Histone deacetylases: Function in tumor development and therapeutic prospects (Review)

RUNLING LIN, YU ZHANG, HONG LI and FAN LIANG

Department of Biochemistry and Molecular Biology, School of Basic Medicine, Shandong Second Medical University, Weifang, Shandong 261000, P.R. China

Received September 1, 2025; Accepted February 5, 2026

DOI: 10.3892/ol.2026.15497

Abstract. Histone deacetylases (HDACs), as key epigenetic regulators, serve a central role in tumorigenesis and progression by modulating chromatin architecture and gene transcription. In recent years, notable advances have been made in elucidating the pan-cancer mechanisms of HDACs and their inhibitors (HDACis), as well as in performing clinical studies, with their antitumor activity becoming a major research focus. The present review summarized the classification and molecular mechanisms of HDACs alongside their roles in various malignancies including ovarian cancer, endometrial carcinoma, glioma, osteosarcoma and multiple myeloma. The present review specifically elaborated on the relationship between particular isoforms, such as HDAC3, HDAC5, HDAC7 and HDAC11, and tumor progression, detailing associated signaling pathways. The present review systematically evaluated the current clinical applications of HDACis, examining both monotherapy and combination therapy efficacy alongside existing challenges. Furthermore, the present review discussed recent progress in structural modifications aimed at enhancing selectivity while reducing toxicity, as well as novel targeting strategies. Concluding with perspectives on HDAC-based therapies, the present review underscores the key importance of precision targeting and combinatorial approaches to improve patient outcomes in the future.

Correspondence to: Professor Fan Liang or Professor Hong Li, Department of Biochemistry and Molecular Biology, School of Basic Medicine, Shandong Second Medical University, 7166 Baotong West Street, Weifang, Shandong 261000, P.R. China
E-mail: liangfan@sdsmu.edu.cn
E-mail: lh@sdsmu.edu.cn

Abbreviations: AKT, protein kinase B; AML, acute myeloid leukemia; Bcl-2, B-cell lymphoma-2; CRC, colorectal cancer; CXCL10, C-X-C motif chemokine ligand 10; DLBCL, diffuse large B-cell lymphoma; DNMTis, DNA methyltransferase inhibitors; DNMTs, DNA methyltransferases; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; FGF18, fibroblast growth factor 18; HCC, hepatocellular carcinoma; HDACs, histone deacetylases; HDACis, HDAC inhibitors; HMTis, histone methyltransferase inhibitors; HSP90, heat-shock protein 90; MDSCs, myeloid-derived suppressor cells; MM, multiple myeloma; NF-κB, nuclear factor-κB; NSCLC, non-small cell lung cancer; PARP, poly(ADP-ribose) polymerase; PARPis, PARP inhibitors; PD-1, programmed cell death protein-1; PI3K, phosphoinositide 3-kinase; PROTACs, proteolysis-targeting chimeras; SATB1, special AT-rich sequence-binding protein 1; TIME, tumor immune microenvironment; TNBC, triple-negative breast cancer; USP38, ubiquitin-specific peptidase 38; VPA, valproic acid

Key words: HDACs, HDACis, combination therapy

Contents

1. Introduction

Histone deacetylases (HDACs), acting as key epigenetic regulators, control chromatin structure and gene expression by removing acetyl groups from histones. HDACs participate in fundamental cellular processes such as proliferation and apoptosis. Dysregulation of their activity is associated with tumorigenesis and progression, endowing them with dual importance both as therapeutic targets and biomarkers (1,2). Within the HDAC family, functional roles and expression patterns exhibit tumor-specific variability. For instance, upregulation of HDAC1 and HDAC2 enhances tumor invasiveness and chemoresistance (3,4). HDACs interact with other enzymes, such as lysine acetyltransferases and DNA methyltransferases (DNMTs), which renders the analysis of the relevant mechanisms more complex (5,6). HDAC inhibitors (HDACis) represent promising therapeutic agents. Notably, several HDACis have gained approval from the USA Food and Drug Administration (FDA) for hematological malignancies. However, their efficacy in solid tumors remains limited

due to off-target effects, poor sensitivity and acquired resistance (7,8). Current research priorities include investigating resistance mechanisms and exploring combination therapies, approaches whose potential have already been demonstrated across multiple tumor types. The development of novel HDACis with enhanced specificity and reduced toxicity is actively being investigated (9-13). The present review comprehensively examines the functions, mechanisms and therapeutic potential of HDACs to inform ongoing research and strategic development.

2. Classification and molecular mechanisms of HDACs

Classification and structural features of the HDAC family. The HDAC family is classified into class I, IIa, IIb and IV, with each subclass exhibiting distinct cellular localization, substrate specificity and functional roles. Members of class I, including HDAC1, HDAC2 and HDAC3, are predominantly localized in the nucleus and serve key roles in regulating gene expression, cell cycle progression and apoptosis. Notably, HDAC3 markedly influences both cell cycle regulation and apoptotic pathways, emerging as a key contributor to tumorigenesis and progression (14). The class IIa subgroup comprises HDAC4, HDAC5, HDAC7 and HDAC9. These enzymes shuttle dynamically between the nucleus and cytoplasm to participate in the modulation of diverse signaling cascades. For instance, HDAC5 and HDAC7 engage with pathways implicated in cancer metastasis, underscoring their oncological relevance (15-17). Class IIb HDACs, represented by HDAC6 and HDAC10, reside primarily in the cytoplasm, where they mediate non-histone deacetylation events, affecting processes such as cell motility and stress responses. Among these, HDAC6 has garnered attention as a promising therapeutic target due to its association with cancer and neurodegenerative disorders (18-20). Class IV histone deacetylase comprises only one isoform, HDAC11. Although the development of selective inhibitors faces numerous challenges due to the lack of crystal structure data, accumulating evidence indicates that this protein is involved in the initiation and progression of tumors and inflammatory diseases. The chemical space, scaffold diversity and key structural features of HDAC11 have been systematically characterized, providing core structural basis and a foundation for the design of selective inhibitors targeting this protein (21). The enzymatic activity of HDAC11 mediates resistance to MEK inhibitors in uveal melanoma, serving as an important molecule driving malignant progression of this tumor (22). In Hodgkin lymphoma cells, HDAC11 plays a central regulatory role in the expression of OX40 ligand, acting as a key factor involved in the formation of the tumor inflammatory microenvironment (23). Structural divergence among HDAC isoforms markedly impacts their interaction profiles with substrates and enzymatic activity. Conserved motifs and specialized domains dictate substrate-binding affinity and specificity, features that are fundamental to their cellular functions. Comprehensive understanding of these classification schemes and structural characteristics is essential in designing selective HDACis, enabling tumor-specific targeting for cancer therapy and other pathologies. Elucidating their precise mechanisms will establish a robust foundation for novel therapeutic interventions in the future (24,25).

HDAC-mediated deacetylation and chromatin remodeling. HDACs exert a central role in regulating chromatin structure and gene expression by catalyzing the deacetylation of lysine residues on histones. This process induces compaction of chromatin conformation, thereby reducing the accessibility of transcriptional machinery to DNA templates and subsequently repressing the transcriptional activity of tumor suppressor genes. HDAC-mediated histone deacetylation enhances the electrostatic interaction between histones and DNA, rendering the chromatin structure more compact and thereby restricting the binding of transcription factors to gene promoters. This process is one of the key epigenetic mechanisms that regulate gene expression in cancer cells (26).

Aberrant expression of HDACs is implicated in various malignant neoplasms. For example, in hepatocellular carcinoma (HCC), dysregulated histone acetylation drives tumorigenesis and progression by silencing tumor suppressor genes (27,28). Furthermore, HDACs extend their regulatory influence beyond histones through deacetylation of non-histone proteins, including transcription factors, thereby modulating cell signaling pathways and altering transcriptional activity. Such post-translational modifications can either enhance or repress target gene expression involved in cell survival, proliferation and metastasis (29,30). This dual regulatory capacity underscores the pivotal role of HDACs in maintaining chromatin dynamics and cellular signaling networks, establishing them as compelling therapeutic targets for cancer treatment. Additionally, HDACs interact with chromatin-remodeling complexes such as switch defective/sucrose non-fermentable; these interactions are key to preserving chromatin architecture and governing gene expression programs. Notably, recruitment of HDACs to specific genomic loci can displace chromatin remodelers, thereby reinforcing transcriptionally repressive environments (31).

Recent studies have revealed the synergistic role of combinatorial histone modifications in chromatin regulation, offering a novel dimension in understanding HDAC function (32,33). Notably, histone modifications can exert synergistic effects through combinatorial modification coding, while HDAC-mediated deacetylation may disrupt the balance of the acetyl-methyl lysine dual modification, thereby altering chromatin accessibility at transcription start sites. The existence of this acetyl-methyl lysine modification has been confirmed in relevant studies (34). For example, in endometrial carcinoma, HDAC1 forms a complex with enhancer of zeste homolog 2. Through deacetylation-methylation, this complex silences tumor suppressor genes such as p21. HDAC1-mediated histone deacetylation compacts chromatin to create conditions for methylation, therefore blocking cell cycle regulatory pathways (35). Furthermore, HDACs do not act independently in epigenetic regulation, but exhibit a close crosstalk with histone methyltransferases and DNMTs. In acute myeloid leukemia (AML), combining HDACis with DNMT inhibitors (DNMTis) disrupts the epigenetic repressive network, reactivates tumor suppressor genes and inhibits cancer cell proliferation (36). In lung cancer models, the interaction between HDAC3 and lysine-specific demethylase 1 affects enhancer activity by regulating histone H3 lysine 4 monomethylation levels, thus highlighting the key role of crosstalk between HDACs and other epigenetic regulators in tumorigenesis (37).

Interaction between HDACs and tumor-associated signaling pathways. HDACs interact with key signaling pathways involving factors such as nuclear factor-κB (NF-κB), p53 and heat-shock protein 90 (HSP90), thereby modulating cellular responses to stress and proliferation signals. For instance, within the constitutively activated NF-κB pathway frequently observed in cancer, HDACs exert post-translational modifications on pathway components via deacetylation, which is an action that fosters tumor cell survival and proliferation (38,39). Similarly, the tumor-suppressive functionality of the classical guardian protein p53 undergoes negative regulation by HDACs. Inhibition of p53 transcriptional activity through deacetylation enables cancer cells to evade apoptosis (5,40). A specific example during cancer progression involves crosstalk between HDAC5 and special AT-rich sequence-binding protein 1 (SATB1), a chromatin architect regulating tumor suppressor gene expression. Previous studies have demonstrated that, in lung adenocarcinoma, HDAC5-mediated deacetylation of SATB1 represses tumor suppressor genes thus not only promoting neoplastic growth and metastasis but also conferring chemoresistance (41,42). The aberrant expression patterns of HDACs across multiple malignancies, including lung cancer, underscore their dual role in oncogenic signaling, acting both as drivers of carcinogenesis and promising therapeutic targets (Fig. 1). Deciphering the intricate interactions between HDACs and these key regulators along with associated signaling cascades offers promising avenues for the development of enhanced cancer treatment modalities. Notably, combining HDACis with conventional therapies represents a strategic approach to overcome drug resistance and improve patient outcomes (19,43,44).

In summary, various subtypes of the HDAC family form a mechanism-phenotype regulatory network through chromatin remodeling, non-histone modification and regulation of signaling pathways (such as the NF-κB and p53 pathways). Aberrant activation of class I HDACs (such as HDAC1/3) can promote cell proliferation by silencing tumor suppressor genes. Class II HDACs (such as HDAC5/7) are involved in tumor metastasis through regulating epithelial-mesenchymal transition (EMT) and angiogenesis. The bidirectional role of class IV HDAC11 is dependent on the specificity of the tumor microenvironment. These mechanistic foundations provide a core theoretical framework for subsequent analysis of the functional differences of HDACs in diverse tumor types.

3. Role of HDACs in different tumor types

This section focuses on ovarian cancer, endometrial cancer, glioma, osteosarcoma and multiple myeloma (MM). These specific cancers were selected to provide a broad yet distinct perspective on HDAC biology across diverse tumor contexts. They represent major malignancies from different organ systems (gynecologic, central nervous system, bone/bone marrow) with unique etiologies, clinical challenges and patterns of HDAC expression/function. This comparative approach allows us to analyze conserved vs. tumor-specific roles of HDACs and their inhibitors, which is crucial for informing future cross-tumor targeting strategies. This section aims to analyze in detail the tumor-specific expression patterns of HDAC subtypes in each cancer type (including the subtype-specific functions of HDAC9 in ovarian cancer and the mechanism by which HDACs regulate ferroptosis in glioma). Additionally, this section aims to compare the core oncogenic pathways mediated by HDACs and the differences in therapeutic responses to HDACis across these different tumor types, thereby providing a reference for cross-tumor targeting strategies in the future.

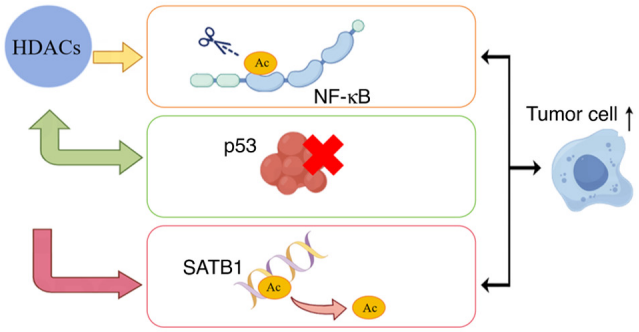

Figure 1. Interaction between histone deacetylases and tumor-related signaling pathways. HDACs can interact with key signaling pathways such as NF-κB and p53, thereby regulating the cellular response to stress and growth signals. HDACs can also deacetylate components of the NF-κB pathway, thus promoting the survival and proliferation of tumor cells. By inhibiting the transcriptional activity of p53, HDACs enable cancer cells to evade apoptosis. Additionally, HDACs can deacetylate SATB1, thereby inhibiting tumor suppressor genes (↑, promotion). HDACs, histone deacetylases; NF-κB, nuclear factor-κB; SATB1, special AT-rich sequence-binding protein 1; Ac, acetylation.

Ovarian cancer. HDACs have emerged as pivotal regulatory factors in the pathogenesis of ovarian cancer, particularly implicated in late-stage diagnosis and chemoresistance (45,46). Dysregulated expression of HDACs is associated with tumor aggressiveness. Their hyperactivation induces chromatin condensation and transcriptional repression of tumor suppressor genes (47,48). This dysregulation markedly contributes to poor clinical outcomes in patients with advanced ovarian cancer by enhancing cancer cell survival under conventional chemotherapy regimens. Notably, elevated expression levels of HDAC9 are associated with adverse prognosis in patients with serous ovarian carcinoma (49). By contrast, this enzyme exhibits tumor-suppressive effects in non-serous subtypes, highlighting histological subtype-specific functionalities among HDAC family members (49). Furthermore, interactions between HDACs and signaling pathways involving forkhead box protein O1 or transforming growth factor-β underscore their role in promoting cell migration and invasion, which are key hallmarks of metastatic progression in ovarian malignancy (50).

