

Histone modifications in cervical cancer: Epigenetic mechanisms, functions and clinical implications (Review)

XUEWEI LI¹, MIN ZHOU¹, JING YU², SHAOHUI YU¹ and ZHENG RUAN³

¹Department of Gynecology, The Affiliated Hospital to Changchun University of Chinese Medicine, Changchun, Jilin 130021, P.R. China;

²Department of Endocrinology, The Affiliated Hospital of Changchun University to Chinese Medicine, Changchun, Jilin 130021,

P.R. China; ³Department of Traditional Chinese Medicine, 964th Hospital, Changchun, Jilin 130062, P.R. China

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Abstract. Cervical cancer (CC) poses a substantial global health challenge and it ranks as the fourth most prevalent malignancy among women worldwide. Management strategies include surgical intervention, radiotherapy, chemotherapy and emerging systemic treatments. Although advancements in immunotherapy and targeted therapies have been achieved, the aggressive metastatic nature of the disease, coupled with immune evasion and drug resistance, continues to limit overall survival rates. Therefore, there remains an urgent need to identify novel treatment modalities and more effective therapeutic agents. As fundamental regulators of epigenetic modifications, histone alterations serve a critical role in controlling gene expression, DNA repair mechanisms and cellular differentiation. These modifications include acetylation, methylation, phosphorylation, ubiquitination, ADP-ribosylation and glycosylation, as well as the more recently identified lactylation and palmitoylation. By restructuring chromatin and facilitating interactions among histones, DNA and regulatory proteins, these modifications exert a substantial influence on cellular functions. Aberrant histone modifications contribute to tumorigenesis, tumor heterogeneity and resistance to conventional anticancer therapies, making them a key focus of oncological research. In recent years, therapeutic strategies targeting histone modifications have gained increasing attention in the treatment of CC. Among these epigenetic alterations, histone acetylation and deacetylation have been extensively studied, with numerous histone deacetylase inhibitors showing promise in preclinical studies. The present review explores the patterns

of histone modifications in CC, emphasizing their molecular roles in tumor progression, metastasis and therapeutic resistance. Additionally, histone modification-driven therapeutic targets are examined, laying the groundwork for future precision medicine approaches in CC treatment.

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1. Introduction

Cervical cancer (CC) is the fourth most frequently diagnosed cancer among women worldwide, accounting for ~266,000 deaths and 528,000 new cases each year (1). CC contributes to 7.5% of all female cancer-related deaths, establishing itself as a notable cause of mortality among women (2). Well-structured screening programs that incorporate affordable treatment techniques, such as cryotherapy, loop electrosurgical excision and thermal ablation, can facilitate the early detection and management of precancerous lesions, thereby reducing the overall disease burden (3).

Nevertheless, in low- and middle-income countries, late-stage CC remains prevalent due to limited access to early diagnostic services and preventive care. Although chemotherapy and radiotherapy continue to serve as the standard treatments for CC, their overall effectiveness remains limited, with a number of patients exhibiting suboptimal responses (4). Notably, targeted therapy and immunotherapy have gained recognition as promising treatment strategies. The approval of PD-1 inhibitors for the management of recurrent or metastatic CC has enhanced host immune responses against human papillomavirus (HPV)-positive malignancies (5). However, despite their potential, several challenges persist, including the immunosuppressive tumor microenvironment, tumor immune

Correspondence to: Dr Zheng Ruan, Department of Traditional Chinese Medicine, 964th Hospital, 4799 Xi'an Road, Lvyuan, Changchun, Jilin 130062, P.R. China
E-mail: tiancai81@163.com

Abbreviations: CC, cervical cancer; HAT, histone acetyltransferase; HDAC, histone deacetylase; HPV, human papillomavirus

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evasion, low patient response rates and acquired drug resistance, all of which compromise treatment (6). In the future, treatment paradigms are expected to emphasize personalized medicine by refining targeted therapies to improve cure rates and extend patient survival.

Eukaryotic chromatin is primarily composed of histones and nucleosomes, with nucleosomes consisting of DNA wrapped around histone proteins. The tail regions of histones frequently undergo a range of post-translational modifications (7), collectively referred to as histone modifications. These modifications influence gene transcription through multiple pathways (8) and are essential for several key biological processes. Common histone modifications include acetylation, methylation and ubiquitination, with acetylation and methylation recognized as the predominant types (9). Recently, additional modifications, such as glycosylation, lactylation and palmitoylation, have been identified, further increasing the complexity of histone regulation (10-13). These modifications are vital for regulating gene expression, repairing DNA damage, and controlling the cell cycle, differentiation, apoptosis and tumor progression (14,15).

Histone modifications may act cooperatively or antagonistically, contributing to the formation of a 'histone code' that fine-tunes cellular functions (16,17). Disruptions in histone modification patterns are closely associated with various diseases, including cancer, neurodegenerative disorders and immune dysfunction, in which these alterations in gene expression contribute to disease progression (18,19). As a result, epigenetic therapies targeting histone modifications have emerged as a critical area of research in precision medicine.

In CC, histone modifications, an essential component of epigenetic regulation, affect key processes such as persistent HPV infection, dysregulation of the cell cycle, immune evasion and treatment resistance. These pathological features arise from chromatin remodeling and aberrant gene expression (20). Epigenetic therapies aimed at correcting abnormal histone modifications, including histone deacetylase (HDAC) inhibitors, are increasingly being recognized as potential treatments for CC (20). Therefore, a comprehensive analysis of the role of histone modifications in CC and their clinical implications may offer valuable insights into precision treatment strategies.

