (Tre-2) and USP8 (UBPY), are essential for cancer development. programmed death-1/programmed cell death protein 1(PD-1/PD-L1) inhibitors can be used in conjunction with USP8/USP7 inhibitors to greatly improve antitumor effectiveness (74). USP9X deubiquitinase is capable of stabilizing oncogenic genes such as β-catenin and MCL1, both of which are involved in tumor development and spread. In addition, USP9X governs epithelial-mesenchymal transition, which raises the chance of tumor metastasis. USP9X also eliminates ubiquitin from PD-L1 cells. Due to this activity, cancer cells can avoid the immune system. MCL1 is destroyed by USP9X inhibitors and cancer cell apoptosis is initiated by this breakdown, suggesting that USP9X may be a therapeutic target. Indeed, USP9X has attracted considerable interest for its potential therapeutic use in neurodegenerative disorders (75). The complex interplay between ubiquitination and deubiquitination is closely associated with several cellular processes. Disruption of this mechanism can result in

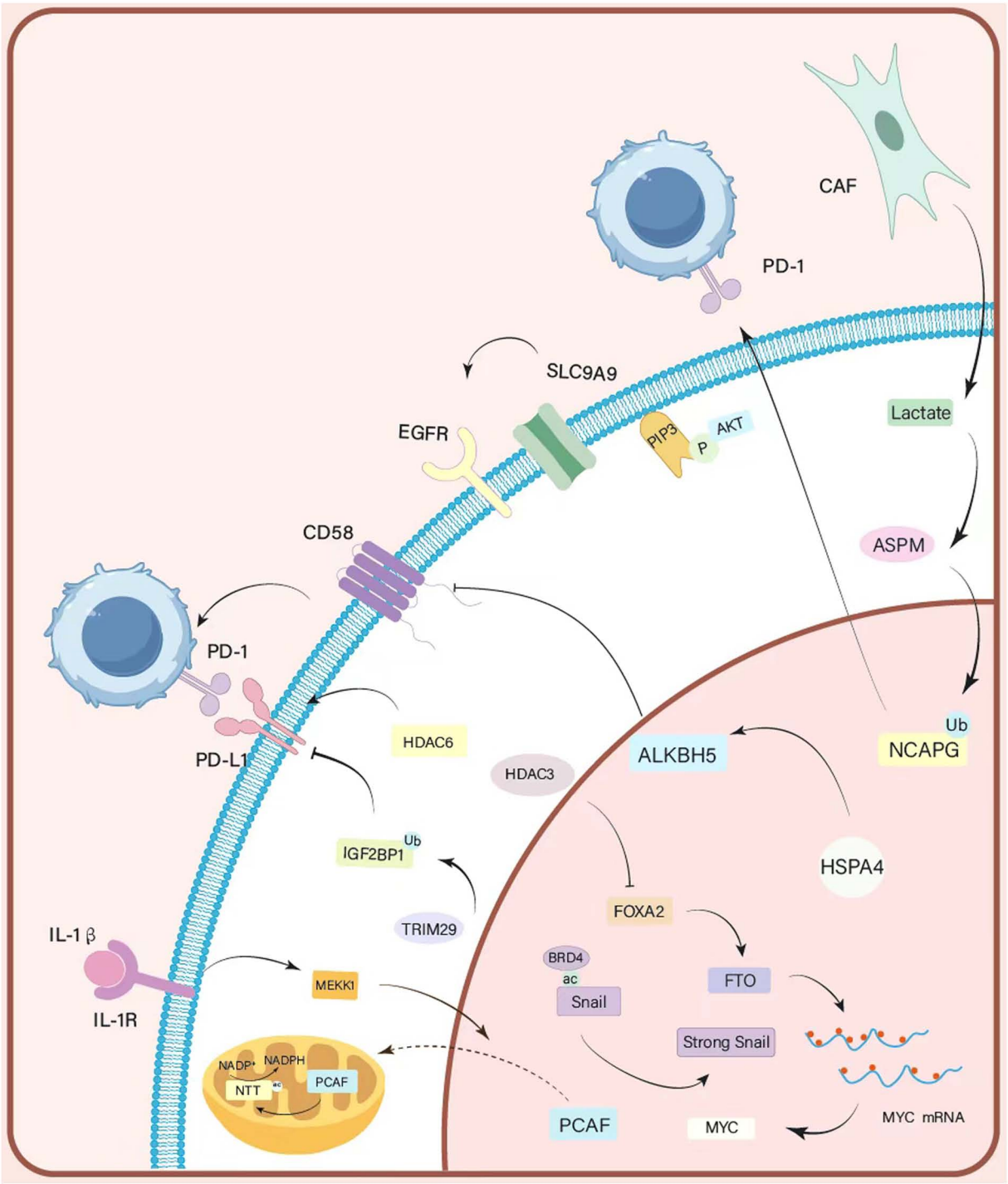

Figure 2. Mechanisms of histone acetylation and ubiquitination. These two major histone modifications regulate the expression of key effector molecules (such as MYC, Snail, NCAPG) and activate downstream signaling pathways (such as EGFR/AKT, IL-1β/MEKK1), thereby directly promoting malignant proliferation and survival of GC cells. MYC, myelocytomatosis oncogene; NCAPG, non-SMC condensin I complex subunit G; EGFR, epidermal growth factor receptor; AKT, protein kinase B; IL-1β, interleukin-1 beta; MEKK1, mitogen-activated protein kinase kinase kinase 1; GC, gastric cancer.

neurodegenerative illnesses, cancer and other illnesses. New approaches for treating these disorders may arise from this association (Table I) (76).

3. Application of histone modifications in gastric cancer

Acetylation modifications and gastric cancer. Several targets for histone acetylation have been identified during GC treatment. Based on acetylation patterns, four lncRNAs (AC114730.1, AL445250.1, LINC01778 and AL163953.1) have been identified as potential chemotherapeutic drugs for adjuvant treatment in various risk categories and to create a prognostic model for the GC response to immunotherapy (77). The responsiveness of patients with GC to immune checkpoint inhibitor treatment can be predicted by histone acetylation-induced upregulation of HSPA4 in GC tumor tissues (78). In cancer cells, the acetylation of nicotinamide nucleotide transferase (NNT) at lysine (K) 1042 (NNT