At the therapeutic strategy level, HDACis have demonstrated promising potential in pre-clinical studies, exhibiting notable anticancer activity against ovarian cancer cells (51-53). However, clinical trials have reported limitations in the efficacy of HDACis when administered as monotherapy, which is a finding that has driven research into combination regimens to enhance therapeutic outcomes. For example, combining HDACis with other anticancer agents has emerged as a highly prospective approach capable of overcoming the constraints associated with single-agent treatments. This

strategy leverages synergistic effects between distinct drugs to amplify therapeutic efficacy while potentially mitigating toxicity associated with high-dose monotherapy (54,55). Recent research has focused on elucidating the combinatorial potential of HDACis with poly(ADP-ribose) polymerase inhibitors (PARPis) and other agents; such regimens have demonstrated enhanced cytotoxic effects in ovarian cancer cell lines (56,57). Furthermore, novel dual-target inhibitors targeting both HDAC and complementary signaling pathways, such as the phosphoinositide 3-kinase (PI3K) pathway, are under development, reflecting an evolutionary trend towards increasingly personalized and efficient treatment modalities for ovarian cancer (Fig. 2) (58).

Endometrial carcinoma. HDACs serve a key role in the pathogenesis of endometrial carcinoma, with their mediated histone deacetylation processes closely associated with tumor invasion and poor clinical outcomes (35). As the most common malignant tumor in the female genital tract, endometrial cancer has a global incidence of ~20.2 per 100,000 women, accounting for 30-40% of all female genital tract malignancies. This tumor typically exhibits an aberrant histone acetylation pattern. Among histone deacetylases, HDAC6 acts as a key member and is highly expressed in 76.8% of endometrial cancer tissues. Such aberrant acetylation serves as a critical factor driving aggressive phenotypes including deep myometrial invasion and lymph node metastasis, as well as advanced-stage disease (46.0% at stages III-IV). It is also closely associated with reduced 5-year disease-free survival (41.3%), representing a key molecular feature underlying poor prognosis (59). Disrupted histone acetylation is strongly associated with high-grade tumors, which are characterized by enhanced invasiveness and metastatic propensity (60). Elevation in HDAC levels is markedly associated with advanced disease stages and diminished survival rates, positioning them as potential prognostic biomarkers (61). Furthermore, upregulation of specific HDAC isoforms (such as HDAC1 and HDAC6) promotes EMT, which enhances cancer cell invasive capabilities. Based on these mechanistic insights, therapeutic strategies targeting HDAC activity emerge as key interventions in restraining tumor progression in endometrial carcinoma (35,62).

The therapeutic potential of HDACis in endometrial carcinoma has garnered notable attention, primarily due to their capacity to induce cell-cycle arrest and apoptosis in cancerous cells. Compounds such as suberoylanilide hydroxamic acid and romidepsin, which are prominent members of the HDACis family, have demonstrated efficacy in pre-clinical models by restoring acetylation levels and reactivating epigenetically silenced tumor suppressor genes (35,60,63). These agents not only suppress tumor growth but also sensitize endometrial cancer cells to conventional chemotherapeutic drugs, thus generating synergistic cytotoxic effects. For instance, combinatorial regimens incorporating HDACis with standard chemotherapy have been reported to enhance DNA damage responses and promote apoptotic pathways in endometrial cancer cell lines (35). Ongoing clinical trials evaluating such combination therapies in patients have yielded preliminary results indicating improved tumor regression rates and overall survival outcomes (35,60,64,65). The strategic deployment of HDACis, particularly when integrated with other treatment modalities, represents a promising approach to enhance therapeutic efficacy and overcome drug resistance in endometrial carcinoma (38,66).

Glioma. HDACs occupy a central position in the regulatory networks governing glioma cells, particularly regarding ferroptosis (a form of regulated cell death driven by iron-dependent lipid peroxidation) (67). As integral components of this pathway, HDACs directly influence tumor progression and therapeutic responses. Inhibition of HDAC activity elevates both histone and non-histone protein acetylation levels, disrupting cellular homeostasis and promoting ferroptotic cell death in glioma cells (68). This mechanism holds particular importance for glioblastoma, which is characterized by high invasiveness and resistance to conventional therapies. The prevalent dysregulation of iron metabolism observed in gliomas is exacerbated by aberrant upregulation of HDACs, thereby sustaining tumor cell survival and proliferation (69,70).

Targeting HDACs to induce ferroptosis represents a promising therapeutic strategy, as previous studies have demonstrated that HDACis enhance the sensitivity of glioma cells to this form of cell death, simultaneously suppressing tumor growth and potentiating the efficacy of existing treatments (67,71). HDACis have emerged as potential therapeutic agents for glioma due to their ability to alter acetylation status in both histone and non-histone proteins, thereby modulating gene expression profiles and cellular behavior. For example, valproic acid (VPA) exhibits notable antineoplastic effects in *in vitro* and *in vivo* models of glioma, demonstrating capabilities to inhibit cell proliferation while increasing responsiveness to radiotherapy and chemotherapy, effects that are likely mediated through the regulation of survival/apoptosis signaling cascades (8,72,73). Mechanistically, HDACis operate via multiple pathways, including reactivating epigenetically silenced tumor suppressor genes, downregulating oncogenic drivers to alter cellular dynamics and driving tumor cell death. Additionally, HDACis contribute to enhancing antitumor immune responses by remodeling the tumor microenvironment and facilitating infiltration of immune effector cells (74,75). Clinically, HDACis have demonstrated promise in improving patient outcomes, particularly for isocitrate dehydrogenase (IDH)-mutant glioma subtypes, where malignant cells display increased sensitivity to HDAC inhibition (76,77). Their therapeutic synergy with immune checkpoint inhibitors further underscores their value in glioma management, while highlighting the increasing demand for personalized medicine based on individualized molecular profiling of tumors.

Osteosarcoma. Osteosarcoma, a highly aggressive bone malignancy predominantly affecting children and adolescents, exhibits HDAC-driven progression through enhanced tumor cell migration and invasion, primarily via regulation of EMT. For example, HDAC6 is markedly upregulated in doxorubicin- and cisplatin-resistant osteosarcoma cells, directly associating with their increased metastatic potential (78). Mechanistically, HDAC6 interacts with estrogen receptor-related proteins to modulate their acetylation status and stability, thereby elevating cancer-cell survival rates

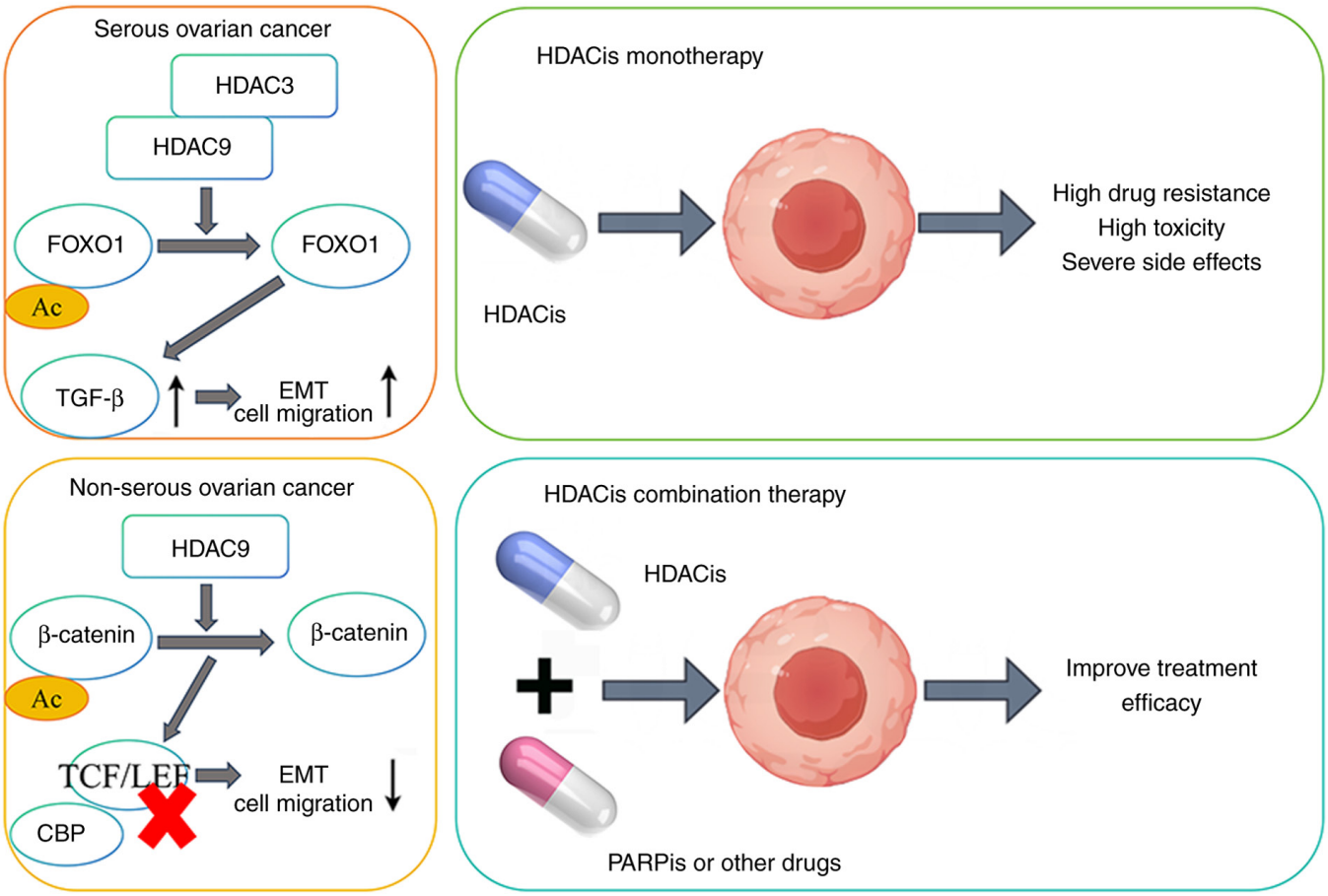

Figure 2. Role of HDACs in ovarian cancer. In serous ovarian cancer, HDAC9 promotes the expression levels of TGF-β by deacetylating FOXO1 and increasing its nuclear accumulation. The upregulated TGF-β enhances cell migration by activating EMT. In non-serous ovarian cancer, HDAC9 inhibits EMT and cell migration by deacetylating β-catenin and reducing its nuclear localization (↑, promotion; ↓ inhibition). Clinical trials have demonstrated that the efficacy of HDACis as a single-agent therapy is limited, while the combination of HDACis with PARPis and other drugs can improve the efficacy of cancer treatment and overcome drug resistance. FOXO1, forkhead box protein O1; TGF-β, transforming growth factor-β; HDACs, histone deacetylases; HDACis, HDAC inhibitors; PARPis, poly(ADP-ribose) polymerase inhibitors; EMT, epithelial-mesenchymal transition; TCF, transcription factor; Ac, acetylation; CBP, CREB-binding protein; LEF, lymphoid enhancer-binding factor.

and conferring apoptosis resistance (79,80). Furthermore, HDACs contribute to the development of chemoresistance and, therefore, inhibiting their activity restores sensitivity to conventional chemotherapeutics, which is a key finding due to the poor prognosis associated with this aggressive disease despite intensive treatment protocols (81). Elevation of HDAC expression in drug-resistant cell lines underscores their promise as therapeutic targets (79,82). Notably, HDACis such as vorinostat and entinostat synergize with doxorubicin in pre-clinical models, enhancing treatment efficacy (83). These agents exert antitumor effects by altering histone/non-histone acetylation landscapes, including reactivating silenced tumor suppressor genes and activating pro-apoptotic pathways; furthermore, when combined with chemotherapy, HDACis exhibit potent combination therapeutic effects, thereby markedly reducing the viability of osteosarcoma cell lines and inducing their apoptosis (84). Additionally, HDACis impede tumor cell motility and invasion (85), while promoting autophagy-induced autonomous cell death (86). Ongoing clinical trials evaluating the safety and efficacy of HDACis combined with standard chemotherapy aim to overcome chemoresistance, improve response rates and, ultimately, enhance patient outcomes in the future (87,88).

MM. HDACis represent a cornerstone therapeutic class for MM, with regulatory approval from the USA FDA for the clinical use of vorinostat, belinostat and romidepsin. Their mechanism of action involves HDAC suppression to disrupt key pathways governing tumor growth and survival, including inhibition of NF-κB signaling cascades, upregulation of cell cycle regulators (including p21 and p53), downregulation of the anti-apoptotic protein B-cell lymphoma-2 (Bcl-2) and induction of apoptotic programs in myeloma cells (89). Concurrently, HDACis enhance antitumor immunity and promote autophagy-mediated cancer cell clearance (90,91). Therapeutic synergy emerges when HDACis are combined with immunomodulatory agents, conventional chemotherapy or targeted therapies, which markedly improves treatment outcomes in patients with MM. For instance, combinatorial regimens incorporating HDACis with proteasome inhibitors (such as bortezomib) demonstrated increased antimyeloma activity and improved survival rates (92), effectively mitigating drug resistance while simultaneously targeting multiple pathogenic pathways implicated in MM pathogenesis. As a classic HDAC inhibitor, vorinostat in combination with the immunomodulatory drug lenalidomide can enhance lenalidomide-mediated CRBN pathway activity through epigenetic

regulation, upregulate the expression of NKG2D ligands and promote the cytotoxic function of NK cells, thereby synergistically inhibiting the proliferation of MM cells (93). When combined with the conventional chemotherapeutic agent bortezomib, vorinostat blocks HDAC-mediated protein deacetylation and jointly inhibits the proteasome/aggregate degradation system with bortezomib, thus overcoming bortezomib resistance and inducing synergistic apoptosis in MM cells (94). The HDAC6 inhibitor ACY-241 in combination with the anti-CD38 targeted therapeutic daratumumab shows unique advantages: It can upregulate CD38 expression on the surface of MM cells, significantly enhance the antibody-dependent cellular cytotoxicity effect of daratumumab and effectively improve the efficiency of targeted elimination of MM cells (95).

