Zhang *et al.*
European Journal of Medical Research (2025) 30:69
https://doi.org/10.1186/s40001-025-02326-8

European Journal
of Medical Research

REVIEW

Open Access

Targeted intervention of tumor microenvironment with HDAC inhibitors and their combination therapy strategies

Wanli Zhang[1], Luqi Ge[1], Yiwen Zhang[2,3,4], Zhentao Zhang[1], Wen Zhang[1], Feifeng Song[2,3*], Ping Huang[2,3,4*] and Tong Xu[2,3*]

Abstract

Histone deacetylation represents a significant epigenetic mechanism that involves the removal of acetyl groups from histones, subsequently influencing gene transcription. Overexpression of histone deacetylases (HDACs) is prevalent across various cancer types, positioning HDAC inhibitors as broadly applicable therapeutic agents. These inhibitors are known to enhance tumor immune antigenicity, potentially slowing tumor progression. Furthermore, the tumor microenvironment, which is intricately linked to cancer development, acts as a mediator in the proliferation of numerous cancers and presents a viable target for oncological therapies. This paper primarily explores how HDAC inhibitors can regulate cancer progression via the tumor microenvironment and suppress tumor growth through multiple pathways, in addition to examining the synergistic effects of combined drug therapies involving HDAC inhibitors.

Keywords Histone deacetylase, Histone deacetylase inhibitors, Tumor, Tumor microenvironment

Introduction

Histone modification is a pivotal epigenetic mechanism implicated in the development and progression of cancer [1]. HDAC and HAT interconversion is shown in Fig. 1A. Acetylation, a key histone modification, is crucial in maintaining physiological equilibrium within the body. Histone deacetylases, a group of proteases, catalyze the deacetylation of lysine residues, which are pivotal in chromosomal structural adjustments and gene expression regulation. The process of histone deacetylation impacts the interaction of DNA with histone octamers, consequently influencing the specific binding of various transcription factors and co-transcription factors to DNA binding sites, thereby modulating gene transcription. HDAC enzymes are ubiquitously present across organisms. In humans, 18 histone deacetylases have been identified and categorized into four major families according to the homology of transcriptional control factor sequences in yeast as class I, class II, class IV, and class III [2]. Notably, class I, II, and IV enzymes are Zn2+-dependent proteins, while class III relies on NAD+as a cofactor. Figure 1B illustrates the classification of HDACs. HDACs play critical roles in various biological processes, such as transcriptional regulation through histone acetylation status, post-translational modification of proteins, and cellular proliferation and

*Correspondence:
Feifeng Song
songfeifeng@hmc.edu.cn
Ping Huang
huangping@hmc.edu.cn
Tong Xu
21619007@zju.edu.cn
[1] Department of Pharmacology, College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou, China
[2] Center for Clinical Pharmacy, Cancer Center, Department of Pharmacy, Zhejiang Provincial People's Hospital(Affiliated People's Hospital), Hangzhou Medical College, Hangzhou, Zhejiang, China
[3] Key Laboratory of Endocrine Gland Diseases of Zhejiang Province, Hangzhou 310014, China
[4] Clinical Research Center for Cancer of Zhejiang Province, Hangzhou, China

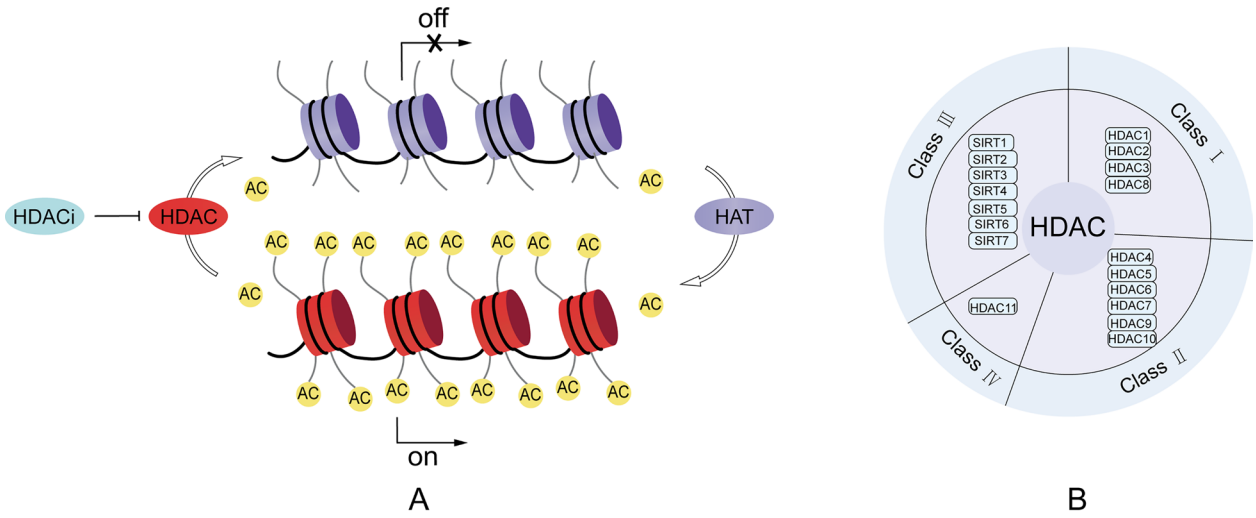

Fig. 1 **A** The regulation of gene transcription mediated by HDAC and HAT. **1B** Based on the sequence homology of transcriptional regulators in yeast, HDACs can be categorized into four main families

differentiation. Furthermore, the overexpression of HDAC is strongly correlated with a wide spectrum of conditions, including different cancers [3–7]neurological disorders [8], and inflammatory diseases [9, 10].

Histone acetylase inhibitors prevent the removal of the N-acetyl group from acetylated lysine residues on histones. This action facilitates the dissociation of DNA from histone octamers, loosens the spatial structure of nucleosomes, and thereby enhances gene transcription. These inhibitors represent a novel class of anticancer agents that exert anti-tumor effects by inducing cell cycle arrest and apoptosis in tumor cells. Furthermore, HDAC inhibitors have the potential to enhance tumor immunogenicity, making them valuable in cancer immunotherapy. The HDAC inhibitors identified thus far are categorized into five main groups based on their structural characteristics, particularly the zinc-binding component: these include isohydroxamic acids, short-chain fatty acids, cyclic peptides, thiols, and benzamide histone deacetylase inhibitors [11]. To date, the U.S. Food and Drug Administration has approved four HDAC inhibitors for clinical use: vorinostat, romidepsin, belinostat, and panobinostat [12]. Additionally, chidamide has been approved by the Chinese Food and Drug Administration for the treatment of relapsed or refractory peripheral T-cell lymphoma (PTCL) [13]. An overview of HDAC inhibitors used in treatment of tumors (Table 1).

The tumor microenvironment encompasses the surrounding milieu where tumor cells reside, composed of adjacent blood vessels, immune cells, fibroblasts, myeloid-derived inflammatory cells, various signaling molecules, and the extracellular matrix. Normal tissue homeostasis and tumor growth rely on the reciprocal communication between cells and their microenvironment. Interactions between tumor cells and this environment can foster cancer progression, impacting disease advancement and prognosis [45]. Notably, interactions like those with tumor-associated macrophages can facilitate metastasis and invasion in pancreatic cancer through epithelial–mesenchymal transformation [46]. Furthermore, the tumor microenvironment, a crucial component of the tumor itself, sustains tumor growth and metastatic dissemination while compromising immune surveillance [47]. For instance, myeloid-derived suppressor cells(MDSCs) can impede innate immunity by converting macrophages from M1 to M2 and suppressing NK cell activity [48].

Acting as a modulator for various cancers, the tumor microenvironment can be targeted for tumor therapy by focusing on constituents like tumor-infiltrating T cells, tumor-associated fibroblasts, tumor-associated macrophages, and tumor-associated neutrophils [49]. With increasing research on the tumor microenvironment and HDAC inhibitors, mounting evidence indicates that HDAC inhibitors play a role in tumor development through the tumor microenvironment. This article offers a comprehensive review of HDAC inhibitors and the tumor microenvironment.

