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Review

Targeting Histone Deacetylases for Cancer Therapy: From Molecular Mechanisms to Clinical Implications

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Abstract

Genetic abnormalities have been conventionally considered as hallmarks of cancer. However, studies over the past decades have demonstrated that epigenetic regulation also participates in the development of cancer. The fundamental patterns of epigenetic components, such as DNA methylation and histone modifications, are frequently altered in tumor cells. Acetylation is one of the best characterized modifications of histones, which is controlled by histone acetyltransferases (HATs) and histone deacetylases (HDACs). HDACs are a group of enzymes which catalyze the removal of the acetyl groups of both histones and non-histone proteins. HDACs are involved in modulating most key cellular processes, including transcriptional regulation, apoptosis, DNA damage repair, cell cycle control, autophagy, metabolism, senescence and chaperone function. Because HDACs have been found to function incorrectly in cancer, various HDAC inhibitors are being investigated to act as cancer chemotherapeutics. The primary purpose of this paper is to summarize recent studies of the links between HDACs and cancer, and further discuss the underlying mechanisms of anti-tumor activities of HDAC inhibitors and clinical implications.

Key words: HDAC, HDAC inhibitor, epigenetic therapy, cancer.

Introduction

In order to carry out cellular functions, histones are subject to about sixteen types of post-translational modifications, such as acetylation, methylation and phosphorylation [1-3]. The enzymes responsible for these reversible modifications include histone acetyltransferases (HATs) and histone deacetylases (HDACs), methyltransferases (KMTs) and demethylases (KDMs), kinases and phosphatases, and so on. Different types of modifications may have different outcomes depending on the biological contexts. For example, trimethylation of H3K4 is generally associated with transcription activation [4], while trimethylation of H3K9 is associated with transcription inactivation [5]. As regards acetylation, it is the first modification identified and one of the best characterized modifications of histones [6]. Reversible acetylation and deacetylation of histones regulated by the opposing effects of HATs and HDACs perturb genetic information flow through interruption of chromosomal structure and the availability of transcription factors to DNA [7]. By removing the negatively charged acetyl groups, HDACs generally act as transcriptional repressors by stabilizing the nucleosomal DNA-histone interaction. HDACs can also bind to

various co-repressors to recruit other histone modifiers, thus regulating other chromatin-based processes. In addition, regulation of non-histone substrates expands the function repertoire of acetylation. The regulatory network of HDACs has now extended to induction of apoptosis, DNA damage repair, cell cycle control, autophagy, metabolism, senescence and so on [8-11].

Cancer is now considered as a disorder of altered genetic and epigenetic regulation [12]. Aberrant epigenome including dysregulatory expression and/or activity of HDACs has been characterized in different tumors [13]. In general, HDACs are cancer permissive despite that certain types of class III HDACs may function as tumor suppressors [14].

The regulatory mechanisms of HDACs in critical cellular properties, with a particular emphasis on classical HDACs will be discussed in this review. The role of this regulatory network in cancer development and the clinical relevance of HDAC inhibitors in cancer treatment will also be reviewed.

An overview of HDACs and HDAC inhibitors

Eighteen distinct HDACs have been identified so far and they are classified into four groups based on their structural divergence, namely class I, II, III and IV HDACs [15, 16]. Class I and II HDACs are considered as 'classical' HDACs while class III is a family of nicotinamide adenine dinucleotide (NAD^+)-dependent proteins. Class IV HDAC is an atypical category of its own, based solely on its DNA sequence similarity to the others (Table 1).