4. Key HDAC isoforms in tumor function and mechanisms

HDAC3. HDAC3 is a key regulatory factor in cancer biology. By catalyzing histone deacetylation, it promotes chromatin condensation and represses the transcription of genes associated with the cell cycle and apoptosis, thus disrupting the balance between cell proliferation and death. In colorectal cancer (CRC), HDAC3 regulates cancer stem cell-associated genes, thereby influencing tumor cell plasticity and chemoresistance. Ubiquitin-specific peptidase 38 (USP38) modulates HDAC3 stability, while pharmacological or genetic inhibition of USP38 induces HDAC3 degradation and promotes the development of aggressive tumor phenotypes. These findings suggest that targeting the HDAC3-USP38 axis may be an effective strategy to overcome chemoresistance (96-98). HDAC3 also impacts the tumor microenvironment via an NF-κB/p65-dependent mechanism, which silences the chemokine gene C-X-C motif chemokine ligand 10 (CXCL10), thus impeding $CD8^+$ T-cell infiltration and fostering an immunosuppressive microenvironment. This mechanism is particularly prominent in KRAS-mutant lung cancer and represents a major cause of its low response rate to immune checkpoint inhibitors (99). Inhibiting HDAC3 increases CXCL10 expression and its combination with anti-programmed cell death protein-1 (PD-1) antibodies markedly enhances tumor regression and T-cell infiltration (37,100). Additionally, HDAC3 inhibition directly induces apoptosis in cancer cells (including breast and lung cancer). Selective HDAC3 inhibitors have demonstrated notable preclinical efficacy; compared with pan-HDAC inhibitors, HDAC3 inhibitors exhibit fewer off-target effects and optimize the therapeutic index (101-103).

HDAC5. HDAC5 serves a key role in transcriptional regulation and is closely associated with the pathogenesis of various cancer types, including lung adenocarcinoma. The core mechanism is that HDAC5 reduces the transcriptional activity of SATB1 via deacetylation at the K411 residue in lung adenocarcinoma, thereby suppressing the expression of tumor suppressor genes and promoting cancer cell migration (42). Downregulation of SATB1 activity enhances metastatic potential by promoting lung adenocarcinoma cell migration. Pharmacological or genetic inhibition of HDAC5 reverses these effects; this not only impedes tumor cell migration, but also reactivates silenced tumor suppressor genes (42). This positions HDAC5 as a promising therapeutic target to prevent invasiveness and restore key antitumor pathways in lung adenocarcinoma. Furthermore, HDAC5 suppression induces cell-cycle arrest, effectively blocking the uncontrolled proliferation of malignant cells (104-106). This dual functionality (simultaneously blocking metastasis and restricting tumor growth) highlights the therapeutic potential of HDAC5 inhibitors. Since aberrant cell cycle progression constitutes a hallmark of malignancy, targeting HDAC5 offers notable value in cancer therapy (Fig. 3). Such intervention could enhance existing treatment modalities and improve patient outcomes, underscoring the need for further investigation into HDAC5 inhibitors as adjunctive therapeutic agents in oncology (107).

HDAC7. HDAC7 is a key regulator driving tumor growth, metastasis and drug resistance through mechanisms intrinsically associated with angiogenic microenvironment modulation. Evidence has demonstrated that HDAC7 is often upregulated in malignancies such as non-small cell lung cancer (NSCLC) and CRC, where these elevated levels are associated with advanced disease stages and poor clinical outcomes (15,108). In NSCLC specifically, HDAC7 potentiates oncogenic signaling by intersecting with fibroblast growth factor 18 (FGF18) pathways, thus enhancing both proliferative capacity and metastatic spread (15). Mechanistically, HDAC7 stabilizes β-catenin (a central mediator of Wnt signaling), facilitating its nuclear translocation and transcriptional complex formation with transcription factor 4 to activate FGF18 expression (Fig. 4) (15). Targeting this axis could disrupt pro-tumorigenic cascades, highlighting the therapeutic vulnerability of HDAC7.

Beyond cellular autonomy, HDAC7 orchestrates extracellular niche formation via dual regulation of angiogenesis and antitumor immunity within the microenvironment. For instance, its role in macrophage polarization and inflammatory reprogramming notably supports metastatic progression (109,110). By engineering pro-vasculature ecosystems conducive to tumor expansion, HDAC7 creates therapeutic challenges through desmoplastic stroma development. Clinically, HDAC7 can serve as both a prognostic biomarker and a therapeutic target. Its high expression predicts poor survival outcomes in patients with various malignancies, including diffuse large B-cell lymphoma (DLBCL), NSCLC, CRC and breast cancer, and can be used for patient risk stratification (108,111). The core mechanism is that high expression of HDAC7 promotes tumor cell proliferation, anti-apoptosis, invasion and metastasis by activating oncogenic pathways such as NF-κB, PI3K/AKT and β-catenin-FGF18, regulating the EMT process and cell cycle-related proteins. Meanwhile, it remodels the immunosuppressive tumor microenvironment and enhances resistance to cancer therapy. Consequently, high HDAC7 expression is closely associated with adverse pathological features including advanced clinical stage, lymph node metastasis and distant metastasis, ultimately leading to shortened overall survival and progression-free survival in patients with DLBCL, NSCLC, CRC and other malignancies, making it a key molecular marker for predicting poor survival outcomes (108,111). Preclinical models have demonstrated that selective inhibition of HDAC7 can sensitize cancer cells to chemotherapy and immunotherapy by disrupting cell survival-related signaling

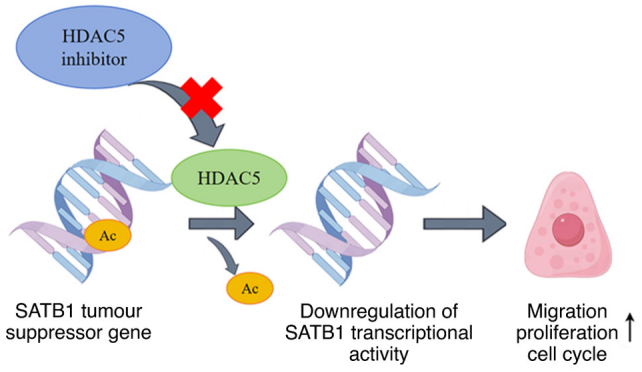

Figure 3. Role of HDAC5 in lung adenocarcinoma. HDAC5-mediated deacetylation of SATB1 reduces its transcriptional activity. The downregulation of SATB1 activity can enhance the migratory ability of lung adenocarcinoma cells, thereby promoting tumor metastasis (↑, promotion). HDAC, histone deacetylase; SATB1, special AT-rich sequence-binding protein 1; Ac, acetylation.

pathways including PI3K/AKT, NF-κB and Wnt/β-catenin, providing a highly promising combination therapeutic strategy to overcome treatment resistance (2,112).

HDAC11. Previous research has revealed the dual role of HDAC11 in oncology, functioning as either an oncogene or tumor suppressor gene depending on the cancer type and microenvironmental context. In HCC, HDAC11 maintains cancer stemness and confers resistance to sorafenib therapy via the microRNA (miR)-145-5p/HDAC11 axis. Downregulation of miR-145-5p elevates HDAC11 expression, thereby enhancing HCC cell survival and proliferative capacity under therapeutic stress (113,114). Within sorafenib-resistant HCC cell lines, dysregulated HDAC11 is associated with augmented drug metabolism and altered signaling pathways driving metastasis. Furthermore, the regulatory influence of HDAC11 over EMT underscores its importance in metastatic progression across multiple malignancies. Its crosstalk with non-coding RNAs, particularly miR-145-5p, forms a key determinant of treatment response in HCC cells, suggesting that the therapeutic targeting of this axis could improve efficacy and overcome chemoresistance (114,115). Clinically, HDAC11 upregulation is associated with poor prognosis in HCC by sustaining stem-like properties and enabling metabolic adaptation for survival under unfavorable conditions. Mechanistically, miR-145-5p suppression elevates HDAC11 levels, which reinforce sorafenib resistance and metastatic potential; by contrast, pharmacological inhibition of HDAC11 restores miR-145-5p abundance, resensitizing HCC cells to sorafenib while attenuating their metastatic abilities (Fig. 5) (113,116). Adding complexity to its functional repertoire, HDAC11 modulates immune evasion pathways and tumor-stroma interactions within the microenvironment, implying that multidimensional therapeutic strategies against HDAC11 may yield notable clinical benefits (116-118).

5. Clinical applications and challenges of HDACis

Pharmacological mechanisms of HDACis. HDACis exert antitumor effects by targeting the active site of HDACs or regulating their interaction with substrates to reverse aberrant epigenetic modifications. Marked differences exist in the mechanisms of action and subtype selectivity among different types of HDACis. Classified by chemical structure and mechanism of action, HDACis mainly fall into four categories: i) Hydroxamic acid derivatives (such as vorinostat), which achieve pan-subtype inhibition of class I and II HDACs by chelating zinc ions in the active site of HDACs. In cutaneous T cell lymphoma, hydroxamic acid derivatives can induce excessive histone acetylation to activate the transcription of tumor suppressor genes such as p21 (119,120); ii) benzamide derivatives (such as entinostat), which exhibit higher selectivity for class I HDACs (HDAC1/2/3). In osteosarcoma models, benzamide derivatives enhance the cytotoxicity of the chemotherapeutic drug doxorubicin by specifically inhibiting HDAC3 (83); iii) cyclic peptide derivatives (such as romidepsin), which bind to the active pocket of HDACs via their unique cyclic peptide structure. In MM, cyclic peptide derivatives can downregulate the expression level of the anti-apoptotic protein Bcl-2 by inhibiting the NF-κB signaling pathway (89); and iv) fatty acid derivatives (such as VPA), which inhibit HDAC activity in a non-competitive manner. In glioma, fatty acid derivatives can promote the expression level of ferroptosis-related genes and enhance the radiosensitivity of tumor cells (67,71). Beyond regulating histone acetylation, HDACis also exert pleiotropic effects through non-histone modifications: i) In lung adenocarcinoma, HDACis can acetylate the transcription factor SATB1, enhancing its regulatory activity on tumor suppressor genes and reversing the pro-metastatic effect mediated by HDAC5 (42); and ii) in CRC, HDACis disrupt the interaction between HSP90 and its target proteins [namely, protein kinase B (AKT)] by acetylating HSP90, thereby inhibiting cell proliferation signaling pathways (96). These mechanisms collectively form the molecular basis for the antitumor activity of HDACis and provide a target basis for the development of subtype-selective inhibitors.

Clinical application status of HDACis. The clinical efficacy of HDACis differs notably between hematological malignancies and solid tumors, with marked limitations in monotherapy and combination therapy has become the core strategy to improve therapeutic outcomes. In terms of monotherapy, the USA FDA has approved five HDACis for clinical use, including: i) Vorinostat, which is approved for cutaneous T cell lymphoma, with an objective response rate (ORR) of 30-40%, but it is associated with dose-limiting toxicities such as fatigue and gastrointestinal disturbances (119,120); ii) belinostat and romidepsin, which are used for peripheral T cell lymphoma, with ORRs of 25 and 35%, respectively, but their survival benefits for advanced patients are limited (121,122); iii) panobinostat, which is combined with bortezomib for MM and as monotherapy, its ORR is <20%; therefore, it is only used as a salvage treatment option for drug-resistant patients (89,92); and iv) VPA. Phase II clinical trials of VPA in glioma have reported that monotherapy achieves a disease control rate (DCR) of ~40%, but it fails to markedly prolong the progression-free survival (PFS) of patients (74,75). Overall, HDACi monotherapy has poor efficacy in solid tumors. For example, the ORR of vorinostat monotherapy in ovarian cancer is only 12% and the DCR of romidepsin

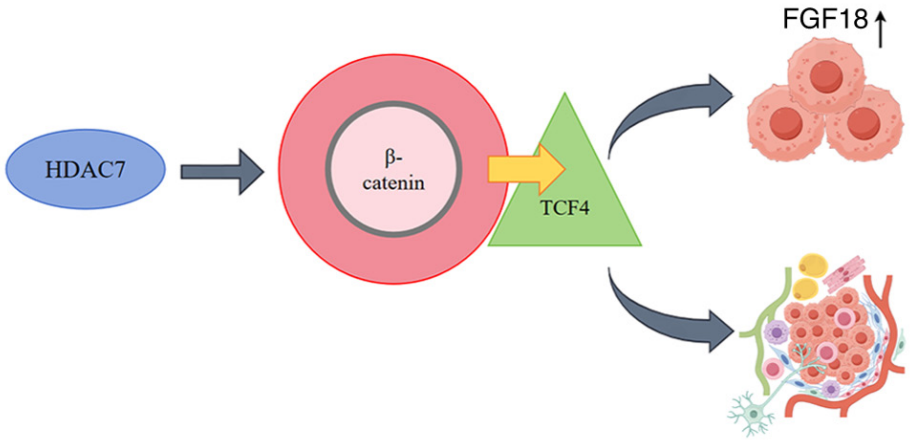

Figure 4. Role of HDAC7 in tumors. HDAC7 is a key regulatory factor that promotes tumor growth, metastasis and drug resistance, and its mechanism of action is closely related to the regulation of the vascular microenvironment. In non-small cell lung cancer, HDAC7 maintains the stability of β-catenin, promotes its nuclear translocation, and subsequent binding to TCF4, thereby activating the expression levels of FGF18. Inhibiting HDAC7 may block this oncogenic signaling cascade. The regulatory role of HDAC7 also extends to the tumor microenvironment, participating in disease progression by influencing angiogenesis and immune responses (↑, promotion). HDAC, histone deacetylase; TCF4, transcription factor 4; FGF18, fibroblast growth factor 18.

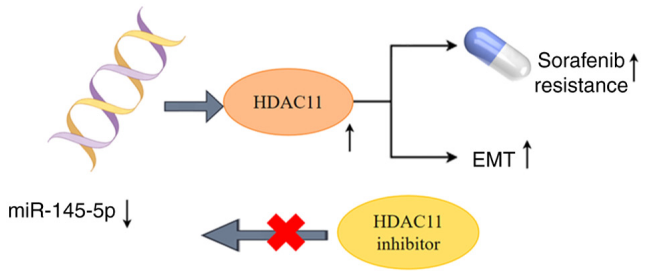

Figure 5. Role of HDAC11 in tumors. In HCC, the inhibition of miR-145-5p leads to an increase in HDAC11 levels, which in turn enhances resistance to sorafenib and the metastatic potential of HCC cells. However, inhibiting HDAC11 activity can restore the level of miR-145-5p, rendering HCC cells sensitive to sorafenib and reducing their metastatic ability (↑, promotion; ↓ inhibition). HDAC, histone deacetylase; HCC, hepatocellular carcinoma; miR, microRNA; EMT, epithelial-mesenchymal transition.

monotherapy in endometrial cancer is <30% (35,54,55,62). Combination therapy strategies have demonstrated synergistic effects in various tumors. In ovarian cancer, the combination of HDACis and PARPis can inhibit the DNA damage repair pathway, increasing the ORR of patients with wild-type BRCA from 15 to 45% without markedly increasing the risk of myelosuppression (56,57). In osteosarcoma, the combination of vorinostat and doxorubicin can downregulate HDAC6 expression, reverse chemoresistance in tumor cells and increase the DCR from 38 to 65% (83,85). In MM, the triple regimen of panobinostat, bortezomib and dexamethasone can markedly prolong the PFS of patients from 9.5 to 12.5 months (92,123). In glioma, the combination of VPA and immune checkpoint inhibitors (anti-PD-1 antibodies) can enhance the infiltration of $CD8^+$ T cells in the tumor microenvironment, increasing the ORR from 18 to 35% (76,77). Furthermore, dual-target inhibitors (for example CUDC-907) that concurrently target HDACs and pathways such as PI3K have exhibited enhanced antitumor activity in preclinical models of ovarian and breast cancer, offering a novel avenue for combination therapy (58,124).