HDAC inhibitors modulate the tumor microenvironment to alleviate tumor progression

The expression of HDAC is intricately linked to the tumor microenvironment and exhibits a negative correlation with infiltrating immune cells, where the microenvironment can supply growth factors for tumor cells, aiding evasion from immune cell attacks. HDAC inhibitors

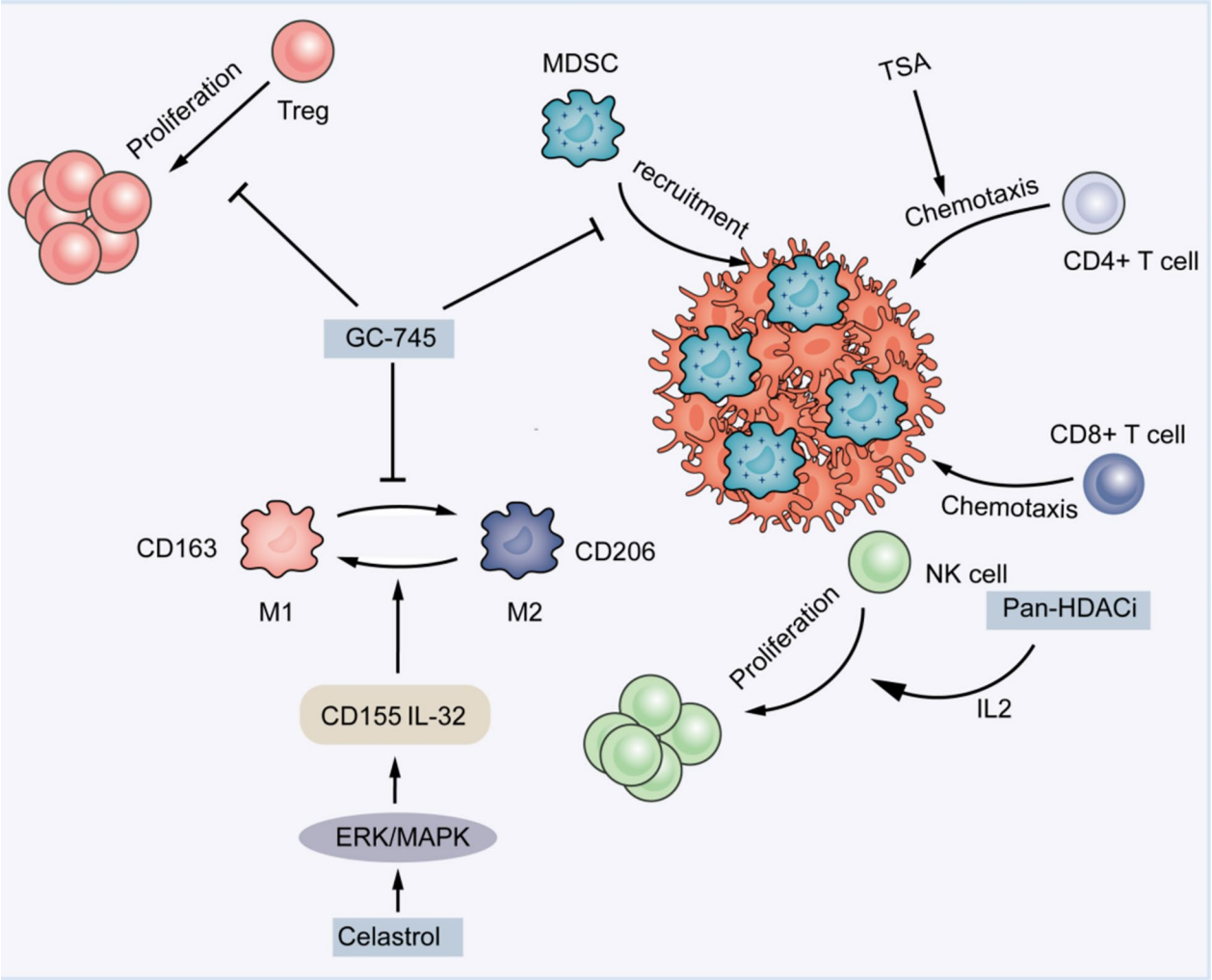

Fig. 2 HDAC inhibitors can promote the proliferation of natural killer cells, inhibit the proliferation of regulatory T cells, and facilitate the migration of $CD8^+$ and $CD4^+$ T cells toward tumor cells. Additionally, HDACs suppress the recruitment of myeloid-derived suppressor cells (MDSCs) to tumor sites and promote the conversion of M2 macrophages to M1 macrophages

hold promise in enhancing tumor immunogenicity, fostering anti-tumor immune responses, and countering the immunosuppressive tumor environment [50]. As shown in Fig. 2, these inhibitors can stimulate anti-tumor immune responses by modulating macrophages, T cells, and MDSCs.

Macrophages, abundant in various cancers, play a pivotal role in regulating cancer progression, thus presenting significant potential for cancer interventions. HDAC inhibitors can bolster anti-tumor capabilities by influencing macrophage phenotype. Not only do they restrict the recruitment of bone marrow-derived suppressor cells in tumors, but they also enhance the anti-tumor profile of tumor-associated macrophages, leading to favorable alterations in the tumor immune landscape [51, 52]. For example, the Chinese medicine Celastrol shifts macrophage polarization from M2 to M1, restraining the growth of colon cancer cells [53]. Moreover, TMP195, a selective class IIa histone deacetylase inhibitor, facilitates macrophage recruitment and differentiation, modulating the anti-tumor characteristics of macrophages and refining the tumor microenvironment [54]. Likewise, TMP195 induces macrophage M1 phenotypic shifts in colon cancer to exert anti-tumor effects [55].

T cells play a pivotal role in anti-tumor immunity, with HDAC inhibitors proving effective in mitigating tumor progression through T cell-mediated mechanisms. For instance, HDAC6 inhibitors demonstrate favorable immunomodulatory effects in chronic lymphocytic leukemia by alleviating T-cell immunosuppression

induced by chronic lymphocytic leukemia [56]. Notably, the class I HDAC inhibitor entinostat counteracts tumor microenvironment suppression in epithelial ovarian carcinoma, enhancing $CD8^+$T-cell activation and improving response rates to other immunotherapies [57]. Similarly, moxidectin reduces the population of T regulatory cells and potential myeloid-derived suppressor cells within the tumor while enhancing the $CD8^+$ cell population within the tumor [58]. Furthermore, HDAC inhibitors are known to recruit T cells to tumor sites, exerting anti-tumor effects. Remarkably, the novel HDAC inhibitor, HPTA, generates anti-tumor effects by enlisting $CXCR3^+CD4^+$ T cells to tumor sites through the chemokine CXCL9/10 axis [59]. Similarly, HDAC3 inhibitors impede tumor growth in murine models by recruiting $CXCR3^+$ T cells to the tumor microenvironment via chemokine signaling [60]. Natural killer(NK) cells are pivotal in the tumor microenvironment, curbing cancer cell proliferation and dissemination. Pan-HDAC inhibitors can enhance IL2-induced NK cell proliferation through the JAK–STAT pathway, preserving their immunoreactivity and activation status [61]. Besides facilitating NK cell proliferation, NK cells can also enhance the expression of the activating receptor NKG2D on their surface, thereby boosting NK cell activity [62]. The abundance of MDSCs in the tumor microenvironment orchestrates immunosuppression, with CN133 showcasing the ability to reshape the tumor microenvironment by reducing polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs) infiltration and bolstering immune response [63]. These findings underscore the potential of HDAC inhibitors in reducing immunosuppression, enhancing anti-tumor efficacy by modulating relevant cells in the tumor microenvironment, and provide a foundation for targeting the tumor microenvironment to impede tumor progression.

Antitumor mechanisms of HDAC inhibitors

Numerous strategies can be employed in cancer therapy, with potential approaches targeting over-immunomodulation, angiogenesis, inflammation, and tumor cell communication with the extracellular matrix. HDAC inhibitors offer an additional avenue to impede tumor growth through diverse mechanisms, including inhibiting angiogenesis, decreasing hypoxia, promoting apoptosis, and modulating the immune response to hinder tumor advancement. Figure 3 shows the anti-tumor mechanism of HDAC inhibitors.