2. CC

CC ranks as the fourth most frequently diagnosed cancer among women worldwide, with ~660,000 new cases reported in 2022 (21). The World Health Organization estimates that CC affects 662,000 individuals globally, including 151,000 women in China (22). Despite a substantial reduction in incidence over the past three decades, CC remains a major global public health concern, with considerable regional disparities in both incidence and mortality rates (23,24). In high-income countries, incidence and mortality rates are notably lower than those in developing regions, largely due to widespread HPV vaccination, comprehensive screening programs and greater access to healthcare resources (25-27). Nevertheless, in the later stages of CC, mortality rates in developed nations can be elevated or comparable to those in developing countries, primarily due to the limited availability of effective treatments for advanced disease (28).

CC can be classified into two primary histological types: Cervical squamous cell carcinoma (CSCC), which arises from squamous cells; and cervical adenocarcinoma, which originates from glandular epithelial cells (29). CSCC accounts for >80% of CC cases worldwide and is associated with high incidence and mortality rates (25). This cancer progresses through a series of well-defined precancerous stages, culminating in cellular dysplasia, cervical intraepithelial neoplasia, and ultimately, squamous cell carcinoma (30).

HPV, a member of the *Papillomaviridae* family, is strongly associated with the development of CC. HPV types associated with CSCC are classified into two groups: Low-risk and high-risk types. Low-risk strains primarily cause genital warts, whereas high-risk strains are implicated in invasive cancer (31). High-risk HPV types 16 and 18 are responsible for ~90% of CC cases. Women infected with high-risk HPV types face a greater likelihood of developing invasive cancer compared with those infected with low-risk types (32).

All HPV types, regardless of risk classification, infect epithelial cells, particularly keratinocytes, leading to cellular immortalization (30). The HPV genome consists of three primary functional regions: The early (E) region, which encodes proteins E1-E7 that are necessary for viral replication; the late (L) region, which produces structural proteins L1 and L2 that are essential for virion assembly; and the long control region, a non-coding segment that contains cis-regulatory elements critical for DNA replication and transcription (33). E1 and E2 are essential for viral DNA replication and act as transcriptional regulators. The viral genome also encodes early genes, such as E5, E6 and E7, which contribute to oncogenic transformation. E5 enhances immune evasion, reduces dependence on growth factors and promotes cellular proliferation (34). E6 interacts with the tumor suppressor protein p53, leading to its degradation (35). E7 binds to retinoblastoma protein, mediating its degradation via the ubiquitin-proteasome system and promoting cell cycle progression (36).

During the later phases of infection, viral late genes become active within the suprabasal layers, initiating circular genome replication and the synthesis of structural proteins. As the virus ascends to the outer layers of the skin or mucosal surfaces, mature viral particles are assembled and subsequently released. Additionally, HPV alters gene expression and activates several signaling pathways, such as those mediated by growth factor receptors, Notch, RAS and PI3K/Akt/mTOR, all of which promote host cell survival and proliferation. These molecular alterations collectively contribute to cervical carcinogenesis (37-39) (Fig. 1).

Given the pivotal role of HPV in the pathogenesis of CC, prevention strategies targeting the virus have proven highly effective. Specifically, vaccination against high-risk HPV types has led to a notable reduction in CC incidence, particularly in developed countries (40). In addition, surgery, radiotherapy and chemotherapy are the standard treatments for locally advanced cervical cancer and have notably reduced the mortality rate of patients with CC; however, their effectiveness in treating more advanced or recurrent disease remains limited (41-43).

Advancements in immunotherapy and targeted therapy have demonstrated considerable promise in cancer treatment. Inhibitors of PD-1/PD-L1, such as nivolumab and