The function and activity of HDACs vary depending on their structure and intracellular localization. Classical HDACs remove the acetyl groups of lysine residues with the presence of a Zn^{2+} ion and a conserved deacetylase core domain, producing an unacetylated lysine and acetate. Class I HDACs (including HDAC1, 2, 3 and 8) are usually located in the nucleus and are found to catalyze a set of non-histone substrates including transcription factors besides histones. Class II HDACs (including HDAC4, 5, 6, 7, 9, 10) show different sequence homology and domain organizations compared with class I HDACs and therefore conducting different downstream functions [17]. They are further divided into two subgroups, namely IIa and IIb. Members of subgroup IIa (including HDAC4, 5, 7 and 9) are localized in both nucleus and cytoplasm. A variety of cytoplasmic proteins are regulated by class IIa HDACs such as structural proteins. HDAC6 and 10 are mostly confined to cytoplasm, and HDAC6 contain two catalytic domains while HDAC10 contains one active deacetylase and one incomplete domain with some similarity to the deacetylase domain [18-22]. Class III HDACs are more generally called sirtuins, which are named after the yeast homologous gene 'silent mating-type information regulation 2'. Sirtuins function as lysine deacetylases with the presence of NAD^+. The functions of sirtuins have been mainly focused on metabolic and senescent regulation [23]. Previously, four of the seven sirtuins (SIRT4, 5, 6 and 7) have been reported to have very weak or even no detectable deacetylase activity towards histones. For example, SIRT5 has desuccinylase and demalonylase activity other than deacetylase and poly-ADP-ribosylase activity shared by most other sirtuins [24], which have variable functions. SIRT1 interacts with KMT Set7/9 to regulate p53 activity [25], and SIRT2 interacts with and deacety-

Table 1. An overview of HDACs. Listed below are the cytogenetic location, subcellular location and tissue distribution of HDACs. Part of the non-histone substrates of different HDACs are also listed including cancer-associated genes like p53 and Rb1. Transcription factors such as E2F1, NF-κB and STAT3, which are also related to cancer, are demonstrated to be catalytic substrates of HDACs. Metabolic enzymes like AMPK and GDH are also found to be regulated by HDACs, especially sirtuins. Non-histone substrates carry out the multiple cellular functions regulated by HDACs.

Classification	HDAC	Cytogenetic location	Subcellular localization	Non-histone substrates (partly shown)
I	HDAC1	1p35.1	nucleus	RB1, SHP, p53, MyoD, E2F1, STAT3, NF-κB, CtIP, AMPK
	HDAC2	6q21	nucleus	GCCR, BCL6, STAT3, YY1
	HDAC3	5q31.3	nucleus	SHP, YY1, GATA1, p65, STAT3, MEF2D
	HDAC8	Xq13.1	nucleus	SMC3, actin
IIa	HDAC4	2q37.3	nucleus/cytoplasm	GATA1, HP1
	HDAC5	17q21.31	nucleus/cytoplasm	SMAD7, HP1
	HDAC7	12q13.11	nucleus/cytoplasm	PLAG1, PLAG2
	HDAC9	7p21.1	nucleus/cytoplasm	---
IIb	HDAC6	Xp11.23	mostly cytoplasm	α-tubulin, HSP90, SHP, SMAD
	HDAC10	22q13.31-q13.33	nucleus/cytoplasm	---
III	SIRT1	10q21.3	nucleus/cytoplasm	p53, β-catenin, Ku70, E2F1, Rb, NF-κB, PGC1α, PPARγ, MyoD, PCAF, FOXO3, HIF1α
	SIRT2	19q13.2	cytoplasm	α-tubulin, FOXO1
	SIRT3	11p15.5	nucleus/mitochondria	IDH2, SDH, CypD, p53, FOXO3A, MRPL10, GDH, LCAD, Ku70, LKB1, NDUFA9
	SIRT4	12q24.31	mitochondria	IDE, ANT2/3, GDH
	SIRT5	6p23	mitochondria	CPS1, Cytochrome C
	SIRT6	19p13.3	nucleus	NF-κB, CtBP, DNA PK, PARP1, HIF1α
	SIRT7	17q25.3	nucleolus	p53
IV	HDAC11	3p25.2	nucleus/cytoplasm	---

*See text for references.

lates FoxO1 to regulate autophagy [26]. Recently, SIRT6 has been demonstrated to catalyze histone H3K9 and H3K56 deacetylation [27, 28]. SIRT7 promotes tumor progression by deacetylation of H3K18 at the promoters of genes related to tumor repression [29], which reflects site specificity for class III HDAC enzymatic activity on histones. SIRT3, a mitochondira-localized sirtuin, is a master regulator of reactive oxidative species (ROS) scavenge and mitochondrial integrity [30]. The regulatory network of sirtuins has been recently reviewed elsewhere [31], and it will not be intensively discussed in this review. Class IV HDAC (HDAC11) contains nine deacetylase motifs shared by both class I and II HDACs [32].