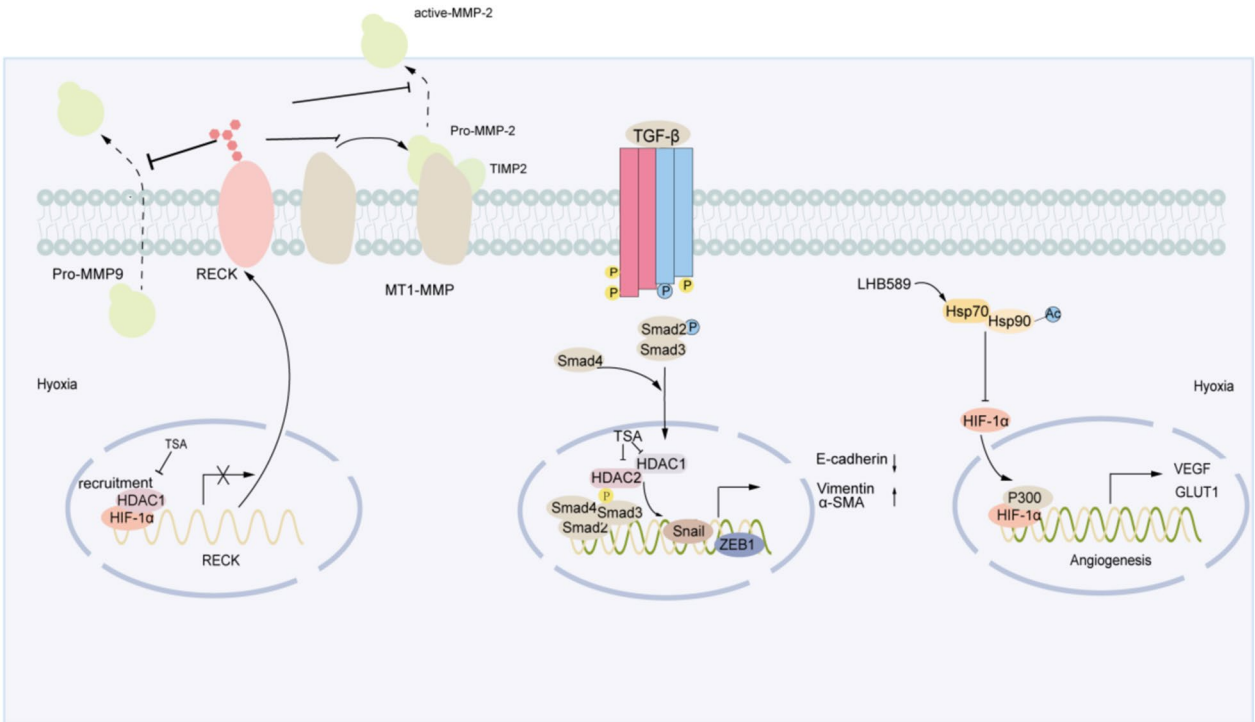

Fig. 3 Under hypoxic conditions, HDAC1 and HIF-1α can bind to the RECK promoter, resulting in the downregulation of RECK expression. However TSA can inhibit this interaction. HDAC inhibitors can suppress EMT-related markers by blocking the TGF-β/Smad pathway and activating phosphorylated p38 MAPK. Furthermore, LBH589 can inhibit the activity of HIF-1α in hypoxic environments, leading to a reduction in VEGF and GLUT1 expression

Anti-angiogenic effects

Hypoxia fosters aggressive tumor characteristics such as abnormal angiogenesis, invasion, metastasis, and resistance to radiation and chemotherapy [64, 65]. Among these, angiogenesis is pivotal in various physiological and pathological processes, notably tumor growth [66–68]. Glioblastoma, known for its strong vascularization, relies on angiogenesis for its growth and survival. HDAC inhibitors such as LBH589 counter the adaptation of glioblastoma cells to hypoxia by curbing hypoxia-inducible factor-1α (HIF-1α) activity and reducing VEGF secretion, thus exerting an anti-angiogenic effect [69]. Similarly, MPT0G157, another HDAC inhibitor, induces the degradation of hypoxia-inducible factor-1α by enhancing the hyperacetylation of heat shock protein 90 (Hsp90), leading to the downregulation of vascular endothelial growth factor expression. Notably, TSA has exhibited enhanced anti-tumor efficacy in various cancers, including breast cancer, colon cancer, and human tongue squamous carcinoma [70–72]. Targeting the tumor survival factor HIF-1α and its downstream gene VEGF, TSA can curb tumor adaptation to hypoxia, thereby restraining the invasion and transmigration of human tongue squamous carcinoma cells [71]. Researches have indicated that RECK is an important regulatory factor in the process of angiogenesis and is expressed at low levels in various types of cancer [73, 74, 74, 75]. Hypoxia induces oncogenic expression in RECK, yet HDAC inhibitors can reverse this effect by targeting the interaction of HDAC1 and HIF-1α at the rHRE2 site on the RECK promoter, downregulating RECK [76] and subsequently hindering the migratory invasion of cancer cells by inhibiting MMP1 and MMP9 activity [64].

Apoptosis

HDAC inhibitors also play a vital role in anticancer mechanisms encompassing apoptosis, cell cycle. For instance, DWP0016 can enhance the acetylation of p53 by promoting the interaction among p300, CBP, and PCAF, thereby facilitating apoptosis and cell cycle arrest in cancer cells [77]. Notably, HDAC inhibitor TW09 also mediates cancer cell death via mitochondrial apoptosis, accompanied by the expression of pro-apoptotic genes such as BIM, NOXA, PUMA, and BMF [78]. Additionally, Vorinostat induces apoptosis and cell cycle arrest in Hodgkin lymphoma cells, resulting in downregulation of Bcl-xL expression and upregulation of P21 expression. MPT0G157 induces apoptosis via a caspase-dependent mechanism [79]. It is noteworthy that HDAC inhibitor can also suppress cancer cell proliferation by regulating the cell cycle protein CDC25 [80]. Furthermore, HDAC inhibitors can promote tumor cell apoptosis via multiple mechanisms, including the Rb-E2F1 pathway, the JNK/AP-1 pathway, and the death receptor 5/TRAIL-R2 pathway [81–83].

Other pathways

HDAC inhibitor can also exert anti-tumor effects through mechanisms involving autophagy and the tumor microenvironment. HDAC inhibitor also exerts immunomodulatory effects by inhibiting STAT6-mediated TH2 cytokine and chemokine secretion within the tumor microenvironment [84]. Additionally, radicicolothionein inhibits tumor growth and activates PENT by downregulating the expression of HDAC6, thereby inducing autophagy in tumor cells [85]. The HDAC inhibitor hydroxyvaleric acid enhances direct interactions between monocytes and tumor cells in the tumor microenvironment, promoting cell death in malignant pleural mesothelioma cells [86]. Furthermore, the inhibition of epithelial–mesenchymal transition and promotion of apoptosis in colon cancer can be achieved through the regulation of TGF-β and p38 MAPK signaling pathways [72]. Collectively, these findings support the notion that HDACs play a crucial role in exerting anti-tumor effects through mechanisms involving the mitigation of hypoxia, inhibition of angiogenesis, promotion of autophagy, and induction of apoptosis.

Drug combinations with HDAC inhibitors

HDAC inhibitors alone may lack efficacy. For instance, at a dosage of 85 mg/day, MGCD0103 shows a lack of efficacy in treating chronic lymphocytic leukemia. However, when the dosage is increased to 110 mg/day, the trial discontinued due to toxic side effects [87]. Likewise, Panobinostat, when utilized as a standalone treatment, primarily exhibits myelosuppressive toxicity in pediatric patients with diffuse intrinsic pontine glioma, which limits the possibility of increasing the dosage [88]. Furthermore, although romidepsin exhibits minimal toxicity in advanced colon cancer, it lacks effectiveness, and its therapeutic efficacy in recurrent or metastatic head and neck cancer remains also limited [89, 90]. The above demonstrates that the efficacy of monotherapy is limited; thus, it is important to consider combination treatments with other drugs to improve efficacy and minimize toxicity.

The combination of immune checkpoints and HDAC inhibitors

HDAC inhibitors alone may have certain limitations, prompting research into their more potent combination therapies. Immune checkpoints remain a focal point in cancer research, as they mediate the immune evasion of tumor cells. The interaction of PD-1 ligands on tumor cells with PD-1 on T cells in the tumor microenvironment establishes an immunosuppressive milieu

promoting cancer immune evasion. Counteracting this process via PD-1 blockers or anti-PD-L1 agents inhibits immune escape. Moreover, HDAC inhibitors are capable of modulating immunogenicity and augmenting anti-tumor immune responses. Numerous studies have highlighted the broad applicability of combining HDAC inhibitors with checkpoint inhibitors. Combinations of HDAC inhibitors and PD-1 blockers have exhibited promising anti-tumor effects and enhanced survival rates across cancer types such as colon cancer, chondrosarcoma, and melanoma [55, 91, 92]. For instance, clinical studies indicate that panobinostat as monotherapy lacks efficacy in melanoma treatment and [93]; however, when paired with PD-1 blockers, it led to more potent anti-tumor effects and improved survival rates [94]. Notably, the HDAC inhibitor CG-745 potentiated the anti-tumor properties of anti-PD-1 antibodies [71]. Additionally, the co-administration of HDAC6 inhibitors with anti-PD-1 blockers reduced tumor growth, enhanced immune cell infiltration, diminished M2-type macrophages, and reshaped the tumor microenvironment [95]. The HDAC inhibitor TSA can promote the conversion of macrophages to the M1 phenotype and, when used in combination with PD-L1, can enhance the tumor-suppressive capabilities of PD-L1 [51].

Additionally, CD47, CTLA-4, and LAG3 are promising immune checkpoints that play significant roles in regulating immune cell function. When combined with HDAC inhibitors, they can synergistically enhance antitumor activity. HDAC inhibitor tacedinaline combined with anti-CD47 effectively eliminates MYC-driven tumor cells, enhances the phagocytic capacity of macrophages, and significantly improves survival rates [96]. Moreover, combining entinostat with anti-CTLA-4 improves immune cell infiltration, decreases the abundance of granulocyte MDSCs in the tumor microenvironment, and boosts the levels of $CD8^+$ effector T cells [97]. Similarly, the combination of the HDAC inhibitor SAHA with anti-LAG-3 significantly enhances tumor suppression compared to monotherapy and promotes the activation of $CD8^+$ T cells [98]. In summary, these findings emphasize the enhanced efficacy achieved through combining HDAC inhibitors with checkpoint inhibitors (Table 1).

