HDACs and HDAC Inhibitors in Cancer Development and Therapy

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Over the last several decades, it has become clear that epigenetic abnormalities may be one of the hallmarks of cancer. Posttranslational modifications of histones, for example, may play a crucial role in cancer development and progression by modulating gene transcription, chromatin remodeling, and nuclear architecture. Histone acetylation, a well-studied posttranslational histone modification, is controlled by the opposing activities of histone acetyltransferases (HATs) and histone deacetylases (HDACs). By removing acetyl groups, HDACs reverse chromatin acetylation and alter transcription of oncogenes and tumor suppressor genes. In addition, HDACs deacetylate numerous nonhistone cellular substrates that govern a wide array of biological processes including cancer initiation and progression. This review will discuss the role of HDACs in cancer and the therapeutic potential of HDAC inhibitors (HDACi) as emerging drugs in cancer treatment.

Histone function is modulated by multiple posttranslational modifications, including reversible acetylation of the amino-terminal ε-group of lysines on histones. Histone acetylation is tightly controlled by a balance between the opposing activities of histone acetyltransferases (HATs) and histone deacetylases (HDACs, also known as lysine deacetylases or KDACs). There are 18 potential human HDACs grouped into four classes. By removing the acetyl groups from the ε-amino lysine residues on histone tails, HDACs may play a critical role in transcription regulation (Seto and Yoshida 2014).

Given that histone modification modulates chromatin structure and gene expression, it is not surprising that abnormal alterations in histone acetylation are associated with cancer development. For example, global loss of acetylation at lysine 16 and trimethylation at lysine 20 of histone H4 is reported to be a common abnormality in human cancer (Fraga et al. 2005), and a low level of histone H3 lysine 18 acetylation (H3K18ac) was found to be a predictor of poor survival in pancreatic, breast, prostate, and lung cancers. In parallel, research increasingly shows aberrant expression of HDACs is frequently observed in various human cancers. Although it is not known whether the changes in histone modification are related to specific alterations in HDACs expression (there are obviously many other mechanisms that can explain why cancer cells might exploit HDACs to support tumorigenesis), they do nevertheless con-

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tribute to the overall principle of targeting HDACs for cancer therapy.

Because approximately equal numbers of genes are activated and repressed by HDAC inhibition, other mechanisms besides histone modification are involved in HDAC-mediated gene regulation. In addition to histones, HDACs also deacetylate a large number of nonhistone proteins. This is consistent with the discovery of many acetylated nonhistone proteins by global analysis in human cells (Choudhary et al. 2009). In tumorigenesis, the finely tuned acetylation status at the whole proteome level is greatly impaired by dysregulated deacetylases (Parbin et al. 2014). Through hyperacetylation of histone and nonhistone targets, HDACi enable the reestablishment of cellular acetylation homeostasis and restore normal expression and function of numerous proteins that may reverse cancer initiation and progression. This article describes recent advances in our understanding of the role of HDACs in cancer and the implications of HDACi in the treatment of cancer.

DYSREGULATION AND MUTATION OF HDACs IN HUMAN CANCER

Based on sequence homology to yeast, 18 human HDACs are grouped into four classes. Class I Rpd3-like enzymes are comprised of HDAC1, 2, 3, and 8. Class II Hda1-like enzymes are further divided into two subclasses: IIa (HDAC4, 5, 6, 7, and 9) and IIb (HDAC6 and 10). Class III Sir2-like enzymes consist of seven sirtuins, which are NAD-dependent protein deacetylases and/or ADP ribosylases. Sirtuins have been shown to regulate many cellular processes including survival, aging, stress response, and metabolism. Class IV contains only HDAC11, which shares sequences similarity to both class I and II proteins.

HDACs are involved in multiple different stages of cancer (Fig. 1). Aberrant expression of classical (class I, II, IV) HDACs has been linked to a variety of malignancies, including solid and hematological tumors (Table 1). In most cases, a high level of HDACs is associated with advanced disease and poor outcomes in patients. For example, high expression of HDAC1, 2, and 3 are associated with poor outcomes in gastric and ovarian cancers (Weichert et al. 2008a,b; Sudo et al. 2011), and high expression of HDAC8 correlates with advanced-stage disease and poor survival in neuroblastoma (Oehme et al. 2009; Rettig et al. 2015). HDACs have also been found broadly dysregulated in multiple myeloma (MM). Overexpression of class I HDACs, particularly HDAC1, is associated with inferior patient outcomes (Mithraprabhu et al. 2014).

The mechanisms by which individual HDACs regulate tumorigenesis are quite diverse. Because HDACs induce a range of cellular and molecular effects through hyperacetylation of histone and nonhistone substrates, HDACs could either repress tumor suppressor gene expression or regulate the oncogenic cell-signaling pathway via modification of key molecules. However, the contribution of HDACs to cancer may not necessarily be related to the level of HDAC expression, because aberrant activity of HDACs is also common in cancer development (West and Johnstone 2014). Certain HDACs function as the catalytic subunits of large corepressor complexes and could be aberrantly recruited to target genes by oncogenic proteins to drive tumorigenesis. For example, the aberrant recruitment of HDAC1, 2, or 3 by oncogenic fusion proteins AML1-ETO and PML-RAR contributes to the pathogenesis of acute myeloid leukemia (AML) (Hug and Lazar 2004; Falkenberg and Johnstone 2014).

Although the broad anticancer effects of HDACi predict an oncogenic role of HDACs in tumor development, in some cancers it has been found that genetic inactivation of HDACs might have tumorigenic effects. *HDAC1* somatic mutations were detected in 8.3% of dedifferentiated liposarcoma and *HDAC4* homozygous deletions occurred in 4% of melanomas (Stark and Hayward 2007; Taylor et al. 2011). Truncating mutations of HDAC2 have been observed in human epithelial cancers with microsatellite instability, which causes a loss of HDAC2 protein expression and confers cells more resistant to HDACi (Ropero et al. 2006). Furthermore, the ectopic expression of

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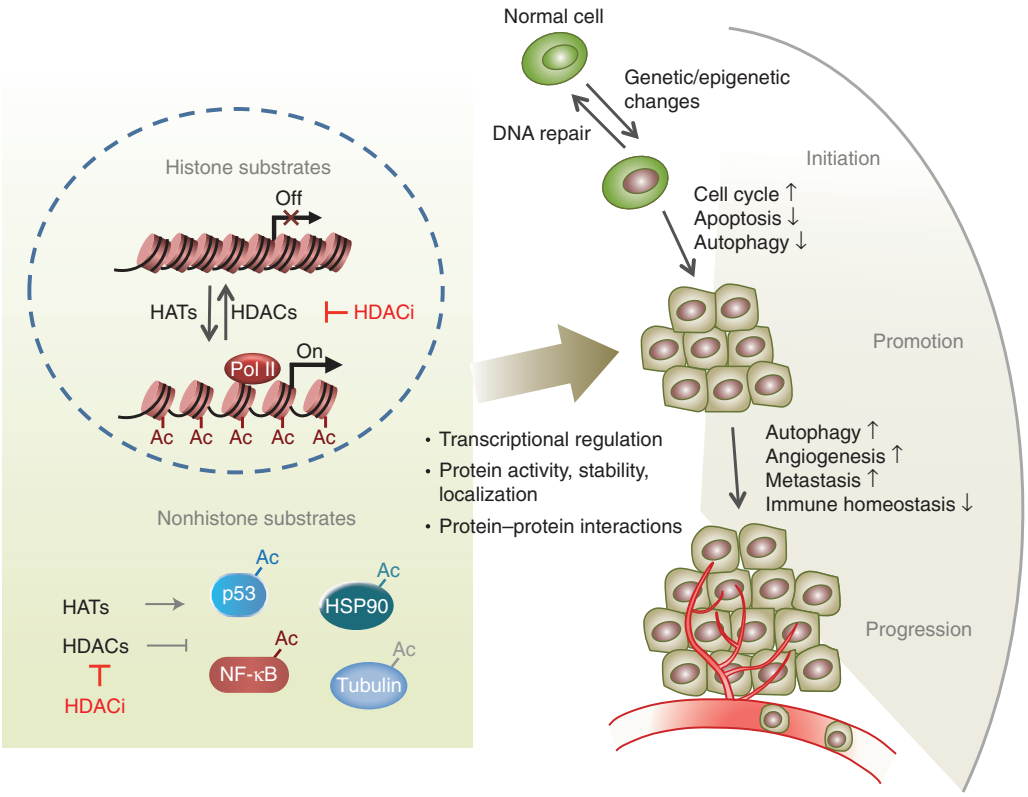

Figure 1. A simplistic illustration of the diverse functions of HDACs and HDACi regulating different stages of cancer through multiple different mechanisms and changing different biological processes. Far right, ↑ indicates promotion or up-regulation, ↓ indicates repression or down-regulation.

HDAC2 in mutant cancer cells induces a reduction of tumor cell growth in vitro and in vivo, suggesting a putative tumor-suppressor role for HDAC2 in this cellular setting. Class II HDACs may also function as tumor suppressor in certain circumstances. Low expression of HDAC10 is associated with poor prognosis in lung and gastric cancer patients (Osada et al. 2004; Jin et al. 2014). HDAC6 is down-regulated in human hepatocellular carcinoma (HCC) tissues, and low expression of HDAC6 is associated with poor prognosis in liver transplantation patients. Knockdown of HDAC6 promotes angiogenesis in HCC by HIF-1α/VEGFA axis (Lv et al. 2015). Also, a recent study revealed a dual role of HDAC1 in cancer initiation and maintenance. HDAC1 antagonizes the oncogenic activity of PML-RAR during the preleukemic stage of acute promyelocytic leukemia (APL), but favors the growth of APL cells at the leukemic stage (Santoro et al. 2013), indicating that elucidation of the role of HDACs at each step of tumorigenesis in different tumor cell types will provide a rationale for targeting HDACs in cancer therapy.