Based on the characterization of HDACs and their unique functions in cancer development, scientists have developed many HDAC inhibitors as a therapeutic strategy to cure cancer. HDAC inhibitors are a group of chemical compounds which reverse the activities of HDACs and are emerging as a class of promising anti-tumor drugs for the treatment of various solid and hematological malignancies [10]. HDAC inhibitors can be categorized into hydroxamic acids, cyclic tetrapeptides, benzamides, aliphatic acids and electrophilic ketones according to their chemical structures (Table 2). These agents exert their inhibitory activities via distinct mechanisms with varying efficiency and specificity. For example, trichostatin A (TSA), the first demonstrated broad-spectrum HDAC inhibitor, functions in a Zn^{2+}-dependent manner [33, 34]. Suberoylanilide hydroxamic acid (SAHA), the first FDA-approved HDAC inhibitor to treat cancer, is a synthetic pan-HDAC inhibitor [35]. Depsipeptide (FK228) shows potent inhibitory activity towards HDAC1 and 2 [36]. Entinostat (MS-275), a benzamide HDAC inhibitor, shows stronger activity towards HDAC1 than HDAC3 and HDAC8 [37]. Butyrate, an aliphatic acid HDAC inhibitor, was found to have anti-tumor activities before HDAC was known to be the target [38]. At least two HDAC inhibitors, SAHA and depsipeptide, have been approved for the treatment of cancer, while many others are under intensive clinical trials [39, 40]. HDAC inhibitors are also implicated in other diseases, such as central nervous system diseases and inflammatory diseases [41, 42].

Biological functions of HDACs and HDAC inhibitors

HDACs are key modulators of chromatin environment, which is the platform of all chromatin-based processes, such as transcription (Fig.1). Here we provide an insight into the roles of HDACs in regulating cellular properties and the underlying mechanisms based on accumulating evidence.

Table 2. HDAC inhibitors currently under clinical investigation. Various HDAC inhibitors are classified into several groups according to their structural patterns. While most inhibitors are at different stages of clinical trials, SAHA and depsipeptide have been approved by FDA for cancer chemotherapeutic intervention.

Group	Compound	HDAC target[1]	Current state
Hydroxamic acid	Vorinostat (SAHA, Zolinza)	class I, II, IV	FDA approved
	Panobinostat (LBH589)	class I, II, IV	phase III CT
	Belinostat (PXD101)	class I, II, IV	phase II CT
	Abexinostat (PCI24781)	class I, II	phase II CT
	Resminostat (RAS2410)	class I, II	phase II CT
	Givinostat (ITF2357)	class I, II	phase II CT
	Dacinostat (LAQ824, NVP-LAQ824)	class I, II	phase I CT
	Pracinostat (SB939)	class I, II	phase II CT
Cyclic tetrapeptide	Romidepsin (Depsipeptide, FK228)	HDAC1, 2	FDA approved
	Apicidin	HDAC2, 3	Phase II CT
	Trapoxin A	HDAC1, 4, 11	ND[2]
Benzamide	Mocetinostat (MGCD0103)	HDAC1, 2, 11	phase II CT
	Entinostat (MS-275, SNDX-275)	HDAC1, 9, 11	phase II CT
	Rocilinostat (ACY-1215)	HDAC6	phase II CT
Aliphatic acid	Valproic acid (VPA)	class I	phase III CT
	Pivanex (AN-9)	ND	phase II CT
	Butyrate	class I, IIa	Phase II CT
Electrophilic ketone	Trifluorometchylketone	ND	ND

*Data partially from www.clinicaltrials.gov, www.cancer.gov. Also see text for references.

[1]Relatively stronger inhibitory effects and lower IC50 dosage than the unlisted HDACs.

[2]ND: no data.