Core challenges in clinical translation. Although HDACis exhibit potential in combination therapy, their clinical translation is limited by three core challenges, namely: i) Drug resistance; ii) off-target toxicity; and iii) a lack of biomarkers. Drug resistance is the primary cause of HDACi treatment failure, with three main mechanisms, including: i) Compensatory upregulation of HDAC subtypes. For example, in AML, prolonged use of pan-HDACis leads to increased HDAC3 expression, which maintains tumor cell survival via enhancement of NF-κB pathway activity (98,125). In osteosarcoma, HDAC6 expression is markedly higher in doxorubicin-resistant cell lines compared with that in doxorubicin-sensitive cells, thus contributing to doxorubicin resistance. This phenotype can be reversed by combination with HDAC6-selective inhibitors (79,85); ii) adaptive activation of signaling pathways. For instance, HDACi treatment induces PI3K/AKT pathway activation in lung cancer (102) and triggers compensatory NF-κB pathway activation in MM (89,92); and iii) tumor microenvironment remodeling, such as increased infiltration of myeloid-derived suppressor cells (MDSCs) in pancreatic cancer following HDACi treatment (126). Furthermore, tumor genomic heterogeneity driven by abnormal mutagenic processes exacerbates HDACi resistance; HDAC dysregulation may impair DNA repair capacity, forming an epigenetic dysregulation, which leads to genomic instability, and in turn induces the drug resistance cascade (127). Off-target toxicity limits dose escalation of HDACis. Due to a lack of subtype selectivity, pan-HDACis cause multi-organ adverse effects, including thrombocytopenia (30%) and neutropenia (25%) in the hematological system (128,129); gastrointestinal disturbances (45%) in the digestive system (130); and grade 3+ fatigue (30%) in systemic reactions (131). The grading and classification of adverse events in this article were based on the Common Terminology Criteria for Adverse Events, the universal standard in clinical oncology. Clinically, adverse effects are mitigated by adjusted dosing regimens (such as twice-weekly vorinostat, low initial dose with gradual escalation of VPA) (74,128) or combination with symptomatic drugs. Certain HDACis (such as vorinostat)

also carry cardiotoxicity risk (QT interval prolongation) (120). The absence of biomarkers hinders precise patient stratification. No clear molecular biomarkers for the prediction of HDACi efficacy exist. The correlation between HDAC9 expression and HDACi sensitivity in ovarian cancer (49,50), IDH mutation status and HDACi efficacy in glioma (76,77) and p53 mutation and HDACi-bortezomib synergy in MM (89) remain unconfirmed, leading to treatment blindness and increased ineffective treatment rates.

Optimization directions for therapeutic strategies. To address the challenges in the clinical translation of HDACis, current research focuses on three key directions: i) Structural modification; ii) targeted delivery; and iii) optimization of combination strategies, aiming to enhance the selectivity and efficacy of HDACis while reducing toxicity.

Structural modification is key to developing subtype-selective HDACis. HDAC3 inhibitors, with an introduced isoquinoline structure, inhibit tumor growth in CRC models without affecting platelet production (103,132). HDAC6 inhibitors, with optimized hydroxamic acid side chain lengths, reduce metastasis rates in triple-negative breast cancer (TNBC) without causing notable gastrointestinal toxicity (18,133). Thiophene derivatives (as HDAC11 inhibitors) can reverse sorafenib resistance in HCC (21,113,114). By contrast, the novel mechanism by which kelch repeat and BTB domain-containing 4 mutations disrupt the ubiquitin-dependent regulation of HDACs suggests that HDAC drug development should consider both HDAC catalytic activity and regulatory networks (134). Furthermore, proteolysis-targeting chimeras (PROTACs) technology enables specific degradation of HDAC subtypes. For example, HDAC7 PROTACs inhibit tumors with low toxicity in lymphoma and overcome compensatory HDAC upregulation in solid tumors (112,134,135).

Targeted delivery focuses on nanocarriers. Liposomes increase drug concentration in osteosarcoma by 8-fold via the enhanced permeability and retention effect (136,137). Epidermal growth factor receptor (EGFR)-targeted polymeric nanocarriers cross the blood-brain barrier, boosting drug concentration in glioma brains by 12-fold (74,138). Inorganic nanocarriers combined with photothermal effects achieve a 55% ORR in breast cancer (135,139). Liver-specific carriers enhance intrahepatic drug concentration in HCC by 6-fold (140,141).

Combination strategies rely on mechanistic synergy. In epigenetic combinations, HDACis plus DNMTis increase ORR from 30 to 60% in AML (36,142). In immune combinations, HDACis plus anti-PD-1 antibodies raise ORR from 25 to 50% in melanoma (143,144). In targeted combinations, HDACis plus PI3K inhibitors improve ORR from 20 to 45% in patients with ovarian cancer who exhibit PI3K pathway activation (58,145).

6. Future research directions and clinical prospects

Based on the aforementioned analysis, three unresolved gaps remain in current HDAC research, including: i) Mechanisms of subtype-specific functions in more solid tumors, which have not been clarified; ii) lack of biomarkers in predicting the efficacy of combination therapy; and iii) relatively low clinical translation efficiency of novel inhibitors. Considering this, the following section proposes future research directions from four dimensions: i) Precise targeting; ii) multi-target combination; iii) immune microenvironment regulation; and iv) drug development.

Precision targeting of HDAC isoforms. The development of HDAC isoform-selective inhibitors represents a novel research direction in cancer therapy. As core molecules in epigenetic regulation, HDACs modulate key cellular processes through deacetylation. Notably, different HDAC isoforms exhibit distinct expression patterns and functions across tumors. For instance, the upregulation of class I HDACs in TNBC is associated with poor prognosis and therapeutic resistance, making them a precise target for intervention. This therapeutic approach not only enhances efficacy but also avoids the off-target effects commonly observed with pan-HDACis (146).

The mechanisms underlying acquired resistance to HDACis are complex, such as the compensatory upregulation of alternative HDAC isoforms in AML (125). Researchers are accelerating the development of novel drugs through various strategies, including combining HDACis with chemotherapy/targeted agents, dynamically adjusting treatment regimens via biomarker monitoring and structure-based drug design or dual-target inhibitors. Additionally, multi-target compounds provide a novel pathway in preventing drug resistance (145,147).

To advance clinical translation, three key research areas should be prioritized over the next 3-5 years: i) Developing HDAC11-selective inhibitors by using structural biology to characterize its active site, addressing sorafenib resistance in HCC and reducing off-target toxicity; ii) establishing patient stratification models based on HDAC isoform expression profiles; for example, designing screening protocols for populations with high class I HDAC expression in TNBC, constructing a multi-dimensional classification system and developing convenient detection kits; and iii) exploring interactions between HDAC isoforms and non-coding RNAs, analyzing key mechanisms such as the miR-145-5p/HDAC11 axis and identifying novel therapeutic targets and candidate biomarkers. These efforts will improve the therapeutic system from three different perspectives.

Combination therapies targeting multiple epigenetic modifiers. The oncology field has increasingly prioritized combinatorial regimens involving HDACis, DNMTis and histone methyltransferase inhibitors (HMTis). This multifaceted approach involves synergistic targeting of interconnected epigenetic pathways driving tumorigenesis. Preclinical evidence demonstrates that co-administration of HDACis with DNMTis achieves coordinated reversal of aberrant epigenetic silencing, reactivating tumor suppressor genes frequently muted in malignancies (36,148). When these epigenetic modifiers are combinatorially inhibited, the tumor microenvironment undergoes notable alterations. This not only enhances the antitumor immune response of the body (preclinical studies have confirmed that HDACis combined with immunotherapy can increase the immunogenicity of tumor cells) but also further improves the therapeutic efficacy of immune checkpoint inhibitors (89,149,150). Mechanistically, this

multi-drug combination strategy can simultaneously block multiple aberrantly activated oncogenic signaling pathways, among which the PI3K/AKT and NF-κB pathways are the most representative targets (151). Incorporating HMTis into combination frameworks amplifies therapeutic impact through layered epigenetic reprogramming. Dual modulation of histone acetylation and methylation status enables comprehensive restoration of silenced tumor suppressor networks key to apoptosis induction (35,152,153). This multitarget strategy overcomes limitations inherent to monotherapy by exploiting synergistic interactions across parallel epigenetic regulatory axes (154). Ongoing clinical trials systematically evaluate diverse combinations with conventional chemotherapy and novel agents, aiming to maximize efficacy while minimizing chemotoxicities associated with traditional cytotoxic regimens (155-159). The integration of multimodal epigenetic therapies represents a paradigm shift towards precision medicine in cancer treatment.

Deciphering the role of HDACs in the tumor immune microenvironment (TIME). HDACs are key regulators of the TIME. By epigenetically modifying immune regulatory genes, HDACs modulate the dynamics of immune cells and facilitate tumor immune evasion. Elevated HDAC activity reduces the infiltration of effector cells such as natural killer and $CD8^+$ T cells, thereby establishing an immunosuppressive microenvironment (12,38,160). Dysregulated HDAC function further exacerbates immune evasion by inhibiting tumor suppressor pathways and upregulating molecules such as programmed cell death-ligand 1 (143,161). For instance, in pancreatic adenocarcinoma, upregulated HDACs impede T cell-mediated antitumor immune responses and recruit MDSCs to form an immune barrier (126).

HDAC-targeted therapy has notable immunomodulatory potential. Combining HDACis with immune checkpoint blockade therapy can reverse immunosuppression (151,162). At the molecular level, HDAC inhibition increases the expression levels of major histocompatibility complex class I molecules on tumor cells and enhances the activity of key components in the antigen-processing system, thus improving T-cell recognition efficiency (2,44). It also reprograms tumor-associated macrophages from the immunosuppressive M2 phenotype to the pro-inflammatory M1 phenotype, thus weakening the ability of the tumor to evade immunity (149,163).

Additionally, HDACs regulate the function of regulatory T cells (Tregs) by interacting with forkhead box protein P3 (FOXP3) regulators. For example, HDAC3 forms a complex with FOXP3 negative regulators to inhibit FOXP3 activity, while HDACis disrupt this complex to relieve the inhibition, reducing Treg-mediated immunosuppression and enhancing the cytotoxicity of effector T cells. The identification of the HDAC-FOXP3-Treg axis provides a theoretical basis for the combination of HDAC-targeted therapy with immunotherapy (164).

Development and evaluation of novel HDACis. Currently, the research and development of novel HDACis focuses on enhancing subtype selectivity, reducing toxicity and overcoming drug resistance, driven by interdisciplinary technologies. By resolving the active pocket structures of HDAC subtypes using X-ray crystallography and cryo-electron microscopy, combined with high-throughput screening, candidate molecules can be rapidly identified. For instance, tetrapheno(α)3-methyl derivatives exhibit nanomolar-level inhibitory activity against HDAC1/6 and demonstrate antiproliferative effects in various cancer cell lines (165,166). Using molecular docking and molecular dynamics simulations to optimize compound structures, dual-target drugs such as 4-arylaminoquinoline derivatives have also been developed, which can simultaneously target the HDAC and EGFR pathways (124,167,168). Additionally, PROTACs technology has emerged as a novel direction; for example, HDAC7 PROTAC degraders can specifically degrade HDAC7 in DLBCL, with antitumor activity >10-fold higher compared with that of traditional inhibitors and low toxicity to normal cells (169).

Preclinical evaluation of novel HDACis requires multi-dimensional validation across the molecular-cell-animal spectrum. At the molecular level, the selectivity for target subtypes is verified; at the cellular level, the effects on drug-resistant strains and other cell types are assessed; and at the animal level, *in situ* xenograft models are used to monitor efficacy and drug distribution. Meanwhile, toxicity to systems such as the hematological, digestive and nervous systems is closely monitored as well. Pharmacokinetic-pharmacodynamic models are employed to optimize dosing regimens or targeted delivery technologies are used to increase drug concentrations in tumor tissues and reduce systemic toxicity. For clinical trials, cancer types and patient groups are selected based on the properties of the drug. For example, HDAC11 inhibitors are first investigated in HCC (113-116), while dual-target drugs are administered to patients with pathway abnormalities (58,124,167,168). In combination therapy trials, relevant molecular markers need to be monitored (37,56,57,100). Although challenges exist, such as the lack of structural data for certain HDAC subtypes and the difficulty of preclinical models in simulating tumor heterogeneity, these can be addressed through homology modeling and patient-derived xenograft models. In the future, integrating biomarker stratification should facilitate the advancement of more HDACis with high efficacy and low toxicity into clinical practice. The key results of recent clinical trials of therapeutic regimens based on histone deacetylase inhibitors are summarized in Table I.

7. Discussion

Mechanistic insights, therapeutic innovations and unresolved questions in HDAC-targeted cancer therapy.

The present review systematically analyzed the role of HDACs in cancer and their therapeutic prospects, demonstrating notable complementarity to and expansion of previous studies (170,171). In terms of research scope, it collates the mechanisms of action of HDAC isoforms across five cancer types, including ovarian cancer, while specifically dissecting the functional differences and regulatory networks of class I isoforms such as HDAC1 and HDAC3. Building on previous studies focused on lung cancer (172), this review further extends the analysis of common mechanisms across cancer types. For instance, HDAC6 can enhance drug resistance in various solid tumors-including lung, breast, hepatocellular, ovarian, pancreatic cancers and CRC-via deacetylation of

Table I. Clinical research on HDAC inhibitors therapy.