POSSIBLE MECHANISMS OF HDACS IN CANCER DEVELOPMENT

Although identification of substrate specificity and biological function for individual HDACs still requires more comprehensive investigations, it is well known that HDACs play crucial roles in cancer by deacetylating histone and nonhistone proteins, which are involved in the regulation of cell cycle, apoptosis, DNA-damage response, metastasis, angiogenesis, autophagy, and other cellular processes (Fig. 1).

Table 1. Dysregulation and mutation of HDACs in human cancer

Cancer types	HDACs	Prognostic relevance	Genetic evidence	Molecular mechanism	References
Solid tumors					
Neuroblastoma	HDAC8	High transcript level correlates with advanced-stage disease and poor survival in neuroblastoma	Knockdown and inhibition of HDAC8 promotes cell-cycle arrest and differentiation, delays cell growth, and induces cell death in vitro and in vivo	HDAC8 inhibition induces $p21^{WAF1/CIP1}$ and *NTRK1/TrkA* gene expression and enhances retinoic acid-mediated differentiation by regulating CREB phosphorylation	Oehme et al. 2009; Rettig et al. 2015
	HDAC10	High expression correlates with poor overall patient survival in advanced INSS stage 4 neuroblastoma	Knockdown and inhibition of HDAC10 in neuroblastoma cells interrupted autophagic flux resulting in an increase of sensitization to cytotoxic drug treatment	HDAC10 controls autophagic processing and resistance to cytotoxic drugs via interaction with Hsp70 family proteins	Oehme et al. 2013
Medulloblastoma	HDAC2	Overexpressed in medulloblastoma subgroups with poor prognosis	HDAC2 depletion induces cell death and attenuates cell growth; MYC amplified and HDAC2 overexpressing cell lines are more sensitive to class I HDACi	N/A	Ecker et al. 2015
	HDAC5, 9	Up-regulated in high-risk medulloblastoma, and their expression is associated with poor survival	Depletion of either HDAC5 or HDAC9 in MB cells resulted in a reduction of cell proliferation and increase in cell death	N/A	Milde et al. 2010

Continued

Table 1. *Continued*

Cancer types	HDACs	Prognostic relevance	Genetic evidence	Molecular mechanism	References
Lung	HDAC1, 3	High expression correlates with a poor prognosis in patients with lung adenocarcinoma	N/A	N/A	Minamiya et al. 2010, 2011
	HDAC2	Abundant expression is observed in lung cancer tissues	HDAC2 inactivation represses tumor cell growth in vitro and in vivo	HDAC2 depletion activates apoptosis via p53 and Bax activation and Bcl2 suppression induces cell-cycle arrest by induction of p21 and suppression of cyclin E2, cyclin D1, and CDK2	Jung et al. 2012
	HDAC5, 10	Low expression is associated with poor prognosis in lung cancer patients	N/A	N/A	Osada et al. 2004
Gastric	HDAC1, 2, 3	High expression is associated with nodal tumor spread and decreased overall patient survival	N/A	N/A	Weichert et al. 2008b; Sudo et al. 2011
	HDAC4	Up-regulated in gastric tumor cells compared with adjacent normal tissues	HDAC4 inhibition has a synergistic effect with docetaxel treatment	HDAC4 inhibition increased the level of cleaved caspases 3 and 9	Colarossi et al. 2014
	HDAC10	Low expression is a poor prognosis marker for gastric cancer patients	N/A	N/A	Jin et al. 2014

Continued

Table 1. *Continued*

Cancer types	HDACs	Prognostic relevance	Genetic evidence	Molecular mechanism	References
Liver	HDAC1	Highly expressed in human HCCs and liver cancer cell lines	HDAC1 inactivation impairs G_1/S cell-cycle transition and causes autophagic cell death	Knockdown of HDAC1 induces p21 and p27 expression and suppresses cyclin D1 and CDK2 expression	Xie et al. 2012
	HDAC1, 2, 3	Up-regulated in human HCCs and liver cancer cell lines	The knockdown of HDAC1–3 leads to increased apoptosis and decreased proliferation	Knockdown and inhibition of HDAC1–3 up-regulates miR-449 and down-regulates c-MET expression, and reduced c-MET dephosphorylates ERK1/2 and inhibits tumor growth	Buurman et al. 2012
	HDAC1, 2, 3	High expression is associated with poor survival in low-grade and early-stage tumors	N/A	N/A	Quint et al. 2011
	HDAC3, 5	Up-regulation is correlated with DNA copy number gains	N/A	N/A	Lachenmayer et al. 2012
	HDAC5	Up-regulated in HCC tissues	Knockdown of HDAC5 promotes cell apoptosis and inhibits tumor cell growth in vitro and in vivo	HDAC5 knockdown promotes apoptosis by up-regulating cyto C, caspase 3, p53, and bax, and induces G_1 phase cell-cycle arrest by up-regulating p21 and down-regulating cyclin D1 and CDK2/4/6	Fan et al. 2014
	HDAC5	Up-regulated in human HCC tissues	Overexpression of HDAC5 promotes tumor cell proliferation, while knockdown of HDAC5 inhibits cell proliferation	HDAC5 promotes cell proliferation by up-regulation of Six1	Feng et al. 2014
	HDAC6	Low expression is associated with poor prognosis in liver transplantation patients	Knockdown of HDAC6 promotes HUVEC migration, proliferation, and tube formation in vitro, and suppresses HCC cell apoptosis and promotes HCC cell proliferation in hypoxia	HDAC6 knockdown promotes angiogenesis in HCC by HIF-1α/VEGFA axis	Lv et al. 2015

Continued

Table 1. *Continued*

Cancer types	HDACs	Prognostic relevance	Genetic evidence	Molecular mechanism	References
Pancreatic	HDAC2	Highly expressed in PDAC	HDAC2 confers resistance toward etoposide in PDAC cells	HDAC2 knockdown up-regulates NOXA expression, which sensitizes tumor cells toward etoposide-induced apoptosis	Fritsche et al. 2009
	HDAC6	Highly expressed in human pancreatic cancer tissues	Knockdown and inhibition of HDAC6 impairs the motility of cancer cells	HDAC6 interacts with CLIP-170 and stimulates the migration of pancreatic cancer cells	Li et al. 2014
	HDAC7	Overexpression is associated with poor prognosis	Knockdown of HDAC7 inhibits tumor cell growth	N/A	Ouaissi et al. 2008, 2014
Colorectal	HDAC2 mutation	Truncating mutations are found in microsatellite unstable sporadic colorectal cancers, which lead to a loss of expression of the protein	HDAC2 mutation renders cells more resistant to antiproliferative and proapoptotic effects of the HDAC inhibitor	N/A	Ropero et al. 2006
	HDAC1, 2, 3	Highly expressed in a subset of colorectal carcinomas; HDAC2 is an independent prognostic factor in colorectal carcinoma	Knockdown of HDAC1 and HDAC2 but not HDAC3 suppresses tumor cell growth	N/A	Weichert et al. 2008d
	HDAC1, 2, 3, 5, 7	Up-regulated in human colorectal cancer; HDAC2 is an early biomarker of colon carcinogenesis	N/A	N/A	Stypula-Cyrus et al. 2013
Breast	HDAC1, 2, 3	HDAC1 was highly expressed in hormone receptor-positive tumors; HDAC2 and 3 are highly expressed in poorly differentiated and hormone receptor negative tumors	N/A	N/A	Zhang et al. 2005; Muller et al. 2013
	HDAC1, 6	High expression is good prognostic factors for estrogen-receptor-positive invasive ductal carcinomas	N/A	N/A	Zhang et al. 2004; Seo et al. 2014

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Table 1. *Continued*

Cancer types	HDACs	Prognostic relevance	Genetic evidence	Molecular mechanism	References
Ovarian	HDAC1, 2, 3	High expression is associated with a poor outcome	Knockdown of HDAC1 reduces cell proliferation via down-regulating cyclin A expression, and knockdown of HDAC3 reduces the cell migration with elevated E-cadherin		Hayashi et al. 2010
	HDAC1, 2, 3	High-level expression is associated with a poor prognosis in ovarian endometrioid carcinomas	N/A	N/A	Weichert et al. 2008a
Cervical	HDAC10	Low expression correlates with lymph node metastasis in cervical cancer	Knockdown of HDAC10 promotes cervical cancer cell migration and invasion	HDAC10 inhibits MMP2 and -9 expression	Song et al. 2013
Prostate	HDAC1, 2, 3	Highly expressed in prostate carcinomas HDAC2 is an independent prognostic marker in prostate cancer cohort	N/A	N/A	Weichert et al. 2008c
Renal	HDAC1, 2	Highly expressed in renal cell cancer, but none of them are associated with patient survival	N/A	N/A	Fritzsche et al. 2008
Bladder	HDAC1, 2, 3	High expression is associated with higher tumor grades; high HDAC1 is a poor prognostic factor in urothelial bladder cancer	N/A	N/A	Poyet et al. 2014
	HDAC2, 4, 5, 7, 8	Up-regulation of HDAC2, 8 and down-regulation of HDAC4, 5, and 7 mRNA are observed in urothelial cancer	N/A	N/A	Niegisch et al. 2013