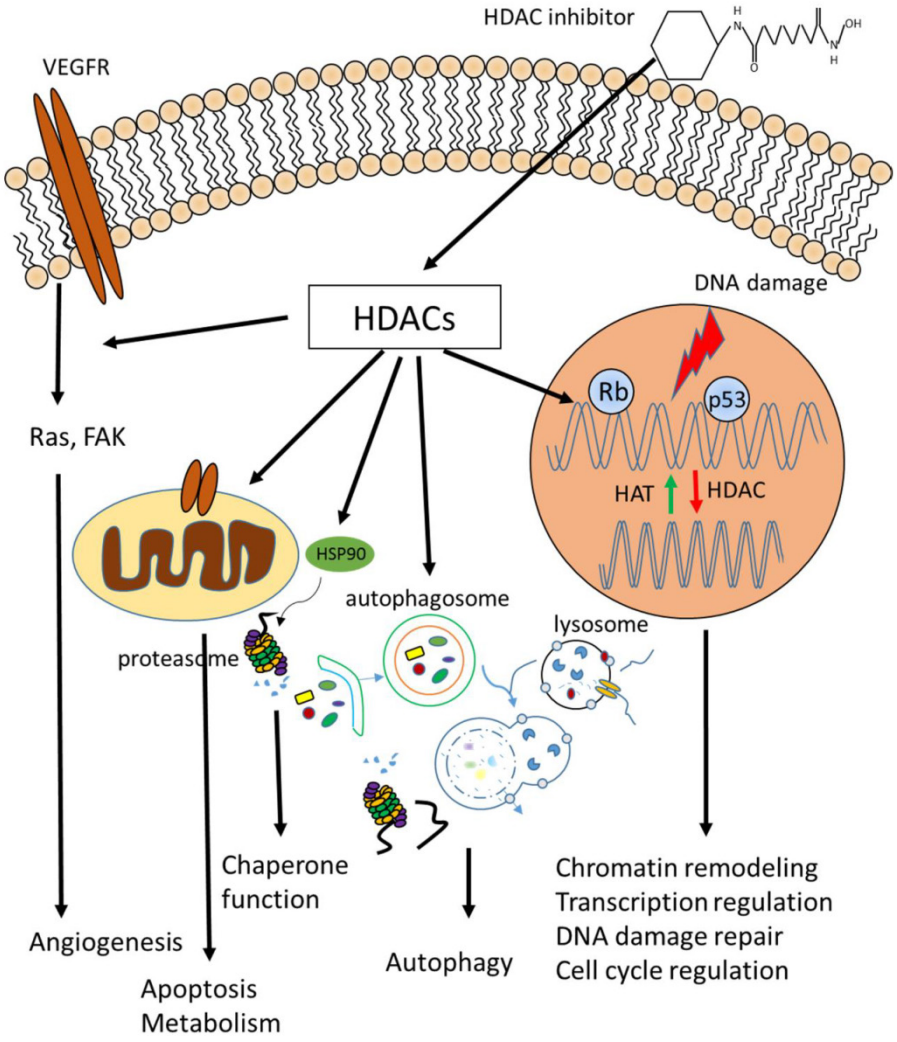

Figure 1. Biological functions of HDACs. Cellular functions regulated by HDACs, including apoptosis, DNA damage repair, cell cycle control, autophagy, metabolism, ageing and many others which are not listed above.

Transcriptional regulation

HDACs have been generally considered to be transcriptional repressive. On the one hand, HDACs stabilize and condense chromosome, making it less available for transcription factors. On the other hand, HDACs act as components of co-repressor complexes. This is convinced by the facts that HDACs are found to cooperate with transcription repressors, and HDAC inhibitors induce expression of certain genes [43, 44]. For example, HDAC1 forms a complex with an adaptor protein RbAp48 and a transcriptional co-repressor mSin3A to mediate gene repression in a deacetylase-dependent manner, and inhibition of HDAC activity blocks this repression [45]. Depsipeptide induces expression of p21 by induction of acetylation of p53 at lysine 373/382 [46]. It is later discovered that depsipeptide actives silenced genes such as p16 and GATA4 by inhibiting CpG and H3K9 methylation on their promoters [47]. HDACs also regulate gene expression by modulating the activity of transcription factors, such as p53 and NF-κB [48-50]. However, accumulated evidences show that HDAC inhibitors can repress certain genes. For example, TSA and sodium butyrate downregulate the expression of Bcl-2 in lymphoma cells [51]. An updated view of HDAC's role in transcriptional regulation is that HDACs function as dynamic transcriptional regulators [52, 53]. Genome-wide screen shows that HDACs are both enriched on the promoters of active and repressive genes [53]. The expression of hundreds of genes are altered when treated with TSA or SAHA using microarray analysis [54]. Although only a small proportion of genes respond to HDAC inhibitor treatment, the role of acetylation and deacetylation as transcriptional regulators should not be underestimated.