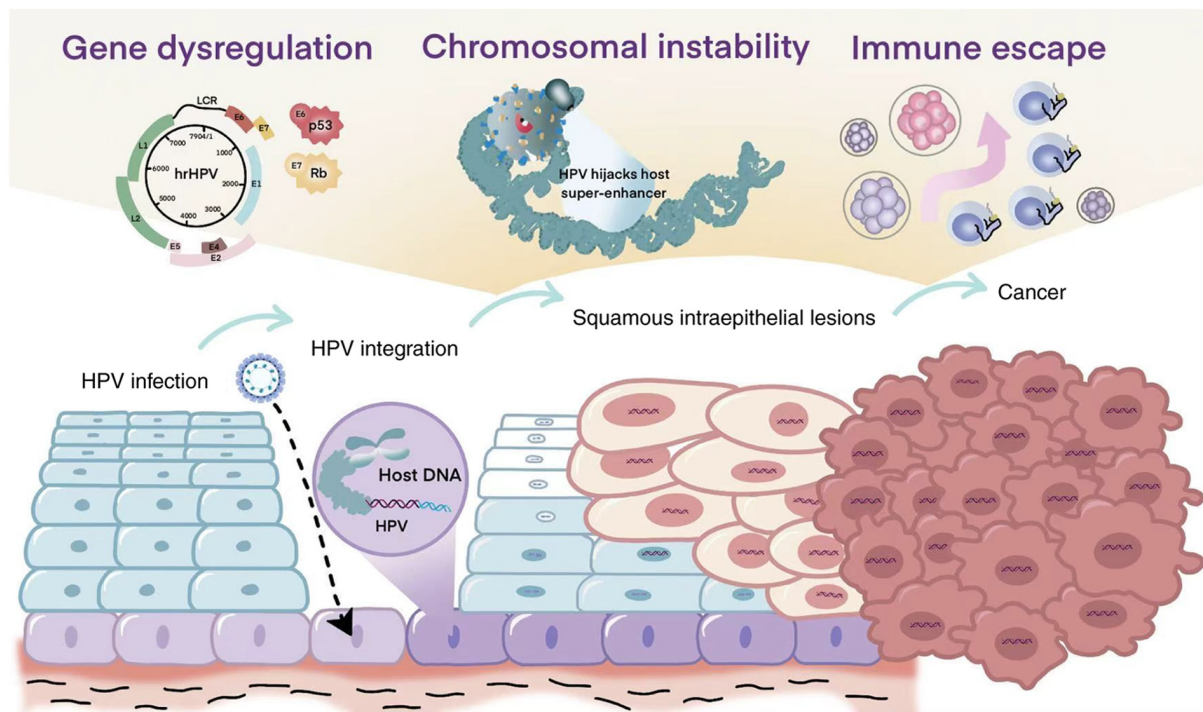


Figure 1. Molecular pathways of HPV-driven cervical carcinogenesis. This image illustrates the molecular pathways through which HPV contributes to cervical cancer development. Upon integration into the host genome, HPV disrupts gene regulation, induces chromosomal instability and facilitates immune evasion. These events promote the formation of squamous intraepithelial lesions, which may progress to invasive cervical carcinoma. The viral oncoproteins E6 and E7 accelerate this transformation by inactivating the p53 and Rb tumor suppressor pathways, thereby facilitating malignant progression. E, early; HPV, human papillomavirus; Rb, retinoblastoma.

pembrolizumab, function by disrupting immune checkpoint pathways, thereby enhancing the ability of the immune system to detect and eliminate cancer cells (44). Additionally, the use of CTLA-4 inhibitors, such as ipilimumab, has been explored as an immune checkpoint-based therapy for CC (45). Emerging evidence has indicated that these therapies exhibit substantial efficacy, particularly when combined with chemotherapy or radiotherapy, in patients with advanced or recurrent disease (46,47).

Although these therapies hold considerable promise, several challenges persist. Immunotherapy can induce immune-related adverse events, such as autoimmune disorders and severe inflammation, and its efficacy is often reduced in tumors exhibiting strong immune tolerance (48-50). Similarly, although targeted therapies are designed to act on specific molecular targets, their effectiveness is limited by tumor heterogeneity and the development of drug resistance, thereby reducing their long-term efficacy (48-50). Moreover, the success of both therapeutic approaches is influenced by individual patient factors and the complexity of the tumor microenvironment (48-50). As a result, future therapeutic strategies should emphasize personalized medicine and the continued development of targeted therapies, with the aim of improving cure rates and extending patient survival.

3. Histone modifications

Histone modifications serve a critical role in regulating biological processes by altering chromatin structure, thereby influencing the expression of specific genes. Although most

research has focused on well-characterized modifications, such as acetylation, methylation and phosphorylation, histones also undergo a variety of other modifications (51). These include citrullination, ubiquitination, ADP-ribosylation and O-GlcNAcylation, as well as less-studied modifications such as propionylation, butyrylation, crotonylation, lactylation and palmitoylation (51). These diverse modifications affect chromatin structure and gene expression, contributing to critical processes such as the cell cycle, DNA repair, differentiation and immune regulation. They also serve a role in the pathogenesis of diseases, including cancer (including CC), neurodegenerative disorders (such as Alzheimer's disease) and metabolic conditions (including diabetes mellitus) (52-54).

The regulation of histone modifications is mediated by 'writers' and 'erasers', enzymes that add or remove modifications, thereby ensuring appropriate gene expression (55). For example, histone acetyltransferases (HATs) introduce acetyl groups, leading to chromatin relaxation and enhanced transcription, whereas HDACs remove acetyl groups, resulting in chromatin condensation and transcriptional repression (56). Similarly, histone methylation is catalyzed by histone methyltransferases (HMTs), whereas histone demethylases are responsible for removing methyl groups. The coordinated activity of these enzymes modulates chromatin architecture and is essential for the regulation of gene expression (57). Notably, certain 'writers' and 'erasers' are capable of regulating multiple types of histone modifications. For example, G9a, a HMT, primarily catalyzes the methylation of lysine 9 on histone H3 (H3K9), but also modulates histone acetylation, thereby influencing gene silencing and chromatin

structure (58). Likewise, p300/CBP, a HAT, facilitates histone acetylation and transcriptional activation (59), and has also been shown to catalyze histone lactylation, a modification particularly relevant under conditions of altered cellular metabolism, such as hypoxia or inflammation (60). Similarly, HDACs primarily remove acetyl groups, leading to chromatin condensation and transcriptional repression; however, certain HDAC family members, such as sirtuin (SIRT)1, serve pivotal roles not only in histone deacetylation but also in regulating non-histone proteins, such as p53, thereby modulating apoptosis and DNA repair (61,62). In addition, lysine-specific demethylase (KDM)1, an ‘eraser’, can remove methyl groups from lysine 4 on histone H3 (H3K4) to suppress gene expression and from H3K9 to promote gene activation (54,63). The cross-regulation by these multifunctional enzymes indicates that histone modification is not a linear process but rather a highly dynamic and interactive network that enables precise control of gene expression, allowing cells to adapt to environmental changes and maintain gene expression homeostasis. A comprehensive summary of the major histone modifications, including ‘writer’ and ‘eraser’ proteins, their family classifications, target sites and functional roles, is presented in Table I.