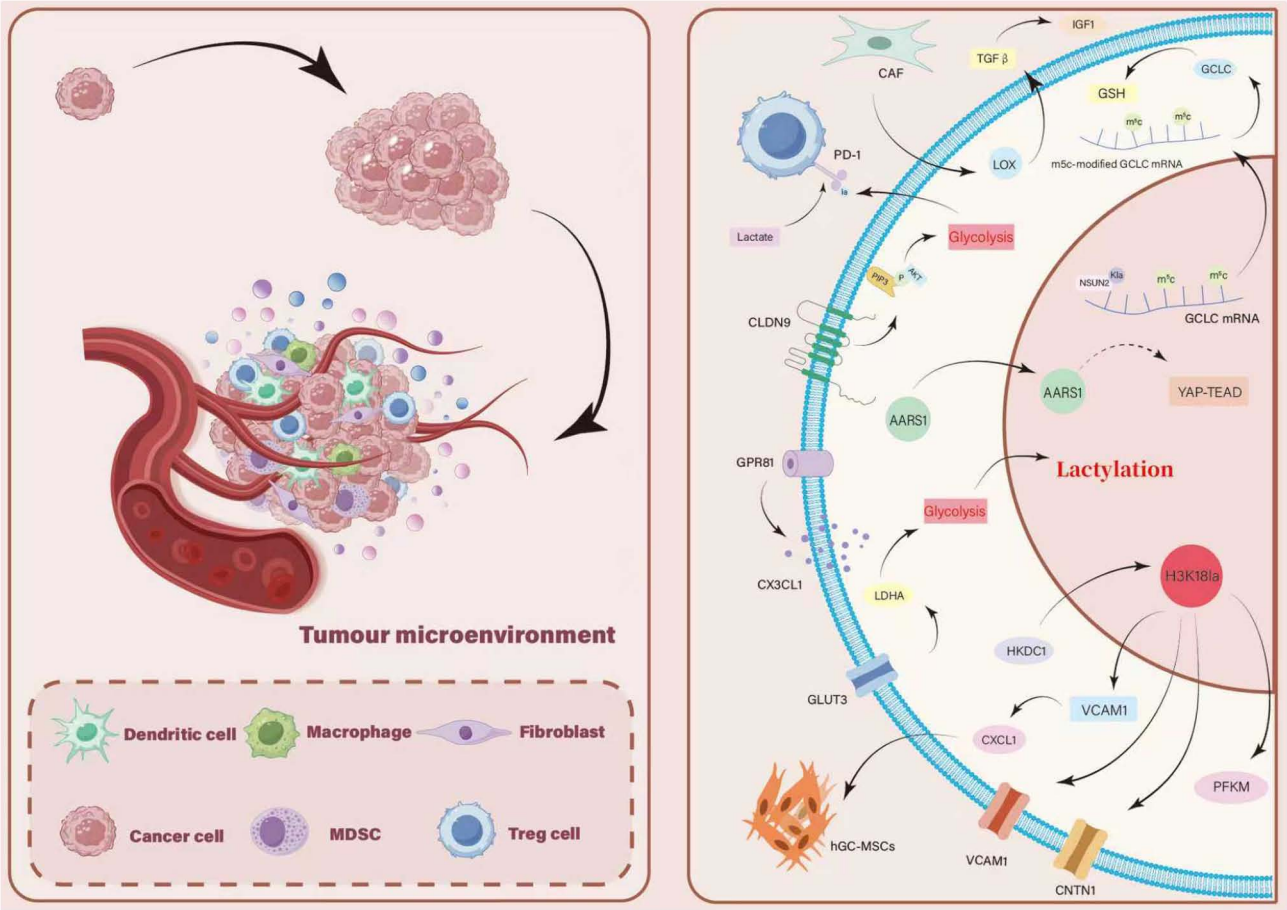

Figure 3. The mechanism of histone lactylation, another critical epigenetic modification. Lactylation acts through distinct downstream pathways (such as YAP-TEAD, glycolysis) to enhance the malignant phenotype of GC cells and convert surrounding stromal cells (such as CAFs, Tregs) into tumor-supportive components. The figure builds a complete causal model from 'epigenetically-driven' to 'cell malignant proliferation', which provides a key mechanism explanation for understanding the rapid development of GC and reveals the potential therapeutic targets. YAP, Yes-associated protein; TEAD, transcriptional enhanced associate domain; CAFs, cancer-associated fibroblasts; Tregs, regulatory T cells); GC, gastric cancer.

K1042ac) under interleukin-1β (IL-1β) stimulation markedly reduces tumor immune escape brought about by IL-1β. By blocking NNT acetylation, therapeutic benefits are attained by interfering with the IL-1β-tumor cell axis (79). By blocking EGFR/PI3K/AKT signaling and preventing GC development, the natural flavonoid pomiferin binds to SLC9A9, a marker of aberrant histone acetylation, in GC cells (2). Owing to their role as epigenetic regulators of chromatin condensation and decondensation (80), HDACs are potential therapeutic candidates for cancer treatment. The hydroxyacetamide derivatives vorinostat and panobinostat are examples of HDAC inhibitors licensed for the treatment of hematologic malignancies (81) and their use in solid tumors is currently under research (82). By contrast, excessive expression of HDAC1 and HDAC3 (83) in GC is associated with poor prognosis, whereas HDAC6 contributes to an increase in important elements of cancer immunotherapy targets, such as PD-1 and PD-L1 receptors (84). Additionally, HDAC3, HDAC4, HDAC5, HDAC6, HDAC7, SIRT3, SIRT5, SIRT6 and SIRT7 seem to be possible prognostic indicators, while HDAC1, HDAC2 (85) and HDAC4 may also be used as predictive biomarkers (86). These results provide a plethora of possible targets and biomarkers for targeted therapy, prognostic evaluation and treatment optimization in GC.

Methylation modifications and gastric cancer. Several malignancies and developmental problems are linked to dysregulation of histone lysine methylation. Thus, histone lysine methylation is a potential therapeutic target (87). Since cancer frequently exhibits aberrant histone methylation caused by gene mutations, translocations, or dysregulation, a number of HMTs and HDMs are possible therapeutic targets (88). The histone methyltransferase EZH2 has been thoroughly investigated in the context of GC pathogenesis (89). Its overexpression in GC is linked to progression, malignancy and poor prognosis and promotes H3K27 trimethylation. Other HMTs involved in GC include SUV39H1 and SUV39H2, which promote H3K9 methylation and play roles in the initiation, progression and spread of GC (90,91). Methylation of the ribosomal protein L40 (rpL40) has been linked to the ribosomal export process in GC by the lysyl methyltransferase SMYD5. One possible component of combination treatment for this cancer is targeting SMYD5 (92).

Although some HDMs exhibit tumor-suppressive properties, their potential functions in cancer are mainly oncogenic. By demethylating H3K4, which silences tumor suppressor genes and promotes tumorigenesis, LSD1, a member of the LSD family of HDMs, functions as a transcriptional co-repressor (93,94). Additionally, numerous KDMs are

Table I. Landscape of major histone modifications and their regulators in GC.