Apoptosis

Apoptosis is the mechanism by which cells undergo programmed cell death upon intrinsic or ex-

trinsic stimuli. This process is modulated by plenty of complex proteins including HDACs (Fig.2). Deletion of HDAC1 suppresses transforming growth factor-β1 (TGF-β1)-induced apoptosis and overexpression of HDAC1 enhances it. HDAC2, however, functions as a negative regulator of TGF-β1-induced apoptosis [55]. Targeted deletion of both HDAC1 and HDAC2 leads to increased apoptosis initiated by p53 hyperacetylation [56]. Caspase-dependent cleavage of HDAC3 leads to its accumulation in the cytoplasm and transcriptional activation of its target pro-apoptotic genes [57]. HDAC4 is also a cleavage target of caspase and the caspase-generated fragment of HDAC4 induces release of mitochondrial cytochrome c and apoptosis [58]. Runt-related transcription factor 2 (RUNX2) restrains the pro-apoptotic activity of p53 in association with HDAC6 [59]. HDAC inhibitors are potent inducers of apoptosis and pro- or anti-apoptotic factors are its modulated targets. Butyrate and TSA induce apoptosis with an activation of caspase-3 or upregulation of pro-apoptotic protein Bad in tumor cells [60, 61]. Ku70 is a DNA repair protein which represses apoptosis by sequestering Bax in the cytosol. Treatment of TSA or nicotinamide, a sirtuin inhibitor, causes Ku70 acetylation and its inability to bind and sequester Bax, resulting in apoptosis [62]. Another pro-apoptotic protein, Bak, is also upregulted by butyrate through increased binding of Sp3 [63]. Depsipeptide activates Bim to initiate apoptosis by acetylation of FoxO1 [64]. Anti-apoptotic proteins are downregulated in response to HDAC inhibitors. For example, TSA and butyrate suppress the expression of Bcl-2 [51]. HDAC inhibitors also increase the expression of Fas and Fas ligand (FasL) to induce apoptosis in various tumor cells, resulting in cytochrome c release and activation of caspase-9 and caspase-3 [65, 66]. The pro-apoptotic effects of HDAC inhibitors seem to be p53-independent because no significant difference of apoptotic cell death is observed in cells expressing wild-type or mutant p53 [67, 68]. However, there are also studies showing that HDAC inhibitors induce apoptosis in a p53-dependent way [69, 70], indicating that HDAC inhibitors may function via both pathways, namely p53-dependent and p53-independent pathways to regulate apoptotic process.