Histone modifications are fundamental to the initiation and progression of cancer, primarily through their effects on chromatin structure and gene expression. Consequently, these modifications influence the transcription of genes involved in tumorigenesis. Aberrant histone modifications, including acetylation, methylation, phosphorylation and ubiquitination, can lead to the silencing of tumor suppressor genes or the activation of oncogenes, thereby facilitating tumor progression. For example, trimethylation of lysine 27 on histone H3 (H3K27me3), a repressive histone mark mediated by EZH2, is frequently observed in breast cancer and hepatocellular carcinoma (HCC), leading to the silencing of key tumor suppressor genes (64,65). For example, EZH2 promotes the stemness of HCC by inducing the transcriptional repression of the tumor suppressor gene TOP2A through H3K27me3-mediated silencing (65). Similarly, elevated levels of histone H3 lysine 9 acetylation (H3K9ac) and H3 lysine 27 acetylation have been associated with oncogene activation, contributing to the progression of colorectal and lung cancer (66). Moreover, histone modifications influence DNA damage repair pathways; for example, phosphorylation of H2AX is activated in response to DNA damage, and affect the tumor microenvironment, such as HDAC-driven immune suppression (67). They are also associated with resistance mechanisms; for example, KDM5A-mediated demethylation enhances chemotherapy resistance (68). As a result, epigenetic therapies targeting histone modifications, including inhibitors of HDACs and HMTs/KDMs, hold notable promise for precision cancer treatment, particularly when used in combination with immunotherapy and molecular targeted therapies.

4. Study of histone modifications in CC

Histone modifications serve a critical role in regulating the initiation, progression and therapeutic response of CC. Modifications such as acetylation, methylation, phosphorylation and ubiquitination are central to modulating gene expression, altering chromatin architecture and influencing

cellular signaling networks, all of which contribute to cancer development. Aberrant histone modifications can lead to the suppression of tumor suppressor genes or the activation of oncogenes, thereby promoting cellular processes, such as proliferation, invasion and immune evasion. Furthermore, histone modifications are closely associated with the development of resistance to therapies, including chemotherapy, radiotherapy and targeted treatments. This section examines the role of histone modifications in the pathophysiology of CC.

Histone acetylation. Histone acetylation, regulated by HATs and HDACs, is a reversible and dynamic process. HATs modify nucleosome structure by promoting chromatin relaxation, thereby facilitating gene transcription (Fig. 2). More than 20 HAT proteins have been identified, with key members belonging to the GNAT, MYST and p300/CBP families (69). Yang *et al* (70) demonstrated that the HAT CSRP2BP markedly promotes epithelial-mesenchymal transition (EMT) and metastasis in CC cells by activating N-cadherin. Notably, in CC tissues, elevated CSRP2BP expression was observed and revealed to be associated with poor prognosis. Furthermore, overexpression of CSRP2BP enhanced the proliferation and metastasis of CC cells in both *in vitro* and *in vivo* models, whereas its silencing had the opposite effect. CSRP2BP was also identified as a key contributor to cisplatin resistance. At the molecular level, CSRP2BP was revealed to catalyze acetylation of histone H4 at lysine residues 5 and 12, to form a complex with the transcription factor SMAD4 and to bind to the SEB2 sequence in the promoter region of N-cadherin, thereby upregulating its transcription. This mechanism may promote EMT and enhance metastasis in CC cells (70). These findings underscore the essential role of histone acetylation in the initiation, progression and development of drug resistance in CC. Similarly, the acetyltransferase p300 catalyzes acetylation of histone H3 at lysine 27 (H3K27), which enhances the activity of the NDUFA8 promoter, thereby stimulating CC cell proliferation (71).

Additional studies by Pan *et al* (72) and Qiao *et al* (73) further support the role of histone acetylation in promoting CC development. Given the significant role of HPV in CC, understanding how HPV infection modulates histone acetylation is essential for elucidating the mechanisms of tumor initiation and progression. Several studies have suggested that HPV-encoded proteins can target HATs, thereby promoting cancer progression (74-77). Conversely, HDAC inhibitors (HDACis) are recognized for their ability to suppress CC initiation and progression. For example, Zhu and Han (78) demonstrated that HDAC10 enhances antitumor responses by modulating the microRNA-223/thioredoxin-interacting protein/Wnt/ β -catenin signaling pathway. Moreover, research has shown that nicotinamide phosphoribosyltransferase suppresses CC by regulating NAD⁺ levels and enhancing the activity of the deacetylase SIRT1. In turn, SIRT1 deacetylates H3K27, alters the subcellular localization of PD-L1, and enhances immune responses (79). In a preclinical study, HDACis have been shown to promote mitophagy by acetylating Parkin, an E3 ubiquitin ligase, thereby suppressing the proliferation of CC cells (80). In addition, HPV-positive CC cells have been treated with the p300 inhibitor C646 to investigate its effect on HPV E6 and E7 expression, and cellular

Table I. Classification of histone modification families.

Category	Histone-modifying enzyme type	Family name	Regulatory modification type	Key action sites	Functional overview	(Refs.)
Writers	Histone acetyltransferases	p300/CBP family, GNAT family, MYST family, TAFII250 family, NAT family	Acetylation	H3K27ac, H3K9ac, H4K16ac	Catalyzes histone acetylation, facilitating chromatin loosening and gene transcription activation	(113-115)
	Histone methyltransferases	EZH family, SUV39 family, SETDB family, G9a/GLP family, SETD family, NSD family, ASH1L family, DOT1L family, PRMT family, SUV420 family	Methylation	H3K4me1/2/3, H3K9me1/2/3, H3K27me3, H3K36me3, H3K79me3	Catalyzes the methylation of histone lysine or arginine residues, modulating gene expression by activation or suppression	(116-118)
	Histone phosphotransferases	Aurora kinase family, cyclin-dependent kinases family, MSK family, JAK family, protein kinase C family, ATM/ATR family, RSK family, checkpoint kinases family	Phosphorylation	H3S10ph, H3T3ph, H2A.XS139ph	Catalyzes histone phosphorylation, modulating cell cycle progression and DNA damage repair	(119,120)
	Histone ubiquitin ligases (E3 ligases)	RING domain E3 family, HECT domain E3 family, Cullin-RING E3 ligase family, U-box domain E3 family, PHD domain E3 family, RBR domain E3 family	Ubiquitination	H2Aub, H2Bub	Catalyzes histone ubiquitination, influencing protein degradation, DNA damage response and gene transcription regulation	(121-123)
	Histone ADP-ribosyltransferases (PARPs)	PARP family, ADP-ribosyltransferase D family, tankyrases family	ADP-ribosylation	H1, H2A, H2B, H3, H4	Catalyzes histone ADP-ribosylation, regulating DNA repair and chromatin remodeling	(124,125)
	Histone lactyltransferases	p300/CBP family, MYST family, GNAT family	Lactylation	H3K18la, H3K9la	Catalyzes histone lactylation, linking cellular metabolism with epigenetic regulation	(126,127)
Erasers	HDACs	HDAC family, SIRT family	Deacetylation	H3K27ac, H3K9ac	Removes acetyl modifications, leading to chromatin condensation and inhibition of gene transcription	(128)

Table I. Continued.