Continued

Table 1. *Continued*

Cancer types	HDACs	Prognostic relevance	Genetic evidence	Molecular mechanism	References
Melanoma	HDAC3, 8	HDAC8 was increased in BRAF-mutated melanoma; HDAC8 and 3 overexpression are associated with improved survival of patients with stage IV metastatic melanoma	N/A	N/A	Wilmott et al. 2015
Hematological tumors					
ALL	HDAC1–9	HDAC2, 3, 6, 7, 8 are up-regulated in ALL samples; HDAC1 and 4 show high expression in T-ALL and HDAC6 and 9 are highly expressed in B-lineage ALL; higher expression of HDAC7 and 9 is associated with a poor prognosis in childhood ALL	N/A	N/A	Moreno et al. 2010
	HDAC4	High expression is associated with high initial leukocyte count, T cell ALL and prednisone poor response	HDAC4 knockdown enhanced etoposide's cytotoxic activity	N/A	Gruhn et al. 2013
CLL	HDAC1, 3, 6, 7, 9, 10, SIRT1 and 6	Higher expressions are associated with poor prognosis and more advanced disease stage	N/A	N/A	Wang et al. 2011
	HDAC6, 7, 10 and SIRT2, 3, 6	Overexpression of HDAC7 and 10 and underexpression of HDAC6 and SIRT3 are correlated with a poor prognosis	N/A	N/A	Van Damme et al. 2012

Continued

Table 1. *Continued*

Cancer types	HDACs	Prognostic relevance	Genetic evidence	Molecular mechanism	References
AML	HDAC5, 6, SIRT1 and 4	HDAC6 and SIRT1 are overexpressed, and HDAC5 and SIRT4 are underexpressed in AML samples	N/A	N/A	Bradbury et al. 2005
DLBCL	HDAC1	Highly expressed in cases of DLBCL and correlated with a poor survival	N/A	N/A	Min et al. 2012
	HDAC2	Highly expressed in nodal lymphomas, which is associated with shorter survival	N/A	N/A	Lee et al. 2014b
	HDAC1, 2, 6	The expression is higher in cases of DLBCL or PTCL; high HDAC6 level is associated with favorable outcome in DLBCL, but with a negative outcome in PTCL	N/A	N/A	Marquard et al. 2009
	HDAC3	Overexpression is observed in phospho STAT3-positive ABC-type DLBCL	HDAC3 knockdown inhibited survival of pSTAT3-positive DLBCL cells	HDAC3 knockdown unregulated STAT3Lys685 acetylation but prevented STAT3Tyr705 phosphorylation	Gupta et al. 2012
CTCL	HDAC2, 6	HDAC2 is highly expressed in aggressive rather than indolent CTCL; HDAC6 is associated with a favorable outcome independent of the subtype	N/A	N/A	Marquard et al. 2008
HL	HDAC1, 2, 3	Overexpressed in HL tissue samples; high HDAC1 expression is correlated with a worse outcome	N/A	N/A	Adams et al. 2010
Myeloma	HDAC1	Overexpression of class I HDAC, particularly HDAC1, is associated with poor prognosis in myeloma	N/A	N/A	Mithraprabhu et al. 2014

HCC, Human hepatocellular carcinoma; PDAC, pancreatic ductal adenocarcinoma; ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; AML, acute myelogenous leukemia; DLBCL, diffuse large B-cell lymphoma; CTCL, cutaneous T-cell lymphomas; HL, Hodgkin's lymphoma.

Cell Cycle

HDAC inhibition has been shown to have antiproliferative effects by inducing cell-cycle arrest in G_1 via up-regulation of cyclin-dependent kinase (CDK) inhibitors or down-regulation of cyclins and CDKs (Chun 2015). HDAC1 and 2 directly bind to the promoters of the $p21^{WAF1/CIP1}$, $p27^{KIP1}$, and $p57^{KIP2}$ genes and negatively regulate their expression (Yamaguchi et al. 2010; Zupkovitz et al. 2010). Loss of HDAC1 and 2 induces expression of CDK inhibitors, leading to a cell-cycle block in G_1. Knockdown of HDAC5 leads to a significant up-regulation of p21 and down-regulation of cyclin D1 and CDK2/4/6, which results in G_1-phase cell-cycle arrest in human HCC cells (Fan et al. 2014). HDAC inhibition might block the cellular G_1/S transition by reactivating Rb function by dephosphorylation and subsequently inhibiting E2F activities in the transcription of genes for G_1 progression. Trichostatin A (TSA) suppressed retinal pigment epithelium (RPE) cell proliferation via a G_1 phase arrest, caused through inhibition of Rb phosphorylation, reduction of cyclinD1/CDK4/6 complexes, and induction of p21 and p27 (Xiao et al. 2014). However, TSA also induced G_1 phase arrest in malignant tumor cells with mutated Rb, indicating an Rb-independent G_1 arrest (Tomosugi et al. 2012).

In addition to controlling the G_1/S transition, HDAC1 knockdown in tumor cells impairs G_2/M transition and inhibits cell growth as evidenced by a reduction of mitotic cells and an increased percentage of apoptotic cells (Senese et al. 2007). HDAC10 regulates the G_2/M transition via modulation of cyclin A2 expression. The effect of HDAC10 on cyclin A2 transcription was dependent on let-7 and HMGA2 (Li et al. 2015b). Consistent with gene knockdown results, inhibition of HDACs by inhibitors including TSA, SAHA, and VPA cause cell-cycle arrest at the G_2/M boundary in a variety of tumor cell lines, supporting pleiotropic roles of HDAC throughout the cell cycle (Juengel et al. 2014).

Besides transcriptional repression of cell-cycle-related genes at the G_1/S and G_2/M cell-cycle checkpoints, HDACs might also regulate cell-cycle progression in a transcription-independent manner. During mitosis, A-kinase-anchoring proteins AKAP95 and HA95 recruit HDAC3 along with Aurora B. In this context, HDAC3 deacetylates histone H3, which in turn allows maximal phosphorylation of Ser10 by Aurora B, leading to HP1β dissociation from mitotic chromosomes. The HDAC3-AKAP95/HA95-Aurora B pathway is required for normal mitotic progression (Li et al. 2006). Indeed, the histone deacetylase inhibitor LBH589 can induce G_2-M cell-cycle arrest and apoptosis in renal cancer cells through degradation of Aurora A and B kinases by targeting HDAC3 and HDAC6 (Cha et al. 2009). Moreover, HDAC3 directly interacts with cyclin A and regulates cyclin A stability by modulating its acetylation status. An abrupt loss of HDAC3 at metaphase facilitates cyclin A acetylation by PCAF/GCN5, which targets cyclin A for degradation. Given that cyclin A is crucial for S phase progression and entry into mitosis, HDAC3 knockdown causes cell accumulation in S and G_2/M phases (Vidal-Laliena et al. 2013). Collectively, HDAC inhibition can arrest the cell cycle at either G_1/S or G_2/M phase, suggesting HDACs as therapeutic targets for abnormal cell growth and proliferation in cancer.

Apoptosis

HDACs have been shown to regulate apoptosis in a variety of cancer cells through changing expression of pro- and antiapoptotic proteins. Treatment of tumor cells with HDACi can either directly activate apoptosis through the extrinsic (death receptor)/intrinsic (mitochondria) pathway, or enhance the susceptibility of tumor cells to apoptosis. The extrinsic apoptosis pathway induced by HDACi is via diverse mechanisms including up-regulation of cell surface death receptors and/or ligands including FAS/APO1-FASL, TNF-TNF receptors and TRAIL-TRAIL receptors, reductions in the level of cytoplasmic FLICE-like inhibitory protein (c-FLIP), and enhanced recruitment of DISC formation (Zhang and Zhong 2014). Two nonselective HDACi, vorinostat and panobinostat,

have been identified as modulators of FLIP expression in several preclinical cancer models (Bangert et al. 2012). Inhibition of HDAC1, 2, and/or 3, but not HDAC6, is necessary for efficient FLIP down-regulation and caspase-8 activation in NSCLC. HDACi sensitized cancer cells for TRAIL-induced apoptosis in a FLIP- and caspase-8-dependent manner (Riley et al. 2013). Depletion of HDAC2 also synergizes pancreatic cancer cells toward TRAIL-induced apoptosis with an increased expression of TRAIL receptor DR5 (TRAIL-R2) (Schuler et al. 2010).

The intrinsic cell death pathway involves the interplay of the pro- and antiapoptotic Bcl-2 superfamily of proteins, and HDAC inhibition could induce the intrinsic pathway by decreasing the expression of antiapoptotic proteins, and increasing the expression of proapoptotic proteins (Zhang and Zhong 2014). HDAC2 depletion results in regression of tumor cell growth and activation of apoptosis via p53 and Bax activation and Bcl2 suppression in human lung cancer cells (Jung et al. 2012). In gastric cancer cells, HDAC2 knockdown selectively induced the expression of proapoptotic factors Bax, AIF, and Apaf-1, but repressed the expression of antiapoptotic Bcl-2 (Kim et al. 2013). HDAC1 and HDAC8 cooperate to repress BMF (Zhang et al. 2006; Kang et al. 2014). Inhibition of HDAC8 by methylselenopyruvate (MSP), a competitive inhibitor of HDAC8, was sufficient to activate BMF transcription and promote BMF-mediated apoptosis in colon cancer cells (Kang et al. 2014). HDAC3 down-regulates PUMA expression in gastric cancer cells and HDACi, like TSA, promotes PUMA expression through enhancing the binding of p53 to the PUMA promoter (Feng et al. 2013). TSA treatment can also effectively overcome resistance to DNA-damage-induced cell death by reactivating PUMA expression in renal cell carcinoma cells (Zhou et al. 2014).