Modification	Enzymatic regulators	Relevance in GC	Key associated molecules/targets in GC
Acetylation	Writers: HATs • p300/CBP • GNAT family • MYST family Erasers: HDACs • Class I/II (Zn^{2+}-dependent) • Class III (NAD^{+}-dependent, SIRTs)	HDAC overexpression correlates with poor prognosis; HDACs inhibitors are promising therapeutic targets. HDAC6 upregulates PD-1/PD-L1. BRD4 promotes GC progression and metastasis.	HDAC1, HDAC3, HDAC6; BRD4; HSPA4; SLC9A9/ pomiferin; NNT K1042ac.
Methylation	Writers: HMTs • EZH2 •SUV39H1/2 • SETD7 • PRMTs Erasers: KMTs/HDMs • LSD1 (KDM1A) • KDM5A/B/C • KDM6B	EZH2 overexpression correlates with progression and poor prognosis. SUV39H1/2 participate in GC initiationand migration. LSD1 and KDM5A/B/C are overexpressed and associated with proliferation and metastasis.	EZH2; SUV39H1, SUV39H2; LSD1 (KDM1A); KDM5A, KDM5B, KDM5C; KDM6B; SETD7/ YAP1
Lactylation	Writers: Lactyltransferases • p300/CBP • AARS1 • KAT2A, HBO1 Erasers: Delactylases • SIRT1-3 • HDAC1-3	H3K18la level is markedly increased in GC and closely related to poor prognosis. Kla drives metabolic reprogramming, proliferation, migration, immune escape and therapy resistance.	H3K18la; AARS1; LDHA; GLUT3; PFKM; HKDC1; NLRP12; PD-L1.
Citrullination	Writers: PADs, especially PAD4 Erasers: (Not well characterized)	PAD4 has genetic susceptibility to GC and its overexpression promotes tumor angiogenesis, proliferation and migration. PAD4 regulates H3R26 citrullination in GC cell lines.	PAD4; H3R26; CXCR2, KRT14, TNF-α.
Ubiquitination	Writers: E3 ubiquitin ligases (e.g., RNF112, TRIM29) Erasers: DUBs (e.g., USP9X, OTUD5)	Ubiquitination regulates glycolytic reprogramming and promotes GC metastasis. TRIM29/IGF2BP1/PD-L1 axis is a potential therapeutic target.	TRIM29/IGF2BP1/ PD-L1;

The table summarizes the five major histone modification types with significant functions in GC. For each modification, the table lists its key 'writer' enzymes and 'eraser' enzymes, outlines the known role of relevance in GC. It provides examples of key associated molecules or targets in GC. This table aims to provide a quick, comprehensive reference framework for understanding the clinical significance of different histone modifications in GC. GC, gastric cancer; HATs, histone acetyltransferases; p300, E1A-associated protein p300; CBP, CREB binding protein; GNAT, GCN5-related N -acetyltransferase; HDACs, histone deacetylase; SIRTs, sirtuins; PD-1/PD-L1, programmed death-1/programmed cell death ligand 1; BRD4, bromodomain containing 4; HSPA4, heat shock protein family A (Hsp70) member 4; SLC9A9, solute carrier family 9 member A9; NNT, nicotinamide nucleotide transhydrogenase; K1042ac, acetylated at lysine (K) 1042; HMTs, histone methyltransferases; EZH2, Enhancer of zeste homolog 2; SUV39H1/2, suppressor of variegation 3-9 homolog 1/2; SETD7, SET domain containing 7; PRMTs, protein arginine methyltransferases; KMTs, lysine methyltransferases; KDMs, lysine demethylases; LSD1, lysine-specific demethylase 1; KDM1A, lysine-specific histone demethylase 1A; KDM5A/B/C, lysine-specific histone demethylase A/B/C; KDM6B, lysine-specific histone demethylase 6A; AARS1, alanyl-tRNA synthetase 1; KAT2A, lysine acetyltransferase 2A; HBO1, Lysine Acetyltransferase 7; H3K18la, histone H3 lysine 18 lactylation; AARS1, alanyl-tRNA synthetase 1; LDHA, lactate dehydrogenase A; GLUT3, glucose transporter 3; PFKM, phosphofructokinase-1; HKDC1, RNA-binding protein hexokinase domain component 1; NLRP12, nucleotide-binding leucine-rich repeat-containing receptor (NLR) family pyrin domain-containing 12; PAD4, Peptidylarginine deiminase 4; H3R26, arginine residue 26 of histone H3; CXCR2, C-X-C motif chemokine receptor 2; KRT14, keratin 14; TNF-α, tumor necrosis factor alpha; RNF112, ring finger protein 112; TRIM29, tripartite motif containing 29; USP9X, ubiquitin-specific peptidase 9, X-linked; OTUD5, ovarian tumor protease deubiquitinase 5; USP9X, ubiquitin-specific peptidase 9, X-linked; IGF2BP1, insulin-like growth factor-2 mRNA-binding protein 1.