Clinical trial no.	Treatment	Cancer	Target
NCT02290431	Drugs: LBH589 (panobinostat); bortezomib and dexamethasone	Relapsed/refractory multiple myeloma	HDAC1, HDAC2, HDAC3, HDAC4, HDAC5, HDAC6, HDAC7, HDAC8, HDAC9, HDAC10, HDAC11, proteasome and GR
NCT01582009	Drugs: Panobinostat and everolimus	Metastatic renal cell carcinoma	mTOR, HDAC1, HDAC2, HDAC3, HDAC4, HDAC5, HDAC6, HDAC7, HDAC8, HDAC9, HDAC10 and HDAC11
NCT02654990	Drugs: Panobinostat capsules, bortezomib injection and dexamethasone tablets	Relapsed or relapsed and refractory multiple myeloma	HDAC1, HDAC2, HDAC3, HDAC4, HDAC5, HDAC6, HDAC7, HDAC8, HDAC9, HDAC10, HDAC11, 26S proteasome and GR
NCT01742988	Drugs: Fimepinostat, rituximab and venetoclax	Refractory or relapsed lymphoma	HDAC1, HDAC2, HDAC3, HDAC6 and phosphoinositide 3-kinase
NCT00901147	Drug: Panobinostat and bortezomib	Relapsed/refractory peripheral T Cell lymphoma or NK/T cell lymphoma	HDAC1, HDAC2, HDAC3, HDAC4, HDAC5, HDAC6, HDAC11 and 26S proteasome
NCT00724984	Drug: PCI-24781	Lymphoma	HDAC1, HDAC2, HDAC3, HDAC6, HDAC8 and HDAC10
NCT00426764	Drug: Romidepsin	Peripheral T cell lymphoma	HDAC1, HDAC2 and HDAC3
NCT02035137	Radiation: 131I-MIBG; drugs: Vincristine, Irinotecan and vorinostat	Neuroblastoma	Noradrenergic neuron-specific marker, tubulin, topoisomerase I, HDAC1, HDAC2, HDAC3 and HDAC6
NCT00843167	Dietary supplement: Broccoli sprout extract; other: Placebo	Breast cancer	Nuclear factor erythroid 2-related factor 2-antioxidant response element signaling pathway, NF-κB inflammatory signaling pathway, cell cycle and apoptosis-related molecules, HDAC1, HDAC2, HDAC3 and HDAC6
NCT00918333	Drugs: Panobinostat and everolimus	Relapsed multiple myeloma, non-Hodgkin lymphoma, or Hodgkin lymphoma	HDAC1, HDAC2, HDAC3, HDAC4, HDAC5, HDAC6, HDAC11 and mTOR
NCT02115282	Drugs: Entinostat, exemestane, goserelin and goserelin acetate	Locally advanced or metastatic relapsed hormone receptor-positive breast cancer	HDAC1, HDAC2, HDAC3 and ER/PR
NCT02833155	Drugs: Entinostat and exemestane	Breast cancer	HDAC1, HDAC2 and HDAC3
NCT00676663	Drugs: Entinostat, exemestane and placebo	Breast cancer	HDAC1, HDAC2, HDAC3 and ER
NCT00574587	Drugs: Vorinostat, paclitaxel, trastuzumab, doxorubicin and cyclophosphamide	Breast cancer	HDAC1, HDAC2, HDAC3, HDAC6, tubulin and DNA
NCT02349867	Drug: Gemcitabine, sorafenib and vorinostat	Pancreatic cancer	Human epidermal growth factor receptor 2/epidermal growth factor receptor, multiple RTKs, HDAC1, HDAC2, HDAC3 and HDAC6
NCT03250273	Drug: Entinostat and nivolumab	Unresectable or metastatic cholangiocarcinoma or pancreatic ductal adenocarcinoma	HDAC1, HDAC2, HDAC3 and PD-1
NCT02836548	Drug: Vorinostat	Resistant advanced melanoma with BRAF V600 mutation	HDAC1, HDAC2, HDAC3 and HDAC6

Table I. Continued.

Clinical trial no.	Treatment	Cancer	Target
NCT02697630	Drug: Pembrolizumab and entinostat	Metastatic uveal melanoma	PD-1, HDAC1, HDAC2 and HDAC3
NCT03215264	Drugs: Hydroxychloroquine, entinostat and regorafenib	Colorectal cancer	RTKs, Raf kinase, autophagy-related pathway, HDAC1, HDAC2 and HDAC3
NCT02512172	Drugs: Oral CC-486, romidepsin and MK-3475	Colorectal cancer	PD-1, HDAC1, HDAC2 and HDAC3
NCT00550277	Drug: LBH589	Refractory clear cell renal cell carcinoma	HDAC1, HDAC2, HDAC3, HDAC4, HDAC5, HDAC6, HDAC7 and HDAC11
NCT02236195	Drug: Mocetinostat	Urothelial carcinoma	HDAC1, HDAC2, HDAC3
NCT01075308	Drug: HDAC inhibitor SB939	Prostate cancer	HDAC1, HDAC2, HDAC3, HDAC4, HDAC5, HDAC6, HDAC7 and HDAC11
NCT02632071	Drugs: ACY-1215 and nab-paclitaxel	Metastatic breast cancer	HDAC6
NCT03018249	Drugs: Entinostat and medroxyprogesterone acetate	Endometrial cancer	PR, HDAC1, HDAC2 and HDAC3
NCT04357873	Drugs: Pembrolizumab and vorinostat	Recurrent and/or metastatic squamous cell carcinoma	PD-1, HDAC1, HDAC2, HDAC3 and HDAC6
NCT02551185	Drug: ACY-241	Advanced solid tumors	HDAC6 and tubulin
NCT04631029	Biological: Atezolizumab; drugs: Carboplatin, entinostat and etoposide	Extensive stage lung small cell carcinoma	HDAC1, HDAC2, HDAC3, programmed cell death-ligand 1, DNA and DNA topoisomerase II
NCT02420613	Drugs: Temsirolimus and vorinostat	Diffuse intrinsic pontine glioma	HDAC1, HDAC2, HDAC3, HDAC6 and mTOR
NCT02780804	Drug: Entinostat	Relapsed or refractory solid tumors (including central nervous system tumors and lymphomas)	HDAC1, HDAC2 and HDAC3

HDAC, histone deacetylase; RTKs, receptor tyrosine kinases; PD-1, programmed cell death protein-1; PR, progesterone receptor; ER, estrogen receptor; GR, glucocorticoid receptor; NF-κB, nuclear factor-κB; NK, natural killer T cells.

α-tubulin (173,174), thereby providing a solid theoretical basis for the development of pan-cancer HDAC-targeted therapeutic strategies (37).

Beyond the expansion of the research scope, the present review also highlighted notable innovations in combination therapy strategies: It proposes a novel HDACi + dual-target drug regimen (for example, combining HDACis with EGFR/PI3K dual-target inhibitors). This strategy achieves synergistic antitumor effects by simultaneously blocking two critical oncogenic pathways: The EGFR signaling pathway and the PI3K/Akt signaling pathway, addressing a key limitation of previous studies that only focused on the combination of HDAC7 PROTAC degraders with immunotherapy (112,175). Notably, a preclinical study on AML reported a synergistic mechanism between HDACs and DNMTs mediated by an acetylation-demethylation crosstalk, further verifying the scientific validity of the multi-targeted epigenetic regulator targeting strategy proposed in the present review (36).

Although this review comprehensively summarizes the research and therapeutic advances related to HDACs, it has certain limitations. First, the tumor coverage is limited, as the functional mechanisms of HDAC isoforms in high-incidence solid tumors such as lung and liver cancer and more hematological malignancies have not been systematically investigated, making it difficult to reflect their pan-cancer regulatory characteristics. Second, research on isoforms such as HDAC8 and HDAC10 is superficial, and the regulatory networks among isoforms remain unclear, precluding a complete understanding of their overall regulatory patterns. Third, clinical data are mostly from traditional regimens, with insufficient data on emerging therapies and Phase III trial evidence for solid tumors. Fourth, tumor microenvironment analysis only focuses on core immune cells, ignoring other components and their cross-regulation with microenvironmental characteristics. Fifth, the clinical validation limitations of potential biomarkers have not been thoroughly

analyzed, nor has the establishment of combined detection systems been explored, which fails to meet the needs of precise treatment.

Due to the complexity of HDAC-related regulatory networks and the multi-faceted challenges in clinical translation, the present review concluded by clarifying the core mechanisms and therapeutic potential of HDACs, while putting forward innovative therapeutic strategies. It also suggested that interdisciplinary collaboration, integrating insights from molecular biology, pharmacology and clinical oncology, is expected to overcome key hurdles in HDAC-targeted therapy, including off-target toxicity, acquired drug resistance and the lack of reliable biomarkers. Therefore, such efforts will accelerate the translation of HDAC-targeted research from basic science to clinical practice and potentially improve the prognosis of patients with cancer in the future.

8. Conclusion

HDACs, as core factors in epigenetic regulation, serve a key role in the oncogenic mechanisms, disease progression and therapeutic resistance of various malignant tumors. Their ability to reshape chromatin structure and regulate gene expression programs makes them highly promising therapeutic targets, a finding that has been validated by the clinical application of HDACis in hematological malignancies; however, translating these advantages into solid tumor therapy remains challenging due to tumor heterogeneity, complex microenvironmental interactions and differences in cellular responses, a discrepancy that underscores the urgency of dissecting subtype-specific functions in different cancer contexts. A key to future progress lies in the development of subtype-selective HDACis that can precisely modulate oncogenic pathways while minimizing off-target effects, as well as rational combination therapy regimens (such as pairing HDACis with immunotherapies, targeted agents or chemotherapy) that hold notable potential through synergistic mechanisms (for example, combination therapy with immune checkpoint blockade can activate antitumor immune responses). Elucidating resistance mechanisms, including compensatory signal activation, altered drug metabolism and microenvironmental adaptation, is equally key to overcoming treatment failure and the identification of biomarkers that predict treatment response or resistance is expected to enable personalized dosing strategies and stratified patient care. Emerging research paradigms advocate for multidisciplinary combination therapies, integrating HDAC-targeted approaches with innovative modalities such as PROTAC degradation systems and dual epigenetic inhibitors. By integrating cutting-edge insights from tumor biology, precision medicine and clinical pharmacology, well-validated HDAC-targeted strategies (supported by rigorous mechanistic studies and clinical trials) have the potential to transform cancer treatment outcomes, with the convergence of these elements expected to shift HDACis from promising experimental tools to core components of modern cancer treatment regimens.

Acknowledgements

Not applicable.

Funding

The present study was supported by the Natural Science Foundation of Shandong (grant no. ZR2023QH453) and the National Natural Science Foundation of China (grant no. 82403344).

Availability of data and materials

Not applicable.

Authors' contributions

RL designed the review article, researched references and wrote the majority of the manuscript. YZ researched references and wrote the manuscript. HL revised and edited the manuscript. FL revised the manuscript and acquired funding. 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.

References

1. Liu YL, Yang PM, Shun CT, Wu MS, Weng JR and Chen CC: Autophagy potentiates the anti-cancer effects of the histone deacetylase inhibitors in hepatocellular carcinoma. Autophagy 6: 1057-1065, 2010.
2. Maciejewski K, Giers M, Oleksiewicz U and Czerwinska P: The epigenetic modifiers HDAC2 and HDAC7 inversely associate with cancer stemness and immunity in solid tumors. Int J Mol Sci 25: 7841, 2024.
3. Bao Q, Li Y, Chen Y, Zheng J, Zhao J and Hu T: Transcriptome-based network analysis related to histone deacetylase genes and identified EMP1 as a potential biomarker for prognosis in bladder cancer. Clin Genitourin Cancer 23: 102262, 2025.
4. Liang T, Wang F, Elhassan RM, Cheng Y, Tang X, Chen W, Fang H and Hou X: Targeting histone deacetylases for cancer therapy: Trends and challenges. Acta Pharm Sin B 13: 2425-2463, 2023.
5. Klieser E, Neumayer B, Di Fazio P, Mayr C, Neureiter D and Kiesslich T: HDACs as an emerging target in endocrine tumors: A comprehensive review. Expert Rev Endocrinol Metab 18: 143-154, 2023.
6. Contreras-Sanzón E, Prado-Garcia H, Romero-Garcia S, Nuñez-Corona D, Ortiz-Quintero B, Luna-Rivero C, Martínez-Cruz V and Carlos-Reyes Á: Histone deacetylases modulate resistance to the therapy in lung cancer. Front Genet 13: 960263, 2022.
7. Liang R, Zhang J, Liu Z, Liu Z, Li Q, Luo X, Li Y, Ye J and Lin Y: Mechanism and molecular network of RBM8A-mediated regulation of oxaliplatin resistance in hepatocellular carcinoma. Front Oncol 10: 585452, 2021.
8. Giordano F, Forestiero M, Leonetti AE, Naimo GD, Marrone A, De Amicis F, Marsico S, Mauro L and Panno ML: Valproic acid reduces invasiveness and cellular growth in 2D and 3D glioblastoma cell lines. Int J Mol Sci 26: 6600, 2025.