The relevance of p53 in HDACi-induced apoptosis is controversial. HDACi can activate p53, but does not necessarily require p53 for induction of anticancer action (Sonnemann et al. 2014). Most studies point to a p53-independent action of HDACi because the anticancer effect of HDACi is not influenced by the tumor's p53 status (Ellis et al. 2009). Other studies, however, suggest an essential role of p53 in the response of tumor cells to HDACi treatment (Bajbouj et al. 2012). Using isogenic HCT-116 colon cancer cell lines with different p53 status, the antitumor effects of vorinostat, apicidin, and VPA were largely independent of p53, whereas entinostat-induced cell death partially depends on p53 (Sonnemann et al. 2014), indicating that HDACi may regulate apoptotic processes via both p53-dependent and independent pathways.

DNA-Damage Response

Numerous studies have shown that HDACs have important roles in DNA-damage repair (DDR) responses because HDACs are critical in modulating chromatin remodeling and maintaining dynamic acetylation equilibrium of DNA-damage-related proteins (Li and Zhu 2014). HDAC1 and HDAC2 are recruited to DNA-damage sites to deacetylate histones H3K56 and H4K16, and facilitate nonhomologous end-joining (NHEJ) (Miller et al. 2010), suggesting a direct role for these two enzymes during DNA replication and double-strand break (DSB) repair. HDAC3 is also associated with DNA-damage control, although it is not localized to DSB DNA-damage sites (Miller et al. 2010). Inactivation of HDAC3 causes genomic instability, and deletion of HDAC3 in the liver leads to hepatocellular carcinoma (Bhaskara et al. 2010). Besides altering histone acetylation status, class I HDACs also regulate other proteins involved in the DNA-damage response, including ATR, ATM, BRCA1, and FUS (Thurn et al. 2013). HDAC inhibition can repress DSB repair and render cancer cells more susceptible to ionizing radiation (IR) and DNA-damaging-agents-induced cell death (Koprinarova et al. 2011).

Among the class II HDACs, HDAC4, HDAC6, HDAC9 and HDAC10, have each been implicated in DNA-damage-repair processes. HDAC4 colocalizes with 53BP to nuclear foci after DSB. Depletion of HDAC4 reduces 53BP1 expression and abrogates the DNA-damage-induced G_2 checkpoint (Kao et al. 2003).

HDAC9 and HDAC10 are reported to be required for homologous recombination (HR). Depletion of HDAC9 or HDAC10 inhibits HR and sensitizes cells to mitomycin C treatment (Kotian et al. 2011). The mismatch repair (MMR) system recognizes DNA mismatches that occur during DNA replication or recombination, and corrects these defects to maintain genomic integrity. MutS protein homolog 2 (MSH2), a key DNA mismatch repair protein, is regulated by class IIb HDACs. HDAC6 sequentially deacetylates and ubiquitinates MSH2, causing a cellular tolerance to DNA damage and decreased cellular DNA mismatch repair activities by down-regulation of MSH2 (Zhang et al. 2014). However, the deacetylation of MSH2 by HDAC10 might promote DNA mismatch repair activity (Radhakrishnan et al. 2015).

SIRT1 is a critical component of the DNA-damage response pathway that regulates multiple steps of DDR, including damage sensing, signal transduction, DNA repair, and apoptosis (Gorospe and de Cabo 2008). SIRT1 interacts with and deacetylates several DDR proteins, including Ku70, NBS1, APE1, XPA, PARP-1, TopBP1, and KAP1 (Luna et al. 2013; Li and Zhu 2014; Wang et al. 2014; Lin et al. 2015). SIRT1 antagonizes p53 acetylation and facilitates cancer cells survival after DNA damage (Luo et al. 2001; Vaziri et al. 2001), making SIRT1 a promising target in cancer therapy. However, SIRT1 also plays an essential role in maintaining genome integrity and stability (Wang et al. 2008; Palacios et al. 2010), so the challenge still remains to modulate SIRT1 function in such a manner that it will be beneficial for cancer therapy. Recent research demonstrated that the role of SIRT1 in response to DNA damage requires posttranslational modifications such as site-specific phosphorylation and ubiquitination. HIPK2 interacts and phosphorylates SIRT1 at Ser682 after DNA damage. Phosphorylation of SIRT1 inhibits SIRT1 deacetylase activity on p53, which in turn potentiates apoptotic p53 target gene expression and DNA-damage-induced apoptosis (Conrad et al. 2015). SIRT1 is also ubiquitinated by MDM2 during DDR, and ubiquitination of SIRT1 affects its function in cell death and survival in response to DNA damage (Peng et al. 2015).

SIRT6, also important in DNA repair, was first found to suppress genomic instability by regulating base excision DNA repair (BER) (Mostoslavsky et al. 2006). Recent studies have demonstrated that SIRT6 is involved in homologous recombination (HR) by deacetylating carboxy-terminal binding protein (CtBP) and interacting protein (CtIP) (Kaidi et al. 2010). SIRT6 is rapidly recruited to DNA-damage sites and stimulates DSB repair by mono-ADP-ribosylation of PARP1(Mao et al. 2011). SIRT6 also recruits the ISWI-chromatin remodeler SNF2H to DSBs, and deacetylates histone H3K56, preventing genomic instability through chromatin remodeling (Toiber et al. 2013). Together, results from these studies suggest that at least some of the class III sirtuins (Sir2 proteins) have an equally critical role in DNA-damage response compared to the classical HDACs.

Metastasis

Epithelial-to-mesenchymal transition (EMT) is a major process in cancer cell invasion and metastasis, and emerging studies have demonstrated the key role of HDACs in EMT regulation in a variety of cancer contexts. EMT is characterized by the loss of epithelial cell markers, namely, epithelial-cadherin (CDH1), and several transcriptional repressors of CDH1 have been identified, including Snail, Slug, Twist, ZEB1, and ZEB2. A mechanism of their action involves recruitment of HDACs to the CDH1 promoter resulting in deacetylation of H3 and H4 histones. Snail recruits HDAC1/2 and Sin3A complex to the CDH1 promoter for histone deacetylation, and the snail/HDAC1/HDAC2 repressor complex contributes to CDH1 silencing in the metastasis of pancreatic cancer (von Burstin et al. 2009). Moreover, the complex of snail/HDAC1/HDAC2 is required for EZH2-mediated CDH1 repression in nasopharyngeal carcinoma cells (Tong et al. 2012). Recruitment of HDACs to the CHD1 promoter is also regulated by ZEB1 in human pancreatic cancer cells (Aghdassi et al. 2012). Given that ZEB1 could also alter the splicing of CDH1 exon 11, a recent

study revealed a dual effect of ZEB1 and its interacting class I HDACs; the decrease in CDH1 is the result of a combination of transcriptional inhibition and aberrant splicing (Liao et al. 2013). Treatment of cells with the HDACs inhibitor, LBH589 (panobinostat), induces CDH1 expression, and represses EMT and metastasis in triple-negative breast cancer (TNBC) cells. Besides preventing ZEB-mediated repression of CDH1 by inhibiting the class I HDACs corepressors, the effect of LBH589 is partially mediated by inhibition of ZEB expression (Rhodes et al. 2014). The expression of ZEB1 is also reduced in pancreatic cancer cells after mocetinostat treatment that sensitizes the undifferentiated, ZEB1-expressing cancer cells for chemotherapy (Meidhof et al. 2015). These findings indicate the therapeutic potential of inhibition of class I HDACs in targeting EMT and metastasis of cancer cells.

The role of SIRT1 in EMT regulation depends on the tumor type. In prostate cancer cells, SIRT1 induces cell migration in vitro and metastasis in vivo by cooperating with ZEB1 to suppress CDH1 transcription (Byles et al. 2012). A recent study reveals a vital role of MPP8-SIRT1 interaction in CDH1 silencing (Sun et al. 2015). The deacetylation of MPP8 at K439 by SIRT1 increases MPP8 protein stability, and MPP8 in turn facilitates SIRT1 recruitment to the CDH1 promoter for H4K16 deacetylation by regulating SIRT1-ZEB1 interaction. Thus, disruption of MPP8-SIRT1 interaction derepresses CDH1 expression and reduces cell motility and invasiveness in prostate cancer cells (Sun et al. 2015). In breast cancer, SIRT1 overexpression is associated with decreased miR-200a. miR-200a negatively regulated SIRT1 expression and reduced EMT (Eades et al. 2011). miR-204 also inhibits EMT in gastric cancer and osteosarcoma cells by directly targeting and repressing SIRT1 at the posttranscriptional level (Shi et al. 2015b). However, an opposite role of SIRT1 in cancer metastasis was indicated by the demonstration that SIRT1 reduces EMT in breast epithelial cells by deacetylating Smad4 and repressing the effect of TGF-β signaling on MMP7 (Simic et al. 2013). A similar mechanism is also found in oral squamous cell carcinoma (OSCC) cells, suggesting the key role of the SIRT1/Smad4/MMP7 pathway in EMT process (Chen et al. 2014).

Angiogenesis

Tumor growth and metastasis depend on angiogenesis. Angiogenesis is triggered by hypoxia or hypoxic microenvironment, and the cellular response to hypoxia is primarily regulated by the transcription factor hypoxia-inducible factors 1 α (HIF-1α). Many HDACs are associated with HIF-1α activity as cell treatment with HDACi causes HIF-1α degradation and functional repression. HDAC1 and HDAC4 directly deacetylate HIF-1α and block degradation of the protein (Yoo et al. 2006; Geng et al. 2011). Instead of regulating HIF-1α acetylation, HDAC5 and HDAC6 facilitate HIF-1α maturation and stabilization by deacetylating its chaperones, HSP70 and HSP90 (Kong et al. 2006; Chen et al. 2015). Inhibition of HDAC5 and 6 results in hyperacetylation of these chaperones, accumulation of the immature HIF-1α complex, and degradation of HIF-1α by the 20S proteasome. HDAC4, HDAC5, and HDAC7 increased transcriptional activity of HIF-1α by promoting its association with p300 (Kato et al. 2004; Seo et al. 2009). In contrast, SIRT1-mediated deacetylation of HIF-1α at Lys674 inhibits HIF-1α activity by blocking p300 recruitment. The suppression of SIRT1 under hypoxic conditions provides a positive feedback loop that maintains a high level of HIF-1 activity (Lim et al. 2010).