Category	Histone-modifying enzyme type	Family name	Regulatory modification type	Key action sites	Functional overview	(Refs.)
	Histone demethylases	Lysine-specific demethylases family and Jumonji C domain demethylases family	Demethylation	H3K4me1/2, H3K9me1/2, H3K27me3	Removes methylation modifications, dynamically regulating gene expression states	(129,130)
	Histone PPs	PP1 family, PP2A family, PP2B family (Calcineurin), PP2C family, PP4 family, PP5 family, PP6 family	Dephosphorylation	H3S10ph, H3Y41ph	Removes histone phosphorylation, regulating cell signaling and stress responses	(131,132)
	Histone deubiquitinases	USP family, UCH family, OTU family, JAMM family, MJD family	Deubiquitination	H2Aub, H2Bub	Removes ubiquitin from histones, affecting protein stability and gene expression regulation	(133)
	Histone delactylases	HDAC family (classical deacetylases) and SIRT family	Delactylation	H3K18la, H3K9la	Removes histone lactylation, balancing metabolism-related epigenetic regulation	(134-136)

HDAC, histone deacetylase; PARP, poly ADP-ribose polymerase; PP, phosphatase; SIRT, sirtuin.

proliferation. The findings indicated that C646 can suppress E6 and E7 transcription, leading to the accumulation of p53 protein. At the same time, cell proliferation is inhibited, glucose metabolism is altered and apoptosis is triggered through the intrinsic apoptosis pathway (81,82). Additionally, several studies have shown that certain non-targeted drugs can act on HDACs to exert anticancer effects. For example, Zhang *et al* (83) reported that trifluoromethyl quinoline derivatives inhibit the proliferation of CC cells by specifically targeting HDAC1. Numerous preclinical studies have emphasized the potential anticancer benefits of HDACis (84-87). In CC, histone acetylation is associated with tumor progression, whereas histone deacetylation has a suppressive role. Notably, the use of HDACis can impede tumor growth. This effect is mediated through multiple mechanisms, including restoration of tumor suppressor gene expression, enhancement of DNA repair processes, stimulation of immune responses, and induction of apoptosis and autophagy, all of which collectively contribute to cancer cell death.

Histone methylation. Histone methylation is a dynamic and reversible process regulated by HMTs and KDMs. Methylation occurs through the activity of HMTs, which add methyl groups to specific histone residues, thereby modifying chromatin structure and function. These modifications are typically associated with either gene activation or repression, depending on the specific site and context (88-90).

Numerous HMTs, including members of the SET, DOT1L and SUV39H families, are involved in regulating gene expression, DNA repair mechanisms and cell cycle progression (88-90). Zhang *et al* (91) demonstrated that HPV18 E6/E7 increases the transcriptional activity of EZH2, resulting in elevated H3K27me3 levels in CC. Furthermore, Beyer *et al* showed that histone modifications, such as H3K9ac and trimethylation of lysine 4 on histone H3 are closely associated with clinicopathological parameters and 10-year survival outcomes, underscoring their prognostic value in CC (92). Chen *et al* (93) reported that NSD2, a HMT, promotes proliferation, migration and invasion of CC cells by activating the endothelial nitric oxide synthase and AKT/MMP-2 signaling pathways. Additionally, Ansari *et al* (94) identified the H3K4-specific methyltransferase MLL as a critical factor in cervical tumor growth. Knockdown of MLL reduced the expression of several key growth and angiogenesis-related factors, including HIF1 α , VEGF and CD31, thereby inhibiting CC progression. Notably, studies have shown interest in histone methylation enzymes as potential therapeutic targets. Zhang *et al* (95) reported that SUV39H1 upregulates DNMT3A expression in CC cells via trimethylation of lysine 9 on histone H3, while simultaneously downregulating immunosuppressive factors, such as Tim-3 and galectin-9. This activity may improve the tumor immune microenvironment and enhance therapeutic efficacy. Moreover, Osawa *et al* (96) showed that the histone demethylase JHDM1D suppresses angiogenesis-related