9. Zheng B, Jiang X, Liu Y, Cheng F, Zhang Y, Niu C, Cong Z, Niu Z and He W: Elevated histone deacetylase 10 expression promotes the progression of clear cell renal cell carcinoma by notch-1-PTEN signaling axis. Discov Oncol 15: 156, 2024.
10. Jungwirth G, Yu T, Liu F, Cao J, Alaa Eddine M, Moustafa M, Abdollahi A, Warta R, Unterberg A and Herold-Mende C: Pharmacological landscape of FDA-approved anticancer drugs reveals sensitivities to ixabepilone, romidepsin, omacetaxine, and carfilzomib in aggressive meningiomas. Clin Cancer Res 29: 233-243, 2023.
11. Lee H, Jung TY, Lim SH, Choi EJ, Lee J and Min DS: Phospholipase D2 is a positive regulator of sirtuin 1 and modulates p53-mediated apoptosis via sirtuin 1. Exp Mol Med 53: 1287-1297, 2021.
12. Lin Y, Jing X, Chen Z, Pan X, Xu D, Yu X, Zhong F, Zhao L, Yang C, Wang B, *et al*: Histone deacetylase-mediated tumor microenvironment characteristics and synergistic immunotherapy in gastric cancer. Theranostics 13: 4574-4600, 2023.
13. Haberland M, Montgomery RL and Olson EN: The many roles of histone deacetylases in development and physiology: Implications for disease and therapy. Nat Rev Genet 10: 32-42, 2009.
14. Kundu R, Banerjee S, Baidya SK, Adhikari N and Jha T: A quantitative structural analysis of AR-42 derivatives as HDAC1 inhibitors for the identification of promising structural contributors. SAR QSAR Environ Res 33: 861-883, 2022.
15. Guo K, Ma Z, Zhang Y, Han L, Shao C, Feng Y, Gao F, Di S, Zhang Z, Zhang J, *et al*: HDAC7 promotes NSCLC proliferation and metastasis via stabilization by deubiquitinase USP10 and activation of β-catenin-FGF18 pathway. J Exp Clin Cancer Res 41: 91, 2022.
16. Yu L, Cao H, Yang JW, Meng WX, Yang C, Wang JT, Yu MM and Wang BS: HDAC5-mediated PRAME regulates the proliferation, migration, invasion, and EMT of laryngeal squamous cell carcinoma via the PI3K/AKT/mTOR signaling pathway. Open Med (Wars) 18: 20230665, 2023.
17. Zhang Y, Ding P, Wang Y, Shao C, Guo K, Yang H, Feng Y, Ning J, Pan M, Wang P, *et al*: HDAC7/c-Myc signaling pathway promotes the proliferation and metastasis of choroidal melanoma cells. Cell Death Dis 14: 38, 2023.
18. Lu B, Qiu R, Wei J, Wang L, Zhang Q, Li M, Zhan X, Chen J, Hsieh IY, Yang C, *et al*: Phase separation of phospho-HDAC6 drives aberrant chromatin architecture in triple-negative breast cancer. Nat Cancer 5: 1622-1640, 2024.
19. Jin J, Meng T, Yu Y, Wu S, Jiao CC, Song S, Li YX, Zhang Y, Zhao YY, Li X, *et al*: Human HDAC6 senses valine abundancy to regulate DNA damage. Nature 637: 215-223, 2025.
20. Pandey UB, Batlevi Y, Baehrecke EH and Taylor JP: HDAC6 at the intersection of autophagy, the ubiquitin-proteasome system and neurodegeneration. Autophagy 3: 643-645, 2007.
21. Bhagat RP, Jyotisha, Dasgupta I, Amin SA, Jakkula P, Bhattacharya A, Qureshi IA and Gayen S: First report on analysis of chemical space, scaffold diversity, critical structural features of HDAC11 inhibitors. Mol Divers 29: 3679-3702, 2025.
22. Sriramareddy SN, Faião-Flores F, Emmons MF, Saha B, Chellappan S, Wyatt C, Smalley I, Licht JD, Durante MA, Harbour JW and Smalley KSM: HDAC11 activity contributes to MEK inhibitor escape in uveal melanoma. Cancer Gene Ther 29: 1840-1846, 2022.
23. Buglio D, Khaskhely NM, Voo KS, Martinez-Valdez H, Liu YJ and Younes A: HDAC11 plays an essential role in regulating OX40 ligand expression in Hodgkin lymphoma. Blood 117: 2910-2917, 2011.
24. Das T, Bhattacharya A, Jha T and Gayen S: Exploration of fingerprints and data mining-based prediction of some bioactive compounds from Allium sativum as histone deacetylase 9 (HDAC9) inhibitors. Curr Comput Aided Drug Des 21: 270-284, 2025.
25. West AC and Johnstone RW: New and emerging HDAC inhibitors for cancer treatment. J Clin Invest 124: 30-39, 2014.
26. Debbarma M, Sarkar K and Sil SK: Dissecting the epigenetic orchestra of HDAC isoforms in breast cancer development: A review. Med Oncol 42: 1, 2024.
27. Sanaei M and Kavoosi F: Histone deacetylase inhibitors, intrinsic and extrinsic apoptotic pathways, and epigenetic alterations of histone deacetylases (HDACs) in hepatocellular carcinoma. Iran J Pharm Res 20: 324-336, 2021.
28. Han S, Fan H, Zhong G, Ni L, Shi W, Fang Y, Wang C, Wang L, Song L, Zhao J, *et al*: Nuclear KRT19 is a transcriptional corepressor promoting histone deacetylation and liver tumorigenesis. Hepatology 81: 808-822, 2025.
29. Jasim SA, Altalbawy FMA, Abohassan M, Oghenemaro EF, Bishoyi AK, Singh RP, Kaur P, Sivaprasad GV, Mohammed JS and Hulail HM: Histone deacetylases (HDACs) roles in inflammation-mediated diseases; current knowledge. Cell Biochem Biophys 83: 1375-1386, 2025.
30. Zhang K, Peng X, Zhou P, Li X, Shen L, Yang L and Zhou Q: HDAC1/2-mediated deacetylation of KLF9 promotes the malignant progression of nasopharyngeal carcinoma via CDH17. Oncogene 44: 3183-3198, 2025.
31. Sahu RK, Dhakshnamoorthy J, Jain S, Folco HD, Wheeler D and Grewal SIS: Nucleosome remodeler exclusion by histone deacetylation enforces heterochromatic silencing and epigenetic inheritance. Mol Cell 84: 3175-3191.e8, 2024.
32. Talom A, Barhoi A, Jirpu T, Dawn B and Ghosh A: Clinical progress and functional modalities of HDAC inhibitor-based combination therapies in cancer treatment. Clin Transl Oncol 28: 71-85, 2026.
33. Sandonà M, Cavioli G, Renzini A, Cedola A, Gigli G, Coletti D, McKinsey TA, Moresi V and Saccone V: Histone deacetylases: Molecular mechanisms and therapeutic implications for muscular dystrophies. Int J Mol Sci 24: 4306, 2023.
34. Lu-Culligan WJ, Connor LJ, Xie Y, Ekundayo BE, Rose BT, Machyna M, Pintado-Urbanc AP, Zimmer JT, Vock IW, Bhanu NV, *et al*: Acetyl-methyllysine marks chromatin at active transcription start sites. Nature 622: 173-179, 2023.
35. Joseph R, Dasari SK, Umamaheswaran S, Mangala LS, Bayraktar E, Rodriguez-Aguayo C, Wu Y, Nguyen N, Powell RT, Sobieski M, *et al*: EphA2- and HDAC-targeted combination therapy in endometrial cancer. Int J Mol Sci 25: 1278, 2024.
36. Blagitko-Dorfs N, Schlosser P, Greve G, Pfeifer D, Meier R, Baude A, Brocks D, Plass C and Lübbert M: Combination treatment of acute myeloid leukemia cells with DNMT and HDAC inhibitors: Predominant synergistic gene downregulation associated with gene body demethylation. Leukemia 33: 945-956, 2019.
37. McGuire CK, Meehan AS, Couser E, Bull L, Minor AC, Kuhlmann-Hogan A, Kaech SM, Shaw RJ and Eichner LJ: Transcriptional repression by HDAC3 mediates T cell exclusion from Kras mutant lung tumors. Proc Natl Acad Sci USA 121: e2317694121, 2024.
38. Yan M, Cao H, Tao K, Xiao B, Chu Y, Ma D, Huang X, Han Y and Ji T: HDACs alters negatively to the tumor immune microenvironment in gynecologic cancers. Gene 885: 147704, 2023.
39. Kim YK, Lee EK, Kang JK, Kim JA, You JS, Park JH, Seo DW, Hwang JW, Kim SN, Lee HY, *et al*: Activation of NF-kappaB by HDAC inhibitor apicidin through Sp1-dependent de novo protein synthesis: Its implication for resistance to apoptosis. Cell Death Differ 13: 2033-2041, 2006.
40. Luo J, Su F, Chen D, Shiloh A and Gu W: Deacetylation of p53 modulates its effect on cell growth and apoptosis. Nature 408: 377-381, 2000.
41. Singh T, Kaur P, Singh P, Singh S and Munshi A: Differential molecular mechanistic behavior of HDACs in cancer progression. Med Oncol 39: 171, 2022.
42. Sharma S, Tyagi W, Tamang R and Das S: HDAC5 modulates SATB1 transcriptional activity to promote lung adenocarcinoma. Br J Cancer 129: 586-600, 2023.
43. Ling R, Wang J, Fang Y, Yu Y, Su Y, Sun W, Li X and Tang X: HDAC-an important target for improving tumor radiotherapy resistance. Front Oncol 13: 1193637, 2023.
44. Mao C, Fan W, Liu J, Yang F, Li W, Li L, Shi Z, Li Q, Yuan Z, Jiang Y and Chu B: Targeting HDAC and PARP enhances STING-dependent antitumor immunity in STING-deficient tumor. Adv Sci (Weinh) 12: e07904, 2025.
45. Rodrigues Moita AJ, Bandolik JJ, Hansen FK, Kurz T, Hamacher A and Kassack MU: Priming with HDAC inhibitors sensitizes ovarian cancer cells to treatment with cisplatin and HSP90 inhibitors. Int J Mol Sci 21: 8300, 2020.
46. Li Z, Wu YH, Guo YQ, Min XJ and Lin Y: Tasquinimod promotes the sensitivity of ovarian cancer cells to cisplatin by down-regulating the HDAC4/p21 pathway. Korean J Physiol Pharmacol 29: 191-204, 2025.
47. Kim M, Lu F and Zhang Y: Loss of HDAC-mediated repression and gain of NF-κB activation underlie cytokine induction in ARID1A- and PIK3CA-mutation-driven ovarian cancer. Cell Rep 17: 275-288, 2016.
48. Feng Q, Hao S, Liu X, Yan Z, Sheng K, Li Y, Zhang P and Sheng X: HDAC7 promotes ovarian cancer malignancy via AKT/mTOR signalling pathway. J Cell Mol Med 28: e70120, 2024.

49. Xu L, Wang J, Liu B, Fu J, Zhao Y, Yu S, Shen L, Yan X and Su J: HDAC9 contributes to serous ovarian cancer progression through regulating epithelial-mesenchymal transition. Biomedicines 10: 374, 2022.
50. Xu L, Yan X, Wang J, Zhao Y, Liu Q, Fu J, Shi X and Su J: The roles of histone deacetylases in the regulation of ovarian cancer metastasis. Int J Mol Sci 24: 15066, 2023.
51. Chi AJ, Hsu JL, Xiao YX, Chern JW, Guh JH, Yu CW and Hsu LC: A novel HDAC6 inhibitor enhances the efficacy of paclitaxel against ovarian cancer cells. Molecules 30: 2793, 2025.
52. Thomine C, Guillemot S, Weiswald LB, Florent R, Abeilard E, Giffard F, Brotin E, Briand M, Dolivet E, Poulain L and Villedieu M: The anticancer effect of the HDAC inhibitor belinostat is enhanced by inhibitors of Bcl-x_L or Mcl-1 in ovarian cancer. Mol Oncol 19: 3325-3341, 2025.
53. Begum S, Irvin SD, Cox CK, Huang Z, Wilson JJ, Monroe JD and Gibert Y: Anti-ovarian cancer migration and toxicity characteristics of a platinum(IV) pro-drug with axial HDAC inhibitor ligands in zebrafish models. Invest New Drugs 42: 644-654, 2024.
54. Natarajan U, Venkatesan T and Rathinavelu A: Effect of the HDAC inhibitor on histone acetylation and methyltransferases in A2780 ovarian cancer cells. Medicina (Kaunas) 57: 456, 2021.
55. Si L, Lai T, Zhao J, Jin Y, Qi M, Li M, Fu H, Shi X, Ma L and Guo R: Identification of a novel pyridine derivative with inhibitory activity against ovarian cancer progression in vivo and in vitro. Front Pharmacol 13: 1064485, 2022.
56. Valdez BC, Tsimberidou AM, Yuan B, Baysal MA, Chakraborty A, Andersen CR and Andersson BS: Synergistic cytotoxicity of histone deacetylase and poly-ADP ribose polymerase inhibitors and decitabine in breast and ovarian cancer cells: Implications for novel therapeutic combinations. Int J Mol Sci 25: 9241, 2024.
57. Qiu J, Ren T, Liu Q, Jiang Q, Wu T, Cheng LC, Yan W, Qu X, Han X and Hua K: Dissecting the distinct tumor microenvironments of HRD and HRP ovarian cancer: Implications for targeted therapies to overcome PARPi resistance in HRD tumors and refractoriness in HRP tumors. Adv Sci (Weinh) 11: e2309755, 2024.
58. Wang Y, Wen J, Sun X, Sun Y, Liu Y, Cheng X, Wu W, Liu Q and Ren F: CUDC-907 exhibits potent antitumor effects against ovarian cancer through multiple in vivo and in vitro mechanisms. Cancer Chemother Pharmacol 93: 295-306, 2024.
59. Zheng Y, Yang X, Wang C, Zhang S, Wang Z, Li M, Wang Y, Wang X and Yang X: HDAC6, modulated by miR-206, promotes endometrial cancer progression through the PTEN/AKT/mTOR pathway. Sci Rep 10: 3576, 2020.
60. Li Y, Zhou W, Li L, Li JW, Li T, Huang C, Lazaro-Camp VJ, Kavlashvili T, Zhang Y, Reyes H, *et al*: Enhancing progestin therapy via HDAC inhibitors in endometrial cancer. Am J Cancer Res 12: 5029-5048, 2022.
61. Nahar S, Yu J, Lee H, Tran DN, Li R, Kim TH, Jung JS, Kim K, Yoo JY and Jeong JW: MIG-6 regulates HDAC1-mediated angiogenesis and tumorigenesis in PTEN-deficient endometrioid endometrial cancer. Mol Cancer Res: Jan 21, 2026 (Epub ahead of print).
62. Psilopatis I, Pergaris A, Giaginis C and Theocharis S: Histone deacetylase inhibitors: A promising therapeutic alternative for endometrial carcinoma. Dis Markers 2021: 7850688, 2021.
63. Edwards K, Yao S, Pisano S, Feltracco V, Brusehafer K, Samanta S, Oommen OP, Gazze SA, Paravati R, Maddison H, *et al*: Hyaluronic acid-functionalized nanomicelles enhance SAHA efficacy in 3D endometrial cancer models. Cancers (Basel) 13: 4032, 2021.
64. Pothuri B, Sawaged Z, Karpel HC, Li X, Lee J, Musa F, Lutz K, Reese E, Blank SV, Boyd LR, *et al*: A phase 2 feasibility study of nab-paclitaxel and carboplatin in epithelial carcinoma of the uterus. Gynecol Oncol 190: 209-214, 2024.
65. Lin CK, Liu ST, Wu ZS, Wang YC and Huang SM: Mechanisms of cisplatin in combination with repurposed drugs against human endometrial carcinoma cells. Life (Basel) 11: 160, 2021.
66. Wu Q, Zhang W, Liu Y, Huang Y, Wu H and Ma C: Histone deacetylase 1 facilitates aerobic glycolysis and growth of endometrial cancer. Oncol Lett 22: 721: 721, 2021.
67. Ma M, Fei X, Jiang D, Chen H, Xie X, Wang Z and Huang Q: Research progress on the mechanism of histone deacetylases in ferroptosis of glioma. Oncol Rev 18: 1432131, 2024.
68. Chen X, Wang Z, Li C, Zhang Z, Lu S, Wang X, Liang Q, Zhu X, Pan C, Wang Q, *et al*: SIRT1 activated by AROS sensitizes glioma cells to ferroptosis via induction of NAD+ depletion-dependent activation of ATF3. Redox Biol 69: 103030, 2024.
69. Pai P, Das I, Reddy Y, Venkidesh BS, Bhandari P, Madalageri M, Sadashivanavar V, Pai KSR, Rao P, Oruganti S, *et al*: Targeting glioblastoma with HDAC inhibitors: Insights into hydroxamic acid-based therapeutic strategies. Acta Neuropathol Commun 14: 9, 2025.
70. Fan F, Liu P, Bao R, Chen J, Zhou M, Mo Z, Ma Y, Liu H, Zhou Y, Cai X, *et al*: A dual PI3K/HDAC inhibitor induces immunogenic ferroptosis to potentiate cancer immune checkpoint therapy. Cancer Res 81: 6233-6245, 2021.
71. Mormino A, Cocozza G, Fontemaggi G, Valente S, Esposito V, Santoro A, Bernardini G, Santoni A, Fazi F, Mai A, *et al*: Histone-deacetylase 8 drives the immune response and the growth of glioma. Glia 69: 2682-2698, 2021.
72. Han W, Yu F, Cao J, Dong B, Guan W and Shi J: Valproic acid enhanced apoptosis by promoting autophagy via Akt/mTOR signaling in glioma. Cell Transplant 29: 963689720981878, 2020.
73. Thotala D, Karvas RM, Engelbach JA, Garbow JR, Hallahan AN, DeWees TA, Laszlo A and Hallahan DE: Valproic acid enhances the efficacy of radiation therapy by protecting normal hippocampal neurons and sensitizing malignant glioblastoma cells. Oncotarget 6: 35004-35022, 2015.
74. Mehndiratta S, Qian B, Chuang JY, Liou JP and Shih JC: N-methylpropargylamine-conjugated hydroxamic acids as dual inhibitors of monoamine oxidase A and histone deacetylase for glioma treatment. J Med Chem 65: 2208-2224, 2022.
75. Kunadis E, Lakiotaki E, Korkolopoulou P and Piperi C: Targeting post-translational histone modifying enzymes in glioblastoma. Pharmacol Ther 220: 107721, 2021.
76. Riyas Mohamed FR and Yaqinuddin A: Epigenetic reprogramming and antitumor immune responses in gliomas: A systematic review. Med Oncol 42: 213, 2025.
77. Ozair A, Bhat V, Alisch RS, Khosla AA, Kotecha RR, Odia Y, McDermott MW and Ahluwalia MS: DNA methylation and histone modification in low-grade gliomas: Current understanding and potential clinical targets. Cancers (Basel) 15: 1342, 2023.
78. Khalid U, Simovic M, Hammann LA, Iskar M, Wong JKL, Kumar R, Jugold M, Sill M, Bolkestein M, Kolb T, *et al*: A synergistic interaction between HDAC- and PARP inhibitors in childhood tumors with chromothripsis. Int J Cancer 151: 590-606, 2022.
79. He Q, Yu C, Li Y, Hao P, Mai H, Guo R, Zhong G, Zhang K, Wong C, Chen Q and Chen Y: ERRα contributes to HDAC6-induced chemoresistance of osteosarcoma cells. Cell Biol Toxicol 39: 813-825, 2023.
80. Wei LH, Torng PL, Hsiao SM, Jeng YM, Chen MW and Chen CA: Histone deacetylase 6 regulates estrogen receptor alpha in uterine leiomyoma. Reprod Sci 18: 755-762, 2011.
81. Stopper D, Biermann L, Watson PR, Li J, König B, Gaynes MN, Pessanha de Carvalho L, Klose J, Hanl M, Hamacher A, *et al*: Exploring alternative zinc-binding groups in histone deacetylase (HDAC) inhibitors uncovers DS-103 as a potent ethylhydrazide-based HDAC inhibitor with chemosensitizing properties. J Med Chem 68: 4426-4452, 2025.
82. Long J, Jia MY, Fang WY, Chen XJ, Mu LL, Wang ZY, Shen Y, Xiang RF, Wang LN, Wang L, *et al*: FLT3 inhibition upregulates HDAC8 via FOXO to inactivate p53 and promote maintenance of FLT3-ITD+ acute myeloid leukemia. Blood 135: 1472-1483, 2020.
83. McGuire JJ, Nerlakanti N, Lo CH, Tauro M, Utset-Ward TJ, Reed DR and Lynch CC: Histone deacetylase inhibition prevents the growth of primary and metastatic osteosarcoma. Int J Cancer 147: 2811-2823, 2020.
84. Sawai T, Yamanegi K, Nishiura H, Futani H and Tachibana T: Sodium valproate enhances semaphorin 3A-mediated anti-angiogenesis and tumor growth inhibition in human osteosarcoma cells. Anticancer Res 43: 2539-2550, 2023.
85. Rossi M, De Martino V, Di Giuseppe L, Battafarano G, Di Gregorio J, Terreri S, Marampon F, Minisola S and Del Fattore A: Anti-proliferative, pro-apototic and anti-migratory properties of HDAC inhibitor PXD-101 on osteosarcoma cell lines. Arch Biochem Biophys 734: 109489, 2023.
86. Magar AG, Morya VK, Koh YH and Noh KC: Synergistic HDAC4/8 inhibition sensitizes osteosarcoma to doxorubicin via pAKT/RUNX2 pathway modulation. Int J Mol Sci 26: 3574, 2025.
87. Collier CD, Getty PJ and Greenfield EM: Targeting the cancer epigenome with histone deacetylase inhibitors in osteosarcoma. Adv Exp Med Biol 1258: 55-75, 2020.