overexpressed in GC tissues. These KDMs include KDM1A, KDM5A, KDM5B and KDM5C, which are involved in cell proliferation and metastasis (95,96) and are members of the H3K4 demethylase family; KDM2A and KDM2B, which drive cell growth and migration and KDM4B and KDM4C, which are members of the H3K9 demethylase family and are involved in tumor growth and invasion (97). Additionally, GC development is linked to excessive expression of the H3K27 demethylase KDM6B. There have been numerous reports of aberrant expression of enzymes controlling histone methylation (91,98). Therefore, there are possible treatment targets for the dysregulation of histone lysine methylation, which is closely associated with developmental problems and cancer. Genetic mutations or other mechanisms frequently cause such dysregulation in GC, with aberrant expression or function of HMTs (e.g., EZH2 and SUV39H2) and HDMs/KDMs (e.g., LSD1 and KDM1A) being pertinent to the initiation, progression and prognosis of GC, respectively, thereby providing possible therapeutic targets.

Other modifications and gastric cancer. Histone citrullination is an increasingly important therapeutic target, which aids in addressing GC (99). PAD4 is an essential enzyme that controls histone citrullination and is crucial in initiating and promoting GC. The PAD4 monomer is composed of two domains, one of which is the N-terminal domain (residues Met1-Pro300) and the other is the C-terminal catalytic domain, which consists of residues Asn301-Pro663. Two immunoglobulin-like subdomains make up the N-terminal domain. Residues Met1-Cys118 are included in subdomain I, while the residues between Ala119 and Pro300 are included in Subdomain II (100). The PAD4 gene is genetically predisposed to GC. GC is strongly associated with tag SNPs at the PAD4 locus. Overexpression of PAD4 converts arginine residues to citrulline residues. By increasing the expression of TNF-α, KRT14 and CXCR2, this effect might encourage tumor angiogenesis, cell proliferation and cell movement. Collectively, these modifications create an immune microenvironment that supports GC development (101). PAD4 is essential for GC cell lines and may increase the citrulline modification of H3R26, supporting the hypothesis that PAD4 contributes to GC development by regulating histone citrullination (102).

In conclusion, the histone citrullination alteration mediated by PAD4 is a potential therapeutic target in GC. By suppressing the activity or expression of PAD4, it is possible to lower the level of histone citrullination and consequently, its regulatory influence on downstream cancer-causing genes. This may open up a novel avenue for GC therapy based on the precise control of histone citrullination and may prevent the spread, movement and angiogenesis of GC cells, ultimately improving patient prognosis. Protein ubiquitination plays a critical role in GC progression by affecting the reprogramming of glycolytic metabolism and advancement of GC metastasis (103). Tripartite motif-containing protein 29 (TRIM29) expression is lower in GC tumor tissues than in normal tissues. The TRIM29/IGF2BP1/PD-L1 axis includes TRIM29 and represents a potential therapeutic target (104). By contrast, the promotion of ubiquitination prevents GC growth and enhances the effectiveness of anticancer medications. Tumor tissues produce more lactate in cancer-associated fibroblasts (CAFs). In GC cells, this lactate encourages the lactylation of H3K18. Deubiquitination of the non-SMC condensin I complex subunit G (NCAPG) is indirectly enhanced by the activation of spindle microtubule assembly factor (ASPM). PD-L1 expression is enhanced by NCAPG. The effectiveness of anti-PD-1 treatment for GC may be enhanced by daturilin, a low-molecular-weight NCAPG antagonist (105).

The intricate regulatory system of histone ubiquitination has great potential for reversing the aberrant proliferation and metastatic behavior of GC cells. This strategy creates new opportunities for precisely targeted therapies based on the control of histone ubiquitination and aids in the creation of more successful GC treatment approaches.

4. Function of histone lactylation in gastric cancer

Kla uses a variety of processes to markedly affect the development and course of GC, which has a profound effect on the course of the illness (106). Kla controls metabolic reprogramming in GC, markedly alters a wide range of proteins in GC cells, affects major metabolic pathways, such as fatty acid metabolism and glycolysis, and simultaneously promotes metabolic abnormalities and malignant progression. Its mode of action involves the aberrant expression of molecules such as AARS1 and NLRP12, as well as lactation-induced changes to histones such as H3K18la. Conversely, Kla modulates histone modification and controls the activity of molecules such Glucose transporter 3 (GLUT3), Phosphofructokinase muscle isoform (PFKM) and HKDC1. By activating the appropriate signaling pathways, Kla promotes the growth, migration and invasiveness of GC cells. Furthermore, GC cells can evade immune system surveillance by influencing PD-L1 expression and regulating the function of tumor microenvironmental components, including cancer-related fibroblasts, macrophages and regulatory T cells. As a result, Kla is a major catalyst for the advancement of GC and management of drug resistance. The method by which these factors are lactylated will then be examined in depth.