The combination of targeted agents and HDAC inhibitors

In addition, HDAC inhibitors exhibit potent synergistic effects when combined with targeted drugs. Following the juxtaposition of the GB2 monoclonal antibody, a targeted therapy for neuroblastoma, with HDAC inhibitors, the latter aids in altering the tumor microenvironment by reducing macrophages and bone marrow immunosuppressive cells with high FGR expression, enhancing the effectiveness of the GD2 monoclonal antibody [99]. In a phase II clinical trial, chidamide showcased remarkable outcomes with higher overall response rates (50%) and complete response rates (40%), as well as sustained responses in patients with angioimmunoblastic T-cell lymphoma [13]. By combining the BTK inhibitor ibrutinib, a targeted therapy, with the HDAC inhibitor chidamide, the modulation of the tumor microenvironment, augmented T-cell infiltration, diminished M2-type macrophages, and intensified T cell-mediated cytotoxicity [100]. Furthermore, the non-toxic effects of the type I HDAC inhibitor entinostat and the mTOR inhibitor sirolimus on monocytes in the tumor microenvironment elucidated significant inhibition of tumor growth, induction of apoptosis, and cell cycle blockade [100]. Phase I clinical investigations unveiled the tolerability of the mTOR inhibitors ridaforolimus and vorinostat at

Table 1 An overview of HDAC inhibitors used in treatment of tumors

HDAC inhibitor	Cancer type	HDAC specificity	Clinical trial	Regulated protein	References
Fimepinostat	Relapsed or refractory diffuse large B cell and high-grade B-cell lymphoma	Class I/II	Phase II	c-Myc	[14–16]
Givinostat	Relapsed or progressive multiple myeloma	Class I/II	Phase II	BRAF, P53	[17–20]
Mocetinostat	Relapsed or refractory lymphoma	Class I/IV	Phase II	E2F6, ZEB1	[21–24]
Abexinostat	Relapsed or refractory lymphoma	Class I/II/IV	Phase I/II	EZH2, RAD51	[25–28]
Domatinostat	Advanced hematological malignancies	Class I	Phase I	FOXM1, HES1	[29–31]
Resminostat	Relapsed or refractory Hodgkin lymphoma	Class I/II	Phase II	CD44	[32, 33]
OBP-801	Advanced solid tumors	Class I	Phase Ia	NOXA	[34, 35]
Belinostat	Relapsed or refractory peripheral or cutaneous T-cell lymphoma	Class I/II	Phase II	P21	[36–38]
SB939	Translocation-associated recurrent/metastatic sarcomas	Class I/II/IV	PhaseII	CDK5	[39, 40]
CKD-581	Lymphoma or multiple myeloma refractory	Class I/II	Phase I	MYC, BCL-2	[41, 42]
Quisinostat	Advanced solid tumors	Class I/II	Phase I	P53	[43, 44]

recommended phase II doses without inducing dose-limiting toxicities [101]. Concurrently, the combination of JQ1, a BET bromodomain inhibitor, and ricolinostat, an HDAC6 inhibitor, facilitated T-cell activation, decreased the inhibitory capacity of immunosuppressive cells, and curtailed tumor growth [102]. In clinical studies, the PI3K inhibitor duvelisib has demonstrated associated pathological toxicities, including elevated transaminases and colitis, in patients with advanced hematologic malignancies [103]. However, the combination of duvelisib with romidepsin has been found to mitigate the liver toxicity induced by the PI3Kδ inhibitor duvelisib in patients with relapsed/refractory T cell lymphomas [104].

The combination of other drugs with HDAC inhibitors

The combination of entinostat and ricolinostat eliminated the suppressive effects on monocyte and polymorphonuclear cell myeloid-derived suppressor cell populations, significantly retarding tumor progression [105]. Moreover, the synergistic interplay of entrestat, N-803, and a vaccine reduced regulatory T cells and bolstered CD8 T-cell infiltration, thereby amplifying the anticancer effect [106]. Study has demonstrated that mucoepidermoid carcinoma cells exhibit a certain level of tolerance to EGFR inhibition. However, the concurrent use of EGFR and HDAC inhibitors can effectively synergize to overcome this EGFR tolerance in mucoepidermoid carcinoma cells [107]. Similarly, SAHA can enhance the expression of PTEN, and inhibit the AKT signaling pathway thereby overcoming resistance to lenvatinib in Hepatocellular Carcinoma [108]. Notably, the combination of panobinostat and NK cells enhances tumor lysis, with panobinostat promoting an increase in the activation receptors of NK cells and facilitating their binding to tumors [109]. Collectively, these findings accentuate the compelling synergy achieved when combining HDAC inhibitors with other pharmacological agents. Clinical trials of HDAC inhibitors in combination with drugs shown in Table 2.

Conclusion and perspectives

Histone deacetylases have garnered significant attention in recent years due to their crucial role in cancer development through the reversible regulation of histone acetylation and non-histone proteins. Acetylation, as an essential epigenetic process of histones, is indispensable for maintaining normal cellular functionality. The use of HDAC inhibitors in cancer therapy has been extensively explored. These inhibitors exhibit anti-tumor effects by inducing cell cycle arrest and apoptosis, while also enhancing the immune antigenic phenotype to bolster immune responses. The tumor microenvironment, where tumor cells reside, is closely linked to cancer progression and influences the development of various cancer types. Targeting the tumor microenvironment has shown promise in alleviating tumor advancement. HDAC

Table 2 Clinical trials of HDAC inhibitor combinations

HDACi	Combined drug	Cancer type	Phase	Curative effect	References
Panobinostat	Carfilzomib	Relapsed or relapsed/refractory multiple myeloma	Phases I/II	The overall objective response of all evaluable patients was 67%, and the clinical benefit rate was 79%	[110]
Entinostat	Pembrolizumab	Metastatic uveal melanoma	Phase II	The overall objective response was 14%. The clinical benefit rate at 18 weeks was 28%	[111]
Valproic acid	S-1	Advanced pancreatic cancer	Phases I/II	The disease control rate of combination therapy was 91.7%	[112]
Valproate	Doxorubicin	Progressing mesothelioma	Phase II	The response rate was 16%, and the optimal control rate was 36%	113
Vorinostat	Lixabepilone	Breast cancer	Phase IB	The ORR and CBR were 22 and 22%	[114]
Mocetinostat	Durvalumab	Non-small cell lung cancer	Phases I/II	The overall objective response was 1 1 .5%	[115]
Ivaltinostat	Gemcitabine, erlotinib	Pancreatic ductal adenocarcinoma	Phases I/II	The ORR and DCR were 25.0% and 93.8%	[116]
Romidepsin, Romidepsin	Tenalisib, 5-Azacytidine	Relapsed/refractory T-cell lymphoma, Peripheral T-cell lymphomas	Phases I/II, Phase II	The overall objective response rate in evaluable patients was 63.0% the ORR and complete response rates were 61% and 48%	[117, 118]

inhibitors interventions can enhance the tumor microenvironment by modulating macrophages, T cells, and NK cells to strengthen the immune response.

HDAC inhibitors exhibit a wide range of therapeutic potential, with five HDAC inhibitors having received approval for cancer therapy. However, the currently approved and clinically researched HDAC inhibitors still present certain limitations in the treatment of cancer. For instance, HDAC inhibitors can induce side effects such as diarrhea, heart problems, and ventricular tachyarrhythmia. Conversely, in some hematologic malignancies, HDAC inhibitors demonstrate efficacy as single-agent anti-tumor therapies. Furthermore, HDAC inhibitors possess the capability to target multiple HDACs, thereby down-regulating their expression and potentially impacting normal physiological processes. As such, the quest for HDAC-specific inhibitors with optimal targeting to enhance tumor cell apoptosis, elevate tumor immunogenicity, and counteract the immunosuppressive tumor microenvironment becomes imperative. Moreover, the pursuit of novel HDAC inhibitors with reduced side effects is essential. Additionally, pillararenes represents a promising class of targeted drug delivery systems. Future developments can focus on designing pillararene-based carriers to transport HDAC inhibitors to the tumor microenvironment, allowing for selective drug release based on the characteristics of that environment.

Combining multiple drugs for cancer treatment can address the limitations of monotherapy, enhancing treatment efficacy and expanding therapeutic possibilities through synergistic or cumulative effects. This approach can mitigate adverse effects and drug resistance by allowing lower doses of drugs in combination. For instance, clinical evidence supports the synergistic and less toxic nature of HDAC inhibitors when combined with other drugs. Nonetheless, some experiments have failed to demonstrate enhanced cancer progression or have even shown adverse effects and notable clinical toxicity when HDAC inhibitors are used in combination. To optimize the anti-tumor potential of HDAC inhibitors, broaden the therapeutic scope, and develop safer and more efficient combinations, advanced studies must meticulously consider the dosage of HDAC inhibitors in combinations and explore novel pairing strategies. Additionally, the combination of HDAC inhibitors with targeted drugs can modulate the tumor microenvironment, suggesting that dosing regimens with targeted agents should be deliberated in later stages of research. In the context of neurological disorders, drugs often face challenges such as poor solubility and inadequate tissue penetration. Furthermore, combining HDAC inhibitors with immune checkpoints offers opportunities to explore additional novel combinations, such as targeting TIM-3. Notably, DDR2 is crucial for tumor proliferation and metastasis, and mutations have been reported in various cancers, highlighting its potential as a therapeutic target. However, there are currently no studies investigating the combination of DDR2 targeting with HDAC inhibitors. Future research could focus on developing dual-target inhibitors or exploring combination therapies that incorporate both approaches.