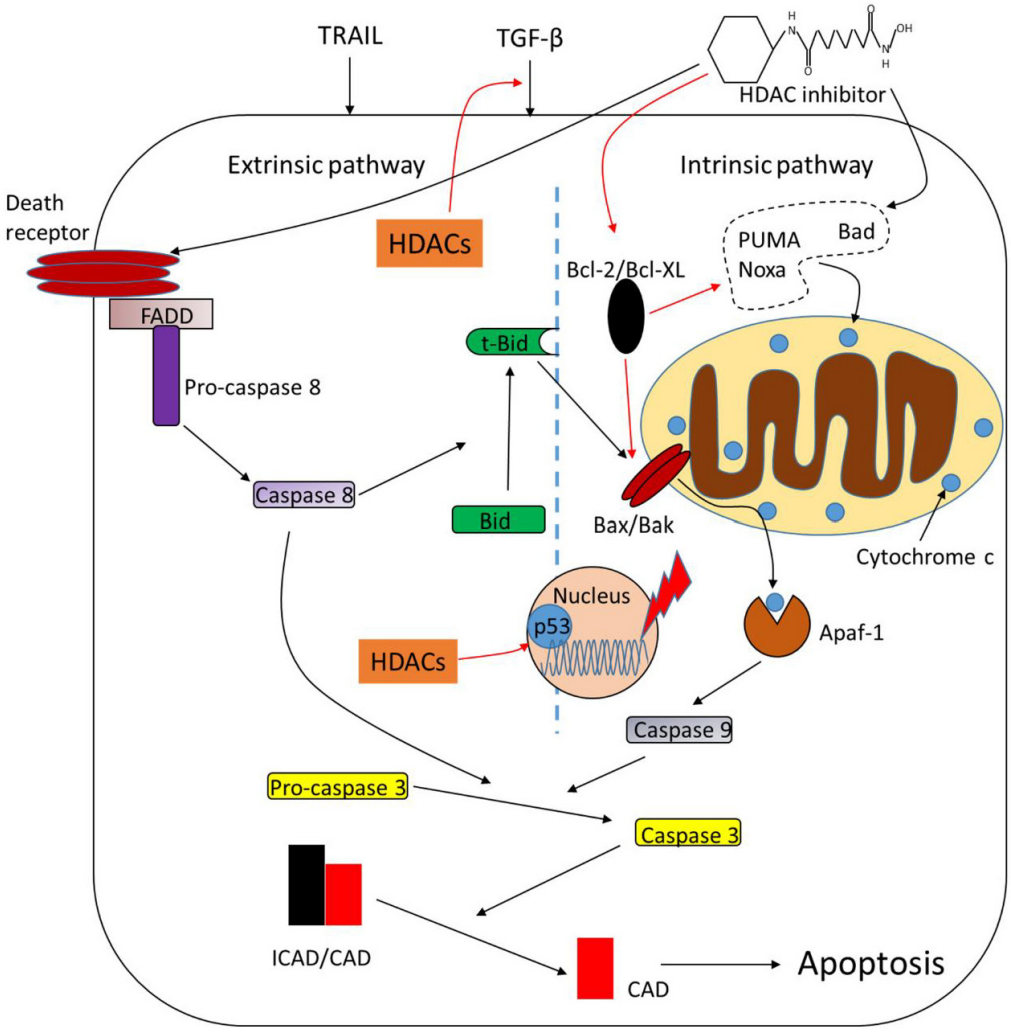

Figure 2. Role of HDACs in regulating apoptosis. HDACs function as apoptotic repressors, while treatment of HDAC inhibitors upregulate pro-apoptotic proteins such as Bad and downregulate anti-apoptotic proteins such as Bcl-2. HDAC inhibitors promote tumor cell apoptosis through both intrinsic and extrinsic pathways. *Arrows in black mean 'promote' while the red ones mean 'inhibit', the same goes with all the figures below.

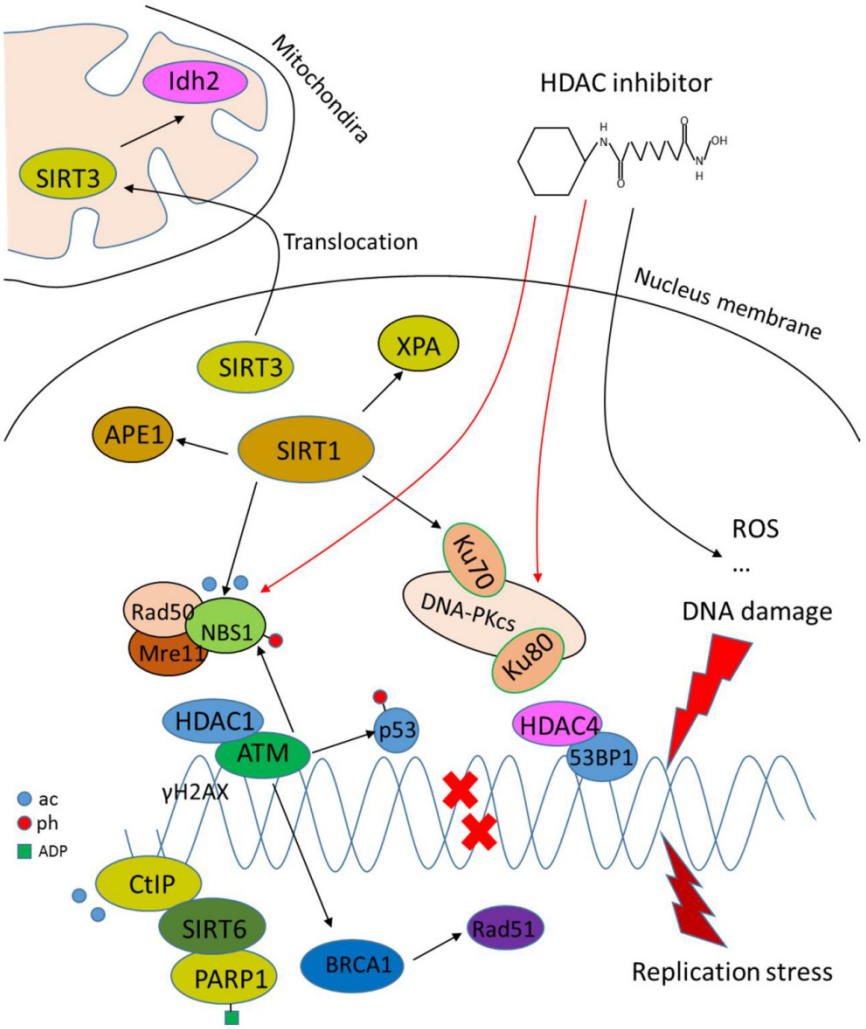

Figure 3. Role of HDACs in regulating DNA damage repair. HDACs interact with DNA damage responsive factors and promote DNA damage repair. HDAC inhibitors induce DNA damage through generation of ROS or suppression of DNA repair proteins.