Lactylation and metabolic reprogramming. Kla is essential for GC development because it controls metabolic reprogramming. According to previous research, the protein Kla varies greatly among the liver cancer, pancreatic cancer, colorectal cancer and GC. A variety of functional routes are enriched in proteins with specific Kla sites, particularly those involved in metabolic processes, such as fatty acid metabolism, glycolysis, glucuronidation and amino acid metabolism (107). Thus, Kla might affect the course of GC by changing the fundamental metabolic pathways (108). A total of 2,375 Kla sites were identified among 1,014 GC cell proteins (109). The fact that the amount of H3K18la is much higher in GC and is strongly associated with poor prognosis is noteworthy, reinforcing the importance of Kla in GC metabolic reprogramming and disease progression, particularly through regulation of metabolic gene expression mediated by histones (57,108). Lactate dehydrogenase A (LDHA) and AARS1 are upregulated in GC and their increased expression is associated with negative patient outcomes. Abnormal expression of AARS1, a crucial enzyme in lactate metabolism, may indirectly control metabolic reprogramming in GC by upsetting the dynamic

equilibrium of Kla, making it a potential marker of metabolic abnormalities and malignancy in GC (52). By contributing to the metabolic reprogramming of GC cells, improving the expression of H3K18la and stabilizing the essential glycolytic enzyme hexokinase 2 (HK2), the NLR family pyrin domain, which includes 12 members (NLRP12), primarily advances the progression of GC (110). Kla, similar to H3K18la, plays a significant role in the metabolic reprogramming of GC by regulating the expression of essential metabolic pathways and associated proteins (e.g., AARS1, NLRP12 and HK2) in GC cells. The significance of Kla in the pathogenesis of GC and its enormous potential in scientific studies and clinical practice have been emphasized.

Promotion of gastric cancer proliferation and migration. Lactate is an important metabolic intermediate, which serves as a mediator for Kla and promotes the development and progression of GC. In this process, several molecules either control Kla or are directly involved in the pathways linked to lactylation. Previous studies have demonstrated that lactate directly promotes tumor cell progression in GC cells (111-113). This mechanism corresponds to the function of lactate as a metabolic intermediate as it facilitates histone modification and promotes the transcription of Vascular Cell Adhesion Molecule 1 (VCAM1) by inducing H3K18la. The AKT-mTOR signaling pathway increases C-X-C Motif Chemokine Ligand 1 (CXCL1) expression via VCAM1. This encourages the recruitment of human GC-derived mesenchymal stem cells, increases immunosuppression and hastens the course of cancer (114). Primary and metastatic GC tumors both exhibit high levels of GLUT3 expression. Its expression is positively associated with lactate-associated pathways and LDHA. By controlling H3 Kla, which facilitates cell proliferation, metastasis and invasion, GLUT3 modulates GC cell activity (115). PFKM is one of the primary rate-limiting enzymes in glycolysis. Its expression is controlled by lactate and is overexpressed in GC. By increasing Contactin-1 (CNTN1) via H3K18la, PFKM promotes GC progression; by decreasing PFKM, GC cell proliferation and migration are inhibited (116,117). Intracellular lactate levels are detected by AARS1, which then translocates to the nucleus. Lactate activates the YAP-TEAD transcription factor complex, which initiates a positive feedback loop that encourages the growth of GC cells. Poor patient prognosis is associated with high AARS1 expression in GC (52,118). In GC, hexokinase domain-containing 1 (HKDC1) protein stimulates the expression of H3K18la. Controlling VCAM1 expression accelerates tumor development (119). Kla changes, such as H3K18la changes, are mediated by lactate via its own activity and by important molecules such as GLUT3, PFKM, AARS1 and HKDC1. This either controls signaling pathways (such as AKT-mTOR and YAP-TEAD) or activates the expression of target genes (such as VCAM1 and CNTN1). Ultimately, it promotes GC development through a variety of methods, including boosting tumor cell activity, attracting immunosuppressive cells and triggering pro-oncogenic signals.