Although the antiangiogenic activity of HDAC inhibition has been demonstrated to be associated with decreased expression of proangiogenic genes, the specific effect of individual HDAC enzymes on angiogenic gene expression is controversial. KLF-4 recruits HDAC2 and HDAC3 at the VEGF promoter and represses its transcription. The up-regulation of VEGF in cancer is associated with loss of KLF-4-HDAC-mediated transcriptional repression (Ray et al. 2013). HDAC5 is another negative regulator of angiogenesis by repressing proangiogenic gene expression, such as FGF2 or Slit2, in endothelial cells (Urbich et al. 2009). Recent

studies demonstrated a dual role of HDAC6 in angiogenesis. HDAC6 promotes angiogenesis by deacetylating cortactin in endothelial cells, thereby regulating endothelial cell migration and sprouting (Kaluza et al. 2011). Another study reported the antiangiogenic effect of HDAC6 in HCC, as depletion of HDAC6 facilitates angiogenesis by up-regulating the expression of HIF-1α and VEGFA (Lv et al. 2015). HDAC7 is crucial in maintaining vascular integrity and endothelial angiogenic functions, such as tube formation, migration and proliferation (Turtoi et al. 2012). HDAC9 positively regulates endothelial cell sprouting and vascular growth by the repression of the miR-17-92 cluster, which reduces the expression of proangiogenic proteins (Kaluza et al. 2013). Taken together, HDACs play important roles in angiogenesis by modulating a multitude of pro- and antiangiogenic factors, indicating that they are potential targets for antiangiogenesis in cancer therapy.

Autophagy

The role of autophagy in cancer is complex. The failure to properly modulate autophagy in response to oncogenic stresses has been implicated both positively and negatively in tumorigenesis. On the one hand, autophagy functions as a surveillance mechanism to remove damaged organelles and cellular components, which might prevent normal cells from transforming to tumor cells. So the loss of autophagy proteins appears to promote cancer development. On the other hand, for established tumors, autophagy can help cancer cell survival under conditions of metabolic stress, and it might also confer resistance to anticancer therapies (Zhi and Zhong 2015). Consistent with the dual role of autophagy in cancer, many HDAC family members show both pro- and antiautophagy activities (Koeneke et al. 2015). Depletion or inhibition of HDAC1 is reported to induce autophagy by promoting accumulation of the autophagosomal marker LC3-II (Xie et al. 2012). However, in mouse models, deletion of both HDAC1 and HDAC2 in skeletal muscle blocks autophagy flux (Moresi et al. 2012). Recent research indicates that the oncogenic role of class IIa HDAC4 and HDAC5 in cancer cells would be derived at least partially via decreasing autophagic flux, but the detailed mechanism needs further investigation.

The key role of HDAC6 in autophagy was first established through the observation that HDAC6 provide an essential link between autophagy and the ubiquitin proteasome system (UPS) in neurodegenerative diseases. When the UPS is impaired, autophagy is strongly activated and acts as a compensatory degradation system in an HDAC6-dependent manner (Pandey et al. 2007). In HDAC6 knockout mouse embryonic fibroblasts (MEFs), HDAC6 appears to be important for ubiquitin-selective quality control (QC) autophagy, but not starvation-induced autophagy (Lee et al. 2010a). A similar mechanism is observed in mitophagy, a selective degradation of mitochondria. The parkin-mediated mitochondrial ubiquitination recruits HDAC6 and p62, which assemble the autophagy machinery and lead to mitochondrial clearance (Lee et al. 2010b). Besides Ub-based selective autophagy, HDAC6 is associated with autophagic clearance of IFN-induced ISG15-conjugated proteins. HDAC6 and p62 independently bind ISG15 and facilitate the autophagosome/lysosome degradation of ISG15 conjugates (Nakashima et al. 2015). The role of HDAC6 in the fusion event is to control acetylation of salt-inducible kinase 2 (SIK2). HDAC6-mediated deacetylation activates SIK2 kinase activity and promotes autophagosome processing (Yang et al. 2013). Although HDAC6 is dispensable for starvation-induced autophagy in MEFs (Lee et al. 2010a), another study demonstrated that HDAC6 is involved in this nonselective degradation by deacetylating LC3-II in HeLa cells (Liu et al. 2013). The acetylation level of LC3B-II is decreased upon serum deprivation and HDAC6 is at least partially responsible for deacetylating LC3-II. In neuroblastoma, depletion and inhibition of HDAC10 disables efficient autophagosome/lysosome fusion and interrupts autophagic flux, resulting in an increase of sensitization to cytotoxic drug treatment (Oehme et al. 2013). The deacetylation of Hsp70 protein families by HDAC10

might contribute to autophagy-mediated cell survival (Oehme et al. 2013). Overall, class IIb HDACs seem to mainly regulate autophagic flux at the level of autophagosome–autolysosome fusion via deacetylation of cytoplasmic proteins (Koeneke et al. 2015).

Sirtuins also participate in regulating autophagy. Sirt1 activity is necessary for the induction of starvation-induced autophagy by directly deacetylating critical regulators of the autophagy machinery, including Atg5, Atg7, Atg8, and LC3 (Lee et al. 2008; Huang et al. 2015a). In embryonic stem cells (ESCs), SIRT1 mediates oxidative stress-induced autophagy at least in part by PI3K/Beclin 1 and mTOR pathways (Ou et al. 2014). SIRT1 and the PI3K/Akt/mTOR pathway are also found to be related to Plumbagin (PLB)-induced autophagy in prostate cancer cells (Zhou et al. 2015). SIRT3, a mitochondrial deacetylase, evokes mitophagy under oxidative stress or starvation conditions (Tseng et al. 2013; Webster et al. 2013). SIRT3 is found to confer cytoprotective effects by activating antioxidant defenses and mitophagy under mitochondrial proteotoxic stress and reestablishing homeostasis in breast cancer cells (Papa and Germain 2014). Two recent reports suggest a connection between autophagy with SIRT5 and SIRT6. SIRT5 reduces ammonia-induced autophagy and mitophagy by regulating glutamine metabolism (Papa and Germain 2014). SIRT6 is involved in autophagy activation during cigarette-smoke-induced cellular senescence via attenuation of IGF-Akt-mTOR signaling (Takasaka et al. 2014). Collectively, a better understanding of the context-dependent effects of individual HDACs enzymes on autophagic process will give us an advantage to treat cancers by exploiting this area in a specifically targeted manner.

ANTICANCER EFFECT OF HDAC INHIBITORS

The availability of HDACi has not only accelerated our understanding of HDAC functions and mechanism of actions, but also presented a promising new class of compounds for cancer treatment. To date, numerous synthetic or natural molecules that target classes I, II, and IV enzymes have been developed and characterized, although interest in the class III Sirtuin family is increasing. Here we only describe the potential role of classical HDACi in cancer therapy. Because classical HDACs display Zn^{2+}-dependent deacetylase activity, the binding of HDACi to the Zn^{2+} ion, which resides at the active site of HDACs, interferes with the activity of HDACs, thereby inhibiting their enzymatic function. On the bases of chemical structures, HDACi are classified into four groups, including hydroxamates, benzamides, short-chain fatty acids, and cyclic peptides (Table 2). Most of these molecules have been developed as anticancer agents with varying specificity and efficiency, pharmacokinetic properties, and toxicological characteristics.

The rationale for targeting HDACs in cancer therapy is that altered HDAC expression and/or function is frequently observed in a variety of cancer types. The disrupted acetylation homeostasis in cells might contribute to tumorigenesis, and the nature of reversible modulation by HDACs makes them attractive targets for cancer treatment. HDACs reversibly modify the acetylation status histones and nonhistones and cause widespread changes in genes expression without a change in DNA sequence. HDACi can counteract the abnormal acetylation status of proteins found in cancer cells and can reactivate the expression of tumor suppressors, resulting in induction of cell-cycle arrest, apoptosis, differentiation, and inhibition of angiogenesis and metastasis (Fig. 1). Furthermore, cancer cells are more sensitive to HDACi-induced apoptosis than normal cells (Ungerstedt et al. 2005), providing additional therapeutic potential of HDACi.

Currently, there are numerous HDACi under clinical development (Table 2), which can be divided into three groups based on their specificity: (1) nonselective HDACi, such as vorinostat, belinostat, and panobinostat; (2) selective HDACi, such as class I HDACi (romidepsin and entinostat) and HDAC6 inhibitor (ricolinostat); and (3) multipharmacological HDACi, such as CUDC-101 and CUDC-907.