DNA damage repair

DNA damage repair involves chromatin remodeling and employs various factors. HDACs play crucial roles in this process since HDACs are core regulators of chromatin remodeling and the acetylation level of DNA damage-related proteins (Fig.3). For example, ataxia telangiectasia mutated (ATM), an early DNA damage sensor, interacts with HDAC1 and their interplay is increased upon ionizing radiation [71]. Further evidence demonstrates that HDAC1 and HDAC2 are rapidly recruited to DNA-damage sites to promote H3K56 hypoacetylation. Depletion of HDAC1 and HDAC2 renders tumor cells more sensitive to DNA-damaging agents and dampens the ability of DNA double strand break repair [72]. HDAC3 has also been implicated in DNA damage repair [73, 74]. Deletion of HDAC3 significantly reduces DNA damage repair ability [74]. HDAC4 is recruited to DNA damage-induced foci and colocalizes with homologous recombination (HR) repair protein 53BP1 following DNA damage [75]. Inhibition of HDAC6 with isoform-specific inhibitor promotes cell death by induction of DNA damage [76]. Knockdown or inhibition of HDAC9 and HDAC10 shows impaired HR repair capacity [77]. Sirtuins are also related to DNA damage repair. SIRT1 interacts and deacetylates several DNA proteins, such as Ku70, NBS1, APE1 and XPA [78-81], reflecting a role of SIRT1 in non-homologous end joining (NHEJ) and HR repair following double strand break damage, and base excision repair and nucleotide excision repair pathway following single-strand DNA damage. Recent studies show that SIRT1 is a chromatin environment regulator at promoters of the housekeeping genes investigated, and inhibition of SIRT1 restores the transcription of genes repressed [82], suggesting an active role of SIRT1 in genomic stability regulation. SIRT6 promotes DNA end resection through deacetylation of C-terminal binding protein-interacting protein (CtIP), while depletion of SIRT6 impairs recruitment of repair proteins at DNA damage sites, leading to reduced HR repair [83]. Later studies show that SIRT6 is recruited to DNA damage sites and stimulates NHEJ and HR repair through mono-ADP-ribosylation of PARP1 on Lys 521, thereby activating PARP1 and enhancing DNA damage repair [84]. SIRT3 is found to translocate to mitochondria from nucleus upon cellular stress, deacetylating and activating Idh2, which is a key regulator of intermediary metabolism and energy production. This leads to an increase in NADPH level and ratio of reduced-to-oxidized glutathione, thus protecting cells from oxidative damage [85, 86].

While HDACs are generally shown to potentiate DNA damage repair capacity, inhibitors that target HDACs are potent inducers of DNA damage in transformed cells. For example, depsipeptide induces DNA damage through generation of ROS [87]. LBH589, a novel broad-spectrum HDAC inhibitor, induces the expression of DNA damage repair genes including FANCG, FoxO3A and GADD45 [88].

HDAC inhibitor PCI-24781 suppresses DNA damage repair by decreasing RAD51 [89]. SAHA induces DNA damage by inhibiting DNA damage proteins such as RAD50 and MRE11 in cancer cells [90]. In a word, HDACs facilitate the DNA damage repair process by either loosening the chromatin for other factors to function or recruiting DNA repair proteins to damage sites, and HDAC inhibitors are thus considered to target HDACs to induce DNA damage.