88. Ding K, Liu H, Yang H, Zhu H, Ma J, Peng H, Huang H, Shi W, Cao L, Wu W, *et al*: A prospective phase 2 study of combination epigenetic therapy against relapsed/refractory peripheral T cell lymphoma. Med 5: 1393-1401.e2, 2024.
89. Pu J, Liu T, Wang X, Sharma A, Schmidt-Wolf IGH, Jiang L and Hou J: Exploring the role of histone deacetylase and histone deacetylase inhibitors in the context of multiple myeloma: Mechanisms, therapeutic implications, and future perspectives. Exp Hematol Oncol 13: 45, 2024.
90. Gössl FJ, Polo P, Helmprobst F, Menzenbach A, Visekruna A, Gress TM, Adhikary T and Lauth M: ER-phagy mediates the anti-tumoral synergism between HDAC inhibition and chemotherapy. Cell Commun Signal 23: 202, 2025.
91. Xu T, Fang Y, Gu Y, Xu D, Hu T, Yu T, Xu YY, Shen HY, Ma P and Shu Y: HDAC inhibitor SAHA enhances antitumor immunity via the HDAC1/JAK1/FGL1 axis in lung adenocarcinoma. J Immunother Cancer 12: e010077, 2024.
92. Ferro A, Graikioti D, Gezer E, Athanassopoulos CM and Cuendet M: Entinostat-bortezomib hybrids against multiple myeloma. Molecules 28: 1456, 2023.
93. Hirano M, Imai Y, Kaito Y, Murayama T, Sato K, Ishida T, Yamamoto J, Ito T, Futami M, Ri M, *et al*: Small-molecule HDAC and Akt inhibitors suppress tumor growth and enhance immunotherapy in multiple myeloma. J Exp Clin Cancer Res 40: 110, 2021.
94. Florean C, Lernoux M, Lorant A, Losson H, Bormans G, Schnekenburger M and Diederich M: HDAC6 inhibitors sensitize resistant t(11;14) multiple myeloma cells to a combination of bortezomib and BH3 mimetics. Haematologica 110: 784-790, 2025.
95. García-Guerrero E, Götz R, Doose S, Sauer M, Rodríguez-Gil A, Nerreter T, Kortüm KM, Pérez-Simón JA, Einsele H, Hudecek M and Danhof S: Upregulation of CD38 expression on multiple myeloma cells by novel HDAC6 inhibitors is a class effect and augments the efficacy of daratumumab. Leukemia 35: 201-214, 2021.
96. Zhan W, Liao X, Liu J, Tian T, Yu L and Li R: USP38 regulates the stemness and chemoresistance of human colorectal cancer via regulation of HDAC3. Oncogenesis 9: 48, 2020.
97. Szigety KM, Liu F, Yuan CY, Moran DJ, Horrell J, Gochnauer HR, Cohen RN, Katz JP, Kaestner KH, Seykora JT, *et al*: HDAC3 ensures stepwise epidermal stratification via NCoR/SMRT-reliant mechanisms independent of its histone deacetylase activity. Genes Dev 34: 973-988, 2020.
98. Dai B, Wang F, Wang Y, Zhu J, Li Y, Zhang T, Zhao L, Wang L, Gao W, Li J, *et al*: Targeting HDAC3 to overcome the resistance to ATRA or arsenic in acute promyelocytic leukemia through ubiquitination and degradation of PML-RARα. Cell Death Differ 30: 1320-1333, 2023.
99. Li L, Hao S, Gao M, Liu J, Xu X, Huang J, Cheng G and Yang H: HDAC3 inhibition promotes antitumor immunity by enhancing CXCL10-mediated chemotaxis and recruiting of immune cells. Cancer Immunol Res 11: 657-673, 2023.
100. Han R, Luo Y, Gao J, Zhou H, Wang Y, Chen J, Zheng G and Ling C: HDAC3: A multifaceted modulator in immunotherapy sensitization. Vaccines (Basel) 13: 182, 2025.
101. Eichner LJ, Curtis SD, Brun SN, McGuire CK, Gushterova I, Baumgart JT, Trefts E, Ross DS, Rymoff TJ and Shaw RJ: HDAC3 is critical in tumor development and therapeutic resistance in Kras-mutant non-small cell lung cancer. Sci Adv 9: eadd3243, 2023.
102. Wu X, Yang C, Sun F, Zhang Y, Wang Y, Li X and Zheng F: Enterotoxigenic bacteroides fragilis (ETBF) enhances colorectal cancer cell proliferation and metastasis through HDAC3/miR-139-3p pathway. Biochem Genet 62: 3904-3919, 2024.
103. Cassandri M, Porrazzo A, Pomella S, Noce B, Zwergel C, Aiello FA, Vulcano F, Milazzo L, Camero S, Pajalunga D, *et al*: HDAC3 genetic and pharmacologic inhibition radiosensitizes fusion positive rhabdomyosarcoma by promoting DNA double-strand breaks. Cell Death Discov 10: 351, 2024.
104. Zhou Y, Jin X, Ma J, Ding D, Huang Z, Sheng H, Yan Y, Pan Y, Wei T, Wang L, *et al*: HDAC5 loss impairs RB repression of pro-oncogenic genes and confers CDK4/6 inhibitor resistance in cancer. Cancer Res 81: 1486-1499, 2021.
105. Fan J, Lou B, Chen W, Zhang J, Lin S, Lv FF and Chen Y: Down-regulation of HDAC5 inhibits growth of human hepatocellular carcinoma by induction of apoptosis and cell cycle arrest. Tumour Biol 35: 11523-11532, 2014.
106. Lyu H, Ishimura A, Suzuki R, Buyanbat K, Batbayar G, Meguro-Horike M, Horike SI, Yano S and Suzuki T: HDAC5, an early osimertinib-responsive gene, is a novel therapeutic target for the drug resistance in EGFR-mutant lung adenocarcinoma cells. Biochem Biophys Rep 42: 102016, 2025.
107. Pan P, Qin G, Wang B, Yu H, Chen J, Liu J, Bing K, Shen J, Ren D, Zhao Y, *et al*: HDAC5 loss enhances phospholipid-derived arachidonic acid generation and confers sensitivity to cPLA2 inhibition in pancreatic cancer. Cancer Res 82: 4542-4554, 2022.
108. Liu C, Zheng D, Pu X and Li S: HDAC7: A promising target in cancer. Front Oncol 14: 1327933, 2024.
109. Lu P, Deng S, Liu J, Xiao Q, Zhou Z, Li S, Xin J, Shu G, Yi B and Yin G: Tweety homolog 3 promotes colorectal cancer progression through mutual regulation of histone deacetylase 7. MedComm (2020) 5: e576, 2024.
110. Gautam N, Chapagain PP, Adhikari NP and Tiwari PB: Characterization of molecular interactions between HDAC7 and MEF2A. J Biomol Struct Dyn: 1-10, 2024 (Epub ahead of print).
111. Lu W, Zhuang G, Guan Y, Li Y, Liu L and Xiao M: Comprehensive analysis of HDAC7 expression and its prognostic value in diffuse large B cell lymphoma: A review. Medicine (Baltimore) 102: e34577, 2023.
112. Jin Y, Qi X, Yu X, Cheng X, Chen B, Wu M, Zhang J, Yin H, Lu Y, Zhou Y, *et al*: Discovery of a potential hematologic malignancies therapy: Selective and potent HDAC7 PROTAC degrader targeting non-enzymatic function. Acta Pharm Sin B 15: 1659-1679, 2025.
113. Bi L, Ren Y, Feng M, Meng P, Wang Q, Chen W, Jiao Q, Wang Y, Du L, Zhou F, *et al*: HDAC11 regulates glycolysis through the LKB1/AMPK signaling pathway to maintain hepatocellular carcinoma stemness. Cancer Res 81: 2015-2028, 2021.
114. Wang W, Ding B, Lou W and Lin S: Promoter hypomethylation and miR-145-5p downregulation-mediated HDAC11 overexpression promotes sorafenib resistance and metastasis of hepatocellular carcinoma cells. Front Cell Dev Biol 8: 724, 2020.
115. Liu Y, Tong X, Hu W and Chen D: HDAC11: A novel target for improved cancer therapy. Biomed Pharmacother 166: 115418, 2023.
116. Chen J, Cheng F, Sahakian E, Powers J, Wang Z, Tao J, Seto E, Pinilla-Ibarz J and Sotomayor EM: HDAC11 regulates expression of C/EBPβ and immunosuppressive molecules in myeloid-derived suppressor cells. J Leukoc Biol 109: 891-900, 2021.
117. Villagra A, Cheng F, Wang HW, Suarez I, Glozak M, Maurin M, Nguyen D, Wright KL, Atadja PW, Bhalla K, *et al*: The histone deacetylase HDAC11 regulates the expression of interleukin 10 and immune tolerance. Nat Immunol 10: 92-100, 2009.
118. Li R, Wu X, Zhao P, Xue K and Li J: A pan-cancer analysis identifies HDAC11 as an immunological and prognostic biomarker. FASEB J 36: e22326, 2022.
119. Zhao C, Dong H, Xu Q and Zhang Y: Histone deacetylase (HDAC) inhibitors in cancer: A patent review (2017-present). Expert Opin Ther Pat 30: 263-274, 2020.
120. Biersack B, Polat S and Höpfner M: Anticancer properties of chimeric HDAC and kinase inhibitors. Semin Cancer Biol 83: 472-486, 2022.
121. Zhou WH, Luo Y, Li RX, Degrace P, Jourdan T, Qiao F, Chen LQ, Zhang ML and Du ZY: Inhibition of mitochondrial fatty acid β-oxidation activates mTORC1 pathway and protein synthesis via Gcn5-dependent acetylation of raptor in zebrafish. J Biol Chem 299: 105220, 2023.
122. Mukherjee A, Zamani F and Suzuki T: Evolution of slow-binding inhibitors targeting histone deacetylase isoforms. J Med Chem 66: 11672-11700, 2023.
123. San-Miguel JF, Hungria VTM, Yoon SS, Beksac M, Dimopoulos MA, Elghandour A, Jedrzejczak WW, Günther A, Nakorn TN, Siritanaratkul N, *et al*: Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: A multicentre, randomised, double-blind phase 3 trial. Lancet Oncol 15: 1195-1206, 2014.
124. Zhang L, Zhang Y, Mehta A, Boufraqech M, Davis S, Wang J, Tian Z, Yu Z, Boxer MB, Kiefer JA, *et al*: Dual inhibition of HDAC and EGFR signaling with CUDC-101 induces potent suppression of tumor growth and metastasis in anaplastic thyroid cancer. Oncotarget 6: 9073-9085, 2015.
125. San José-Enériz E, Gimenez-Camino N, Rabal O, Garate L, Miranda E, Gómez-Echarte N, García F, Charalampopoulou S, Sáez E, Vilas-Zornoza A, *et al*: Epigenetic-based differentiation therapy for acute myeloid leukemia. Nat Commun 15: 5570, 2024.