Lactylation and immune microenvironment. Kla is a vital mechanism that facilitates the progression of GC, influencing tumor-immune interactions in a variety of ways during its development (120). According to previous research, there is a clear link between lactate and tumor immune evasion; the amount of lactate released by tumor tissues is markedly higher than that released by healthy tissues. Increased lactate concentrations in GC tissues lead to much higher PD-L1 expression than that in the normal control group, demonstrating that lactate aids cancer cells in evading the immune system (121). Lactic-acid-mediated immune escape also involves cellular elements in the tumor microenvironment (TME) (122). Expression of the closely linked protein-9 (CLDN9) gene and interleukin IL-4 both cause CD8+ T cell dysfunction in GC, which contributes to immune escape. Through the PI3K/AKT/HIF1α signaling pathway, CLDN9 promotes the glycolysis pathway while also fostering the production and stability of PD-L1 lactate (123). By boosting ATP synthesis and increasing sugar fermentation, inducing lactate production, upregulating the expression of FcγRIIB on the surface of macrophages and inducing PD-1 antibody to treat drug resistance, IL-4 stimulates macrophage metabolic changes, activates the PI3K/AKT/mTOR pathway and facilitates immune escape (124,125). By lowering the inhibitory effect on CD8+ T cell activity, deletion of G protein-coupled receptor 81 (GPR81) reduces the entry of regulatory T cells into the TME and slows the development of GC (113). By controlling the release of lysyl oxidase (LOX) and CLDN9 by CAFs, activating the PI3K/AKT/HIF1α pathway and inducing macrophage metabolic changes caused by IL-4, Kla directly encourages the expression of PD-L1 in tumor cells and mediates immunity throughout the development of GC. Kla also promotes medication resistance in GC therapy by influencing Treg cell infiltration through GPR81. In conclusion, lactylation is an essential primary immune-related process in GC development.

Lactylation and therapy resistance. Lactate plays an essential role in the mechanism of tumor drug resistance by controlling the immune microenvironment, DNA repair, gene expression and metabolic pathways (126) and contributes to drug resistance in various tumor types (127). In the context of immunological drug resistance, lactate induces the expression of chemokine CX3CL1 by activating the GPR81 signaling pathway, which promotes the entry of regulatory T cells into the TME. By reducing regulatory T cell infiltration and mitigating its inhibitory effect on CD8+ T cell function, GPR81 deletion can prevent the central lymph node from progressing (117). Kla is widely involved in various drug resistance mechanisms, providing key theoretical support and potential ways to develop new Kla targeting strategies to overcome tumor drug resistance.

5. Clinical significance of histone lactylation modifications

Biomarkers for gastric cancer diagnosis and prognosis. The spread and invasion of GC cells is facilitated by GLUT3. In GC cells, LDH activity, L-lactic acid concentration and Kla levels can be markedly reduced by knocking out GLUT3, indicating that it may be used as a possible diagnostic marker of GC (128). The gene associated with hypoxic-glycolysis-lactic acidation mirrors the intrinsic metabolic condition, drug reactivity and immunological microenvironment makeup of GC, which aids

in improving prognostic assessment (129). The SIRT family is a subset of class III HDACs. The combination of oxamate and a low dose of the SIRT1 activator SRT2104 may markedly limit the proliferation of GC cells (57). The efficacy of these treatment strategies, which are regulated by lactylation, supports the use of lactylation-related chemicals as prognostic indicators.

Models that incorporate numerous genes related to lactylation reflect disease features more accurately than models that focus on a single molecule. The lactate production scoring model is a promising diagnostic biomarker for GC because database analysis has revealed four basic lactylation-related pathways in GC tissues, which led to the selection of six lactylation-related genes for model development (130). Based on the Cancer Genome Atlas study, a risk model for lactate production-related genes efficiently differentiates molecular and immunological features in patients with GC, laying the groundwork for prognostic evaluation (121).