Abbreviations

HDAC	Histone deacetylase
HAT	Histone acetyltransferase
HDACi	Histone deacetylase inhibition
PTCL	Peripheral T-cell lymphoma
MDSCs	Myeloid-derived suppressor cells
NK cells	Natural killer cells
Treg	Regulatory T
PMN-MDSCs	Polymorphonuclear Myeloid-derived suppressor cells
HIF-1α	Hypoxia-inducible factor-1α
VEGF	Vascular endothelial growth factor
HSP90	Heat Shock Protein 90
RECK	Reversion inducing cysteine rich protein with Kazal motifs
MMP1	Matrix metallopeptidase 1
MMP9	Matrix metallopeptidase 9
CBP	CREB-binding protein
PCAF	P300/CBP-associated factor
BIM	Bcl-2 interacting mediator of cell death
PUMA	P53 upregulated modulator of apoptosis
BMF	Bcl-2 modifying factor
CDC25	Cell division cycle 25
PTEN	Phosphatase and tensin homolog deleted on chromosome ten
EMT	Epithelial–mesenchymal transition
TGF-β	Transforming growth factor β
MAPK	Mitogen-activated protein kinase
STAT6	Signal transducer and activator of transcription 6
PD-L1	Programmed cell death 1 ligand 1
PD-1	Programmed cell death protein-1
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
LAG-3	Lymphocyte Activation Gene-3
CD47	Cluster of differentiation 47
GLUT1	Facilitative glucose transporter
EGFR	Epidermal growth factor receptor
TIM-3	T cell immunoglobulin domain and mucin domain-3

Acknowledgements
The article was funded by the Chinese Medicine Research Program of Zhejiang Province (No. 2024ZL275 and 2024ZL242); National Natural Science Foundation of China (No. 82203858 and 82161138019).

Author contributions
Wanli Zhang: Conceptualization, Investigation, Writing—original draft,Writing—review & editing. Luqi Ge: Conceptualization, Supervision Yiwen Zhang: Conceptualization, Writing—review & editing. Zhentao Zhang: Conceptualization, Project administration Wen Zhang: Conceptualization,Supervision Feifeng Song: Conceptualization, Funding acquisition, Project administration Ping Huang: Funding acquisition, Project administration Tong Xu: Funding acquisition, Supervision.

Funding
The research was supported by the Chinese Medicine Research Program of Zhejiang Province (Grant numbers [No.2024ZL275 and [No.2024ZL242]); National Natural Science Foundation of China (Grant numbers[No.82203858] and [No.82161138019]).

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 21 August 2024 Accepted: 23 January 2025
Published online: 04 February 2025

References

1. Yang G, Yuan Y, Yuan H, et al. Histone acetyltransferase 1 is a succinyltransferase for histones and non-histones and promotes tumorigenesis. EMBO Rep. 2021;22(2): e50967. https://doi.org/10.15252/embr.202050967.
2. Witt O, Deubzer HE, Milde T, Oehme I. HDAC family: what are the cancer relevant targets? Cancer Lett. 2009;277(1):8–21. https://doi.org/10.1016/j.canlet.2008.08.016.
3. Ma L, Qi L, Li S, et al. Aberrant HDAC3 expression correlates with brain metastasis in breast cancer patients. Thoracic Cancer. 2020;11(9):2493–505. https://doi.org/10.1111/1759-7714.13561.
4. Mori M. Histone deacetylase 1 expression in gastric cancer. Oncol Rep. 2011. https://doi.org/10.3892/or.2011.1361.
5. Li D, Sun X, Zhang L, et al. Histone deacetylase 6 and cytoplasmic linker protein 170 function together to regulate the motility of pancreatic cancer cells. Protein Cell. 2014;5(3):214–23. https://doi.org/10.1007/s13238-013-0010-3.
6. OuYang C, Shu G, Liu J, et al. HDAC5, negatively regulated by miR -148a-3p, promotes colon cancer cell migration. Cancer Sci. 2022;113(8):2560–74. https://doi.org/10.1111/cas.15399.
7. Weichert W. HDAC expression and clinical prognosis in human malignancies. Cancer Lett. 2009;280(2):168–76. https://doi.org/10.1016/j.canlet.2008.10.047.
8. Kassis H, Shehadah A, Li C, et al. Class IIa histone deacetylases affect neuronal remodeling and functional outcome after stroke. Neurochem Int. 2016;96:24–31. https://doi.org/10.1016/j.neuint.2016.04.006.
9. Falkenberg KJ, Johnstone RW. Histone deacetylases and their inhibitors in cancer, neurological diseases and immune disorders. Nat Rev Drug Discov. 2014;13(9):673–91. https://doi.org/10.1038/nrd4360.
10. Zhong Y, Huang T, Huang J, et al. The HDAC10 instructs macrophage M2 program via deacetylation of STAT3 and promotes allergic airway inflammation. Theranostics. 2023;13(11):3568–81. https://doi.org/10.7150/thno.82535.
11. Fan W, Zhang L, Jiang Q, Song W, Yan F, Zhang L. Histone deacetylase inhibitor based prodrugs. Eur J Med Chem. 2020;203: 112628. https://doi.org/10.1016/j.ejmech.2020.112628.
12. Zhao C, Dong H, Xu Q, Zhang Y. Histone deacetylase (HDAC) inhibitors in cancer: a patent review (2017-present). Expert Opin Ther Pat. 2020;30(4):263–74. https://doi.org/10.1080/13543776.2020.1725470.
13. Shi Y, Dong M, Hong X, et al. Results from a multicenter, open-label, pivotal phase II study of chidamide in relapsed or refractory peripheral T-cell lymphoma. Ann Oncol. 2015;26(8):1766–71. https://doi.org/10.1093/annonc/mdv237.
14. Landsburg DJ, Barta SK, Ramchandren R, et al. Cancer network disruption by a single molecule inhibitor targeting both histone deacetylase activity and phosphatidylinositol 3-kinase signaling. Br J Haematol. 2021;195(2):201–9. https://doi.org/10.1111/bjh.17730.
15. Qian C, Lai CJ, Bao R, et al. Cancer network disruption by a single molecule inhibitor targeting both histone deacetylase activity and phosphatidylinositol 3-kinase signaling. Clin Cancer Res. 2012;18(15):4104–13. https://doi.org/10.1158/1078-0432.CCR-12-0055.
16. Fu XH, Zhang X, Yang H, et al. CUDC-907 displays potent antitumor activity against human pancreatic adenocarcinoma in vitro and in vivo through inhibition of HDAC6 to downregulate c-Myc expression. Acta Pharmacol Sin. 2019;40(5):677–88. https://doi.org/10.1038/s41401-018-0108-5.
17. Rambaldi A, Dellacasa CM, Finazzi G, et al. A pilot study of the histone-deacetylase inhibitor Givinostat in patients with JAK2V617F positive chronic myeloproliferative neoplasms. Br J Haematol. 2010;150(4):446–55. https://doi.org/10.1111/j.1365-2141.2010.08266.x.
18. Carlisi D, Vassallo B, Lauricella M, et al. Histone deacetylase inhibitors induce in human hepatoma HepG2 cells acetylation of p53 and histones in correlation with apoptotic effects. Int J Oncol. 2008. https://doi.org/10.3892/ijo.32.1.177.
19. Li S, Fossati G, Marchetti C, et al. Specific inhibition of histone deacetylase 8 reduces gene expression and production of proinflammatory cytokines in vitro and in Vivo. J Biol Chem. 2015;290(4):2368–78. https://doi.org/10.1074/jbc.M114.618454.
20. Celesia A, Notaro A, Franzò M, et al. The histone deacetylase inhibitor ITF2357 (Givinostat) targets oncogenic BRAF in melanoma cells and promotes a switch from pro-survival autophagy to apoptosis. Biomedicines. 2022;10(8):1994. https://doi.org/10.3390/biomedicines10081994.
21. Batlevi CL, Crump M, Andreadis C, et al. A phase 2 study of mocetinostat, a histone deacetylase inhibitor, in relapsed or refractory lymphoma. Br J Haematol. 2017;178(3):434–41. https://doi.org/10.1111/bjh.14698.
22. Fournel M, Bonfils C, Hou Y, et al. MGCD0103, a novel isotype-selective histone deacetylase inhibitor, has broad spectrum antitumor activity *in vitro* and *in vivo*. Mol Cancer Ther. 2008;7(4):759–68. https://doi.org/10.1158/1535-7163.MCT-07-2026.
23. Zhang Q, Sun M, Zhou S, Guo B. Class I HDAC inhibitor mocetinostat induces apoptosis by activation of miR-31 expression and suppression of E2F6. Cell Death Discovery. 2016;2(1):16036. https://doi.org/10.1038/cddiscovery.2016.36.
24. Meidhof S, Brabletz S, Lehmann W, et al. ZEB 1-associated drug resistance in cancer cells is reversed by the class I HDAC inhibitor mocetinostat. EMBO Mol Med. 2015;7(6):831–47. https://doi.org/10.15252/emmm.201404396.
25. Evens AM, Balasubramanian S, Vose JM, et al. A phase I/II multicenter, open-label study of the oral histone deacetylase inhibitor abexinostat in relapsed/refractory lymphoma. Clin Cancer Res. 2016;22(5):1059–66. https://doi.org/10.1158/1078-0432.CCR-15-0624.
26. Zhang W, Lv S, Liu J, et al. PCI-24781 down-regulates EZH2 expression and then promotes glioma apoptosis by suppressing the PIK3K/Akt/mTOR pathway. Genet Mol Biol. 2014;37(4):716–24. https://doi.org/10.1590/S1415-47572014005000011.
27. Buggy JJ, Cao ZA, Bass KE, et al. CRA-024781: a novel synthetic inhibitor of histone deacetylase enzymes with antitumor activity *in vitro* and *in vivo*. Mol Cancer Ther. 2006;5(5):1309–17. https://doi.org/10.1158/1535-7163.MCT-05-0442.
28. Adimoolam S, Sirisawad M, Chen J, Thiemann P, Ford JM, Buggy JJ. HDAC inhibitor PCI-24781 decreases RAD51 expression and inhibits homologous recombination. Proc Natl Acad Sci USA. 2007;104(49):19482–7. https://doi.org/10.1073/pnas.0707828104.
29. Srinivas N, Song L, Lei KC, et al. The HDAC inhibitor domatinostat induces type I interferon α in Merkel cell carcinoma by HES1 repression. J Cancer Res Clin Oncol. 2023;149(11):8267–77. https://doi.org/10.1007/s00432-023-04733-y.
30. Von Tresckow B, Sayehli C, Aulitzky WE, et al. Phase I study of domatinostat (4 SC -202), a class I histone deacetylase inhibitor in patients with advanced hematological malignancies. Euro J Haematol. 2019;102(2):163–73. https://doi.org/10.1111/ejh.13188.
31. Roca MS, Moccia T, Iannelli F, et al. Correction to: HDAC class I inhibitor domatinostat sensitizes pancreatic cancer to chemotherapy by targeting cancer stem cell compartment via FOXM1 modulation. J Exp Clin Cancer Res. 2022;41(1):138. https://doi.org/10.1186/s13046-022-02324-2.
32. Walewski J, Paszkiewicz-Kozik E, Borsaru G, et al. Resminostat in patients with relapsed or refractory Hodgkin lymphoma: results of the phase II SAPHIRE study. Leuk Lymphoma. 2019;60(3):675–84. https://doi.org/10.1080/10428194.2018.1492122.
33. Soukupova J, Bertran E, Peñuelas-Haro I, et al. Resminostat induces changes in epithelial plasticity of hepatocellular carcinoma cells and sensitizes them to sorafenib-induced apoptosis. Oncotarget. 2017;8(66):110367–79. https://doi.org/10.18632/oncotarget.22775.
34. Heath EI, Weise A, Vaishampayan U, Danforth D, Ungerleider RS, Urata Y. Phase Ia dose escalation study of OBP-801, a cyclic depsipeptide