Table 2. HDAC inhibitors currently under clinical investigations

HDACis	Specificity	Cancer types	Clinical trial	References
Hydroxamic acid				
Vorinostat (SAHA)	Classes I, II, and IV	CTCL	FDA approved in 2006	Mann et al. 2007
Belinostat (Beleodaq/ PXD101)	Classes I, II, and IV	PTCL	FDA approved in 2014	McDermott and Jimeno 2014
Panobinostat (LBH-589)	Classes I, II, and IV	MM	FDA approved in 2015	Richardson et al. 2015
Resminostat (4SC-201)	Classes I and II	Advanced colorectal and hepatocellular carcinoma; HL	Phase II trial	Brunetto et al. 2013; Zhao and Lawless 2015
Givinostat (ITF2357)	Classes I and II	CLL; MM; HL	Phase II trial	Galli et al. 2010; Locatelli et al. 2014
Pracinostat (SB939)	Classes I, II, and IV	AML	Phase II trial	Zorzi et al. 2013
Abexinostat (PCI-24781)	Classes I and II	Metastatic solid tumors; HL; non-HL; CLL	Phase I trial	Choy et al. 2015; Morschhauser et al. 2015
Quisinostat (JNJ-26481585)	Class I and II HDACs	Advanced solid tumor; lymphoma; CTCL	Phase I and II trial	Venugopal et al. 2013
MPT0E028	HDAC1, 2, 6	Advanced solid tumor	Phase I trial	Zwergel et al. 2015
CHR-3996	Class I	Solid tumor	Phase I trial	Banerji et al. 2012
CUDC-101	Classes I and II HDAC, EGFR, HER2	Solid tumor	Phase I trial	Shimizu et al. 2015
CUDC-907	Classes I and II HDAC, PI3K	MM; lymphoma; solid tumor	Phase I trial	Qian et al. 2012
Benzamides				
Entinostat (MS-275)	Class I	Solid and hematological malignancies	Phase I and II trial	Knipstein and Gore 2011
Mocetinostat (MGCD0103)	Class I and IV	Solid and hematological malignancies	Phase I and II trial	Younes et al. 2011
Tacedinaline (CI-994)	Class I	MM; lung and pancreatic cancer	Phase II and III trial	Pauer et al. 2004
Ricolinostat (ACY-1215)	HDAC6	MM; lymphoma	Phase I and II trial	Santo et al. 2012
Chidamide (CS055/ HBI-8000)	HDAC1, 2, 3, and 10	Breast cancer; NSCLC	Phase II and III trial	Dong et al. 2012; Shi et al. 2015a
Cyclic peptides				
Romidepsin (Depsipeptide/ FK228)	Class I	CTCL; PTCL	FDA approved in 2009 and 2011	Frye et al. 2012
Aliphatic fatty acids				
Valproic acid (VPA)	Class I and II	Solid and hematological malignancies	Phase I and II trial	Bilen et al. 2015
Phenylbutyrate	Classes I and II	Solid and hematological malignancies	Phase I and II trial	Iannitti and Palmieri 2011
AR-42	Class I and IIb	AML	Phase I trial	Guzman et al. 2014
Pivanex (AN-9)	Classes I and II	NSCLC; myeloma; CLL	Phase II trial	Reid et al. 2004

AML, Acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CTCL, cutaneous T-cell lymphoma; HL, Hodgkin's lymphoma; MM, multiple myeloma; NSCLC, non-small-cell lung cancer; PTCL, peripheral T-cell lymphoma.

Nonselective Broad-Spectrum HDAC Inhibitors

The most extensively studied and commonly used HDACi are nonselective HDACi. For example, vorinostat (SAHA), a hydroxamate class agent, was the first histone deacetylase inhibitor approved by the Food and Drug Administration (FDA) to treat patients with cutaneous T-cell lymphoma (CTCL). Like TSA, SAHA inhibits all zinc-dependent HDACs in low nanomolar ranges, although more recent studies suggest that most hydroxamate-based HDACi have a weak effect on class IIa enzymes (Bradner et al. 2010). Preclinical studies have demonstrated that SAHA induces apoptosis and cell-cycle arrest, and reduces the proliferation and metastatic potential of tumor cells. SAHA also sensitized tumor cells to chemotherapy and/or radiotherapy (Shi et al. 2014; Xue et al. 2015). In addition to SAHA, two hydroxamate-based nonselective HDACi, belinostat (Beleodaq/PXD101) and panobinostat (LBH-589), were recently approved by the FDA to treat peripheral T-cell lymphomas (PTCL) and multiple myeloma, respectively. Both of these drugs are also under investigation in combination therapies for solid tumors.

Selective HDAC Inhibitors

To date, there are relatively few highly selective HDACi, but compounds with proposed selectivity for several class I and class II HDACs have been developed (Table 3).

Class I HDACi

HDAC1 and HDAC2. Romidepsin (FK-228), the second histone deacetylase inhibitor approved for the treatment of CTCL and PTCL, exhibits a stronger inhibition toward HDAC1 and HDAC2 enzymes at low nanomolar levels (Furumai et al. 2002). Its antitumor efficacy has been demonstrated in different cancer models (McGraw 2013; Karthik et al. 2014). BRD8430, compound 60 and MRLB-223 are three novel HDAC1 and HDAC2 inhibitors under preclinical studies. The selective inhibition of HDAC1 and HDAC2 by BRD8430 and compound 60 induced differentiation and cell death in neuroblastoma cells, and synergistically activated retinoic acid signaling in combination treatment with 13-*cis* retinoic acid (Frumm et al. 2013). MRLB-223 induced tumor cell death via the intrinsic apoptotic pathway in a p53-independent manner. However, MRLB-223 had less effect on induction of apoptosis and therapeutic efficacy as seen using the broad-spectrum histone deacetylase inhibitor vorinostat (Newbold et al. 2013).

HDAC3. RGFP966 is an *N*-(*o*-aminophenyl) carboxamide HDAC3-selective inhibitor (Malvaez et al. 2013). RGFP966 decreased growth and increased apoptosis of refractory CTCL cells by targeting DNA replication (Wells et al. 2013). Consistent with previous research demonstrating the contribution of HDAC3 to the effects of SAHA on DNA replication (Conti et al. 2010), HDAC3 inhibition by RGFP966 reduces DNA replication fork velocity and causes replication stress in CTCL cells (Wells et al. 2013).

A recent preclinical study demonstrated that HDAC3 represents a promising therapeutic target in multiple myeloma (MM) (Minami et al. 2014). HDAC3 inhibition by BG45, a HDAC3-selective inhibitor, induces significant apoptosis in MM cells, without affecting normal donor PBMCs. BG45-induced MM cell toxicity might be associated with hyperacetylation and hypophosphorylation of STAT3. HDAC3 inhibition, but not HDAC1 or HDAC2, significantly enhances bortezomib-induced cell death in vitro and in vivo, providing the preclinical rationale for combination treatment of MM with HDAC3 and proteasome inhibitors.

T247 and T326 are identified as HDAC3-selective inhibitors by screening a series of compounds assembled using "click chemistry" (Suzuki et al. 2013). In cell-based assays, T247 and T326 selectively enhance the acetylation of NF-κB, a substrate of HDAC3, but did not regulate HDAC1 and HDAC6 substrates, suggesting they are HDAC3-selective inhibitors. T247 and T326 inhibited the growth of colon and prostate cancer cells (Suzuki et al. 2013). In TMEM16A-expressing cancer cells, T247 also exerts a suppressive effect on cancer cell viability via downregulating TMEM16A (Matsuba et al. 2014).

Table 3. Specific HDAC inhibitors in cancer therapy

HDACis	Specificity	Cancer types	Stage	References
Class I				
Romidepsin (Depsipeptide/ FK228)	HDAC1, 2	CTCL and PTCL	FDA approved	Furumai et al. 2002; Frye et al. 2012
BRD8430	HDAC1, 2	Neuroblastoma	Preclinical	Frumm et al. 2013
Compound 60	HDAC1, 2	Neuroblastoma	Preclinical	Methot et al. 2008; Frumm et al. 2013; Schroeder et al. 2013
MRLB-223	HDAC1, 2	Lymphomas	Preclinical	Newbold et al. 2013
Entinostat (MS-275)	HDAC1, 2, 3	Multiple cancer cells	Clinical trial	Hu et al. 2003; Khan et al. 2008; Knipstein and Gore 2011
CHR-3996	HDAC1, 2, 3	Multiple cancer cells	Clinical trial	Moffat et al. 2010; Banerji et al. 2012
Tacedinaline (CI-994)	HDAC1, 2, 3	Multiple myeloma; lung and pancreatic cancer	Clinical trial	Kraker et al. 2003; Pauer et al. 2004
Apicidin	HDAC1, 2, 3	Multiple cancer cells	Preclinical	Olsen et al. 2012; Ahn et al. 2015
RGFP966	HDAC3	CTCL	Preclinical	Wells et al. 2013
BG45	HDAC3	Myeloma	Preclinical	Minami et al. 2014
T247 and T326	HDAC3	Colon and prostate cancer	Preclinical	Suzuki et al. 2013
PCI-34051	HDAC8	Lymphoma, neuroblastoma	Preclinical	Balasubramanian et al. 2008; Oehme et al. 2009; Rettig et al. 2015
Compound 2 (Cpd2)	HDAC8	Neuroblastoma	Preclinical	Krennhrubec et al. 2007; Oehme et al. 2009; Rettig et al. 2015
C149 (NCC149)	HDAC8	Multiple cancer cells	Preclinical	Suzuki et al. 2012; Suzuki et al. 2014
Compound 22 d	HDAC8	Lung cancer	Preclinical	Huang et al. 2012
Class IIa				
TMP269	HDAC4, 5, 7, 9	Multiple myeloma	Preclinical	Lobera et al. 2013; Kikuchi et al. 2015
MC1568	HDAC4, 5, 6, 7, 9	Gastric, colorectal, pancreatic and breast cancer	Preclinical	Mai et al. 2005; Duong et al. 2008; Wang et al. 2012; Colarossi et al. 2014; Ishikawa et al. 2014
LMK235	HDAC4, 5	Multiple cancer cells	Preclinical	Marek et al. 2013
Class IIb				
Ricolinostat (ACY-1215)	HDAC6	Multiple myeloma, lymphoma, glioblastoma	Clinical trial	Santo et al. 2012; Amengual et al. 2015; Li et al. 2015a; Mishima et al. 2015
Tubacin	HDAC6	Multiple cancer cells	Preclinical	Haggarty et al. 2003; Aldana-Masangkay et al. 2011
Tubastatin A	HDAC6	Multiple cancer cells	Preclinical	Butler et al. 2010
C1A	HDAC6	Multiple cancer cells	Preclinical	Kaliszczak et al. 2013
HPOB	HDAC6	Multiple cancer cells	Preclinical	Lee et al. 2013
Nexturastat A (Compound 5g)	HDAC6	Melanoma	Preclinical	Bergman et al. 2012
Compound 12	HDAC6	Colorectal cancer	Preclinical	Lee et al. 2014a
Befexamac	HDAC6, 10	Neuroblastoma, lung cancer	Preclinical	Bantscheff et al. 2011; Oehme et al. 2013; Li et al. 2015b; Scholz et al. 2015

CTCL, Cutaneous T-cell lymphoma; PTCL, peripheral T cell lymphoma.