Therapeutic targets. Extensive studies have shown that epigenetic drugs can suppress oncogenes or activate tumor suppressor genes to treat specific cancers. In research on lactate-related therapeutic targets for GC, molecules involved in lactate metabolism and transport are important research directions (131). As a key enzyme in lactate production, LDHA has shown potential in preclinical studies on targeted drugs (132). Zhao *et al* (128) conducted experiments using samples from patients who underwent gastrectomy and found that oxamate, a widely used LDHA inhibitor, suppressed GC cell proliferation when used alone. However, this has not been clinically validated. Lactate transporters are closely associated with LDHA. A previous study suggested that inhibiting monocarboxylate transporters targeting glycolytic and oxidative tumor cells disrupts the lactate shuttle, thereby overcoming immune evasion, enhancing immunity and strengthening antitumor effects (126). Among them, the MCT1 inhibitor AZD3956 has entered clinical trials and is expected to further inhibit GC progression by blocking lactate transport. However, it should be noted that studies have identified cases of malignant hyperlactemic acidosis occurring in patients with metastatic melanoma immediately after their first exposure to AZD3965. Therefore, the efficacy and safety of AZD3956 in GC still require confirmation in clinical trials (127). β-Aminopropionitrile, a LOX inhibitor compound, has been shown to be effective in treating breast cancer by inhibiting LOX. In GC, subsequent studies have clarified that CAFs can drive tumor progression through the LOX/transforming growth factor β(TGFβ)/IGF1 pathway. Earlier experiments revealed that dextran sulfate can simultaneously reduce the expression of LOX and TGF-β under hypoxic conditions, while inhibiting the invasion and migration of GC cells. Although this early study did not explicitly link these molecules to a single pathway, its findings align closely with the subsequently elucidated pathway inhibition effects. Therefore, β-aminopropionitrile likely exerts its anti-GC activity by inhibiting the same LOX/TGFβ/IGF1 pathway, though this remains to be confirmed through targeted experimental validation (133-135). Monocarboxylate transporter 4 is highly overexpressed in malignant GC cells with peritoneal carcinomatosis and silencing this protein reduces tumor cell proliferation and lactate uptake in malignant ascites, making it a clinically specific target for GC (136). In addition, there are multiple notable targets for lactylation-related epigenetic regulation and cell death mechanisms. Tumor stemness refers to tumor cells with stem cell behavior and characteristics that play key roles in tumorigenesis (137). METTL14 expression is upregulated by histone H3Lys18 lactylation, which inhibits GC stemness by mediating m6A modification of ATF5 mRNA; knocking down METTL14 activates the WDR74/β-catenin axis to promote stemness and reduced METTL14 expression levels in patients with GC correlate with poor prognosis, making it a potential therapeutic target (138). In GC therapeutic research, these targets have shown potential for inhibiting disease progression and improving prognosis, providing multidimensional approaches for precision treatment.

Current limitations and unresolved questions in histone lactylation research in GC. Currently, it is quite difficult to identify Kla, especially at particular histone locations such as H3K18la, owing to the lack of antibody specificity. According to recent research, most PTMs have not yet been isolated. Instead, it has been suggested that two or more separate PTMs could interact with each other. Due to the potential for cross-reactivity with other acylation changes, such as acetylation, the validity of existing antibodies may be jeopardized (49). Second, mass spectrometry analysis struggles with signal interference because lactyl-lysine and N6-carboxyethyl lysine are isomers with the same molecular weight, making it difficult to distinguish them. Additionally, lactoyl-CoA, the major substrate, is found at very low concentrations in cells and traditional mass spectrometry techniques are not sufficiently sensitive to identify it. This constraint prevents precise measurements and dynamic tracking investigations (50). Most importantly, most of the possible targets mentioned in the present review, such as GLUT3, LDHA and MCT1, are still in the early stages of research, underscoring the universal difficulties in translating histone Kla research from basic mechanisms to therapeutic uses. For example, CLDN9 is essential for GC immune evasion. Systemic suppression of this protein, which regulates several cellular processes, may have significant systemic consequences. Therefore, it is essential to develop therapies that target CLDN9, particularly for the treatment of GC, without causing harm to the body. However, modern technologies are still unable to satisfy this need.

6. Outlook

GC is one of the most prevalent types of cancers worldwide. The pathogenesis is complex and exhibits significant heterogeneity. Clinical diagnosis and treatment still face numerous challenges, including difficulties in early detection, drug resistance and poor prognosis. Overall, the pivotal role of epigenetic regulation in tumor development has become increasingly prominent.

Epigenetic regulation constitutes a multilevel network for the occurrence and development of GC, in which classic mechanisms such as DNA methylation, chromatin remodeling complexes and non-coding RNA work together with histone modifications to regulate gene expression and cell fate. As important epigenetic regulatory machinery, histone modifications dynamically regulate chromatin structure and gene expression through acetylation, ubiquitination and Kla. These modifications are involved in numerous biological processes such as proliferation, migration,

metabolic reprogramming and immune escape of tumor cells, representing hot spots in GC research.

The present review focused on histone modification in GC and systematically reviewed its molecular mechanism, functional role and clinical transformation potential. It outlined how different types of modifications regulate the development of GC and explain how they affect the process of metabolism, proliferation, migration and immunity to drive the progression of tumors. It also focused on the clinical value of histone modification (especially Kla modification) in GC as a diagnostic biomarker and treatment target, as well as the prospect of application in analyzing the mechanism of drug resistance. Ultimately, the present review combined existing research results to further transform these findings into clinical practice.

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Competing interests

The authors declare that they have no competing interests.

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