class I histone deacetylase inhibitor, in patients with advanced solid tumors. Invest New Drugs. 2022;40(2):300–7. https://doi.org/10.1007/s10637-021-01180-9.
35. Sugimoto Y, Katsumi Y, Iehara T, et al. The novel histone deacetylase inhibitor, OBP-801, induces apoptosis in rhabdoid tumors by releasing the silencing of *NOXA*. Mol Cancer Ther. 2020;19(10):1992–2000. https://doi.org/10.1158/1535-7163.MCT-20-0243.
36. Buckley MT, Yoon J, Yee H, et al. The histone deacetylase inhibitor belinostat (PXD101) suppresses bladder cancer cell growth in vitro and in vivo. J Transl Med. 2007;5(1):49. https://doi.org/10.1186/1479-5876-5-49.
37. Foss F, Advani R, Duvic M, et al. A Phase II trial of Belinostat (PXD 101) in patients with relapsed or refractory peripheral or cutaneous T-cell lymphoma. Br J Haematol. 2015;168(6):811–9. https://doi.org/10.1111/bjh.13222.
38. Ramalingam SS, Belani CP, Ruel C, et al. Phase II study of belinostat (PXD101), a histone deacetylase inhibitor, for second line therapy of advanced malignant pleural mesothelioma. J Thorac Oncol. 2009;4(1):97–101. https://doi.org/10.1097/JTO.0b013e318191520c.
39. AphaseIIstudyofSB939,anovelpan-histone.pdf.
40. Liang XL, Ouyang L, Yu NN, et al. Histone deacetylase inhibitor pracinostat suppresses colorectal cancer by inducing CDK5-Drp1 signaling-mediated peripheral mitofission. J Pharma Anal. 2023;13(10):1168–82. https://doi.org/10.1016/j.jpha.2023.06.005.
41. Cho H, Yoon DH, Kim KP, et al. Phase I study of CKD-581, a pan-histone deacetylase inhibitor, in patients with lymphoma or multiple myeloma refractory to standard therapy. Invest New Drugs. 2018;36(5):877–85. https://doi.org/10.1007/s10637-018-0582-0.
42. Kim SJ, Kim UJ, Yoo HY, Choi YJ, Kang KW. Anti-cancer effects of CKD-581, a potent histone deacetylase inhibitor against diffuse large B-cell lymphoma. IJMS. 2020;21(12):4377. https://doi.org/10.3390/ijms21124377.
43. Venugopal B, Baird R, Kristeleit RS, et al. A phase I study of quisinostat (JNJ-26481585), an oral hydroxamate histone deacetylase inhibitor with evidence of target modulation and antitumor activity, in patients with advanced solid tumors. Clin Cancer Res. 2013;19(15):4262–72. https://doi.org/10.1158/1078-0432.CCR-13-0312.
44. Bao L, Diao H, Dong N, et al. Histone deacetylase inhibitor induces cell apoptosis and cycle arrest in lung cancer cells via mitochondrial injury and p53 up-acetylation. Cell Biol Toxicol. 2016;32(6):469–82. https://doi.org/10.1007/s10565-016-9347-8.
45. Joyce JA, Pollard JW. Microenvironmental regulation of metastasis. Nat Rev Cancer. 2009;9(4):239–52. https://doi.org/10.1038/nrc2618.
46. Xiong C, Zhu Y, Xue M, et al. Tumor-associated macrophages promote pancreatic ductal adenocarcinoma progression by inducing epithelial-to-mesenchymal transition. Aging. 2021;13(3):3386–404. https://doi.org/10.18632/aging.202264.
47. Pitt JM, Marabelle A, Eggermont A, Soria JC, Kroemer G, Zitvogel L. Targeting the tumor microenvironment: removing obstruction to anticancer immune responses and immunotherapy. Ann Oncol. 2016;27(8):1482–92. https://doi.org/10.1093/annonc/mdw168.
48. Sinha P, Clements VK, Bunt SK, Albelda SM, Ostrand-Rosenberg S. Cross-talk between myeloid-derived suppressor cells and macrophages subverts tumor immunity toward a type 2 response. J Immunol. 2007;179(2):977–83. https://doi.org/10.4049/jimmunol.179.2.977.
49. Xiao Y, Yu D. Tumor microenvironment as a therapeutic target in cancer. Pharmacol Ther. 2021;221: 107753. https://doi.org/10.1016/j.pharmthera.2020.107753.
50. Stimson L, Wood V, Khan O, Fotheringham S, La Thangue NB. HDAC inhibitor-based therapies and haematological malignancy. Ann Oncol. 2009;20(8):1293–302. https://doi.org/10.1093/annonc/mdn792.
51. Li X, Su X, Liu R, et al. HDAC inhibition potentiates anti-tumor activity of macrophages and enhances anti-PD-L1-mediated tumor suppression. Oncogene. 2021;40(10):1836–50. https://doi.org/10.1038/s41388-020-01636-x.
52. Kim YD, Park SM, Ha HC, et al. inhibition of histone deacetylase attenuates hypoxia-induced migration and invasion of cancer cells via the restoration of RECK expression. J Cancer. 2020;11(14):4059–72. https://doi.org/10.7150/jca.44622.
53. Wang S, Hu G, Chen L, et al. Celastrol acts as a new histone deacetylase inhibitor to inhibit colorectal cancer cell growth via regulating macrophage polarity. Cell Biol Int. 2023;47(2):492–501. https://doi.org/10.1002/cbin.11952.
54. Guerriero JL, Sotayo A, Ponichtera HE, et al. Class IIa HDAC inhibition reduces breast tumours and metastases through anti-tumour macrophages. Nature. 2017;543(7645):428–32. https://doi.org/10.1038/nature21409.
55. Han Y, Sun J, Yang Y, et al. TMP195 exerts antitumor effects on colorectal cancer by promoting M1 macrophages polarization. Int J Biol Sci. 2022;18(15):5653–66. https://doi.org/10.7150/ijbs.73264.
56. Chiappinelli K, Seiffert M, Sahakian E, Sahakian E. HDAC6 inhibition alleviates CLL-induced T-cell dysfunction and enhances immune checkpoint blockade Effi Cacy in the Em-TCL1 model. Front Immunol. 2020. https://doi.org/10.3389/fimmu.2020.59007.
57. McCaw TR, Goel N, Brooke DJ, et al. Class I histone deacetylase inhibition promotes CD8 T cell activation in ovarian cancer. Cancer Med. 2021;10(2):709–17. https://doi.org/10.1002/cam4.3337.
58. Briere D, Sudhakar N, Woods DM, et al. The class I/IV HDAC inhibitor mocetinostat increases tumor antigen presentation, decreases immune suppressive cell types and augments checkpoint inhibitor therapy. Cancer Immunol Immunother. 2018;67(3):381–92. https://doi.org/10.1007/s00262-017-2091-y.
59. Chen C, Lim D, Cai Z, et al. HDAC inhibitor HPTA initiates anti-tumor response by CXCL9/10-recruited CXCR3+CD4+T cells against PAHs carcinogenicity. Food Chem Toxicol. 2023;176: 113783. https://doi.org/10.1016/j.fct.2023.113783.
60. Li L, Hao S, Gao M, et al. HDAC3 inhibition promotes antitumor immunity by enhancing CXCL10-mediated chemotaxis and recruiting of immune cells. Cancer Immunol Res. 2023;11(5):657–73. https://doi.org/10.1158/2326-6066.CIR-22-0317.
61. Zheng J, Lu Y, Xiao J, et al. Pan-HDAC inhibitors augment IL2-induced proliferation of NK cells via the JAK2-STAT5B signaling pathway. Int Immunopharmacol. 2023;116: 109753. https://doi.org/10.1016/j.intimp.2023.109753.
62. Chu Y, Yahr A, Huang B, Ayello J, Barth M. Romidepsin alone or in combination with anti-CD20 chimeric antigen receptor expanded natural killer cells targeting Burkitt lymphoma *in vitro* and in immunodeficient mice. Oncolmmunology. 2017. https://doi.org/10.1080/2162402X.2017.1341031.
63. Chen Z, Yang X, Chen Z, et al. A new histone deacetylase inhibitor remodels the tumor microenvironment by deletion of polymorphonuclear myeloid-derived suppressor cells and sensitizes prostate cancer to immunotherapy. BMC Med. 2023;21(1):402. https://doi.org/10.1186/s12916-023-03094-0.
64. Jeon HW, Lee YM. Inhibition of histone deacetylase attenuates hypoxia-induced migration and invasion of cancer cells via the restoration of RECK expression. Mol Cancer Ther. 2010;9(5):1361–70. https://doi.org/10.1158/1535-7163.MCT-09-0717.
65. Zhou J, Schmid T, Schnitzer S, Brüne B. Tumor hypoxia and cancer progression. Cancer Lett. 2006;237(1):10–21. https://doi.org/10.1016/j.canlet.2005.05.028.
66. Zhou M, Lu W, Li B, Liu X, Li A. TARBP2 promotes tumor angiogenesis and metastasis by destabilizing antiangiogenic factor mRNAs. Cancer Sci. 2021;112(3):1289–99. https://doi.org/10.1111/cas.14820.
67. He L, Zhu W, Chen Q, et al. Ovarian cancer cell-secreted exosomal miR-205 promotes metastasis by inducing angiogenesis. Theranostics. 2019;9(26):8206–20. https://doi.org/10.7150/thno.37455.
68. Kim ES, Serur A, Huang J, et al. Potent VEGF blockade causes regression of coopted vessels in a model of neuroblastoma. Proc Natl Acad Sci USA. 2002;99(17):11399–404. https://doi.org/10.1073/pnas.172398399.
69. Yao ZG, Li WH, Hua F, et al. LBH589 inhibits glioblastoma growth and angiogenesis through suppression of HIF-1α expression. J Neuropathol Exp Neurol. 2017;76(12):1000–7. https://doi.org/10.1093/jnen/nlx088.
70. Noh H, Park J, Shim M, Lee Y. Trichostatin A enhances estrogen receptor-alpha repression in MCF-7 breast cancer cells under hypoxia. Biochem Biophys Res Commun. 2016;470(3):748–52. https://doi.org/10.1016/j.bbrc.2016.01.022.
71. Wang ZL. HDAC inhibitor, CG-745, enhances the anti-cancer effect of anti-PD-1 immune checkpoint inhibitor by modulation of the immune microenvironment. Oncol Rep. 2012. https://doi.org/10.3892/or.2012.1784.