126. Sim W, Lim WM, Hii LW, Leong CO and Mai CW: Targeting pancreatic cancer immune evasion by inhibiting histone deacetylases. World J Gastroenterol 28: 1934-1945, 2022.
127. Li X, Wang Y, Deng S, Zhu G, Wang C, Johnson NA, Zhang Z, Tirado CR, Xu Y, Metang LA, *et al*: Loss of SYNCRIP unleashes APOBEC-driven mutagenesis, tumor heterogeneity, and AR-targeted therapy resistance in prostate cancer. Cancer Cell 41: 1427-1449.e12, 2023.
128. Yang L, Qiu Q, Wang J, Wen Y, Li H, Liang R, Feng Y, Wang F, Lin X, Tang M, *et al*: Preclinical and first-in-human of purinostat mesylate, a novel selective HDAC I/IIb inhibitor, in relapsed/refractory multiple myeloma and lymphoma. Signal Transduct Target Ther 10: 201, 2025.
129. Bishton MJ, Harrison SJ, Martin BP, McLaughlin N, James C, Josefsson EC, Henley KJ, Kile BT, Prince HM and Johnstone RW: Deciphering the molecular and biologic processes that mediate histone deacetylase inhibitor-induced thrombocytopenia. Blood 117: 3658-3668, 2011.
130. Liu YM and Liou JP: An updated patent review of histone deacetylase (HDAC) inhibitors in cancer (2020-present). Expert Opin Ther Pat 33: 349-369, 2023.
131. Song S, Wen Y, Tong H, Loro E, Gong Y, Liu J, Hong S, Li L, Khurana TS, Chu M and Sun Z: The HDAC3 enzymatic activity regulates skeletal muscle fuel metabolism. J Mol Cell Biol 11: 133-143, 2019.
132. Bülbül EF, Robaa D, Sun P, Mahmoudi F, Melesina J, Zessin M, Schutkowski M and Sippl W: Application of ligand- and structure-based prediction models for the design of alkylhydrazide-based HDAC3 inhibitors as novel anti-cancer compounds. Pharmaceuticals (Basel) 16: 968, 2023.
133. Ren Y, Li S, Zhu R, Wan C, Song D, Zhu J, Cai G, Long S, Kong L and Yu W: Discovery of STAT3 and histone deacetylase (HDAC) dual-pathway inhibitors for the treatment of solid cancer. J Med Chem 64: 7468-7482, 2021.
134. Xie X, Zhang O, Yeo MJR, Lee C, Tao R, Harry SA, Payne NC, Nam E, Paul L, Li Y, *et al*: Converging mechanism of UM171 and KBTBD4 neomorphic cancer mutations. Nature 639: 241-249, 2025.
135. Gao J, Hou B, Zhu Q, Yang L, Jiang X, Zou Z, Li X, Xu T, Zheng M, Chen YH, *et al*: Engineered bioorthogonal POLY-PROTAC nanoparticles for tumour-specific protein degradation and precise cancer therapy. Nat Commun 13: 4318, 2022.
136. Sun J, Lian X, Lv C, Li H, Lin Z, Luo S, Liu Y, Xu Y, Jiang X, Xu W, *et al*: Trps1 acts as a regulator of Sf-1 transcription and testosterone synthesis in mouse Leydig cells. Cell Biol Toxicol 39: 3141-3157, 2023.
137. Chen M, Wang C, Wang X, Tu Z, Ding Z and Liu Z: An 'AND' logic-gated prodrug micelle locally stimulates antitumor immunity. Adv Mater 36: e2307818, 2024.
138. Li S, Liu Y, Tian T, Zhang T, Lin S, Zhou M, Zhang X, Lin Y and Cai X: Bioswitchable delivery of microRNA by framework nucleic acids: Application to bone regeneration. Small 17: e2104359, 2021.
139. Xing X, Zhong W, Tang P, Tao Q, Lu X and Zhong L: Tracking intracellular nuclear targeted-chemotherapy of chidamide-loaded Prussian blue nanocarriers by SERS mapping. Colloids Surf B Biointerfaces 229: 113469, 2023.
140. Hong L, Ni M, Xue F, Jiang T, Wu X, Li C, Liang S, Chen T, Luo C and Wu Q: The role of HDAC3 in pulmonary diseases. Lung 203: 47, 2025.
141. Zhang F, Yue K, Sun S, Lu S, Jia G, Zha Y, Zhang S, Chou CJ, Liao C, Li X and Duan Y: Targeting histone deacetylase 11 with a highly selective inhibitor for the treatment of MASLD. Adv Sci (Weinh) 12: e2412903, 2025.
142. Pramanik SD, Kumar Halder A, Mukherjee U, Kumar D, Dey YN and R M: Potential of histone deacetylase inhibitors in the control and regulation of prostate, breast and ovarian cancer. Front Chem 10: 948217, 2022.
143. Woods DM, Sodré AL, Villagra A, Sarnaik A, Sotomayor EM and Weber J: HDAC inhibition upregulates PD-1 ligands in melanoma and augments immunotherapy with PD-1 blockade. Cancer Immunol Res 3: 1375-1385, 2015.
144. Baretti M and Yarchoan M: Epigenetic modifiers synergize with immune-checkpoint blockade to enhance long-lasting antitumor efficacy. J Clin Invest 131: e151002, 2021.
145. Qian C, Lai CJ, Bao R, Wang DG, Wang J, Xu GX, Atoyan R, Qu H, Yin L, Samson M, *et al*: Cancer network disruption by a single molecule inhibitor targeting both histone deacetylase activity and phosphatidylinositol 3-kinase signaling. Clin Cancer Res 18: 4104-4113, 2012.
146. Zhou L and Yu CW: Epigenetic modulations in triple-negative breast cancer: Therapeutic implications for tumor microenvironment. Pharmacol Res 204: 107205, 2024.
147. Venneker S, van Eenige R, Kruisselbrink AB, Palubeckaitė I, Taliento AE, Briaire-de Bruijn IH, Hogendoorn PCW, van de Sande MAJ, Gelderblom H, Mei H, *et al*: Histone deacetylase inhibitors as a therapeutic strategy to eliminate neoplastic 'stromal' cells from giant cell tumors of bone. Cancers (Basel) 14: 4708, 2022.
148. Guo F and Wang H: Potential of histone deacetylase inhibitors for the therapy of ovarian cancer. Front Oncol 12: 1057186, 2022.
149. Li X, Su X, Liu R, Pan Y, Fang J, Cao L, Feng C, Shang Q, Chen Y, Shao C and Shi Y: HDAC inhibition potentiates anti-tumor activity of macrophages and enhances anti-PD-L1-mediated tumor suppression. Oncogene 40: 1836-1850, 2021.
150. Nguyen A, Ho L, Hogg R, Chen L, Walsh SR and Wan Y: HDACi promotes inflammatory remodeling of the tumor microenvironment to enhance epitope spreading and antitumor immunity. J Clin Invest 132: e159283, 2022.
151. Zhang W, Ge L, Zhang Y, Zhang Z, Zhang W, Song F, Huang P and Xu T: Targeted intervention of tumor microenvironment with HDAC inhibitors and their combination therapy strategies. Eur J Med Res 30: 69, 2025.
152. Jing L, Qian Z, Gao Q, Sun R, Zhen Z, Wang G, Yang X, Li H, Guo T and Zhang W: Diffuse midline glioma treated with epigenetic agent-based immunotherapy. Signal Transduct Target Ther 8: 23, 2023.
153. Fresquet V, Garcia-Barchino MJ, Larrayoz M, Celay J, Vicente C, Fernandez-Galilea M, Larrayoz MJ, Calasanz MJ, Panizo C, Junza A, *et al*: Endogenous retroelement activation by epigenetic therapy reverses the warburg effect and elicits mitochondrial-mediated cancer cell death. Cancer Discov 11: 1268-1285, 2021.
154. Jenke R, Reßing N, Hansen FK, Aigner A and Büch T: Anticancer therapy with HDAC inhibitors: Mechanism-based combination strategies and future perspectives. Cancers (Basel) 13: 634, 2021.
155. Chen Y, Su J, Li S, Chen F, Zhang Y, Wang X, Zhang Y, Wang X, Yuan Z, Ren S, *et al*: Structural modifications and prospects of histone deacetylase (HDAC) inhibitors in cancer. Curr Med Chem 32: 8530-8555, 2025.
156. Zou Q, Zhang Y, Zhou H, Lai Y, Cao Y, Li Z, Su N, Li W, Huang H, Liu P, *et al*: Chidamide, a histone deacetylase inhibitor, combined with R-GemOx in relapsed/refractory diffuse large B-cell lymphoma (TRUST): A multicenter, single-arm, phase 2 trial. Cancer Med 14: e70919, 2025.
157. Wang L, Gao M, Wang T, Cui P, Chen G, Han X, Ma Z, Yang W, Jing F, Ma J, *et al*: First-line treatment with HDACis plus tislelizumab combined with chemotherapy in advanced NSCLC: A single-arm phase II study. Oncologist 30: oyaf155, 2025.
158. Wieduwilt MJ, Pawlowska N, Thomas S, Olin R, Logan AC, Damon LE, Martin T, Kang M, Sayre PH, Boyer W, *et al*: Histone deacetylase inhibition with panobinostat combined with intensive induction chemotherapy in older patients with acute myeloid leukemia: Phase I study results. Clin Cancer Res 25: 4917-4923, 2019.
159. Gu S, Hou Y, Dovat K, Dovat S, Song C and Ge Z: Synergistic effect of HDAC inhibitor chidamide with cladribine on cell cycle arrest and apoptosis by targeting HDAC2/c-Myc/RCC1 axis in acute myeloid leukemia. Exp Hematol Oncol 12: 23, 2023.
160. Liu S, Ma S, Liu G, Hou L, Guan Y, Liu L, Meng Y, Yu W, Liu T, Zhou L, *et al*: CK2B induces $CD8^+$ T-cell exhaustion through HDAC8-mediated epigenetic reprogramming to limit the efficacy of anti-PD-1 therapy in non-small-cell lung cancer. Adv Sci (Weinh) 12: e2411053, 2025.
161. Chen C, Li X, Zhao H, Liu M, Du J, Zhang J, Yang X, Hou X and Fang H: Discovery of DNA-targeting HDAC inhibitors with potent antitumor efficacy in vivo that trigger antitumor immunity. J Med Chem 65: 3667-3683, 2022.
162. Liang R, Ding D, Li Y, Lan T, Ryabtseva S, Huang S, Ren J, Huang H and Wei B: HDACi combination therapy with IDO1i remodels the tumor microenvironment and boosts antitumor efficacy in colorectal cancer with microsatellite stability. J Nanobiotechnology 22: 753, 2024.
163. Guerriero JL, Sotayo A, Ponichtera HE, Castrillon JA, Pourzia AL, Schad S, Johnson SF, Carrasco RD, Lazo S, Bronson RT, *et al*: Class IIa HDAC inhibition reduces breast tumours and metastases through anti-tumour macrophages. Nature 543: 428-432, 2017.

164. Chen KY, Kibayashi T, Giguelay A, Hata M, Nakajima S, Mikami N, Takeshima Y, Ichiyama K, Omiya R, Ludwig LS, *et al*: Genome-wide CRISPR screen in human T cells reveals regulators of FOXP3. Nature 642: 191-200, 2025.
165. Gediya P, Vyas VK, Carafa V, Sitwala N, Della Torre L, Poziello A, Kurohara T, Suzuki T, Sanna V, Raguraman V, *et al*: Discovery of novel tetrahydrobenzo[b]thiophene-3-carbonitriles as histone deacetylase inhibitors. Bioorg Chem 110: 104801, 2021.
166. Elmezayen AD, Al-Obaidi A and Yelekçi K: Discovery of novel isoform-selective histone deacetylases 5 and 9 inhibitors through combined ligand-based pharmacophore modeling, molecular mocking, and molecular dynamics simulations for cancer treatment. J Mol Graph Model 106: 107937, 2021.
167. Yao K, Li Y, Wei W, Liu S, Wang X, Xu J, Zhang R, Wu Z, Guo C, Yang L and Hu L: Synthesis and biological evaluation of novel 4-Arylaminoquinolines derivatives as EGFR/HDAC inhibitors. Bioorg Med Chem Lett 122: 130214, 2025.
168. Parag-Sharma K, Tasoulas J, Musicant AM, do Nascimento-Filho CHV, Zhu Z, Twomey C, Liu P, Castilho RM and Amelio AL: Synergistic efficacy of combined EGFR and HDAC inhibitors overcomes tolerance to EGFR monotherapy in salivary mucoepidermoid carcinoma. Oral Oncol 115: 105166, 2021.
169. Cao J, Zhao W, Zhao C, Liu Q, Li S, Zhang G, Chou CJ and Zhang Y: Development of a bestatin-SAHA hybrid with dual inhibitory activity against APN and HDAC. Molecules 25: 4991, 2020.
170. Zhang Y, Wang H, Zhan Z, Gan L and Bai O: Mechanisms of HDACs in cancer development. Front Immunol 16: 1529239, 2025.
171. Hai R, Yang D, Zheng F, Wang W, Han X, Bode AM and Luo X: The emerging roles of HDACs and their therapeutic implications in cancer. Eur J Pharmacol 931: 175216, 2022.
172. Sanaei M and Kavoosi F: Histone deacetylases and histone deacetylase inhibitors: Molecular mechanisms of action in various cancers. Adv Biomed Res 8: 63, 2019.
173. Oliveira-Silva JM, de Oliveira LS, Tagliéri JVM, Lopes LB, de Souza CVE, Batistão HKA and Castro-Gamero AM: HDAC6: Tumor progression and beyond. Curr Cancer Drug Targets: Jan 7, 2025 (Epub ahead of print).
174. Jo H, Shim K and Jeoung D: Targeting HDAC6 to overcome autophagy-promoted anti-cancer drug resistance. Int J Mol Sci 23: 9592, 2022.
175. Kadier K, Niu T, Ding B, Chen B, Qi X, Chen D, Cheng X, Fang Y, Zhou J, Zhao W, *et al*: PROTAC-mediated HDAC7 protein degradation unveils its deacetylase-independent proinflammatory function in macrophages. Adv Sci (Weinh) 11: e2309459, 2024.

Copyright © 2026 Lin et al. This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.