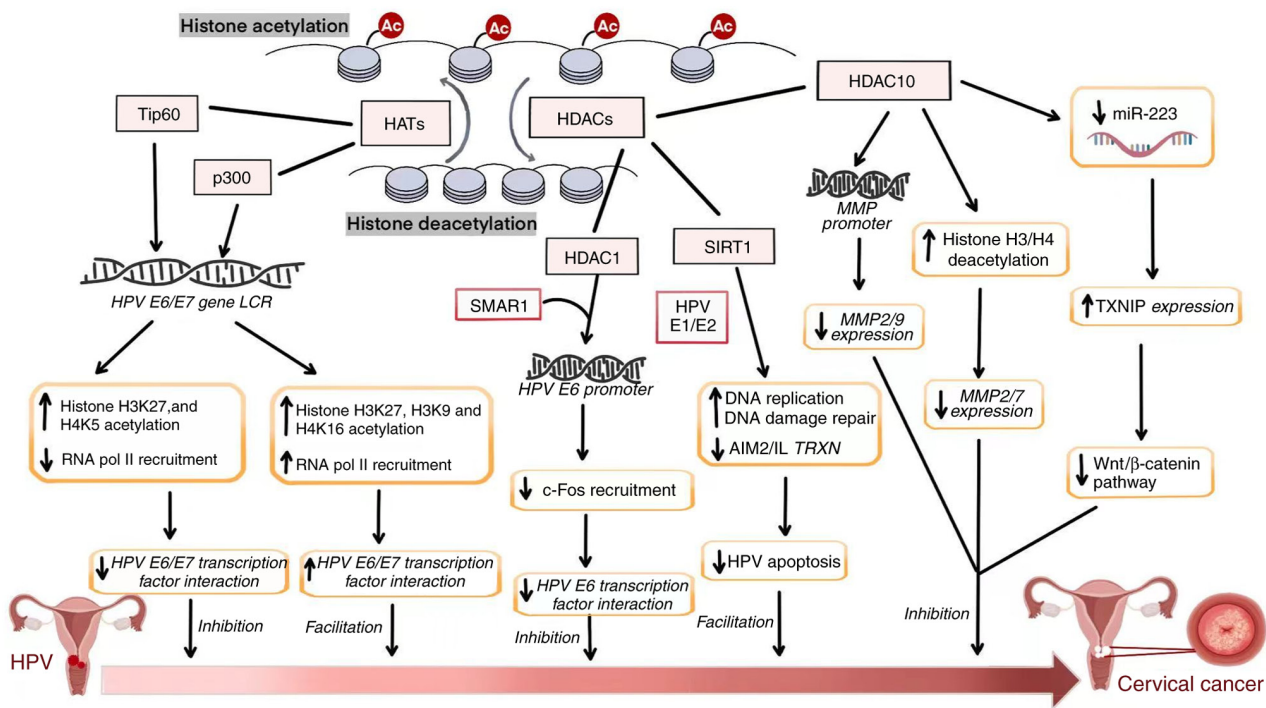


Figure 2. Mechanisms of histone acetylation in cervical cancer. Histone acetylation and deacetylation are regulated by HATs and HDACs, respectively, and represent highly dynamic processes. HATs, such as Tip60 and p300, promote chromatin relaxation and transcriptional activation, whereas HDACs, including HDAC1, HDAC10 and SIRT1, promote chromatin condensation by removing acetyl groups. These opposing activities critically modulate gene expression and influence cervical cancer progression through multiple signaling pathways. Inhibition and facilitation refer to the effects on cervical cancer. E, early; HAT, histone acetyltransferase; HDAC, histone deacetylase; HPV, human papillomavirus; LCR, long control region; miR, microRNA; SIRT, sirtuin 1; TXNIP, thioredoxin-interacting protein.

factors, including VEGF-B and angiopoietin, under conditions of nutrient deprivation, thereby limiting angiogenesis and exerting tumor-suppressive effects.

In summary, studies have identified the critical roles of histone methylation and demethylation in tumor progression, immune regulation, cell invasion and angiogenesis, all of which markedly contribute to CC development.

Histone phosphorylation. The regulation of histone phosphorylation involves histone kinases (HKs) and phosphatases (PPs), with both enzymatic processes being dynamic and reversible. Histone phosphorylation, catalyzed by HKs, modifies chromatin structure and function, typically influencing gene transcription by either activating or repressing it (97,98). Several HKs, including members of the Aurora, CDK and MSK families, serve essential roles in gene expression, DNA repair, cell cycle progression and signal transduction (97,98). In CC cells, phosphorylation of histone H2AX serves as a key indicator of DNA damage, reflecting cellular sensitivity to radiation and the efficiency of DNA repair mechanisms; this makes H2AX phosphorylation a promising biomarker for evaluating the therapeutic response to radiotherapy in CC (99). Zhao *et al* (100) also reported that alterations in H2AX phosphorylation levels before and after neoadjuvant chemotherapy provide valuable insights for assessing treatment response in patients with CC. Several additional studies have investigated histone phosphorylation as a potential biomarker for prognosis and treatment efficacy in CC (101-103).

Preclinical studies have further suggested that targeting PPs or their upstream kinases can effectively inhibit tumor

growth. For example, Zhang and Zhang (104) demonstrated that ZM447439, a potent Aurora kinase B inhibitor, suppresses the proliferation of SiHa CC cells while enhancing cisplatin sensitivity. Similarly, Cheung *et al* (105) reported that BPR1K653, a novel Aurora kinase inhibitor, exhibits strong antiproliferative effects in multidrug-resistant cancer cells mediated by MDR1 (P-gp170).

In conclusion, although histone phosphorylation has been extensively studied in various tumors, research specifically focusing on CC remains limited. Most studies have investigated phosphorylated histones as potential biomarkers or examined HKs that suppress CC progression. However, these investigations are still relatively preliminary and lack comprehensive mechanistic insights.