72. Huang C, Wu X-F, Wan X-l. Trichostatin a inhibits phenotypic transition and induces apoptosis of the TAF-treated normal colonic epithelial cells through regulation of TGF-β pathway. Int J Biochem Cell Biol. 2019. https://doi.org/10.1016/j.biocel.2019.105565.
73. Noda M, Takahashi C. Recklessness as a hallmark of aggressive cancer. Cancer Sci. 2007;98(11):1659–65. https://doi.org/10.1111/j.1349-7006.2007.00588.x.
74. Zhang Y, Cheng S, Zhang G, et al. Low expression of RECK indicates a shorter survival for patients with invasive breast cancer. Cancer Sci. 2012;103(6):1084–9. https://doi.org/10.1111/j.1349-7006.2012.02265.x.
75. Rhee J. RECKing MMP function: implications for cancer development. Trends Cell Biol. 2002;12(5):209–11. https://doi.org/10.1016/S0962-8924(02)02280-8.
76. Lee KJ, Lee KY, Lee YM. 2010 Downregulation of a tumor suppressor RECK by hypoxia through recruitment of HDAC1 and HIF-1α to reverse HRE site in the promoter. Biochimica et Biophysica Acta Mol Cell Res. 1803;5:608–16. https://doi.org/10.1016/j.bbamcr.2010.01.004.
77. Jin H, Liang L, Liu L, Deng W, Liu J. HDAC inhibitor DWP0016 activates p53 transcription and acetylation to inhibit cell growth in U251 glioblastoma cells. J Cell Biochem. 2013;114(7):1498–509. https://doi.org/10.1002/jcb.24491.
78. Laszig S, Boedicker C, Weiser T, Knapp S, Fulda S. The novel dual BET/HDAC inhibitor TW09 mediates cell death by mitochondrial apoptosis in rhabdomyosarcoma cells. Cancer Lett. 2020;486:46–57. https://doi.org/10.1016/j.canlet.2020.05.008.
79. Huang YC, Huang FI, Mehndiratta S, Lai SC, Liou JP, Yang CR. Anticancer activity of MPT0G157, a derivative of indolylbenzenesulfonamide, inhibits tumor growth and angiogenesis. Oncotarget. 2015;6(21):18590–601. https://doi.org/10.18632/oncotarget.4068.
80. Naldini A, Filippi I, Cini E, Rodriquez M, Carraro F, Taddei M. Down-regulation of hypoxia-related responses by novel antitumor histone deacetylase inhibitors in MDAMB231 breast cancer cells. ACAMC. 2012;12(4):407–13. https://doi.org/10.2174/187152012800228706.
81. Zhao Y, Tan J, Zhuang L, Jiang X, Liu ET, Yu Q. Inhibitors of histone deacetylases target the Rb-E2F1 pathway for apoptosis induction through activation of proapoptotic protein Bim. Proc Natl Acad Sci USA. 2005;102(44):16090–5. https://doi.org/10.1073/pnas.0505585102.
82. Li X, Guo Y, Kuang X, et al. Histone deacetylase inhibitor LMK-235-mediated HO-1 expression induces apoptosis in multiple myeloma cells via the JNK/AP-1 signaling pathway. Life Sci. 2019;223:146–57. https://doi.org/10.1016/j.lfs.2019.03.011.
83. Nakata S, Yoshida T, Horinaka M, Shiraishi T, Wakada M, Sakai T. Histone deacetylase inhibitors upregulate death receptor 5/TRAIL-R2 and sensitize apoptosis induced by TRAIL/APO2-L in human malignant tumor cells. Oncogene. 2004;23(37):6261–71. https://doi.org/10.1038/sj.onc.1207830.
84. Buglio D, Georgakis GV, Hanabuchi S, et al. Vorinostat inhibits STAT6-mediated TH2 cytokine and TARC production and induces cell death in Hodgkin lymphoma cell lines. Blood. 2008;112(4):1424–33. https://doi.org/10.1182/blood-2008-01-133769.
85. Yang F, Wang F, Liu Y, et al. Sulforaphane induces autophagy by inhibition of HDAC6-mediated PTEN activation in triple negative breast cancer cells. Life Sci. 2018;213:149–57. https://doi.org/10.1016/j.lfs.2018.10.034.
86. Hoyos C, Fontaine A, Jacques JR, et al. HDAC inhibition with valproate improves direct cytotoxicity of monocytes against mesothelioma tumor cells. Cancers. 2022;14(9):2164. https://doi.org/10.3390/cancers14092164.
87. Blum KA, Advani A, Fernandez L, et al. Phase II study of the histone deacetylase inhibitor MGCD0103 in patients with previously treated chronic lymphocytic leukaemia. Br J Haematol. 2009;147(4):507–14. https://doi.org/10.1111/j.1365-2141.2009.07881.x.
88. Monje M, Cooney T, Glod J, et al. Phase I trial of panobinostat in children with diffuse intrinsic pontine glioma: a report from the Pediatric Brain Tumor Consortium (PBTC-047). Neuro Oncol. 2023;25(12):2262–72. https://doi.org/10.1093/neuonc/noad141.
89. Whitehead RP, Rankin C, Hoff PMG, et al. Phase II trial of romidepsin (NSC-630176) in previously treated colorectal cancer patients with advanced disease: a Southwest Oncology Group study (S0336). Invest New Drugs. 2009. https://doi.org/10.1007/s10637-008-9190-8.
90. Haigentz M, Kim M, Sarta C, et al. Phase II trial of the histone deacetylase inhibitor romidepsin in patients with recurrent/metastatic head and neck cancer. Oral Oncol. 2012;48(12):1281–8. https://doi.org/10.1016/j.oraloncology.2012.05.024.
91. Que Y, Zhang XL, Liu ZX, et al. Frequent amplification of HDAC genes and efficacy of HDAC inhibitor chidamide and PD-1 blockade combination in soft tissue sarcoma. J Immunother Cancer. 2021;9(2):e001696. https://doi.org/10.1136/jitc-2020-001696.
92. Bretz AC, Parnitzke U, Kronthaler K, et al. Domatinostat favors the immunotherapy response by modulating the tumor immune microenvironment (TIME). J Immunother Cancer. 2019;7(1):294. https://doi.org/10.1186/s40425-019-0745-3.
93. Ibrahim N, Buchbinder EI, Granter SR, et al. A phase I trial of panobinostat (LBH 589) in patients with metastatic melanoma. Cancer Med. 2016;5(11):3041–50. https://doi.org/10.1002/cam4.862.
94. Woods DM, Sodré AL, Villagra A, Sarnaik A, Sotomayor EM, Weber J. Selective HDAC6 inhibitors improve anti-PD-1 immune checkpoint blockade therapy by decreasing the anti-inflammatory phenotype of macrophages and down-regulation of immunosuppressive proteins in tumor cells [published correction appears in Sci Rep. Cancer Immunol Res. 2015;3(12):1375–85. https://doi.org/10.1158/2326-6066.CIR-15-0077-T.
95. Knox T, Sahakian E, Banik D, et al. Selective HDAC6 inhibitors improve anti-PD-1 immune checkpoint blockade therapy by decreasing the anti-inflammatory phenotype of macrophages and down-regulation of immunosuppressive proteins in tumor cells. Sci Rep. 2019;9(1):6136. https://doi.org/10.1038/s41598-019-42237-3.
96. Marquardt V, Theruvath J, Pauck D, et al. Tacedinaline (CI-994), a class I HDAC inhibitor, targets intrinsic tumor growth and leptomeningeal dissemination in MYC-driven medulloblastoma while making them susceptible to anti-CD47-induced macrophage phagocytosis via NF-kB-TGM2 driven tumor inflammation. J Immunother Cancer. 2023;11(1): e005871. https://doi.org/10.1136/jitc-2022-005871.
97. Christmas BJ, Rafie CI, Hopkins AC, et al. Entinostat converts immune-resistant breast and pancreatic cancers into checkpoint-responsive tumors by reprogramming tumor-infiltrating MDSCs. Cancer Immunol Res. 2018;6(12):1561–77. https://doi.org/10.1158/2326-6066.CIR-18-0070.
98. Xu T, Fang Y, Gu Y, et al. HDAC inhibitor SAHA enhances antitumor immunity via the HDAC1/ JAK1/FGL1 axis in lung adenocarcinoma. *Open access*.
99. Kroesen M, Büll C, Gielen PR, et al. Anti-GD2 mAb and Vorinostat synergize in the treatment of neuroblastoma. OncoImmunology. 2016;5(6): e1164919. https://doi.org/10.1080/2162402X.2016.1164919.
100. Yu H, Mi L, Zhang W, Michalowski A, et al. TORC1 and class I HDAC inhibitors synergize to suppress mature B cell neoplasms. Hematol Oncol. 2022;40(5):894–905. https://doi.org/10.1002/hon.3056.
101. Zibelman M, Wong YN, Devarajan K, et al. Phase I study of the mTOR inhibitor ridaforolimus and the HDAC inhibitor vorinostat in advanced renal cell carcinoma and other solid tumors. Invest New Drugs. 2015;33(5):1040–7. https://doi.org/10.1007/s10637-015-0261-3.
102. Adeegbe DO, Liu Y, Lizotte PH, et al. Synergistic immunostimulatory effects and therapeutic benefit of combined histone deacetylase and bromodomain inhibition in non-small cell lung cancer. Cancer Discov. 2017;7(8):852–67. https://doi.org/10.1158/2159-8290.CD-16-1020.
103. Flinn IW, O'Brien S, Kahl B, et al. Duvelisib, a novel oral dual inhibitor of PI3K-δ, γ, is clinically active in advanced hematologic malignancies. Blood. 2018;131(8):877–87. https://doi.org/10.1182/blood-2017-05-786566.
104. Horwitz SM, Nirmal AJ, Rahman J, et al. Duvelisib plus romidepsin in relapsed/refractory T cell lymphomas: a phase 1b/2a trial. Nat Med. 2024;30(9):2517–27. https://doi.org/10.1038/s41591-024-03076-6.
105. Hashimoto A, Fukumoto T, Zhang R, Gabrilovich D. Selective targeting of different populations of myeloid-derived suppressor cells by histone deacetylase inhibitors. Cancer Immunol Immunother. 2020;69(9):1929–36. https://doi.org/10.1007/s00262-020-02588-7.
106. Hicks KC, Knudson KM, Lee KL, et al. Cooperative immune-mediated mechanisms of the HDAC inhibitor Entinostat, an IL15 superagonist, and a cancer vaccine effectively synergize as a novel cancer therapy.