HDAC8. HDAC8 has proven to be the most promising target to achieve selectivity. The unique features of HDAC8, such as conformational variability of the L1 and L2 loop segments (Dowling et al. 2008) and the presence of serine 39 phosphorylation near the active site (Lee et al. 2004), led to the design of higher selective inhibitors for HDAC8.

Modifications to the hydroxamic acid scaffold resulted in the discovery of PCI-34051, a potent HDAC8-specific inhibitor with a >200-fold selectivity over other HDACs. It induces caspase-dependent apoptosis in T-cell-derived malignant cells, but not in a panel of solid tumor cell lines or other hematopoietic cells. Mechanistically, PLCγ1-dependent calcium mobilization from the endoplasmic reticulum (ER) and, in turn, release of cytochrome *c* from mitochondria might contribute to PCI-34051-induced cell death (Balasubramanian et al. 2008). Besides T-cell leukemia and lymphoma, human and murine-derived malignant peripheral nerve sheath tumors (MPNST) cells also exhibited "sensitivity" to HDAC8 inhibitors: PCI-34051 and its variant PCI-48012 (Lopez et al. 2015). HDAC8 inhibition-induced S phase cell-cycle arrest and apoptosis in MPNST cells, but the underlying mechanism remains unclear. Given that high HDAC8 expression is significantly correlated with advanced stage and poor outcome in neuroblastoma (Oehme et al. 2009), HDAC8 inhibition by selective inhibitors, compound 2 (Cpd2) and PCI-34051, induced cell differentiation, cell-cycle arrest, and cell death in neuroblastoma cells, while untransformed cells were not affected (Rettig et al. 2015). PCI-48012, an in vivo stable variant of PCI-34051 with improved pharmacokinetic properties, displayed a significant antitumor activity without toxicity in xenograft mouse models. PCI-48012 in combination with retinoic acid further enhanced differentiation in neuroblastoma cells and delayed tumor growth in vivo (Rettig et al. 2015).

Class IIa HDACi

In contrast to class I HDACs, much less is known about the molecular mechanisms and therapeutic potential of targeting class IIa HDACs (HDAC4, 5, 7, and 9), and there is a lack of pharmacological tools to specifically probe class IIa HDAC activities (Lobera et al. 2013). A high-throughput screen (HTS) identified trifluoromethyloxadiazole (TMFO) derivatives as inhibitors selective for class IIa HDACs. Although TMP269, a compound in the TFMO series, has a modest growth inhibitory effect in multiple myeloma (MM) cell lines, it enhances protease inhibitor carfilzomib-induced apoptosis by activating ER stress signaling (Kikuchi et al. 2015), providing the combination of the inhibition of both proteasome and class IIa HDACs as a novel treatment strategy in MM.

MC1568 and MC1575 are derivatives of aroyl-pyrrolyl-hydroxyamides (APHAs), showing selectivity toward class IIa HDACs and HDAC6 (Mai et al. 2005; Fleming et al. 2014). Although class IIa HDACs are mainly involved in tissue-specific growth and differentiation, rather than in cell proliferation, MC1568 and MC1575 treatment still displayed antiproliferative effects in estrogen-receptor-positive breast cancer cells (Duong et al. 2008) as well as human melanoma cells (Venza et al. 2013). MC1568 significantly enhanced MGCD0103-induced apoptosis and G_2/M arrest in pancreatic cancer cells (Wang et al. 2012). The additional treatment with MC1568 to simvastatin led to further induction of p27 expression and displayed a considerable synergistic antiproliferative effect in colorectal cancer cells (Ishikawa et al. 2014). MC1568 also had a synergistic effect with docetaxel treatment to increase cytotoxicity in gastric cancer cells (Colarossi et al. 2014).

Another new hydroxamate-based histone deacetylase inhibitor, LMK235, showed high selectivity for HDAC4 and HDAC5 (Marek et al. 2013). Compared with SAHA, LMK235 is less toxic and more suitable for the treatment of some cancers. Consistent with a recent study where silencing of HDAC4 was able to sensitize ovarian cancer cells to cisplatin (Stronach et al. 2011), the combination of LMK235 with cisplatin-enhanced cisplatin sensitivity in resistant cells (Marek et al. 2013).

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YK-4-272 and tasquinimod are two novel unconventional HDACi, which either target HDAC nuclear-cytoplasmic shuttling or alter the interaction of class IIa HDACs with their partners. YK-4-272 represses the growth of human prostate cancer cells in vitro and in vivo (Kong et al. 2012). YK-4-272 binds HDAC4, and the localization of YK-4-272 in the cytoplasm traps and sequestrates HDAC4 in cytoplasm, resulting in increased acetylation of tubulin and nuclear histones in prostate cancer cells. However SAHA treatment also causes an accumulation of HDAC4 in cytoplasm similar to YK-4-272, which suggests the possibility that cytoplasmic restriction of class II HDACs is an indirect effect of class I inhibition. So far, the cytoplasmic functions of class IIa HDACs is not well known and this uncertain function could be amplified by inhibition of HDAC nuclear transport, limiting the use of the HDAC shuttling inhibitor.

Class IIb HDACi

HDAC6 inhibition has been intensively studied and a number of HDAC6-selective inhibitors are developed, such as tubacin and tubastatin A; however, their poor pharmacokinetic properties prevented them from further clinical development. Among HDAC6-specific inhibitors available, ricolinostat (ACY-1215) was the first one entered in clinical studies of patients with relapsed/refractory multiple myeloma or lymphoma (Santo et al. 2012; Amengual et al. 2015). In multiple myeloma, the highly secretory antibody-producing cells are heavily reliant on protein handling pathways, including the unfolded protein response (UPR), proteasome, aggresome, and autophagy pathways. So targeting both of the proteasome and aggresome degradation pathways by proteasome and HDAC6 inhibitors, respectively, induces accumulation of polyubiquitinated proteins, followed by activation of apoptotic cascades and synergistic cytotoxicity. ACY-1215 in combination with bortezomib triggered synergistic anti-MM activity without significant adverse effects (Santo et al. 2012), and similar anti-MM effects were obtained by combination treatment of ACY-1215 with another proteasome inhibitor, carfilzomib (Mishima et al. 2015). Besides hematological tumors, recent research indicated that ACY-1215 also significantly inhibited glioblastoma multiforme (GBM) cell growth (Li et al. 2015a). C1A is another HDAC6-selective inhibitor, which modulates HDAC6 downstream targets (α-tubulin and HSP90) and induces growth inhibition of a panel of cancer cell lines. To date, HDAC10-specific inhibitors are not yet available. Like other selective HDAC inhibitors, development of HDAC10-selective inhibitors might help clarify the function and mechanism of action of HDAC10, and potentially provide additional anticancer drugs.

Multipharmacological HDAC Inhibitors

Tumor heterogeneity requires a comprehensive approach to target multiple pathways underlying the initiation and progression of cancers. To enhance the therapeutic efficacy of HDACi, the combination with other anticancer agents have been explored and evaluated in preclinical and clinical studies. Another promising approach is to generate a single chemical compound that acts on multiple targets. CUDC-101, with a potent inhibitory activity against EGFR, HER2, and HDACs, is currently being evaluated in clinical trials as a treatment for advanced solid tumors, such as head and neck, gastric, breast, liver, and non-small-cell lung cancer tumors (Cai et al. 2010; Galloway et al. 2015). Recent research also indicates the antitumor effect of CUDC-101 in EGFR-overexpressing glioblastoma and anaplastic thyroid cancer (Liffers et al. 2015; Zhang et al. 2015a). CUDC-907 is another dual-acting agent developed by the same research group to inhibit both HDACs and phosphoinositide 3-kinase (PI3K) (Qian et al. 2012) and its clinical trials are underway for the treatment of lymphoma and multiple myeloma as well as advanced/relapsed solid tumors. Romidepsin (FK228, depsipeptide) is a potent class I histone deacetylase inhibitor that has FDA approval for the treatment of cutaneous and peripheral T-cell lymphomas, and recent research demonstrated that FK228 and its analogs (FK-A5 and FK-A11) act as HDACs and

PI3K dual inhibitors (Saijo et al. 2012; Saijo et al. 2015).

Numerous chemical hybrid molecules containing both HDACi activities and an additional anticancer module are under development, dual targeting HDACs and estrogen receptor (Gryder et al. 2013; Tang et al. 2015), retinoid X receptor (RXR) (Wang et al. 2015), topoisomerase I/II (Guerrant et al. 2013), 1α, 25-vitamin D (Lamblin et al. 2010), receptor tyrosine kinases (RTKs) (Zhang et al. 2013), tubulin (Zhang et al. 2015b), or DNA methyltransferase (Shukla et al. 2015), potentially leading to a rational efficacy in cancer therapy. Additionally, the hybrid of a nitric oxide (NO) donor and a histone deacetylase inhibitor has been developed and displayed outstanding antiproliferative activity in tumor cells (Duan et al. 2015).