Histone lactylation. Histone lactylation is a newly identified epigenetic modification in which lactate molecules are covalently attached to lysine residues on histones, resulting in altered chromatin structure and changes in gene transcription. This modification has attracted increasing scientific attention over the past 3 years (106). In CC, a previous study has shown that DPF2, a member of the DPF protein family, recognizes lactylated histones and facilitates gene activation. Specifically, DPF2 binds to lactylated histones and promotes the transcription of target genes (SEMA5A, FUT8, ROCK1 and SOAT1), thereby contributing to the initiation and progression of CC. Histone lactylation is closely associated with cellular metabolism and transcriptional regulation, and serves a substantial role in CC development. These findings suggest that DPF2 may serve as a promising therapeutic target for CC (106). In

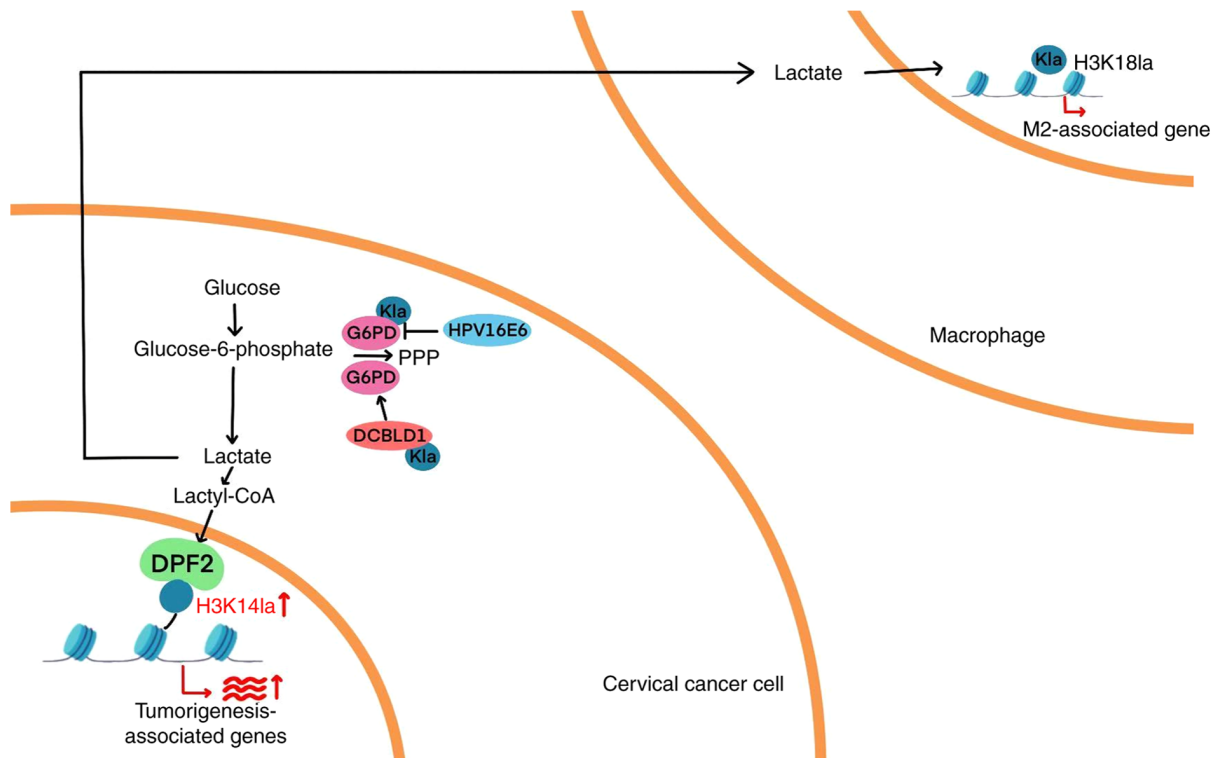


Figure 3. Mechanisms of histone lactylation in cervical cancer. Cervical cancer cells enhance glycolysis to regulate their own histone modifications, thereby promoting oncogene transcription. Concurrently, lactate secreted by tumor cells induces histone lactylation in macrophages, skewing their polarization toward the tumor-promoting M2 phenotype. Additionally, HPV contributes to tumor progression via the PPP, modulating the lactylation of G6PD. Lactylation of the DCBLD1 protein stabilizes G6PD by preventing its degradation, further supporting tumor growth. DCBLD1, discoidin domain-containing receptor 1; DPF2, D2 zinc finger protein 2; G6PD, glucose-6-phosphate dehydrogenase; HPV, human papillomavirus; PPP, pentose phosphate pathway.

addition, histone lactylation presents potential therapeutic targets for metabolic and immune-based interventions. Huang *et al* (107) investigated how CC cells modulate histone lactylation in macrophages through lactate secretion. Their findings revealed that lactate released by CC cells upregulates lactylation of lysine 18 on histone and M2 macrophage markers (arginase-1), while downregulating M1 markers (inducible nitric oxide synthase). Overall, lactate was shown to enhance GPD2 expression via histone lactylation, promoting M2 macrophage polarization and facilitating tumor progression. In summary, although histone lactylation is a relatively recent discovery with limited research in CC, its critical role in other malignancies underscores the importance of further investigation (Fig. 3).

Other histone modifications. Crotonylation is a histone modification in which a crotonyl group, an unsaturated short-chain fatty acid, is added to lysine residues on histones. This modification is associated with gene activation and the regulation of cellular metabolism. Over the past 3 years, crotonylation has garnered increasing attention in epigenetics research (108). In CC, a previous study has shown that p300-mediated crotonylation enhances the proliferation, invasion and migration of HeLa cells by promoting the activity of heterogeneous nuclear ribonucleoprotein A1 (hnRNP A1). Specifically, p300 modulates hnRNP A1 function by catalyzing histone crotonylation, which subsequently influences transcriptional and epigenetic regulation. This pathway serves a critical role in tumor growth and metastasis (108).

Several other histone modifications, such as ubiquitination, ADP-ribosylation, palmitoylation, propionylation and butyrylation, remain either rare or relatively newly characterized, thereby limiting their current investigation in CC. However, these modifications are expected to become important areas of future research, offering considerable potential for understanding the epigenetic regulation of CC.

5. Clinical application of targeting histone modifications in CC

Numerous preclinical studies have explored the potential of targeting histone-modifying enzymes as a therapeutic approach for CC. Histone modifications, such as acetylation and methylation, serve essential roles in regulating cancer cell proliferation, metastasis and resistance to therapy. For example, small-molecule inhibitors (such as p-coumaric acid, ferulic acid, sinapinic acid and resveratrol) that target HDACs or HMTs have demonstrated efficacy in reducing the proliferation and migration of CC cells, thereby inhibiting tumor progression (109-112).