Clin Cancer Res. 2020;26(3):704–16. https://doi.org/10.1158/1078-0432.CCR-19-0727.
107. Synergistic Efficacy of Combined EGFR and HDAC Inhibitors Overcomes Tolerance to EGFR Monotherapy in Salivary Mucoepidermoid Carcinoma.
108. HDAC Inhibition Sensitize Hepatocellular Carcinoma to Lenvatinib via Suppressing AKT Activation.pdf.
109. Afolabi LO, Bi J, Li X, et al. Synergistic tumor cytolysis by NK cells in combination with a pan-HDAC inhibitor. Panobinostat Front Immunol. 2021;12: 701671. https://doi.org/10.3389/fimmu.2021.701671.
110. Berdeja JG, Gregory TK, Faber EA, et al. A phase I/ II study of the combination of panobinostat and carfilzomib in patients with relapsed or relapsed/refractory multiple myeloma: final analysis of second dose-expansion cohort. American J Hematol. 2021;96(4):428–35. https://doi.org/10.1002/ajh.26088.
111. Ny L, Jespersen H, Karlsson J, et al. The PEMDAC phase 2 study of pembrolizumab and entinostat in patients with metastatic uveal melanoma. Nat Commun. 2021;12(1):5155. https://doi.org/10.1038/s41467-021-25332-w.
112. Iwahashi S, Utsunomiya T, Imura S, et al. Effects of valproic acid in combination with S-1 on advanced pancreatobiliary tract cancers: clinical study phases I/II. Anti Res. 2014. https://doi.org/10.1200/jco.2014.32.3_suppl.306.
113. Scherpereel A, Berghmans T, Lafitte JJ, et al. Valproate-doxorubicin: promising therapy for progressing mesothelioma a phase II study. Euro Res J. 2011;37(1):129–35. https://doi.org/10.1183/09031936.00037310.
114. Luu T, Kim K, et al. Phase IB trial of ixabepilone and vorinostat in metastatic breast cancer. Breast Cancer Res Treat. 2018;167(2):469–78. https://doi.org/10.1007/s10549-017-4516-x.
115. Johnson ML, Strauss J, Patel MR, et al. Mocetinostat in combination with durvalumab for patients with advanced NSCLC: results from a phase I/II study. Clin Lung Cancer. 2023;24(3):218–27. https://doi.org/10.1016/j.cllc.2023.01.013.
116. MI J, James S, Mr P, et al. A phase I/II study of ivaltinostat combined with gemcitabine and erlotinib in patients with untreated locally advanced or metastatic pancreatic adenocarcinoma. Clin Lung Cancer. 2023. https://doi.org/10.1016/j.cllc.2023.01.013.
117. Iyer SP, Huen A, Ai WZ, et al. Safety and efficacy of tenalisib in combination with romidepsin in patients with relapsed/refractory T-cell lymphoma results from a phase I/II open-label multicenter study. Haematol. 2023. https://doi.org/10.3324/haematol.2022.281875.
118. Falchi L, Ma H, Klein S, et al. Combined oral 5-azacytidine and romidepsin are highly effective in patients with PTCL: a multicenter phase 2 study. Blood. 2021;137(16):2161–70. https://doi.org/10.1182/blood.2020009004.

Publisher's Note