CLINICAL LANDSCAPE OF HDAC INHIBITORS IN CANCER THERAPY

After vorinostat (SAHA) was approved to treat CTCL in 2006, the other three HDACi, romidepsin, belinostat, and panobinostat, have since been approved by the FDA for the treatment of cancer. Currently, more than 20 different HDACi are in different phases of clinical trials as single agents or in combination with chemotherapy or radiation therapy in patients with hematologic or solid tumors.

The efficacy of HDACi tested in clinical trials has been largely restricted to hematological malignancies, with positive therapeutic responses in leukemias, lymphomas, and multiple myeloma; however, the clinical outcomes in solid tumors are disappointing when used as monotherapy. It is not entirely clear why HDACi are more effective in hematological malignancies. One reason might be the poor pharmacokinetic properties of some HDACi, such as a short drug half-life that restricts them to distribute to solid tumors. Selective and accurate drug delivery of HDACi may help to overcome the issues associated with inefficient bioavailability. For example, HDACi conjugated to folic and pteroic acids selectively targets folate receptor (FR)-overexpressed solid tumors (Sodji et al. 2015). The other reason might be that HDACi do not target solid tumors. Identifying those cancers or patients where HDAC deregulation is important for tumor development might contribute to rational cancer therapy.

Another obstacle that limits the use of HDACi in patients is their side effects and toxicity displayed during early-phase clinical trials. The common toxicities related to vorinostat, romidepsin, and belinostat were nausea, vomiting, anorexia, and fatigue that are mostly manageable, but some may cause more serious adverse events. In general, acute toxicity of nonselective HDACi is mainly through HDAC1-3 inhibition, so these compounds from unrelated chemical classes have a similar toxicity profile. HDACi have a broad effect on chromatin and can reverse the aberrant epigenetic changes in cancers. However, although the inhibition of HDACs may reactivate some tumor suppressors, they can also affect numerous other genes (Guha 2015). Although the second-generation of HDACi have been developed with improved pharmacodynamic and pharmacokinetic values, given that these new agents possess similar specificity profiles as their parental compounds, it is unclear whether these newer agents will have improved and less toxic clinical outcomes. Currently, major efforts in therapeutic strategies are focused on developing selective inhibitors and studying combination therapies, with the aim of increasing potency against specific cancer types and overcoming drug toxicity and resistance.

HDACi are continuously explored for used in combination with other antitumor agents to optimize their efficacy and toxicity. Combining HDACi with primary chemotherapeutic agents that induce DNA damage or apoptosis has shown very promising results in preclinical research studies. HDAC inhibition might resensitize tumor cells to the primary agents and overcome therapy resistance. For example, hypoxia-induced cisplatin resistance in NSCLC can be overcome by combining cisplatin with panobinostat by increasing histone acetylation and destabilization of HIF-1α (Fischer et al. 2015). ERCC1 and p53 were reported to have a predictive role for the efficacy of combined panobino-

stat and cisplatin treatment (Fischer et al. 2015). HDAC inhibitions could also overcome resistance to mTOR inhibitors (e.g., everolimus, temsirolimus, sirolimus, and ridaforolimus) in advanced solid tumors or lymphoma (Dong et al. 2013; Beagle et al. 2015; Zibelman et al. 2015).

Given that cross talk exists between DNA methylation and histone deacetylation in gene expression, a combination of HDACi and DNA methyltransferases (DNMTs) have been shown to produce a synergistic effect on reactivation of tumor-suppressor genes and represent a promising future therapeutic approach. Large phase I and II trials are currently underway to assess the efficacy of two chromatin-modifying agents, azacitidine and entinostat, for the treatment of chronic myelomonocytic leukemia, acute myeloid leukemia, NSCLC, advanced breast cancer, and metastatic colorectal cancer (Juergens et al. 2011; Prebet et al. 2014). Recent research demonstrated that combined MS-275 and azacitidine treatment is more efficient and selectively targeted esophageal cancer cells by inducing DNA damage, cell viability loss, apoptosis, and decreasing cell migration (Ahrens et al. 2015).

Preclinical studies also indicate a synergistic antitumor effect of HDACi with other epigenetic-targeted drugs, such as lysine-specific histone demethylase inhibitors (Vasilatos et al. 2013; Fiskus et al. 2014). These observations are consistent with recent findings that broad-acting HDAC inhibitors have minimal effect on promoter acetylation, but rather they promote H3K27 trimethylation, a silencing-associated histone modification (Halsall et al. 2015). These and other studies on the basic mechanisms of HDACs, HDACi, and their relationships with other histone modifications will no doubt guide the choice of future combination therapies.

Similarly, preclinical evidence from studies of HDACi together with proteasome inhibitors (e.g., bortezomib, carfilzomib, and marizomib) provides a strong scientific rationale for combination therapy. Given that HDAC6 facilitates misfolded protein aggresome formation for proteosome-independent proteolysis, dual targeting of HDAC6 and proteasomes can produce synergistic effects in lymphoma and multiple myeloma (Amengual et al. 2015; Mishima et al. 2015). However, the combination of proteasome and class I HDAC-specific inhibitors in nasopharyngeal carcinoma cells induced a significant apoptosis through an ROS-dependent and ER stress-induced mechanism, independent of HDAC6 inhibition (Hui and Chiang 2014). Because vorinostat and bortezomib are both FDA-approved drugs for the treatment of CTCL and multiple myeloma, respectively, the combination of these two agents has been tested in a variety of preclinical models and in clinical trials. Recent research explored the synergistic effect of vorinostat and bortezomib on host immune response and found cotreatment of HPV-expressing cervical cancer cells with bortezomib and vorinostat led to a tumor-specific immunity by rendering tumor cells more susceptible to killing by antigen-specific $CD8^+$ T cells, suggesting that activated host immune surveillance contributes to antitumor effects (Huang et al. 2015b).

HDACi have also been evaluated in combination with a hormone antagonist for the treatment of patients whose tumors express hormone receptors. Three phase II clinical trials are currently carried out with vorinostat and tamoxifen for the treatment of breast cancer (Munster et al. 2011). Although histone deacetylation plays a key role in estrogen receptor gene silencing, it remains unclear whether the addition of HDACi actually reactivates functional estrogen receptor α expression (de Cremoux et al. 2015). A recent study demonstrates that Bcl-2 down-regulation and induction of proapoptotic proteins by combined estrogen receptor and HDAC inhibition leads to apoptotic cell death of tamoxifen-resistant cells (Raha et al. 2015).

HDACi have been shown to enhance the immunogenicity of cancer cells (Murakami et al. 2008; Christiansen et al. 2011; Jazirehi et al. 2014), and the antitumor efficacy of HDACi in vivo also relies on an intact immune system (West et al. 2013, 2014), so the combination of HDACi with immunotherapy is a promising strategy for the treatment of cancer. The efficacy of HDACi can be significantly enhanced by the concurrent administration of

various immunotherapeutic approaches, such as cancer vaccines, adoptive T-cell transfer, and immune checkpoint inhibitors (Park et al. 2015). For example, coadministration of HDACi with antibodies against cytotoxic T-lymphocyte antigen 4 (CTLA4) could further enhance the infiltration of $CD4^+$ T cells and achieve a synergistic therapeutic effect on tumors by promoting antitumor immune responses (Cao et al. 2015). A recent preclinical study indicated that HDACi in combination with immunomodulatory drugs, such as lenalidomide and pomalidomide, showed a synergistic cytotoxicity in multiple myeloma by down-regulating c-Myc expression. A phase I trial is currently underway to assess the effect of ACY-241, a next-generation selective inhibitor of HDAC6, with and without pomalidomide and low-dose dexamethasone for treatment of multiple myeloma. Another phase II clinical trial evaluated the class I histone deacetylase inhibitor romidepsin in combination with lenalidomide in patients with peripheral T-cell lymphoma.

There is also substantial evidence that HDACi such as vorinostat enhance radiation sensitization by inhibiting DNA-damage repair, inducing apoptosis, inhibiting proliferation and angiogenesis, and enhancing immune surveillance for cancer (Son et al. 2014).

SUMMARY AND PERSPECTIVE

Studies over the past few decades have demonstrated that HDACs play a critical role in the development of cancer by reversibly modulating acetylation status of histone and nonhistone proteins. As an eraser of histone acetylation and a key regulator of epigenetics, HDACs have been found to dysregulate and/or function incorrectly in cancer, providing a crucial attractive target against cancer. However, the precise function of HDACs as a central mediator of proliferation and tumorigenic capacity still remains a conundrum. Although genetic knockdown or knockout of HDACs in a variety of cancer cells induces cell-cycle arrest and apoptosis, a putative tumor suppressor role of HDACs is also observed in certain circumstances. More studies are needed to systematically dissect the role of individual HDACs in different cancer types at different stages of tumorigenesis. Clearly, the development of HDACi, in particular selective inhibitors, could help clarify the function of distinct HDACs, and a better comprehension of HDACs in cancer will give us a mechanistic-based rationale for the clinical use of HDACi as antitumor agents. So far, the most common HDACi under preclinical and clinical evaluation are broad spectrum nonselective HDACi. The effectiveness of nonselective HDACi for the treatment of cancer relies on its broad-spectrum inhibition against HDACs, which is also the major reason for toxicity of these agents. Therefore, current emphasis is placed on developing HDACi with higher target specificity that might be more efficacious with less toxicity. In parallel, research is increasingly showing that combination therapy might be another important direction to enhance the therapeutic efficacy of HDACi. Further elucidation of the mechanisms of action of HDACs and HDACi will provide a bright future for the use of HDACi as one of many tools in the fight against cancer.

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