In addition, some clinical studies have begun investigating the utility of histone modifications as prognostic biomarkers (97,103). By examining specific histone modification patterns in CC tissues, clinicians can obtain early insights into disease progression, recurrence risk and treatment response. Changes in histone modifications may be associated with tumor invasiveness, metastatic potential and resistance to

Table II. Histone-modifying drugs evaluated in clinical trials.

Histone modification type	Inhibitor name	Target enzyme	Clinical cancer types	Side effects	(Refs.)
Methylation	Tazemetostat	EZH2	Used in combination with atezolizumab for DLBCL; used with other EZH2 mutations, SMARCB1 loss or SMARCA4 loss in pediatric tumors; used with BAP1-inactivated malignant pleural mesothelioma	Anemia, neutropenia, hepatotoxicity	(137,138)
	Valemetostat	EZH2	NHL, including adult T-cell leukemia/lymphoma, B-cell lymphoma and peripheral T-cell lymphoma	Anemia, neutropenia, hepatotoxicity	(139,140)
	GSK126	EZH2	Lymphoma and solid tumors	Fatigue, nausea, diarrhea	(141)
	MAK683	EZH2	DLBCL and solid tumors (expected to complete clinical trial in fall 2026)	Fatigue, nausea, diarrhea	(142)
	Pinometostat	EZH2	MLL-rearranged leukemia	Fatigue, nausea, diarrhea	(143)
	Revumenib	Menin	Ewing's sarcoma	Fatigue, nausea, diarrhea	(144,145)
	Ziftomenib	Menin and LSD1	Ewing's sarcoma, used with other therapies	Anemia, neutropenia, hepatotoxicity	(146)
	Seclidemstat (SP-2577)	Menin and LSD1	NHL and advanced solid tumors; small cell lung cancer and LUSC, used with nivolumab	Anemia, neutropenia, hepatotoxicity	(147)
	Pulrodestat (CC-90011)	Menin and LSD1	Used for marginal zone lymphoma or other lymphomas when LSD1 expression is high; various neuroendocrine tumors, used with chemotherapy or immunotherapy	Fatigue, nausea, diarrhea	(148)
	Tranlycypromine	LSD1	AML and myelodysplastic syndromes, used with ATRA	Fatigue, nausea, diarrhea	(149,150)
	Chidamide	LSD1	Relapsed or refractory peripheral T-cell lymphoma	Hepatotoxicity	(151)
	Mocetinostat	LSD1	Hematological cancer (such as lymphoma and leukemia) and solid tumors (pancreatic cancer)	Appetite suppression	(152,153)
Acetylation	Citarinostat	HDAC	Lung cancer	Peripheral neuropathy	(154)
	Tucidinostat	HDAC	Non-small cell lung cancer, gastric cancer and hepatocellular carcinoma	Anemia	(155)
	Vorinostat	HDAC	Hodgkin's lymphoma	Fatigue, nausea, diarrhea	(156,157)
	Panobinostat	HDAC	Multiple myeloma	Fatigue, nausea, diarrhea	(158)
	Romidepsin	HDAC	NHL	Fatigue, nausea, anemia	(159)
	Belinostat	HDAC	Peripheral T-cell lymphoma	Fatigue, nausea, vomiting	(160)

AML, acute myeloid leukemia; ATRA, all-trans retinoic acid; DLBCL, diffuse large B-cell lymphoma; LUSC, lung squamous cell carcinoma; NHL, non-Hodgkin lymphoma.

standard therapies, offering valuable guidance for personalized treatment planning.

Although the clinical application of histone modification-targeted therapies in CC is still in its infancy, such agents, especially in the context of hematologic malignancies, have already advanced to large-scale clinical trials and have demonstrated encouraging results (Table II). Ongoing research suggests that these strategies may evolve into effective therapeutic options for CC. In the future, precise modulation of histone modification pathways could lead to advancements in early detection, prognostic evaluation and the development of individualized treatment strategies.

6. Conclusion

Histone modifications serve a crucial role in regulating the proliferation, migration, invasion and drug resistance of CC cells by altering chromatin structure and modulating gene expression. Although research into therapies targeting histone modifications in CC is still in its early stages, preclinical studies have suggested that enzymes such as HDACs and HMTs may effectively inhibit tumor growth and metastasis.

Moreover, histone modifications hold promise as biomarkers for early diagnosis, prognostic assessment and monitoring therapeutic responses. Distinct histone modification patterns may help predict tumor invasiveness and response to treatment. While drugs targeting histone modifications have not yet undergone widespread clinical testing in CC, emerging research indicates that these therapies may represent a novel option for personalized treatment strategies.

However, in low- and middle-income countries, the high cost and limited accessibility of histone modification-targeting therapies present substantial barriers to their use. Challenges such as inadequate healthcare infrastructure, unstable drug supply chains and restricted insurance coverage prevent a number of patients from receiving timely and effective treatments (113-115). Therefore, reducing drug costs, enhancing access to therapies and strengthening public health policy support are critical steps toward expanding the availability of these promising treatments, particularly for CC, which has a disproportionately high incidence in resource-limited settings.

In conclusion, histone modifications are integral to the pathogenesis of CC and offer substantial clinical potential. Future research should focus on elucidating the molecular mechanisms underlying these modifications and advancing clinically applicable therapies for early detection, individualized treatment and prognostic prediction.

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Authors' contributions

All authors contributed to the conception and design of the study. XL, MZ and ZR drafted the initial manuscript and prepared the figures. JY and SY provided constructive feedback. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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