Cell cycle control

Cell cycle progression involves a series of events that lead to replication and division of cellular contents. Duplication of nuclear materials and information needs overall chromatin reconstruction, in which HDACs are key regulators. Other cell cycle regulators, such as cyclins and CDKs, are also regulated by HDACs. Genomewide profiling in yeast reveals that HDACs function as regulators of genes involved in cell cycle [91]. The cell cycle transcription factor E2F plays a major role during G1/S transition. Retiboblastoma protein (Rb) interacts with HDAC1 to repress E2F-mediated transcription of cell cycle proteins such as cyclin E, while TSA treatment abrogates this repression [92-94]. However, later studies shows that the cell cycle inhibitory function of Rb is not necessarily dependent on the activity of HDACs [95, 96]. TSA fails to restore cyclin A and it has no significant effect on cell cycle distribution [95], indicating that HDACs may employ other mechanisms instead of Rb-mediated transcriptional repression to influence cell cycle. HDAC1 knockdown can arrest cell cycle at either G1 phase or G2/M transition [97]. Combined genetic inactivation of HDAC1 and HDAC2 causes a senescence-like G1 arrest in a p53-independent manner [98]. HDAC3 is later proved to a master regulator of mitosis. HDAC3-dependent deacetylation of histone H3 creates a hypoacetylated environment for kinase Aurora B [99]. Phosphorylation of H3S10 by Aurora B is essential for the onset of mitosis. LBH589 induces G2/M arrest through degradation of Aurora A and B [100]. HDAC3 knockdown results in spindle assembly checkpoint activation and sister chromatid dissociation, which may be related to centromeric H3K4 acetylation and loss of dimethylation at the same site [101]. Collapsed mitotic spindle is also observed in HDAC3 knockdown cells and TSA treatment results in similar defects [102]. HDAC inhibition by trapoxin arrests cell cycle at G1 and G2 phase by increasing the transcription of cyclin E [103]. TSA induces G0/G1 arrest in human liver cancer cells [104]. TSA also induces delay of G2/M transition in a transcription-dependent way [105]. Inhibition of HDAC activity can also lead to dysregulation of mitotic checkpoint activation [106]. In summary, HDACs are important elements in cell cycle regulatory machinery and HDAC inhibitors alter cell cycle progress by interacting with cell cycle regulators, resulting in cell cycle arrest at certain phases and detention of proliferation.

Autophagy

Autophagy is the process of self-degradation of unnecessary or dysfunctional cellular components through the lysosomal machinery, which ensures cell survival during starvation [107]. Autophagy has a close relationship with cancer and its role in cancer development is still under hot debate [108, 109]. It has gradually come to a common understanding that autophagy is regulated by acetylation. SAHA and butyrate can induce caspase-independent autophagic cell death [110]. SAHA activates autophagy through inactivation of mammalian target of rapamycin (mTOR) [111]. Genetic knockdown or inhibition of HDAC1 significantly induces autophagy [112]. Later in Huntington's disease model, it is reported that mutant huntington protein (Htt) is deacetylated by HDAC1 and inhibition of HDAC1 facilitates mutant Htt clearance through induction of autophagy [113]. HDAC inhibition-induced autophagy is also related to DNA damage repair [11]. However, some other studies come to an opposite conclusion. HDAC6, a microtubule-associated deacetylase, is also involved in autophagy. HDAC6 provides a link between autophagy and ubiquitin-proteasome system, and expression of HDAC6 is sufficient to induce autophagy [114]. It is later confirmed that HDAC6 is not required for autophagy activation but the fusion of autophagosomes to lysosomes [115]. It is recently found out that HDAC10 promotes autophagy-mediated survival, while inhibition of HDAC10 disrupts autophagy associated with increased sensitization to chemotherapeutic drugs in cancer cells [116]. These data indicates that HDACs and HDAC inhibitors may have pleiotropic roles in the regulation of autophagy. Sirtuins also participate in regulating autophagy. Acetylation of FoxO1 by dissociation from SIRT2 is essential for the induction of autophagy [26, 117]. SIRT1 forms a complex with critical regulators of the autophagy machinery, such as autophagy genes (Atg)5, Atg7 and Atg8 [118]. The role of HDACs in either promoting or restraining autophagy are still under investigation, and evidence supporting both sides is accumulated. The therapeutic effects of HDAC inhibitors may be explained by the dual role of autophagy in disease progress.

Metabolism and senescence

Acetylation of either histones or non-histone proteins has been demonstrated to be tightly corre-

lated with metabolism (Fig.4) [119, 120]. The role of sirtuins in metabolism has been well characterized and reviewed elsewhere [23, 121, 122]. Classical HDACs, however, are also related to metabolism regulation. AMP-activated protein kinase (AMPK), a critical sensor and regulator of metabolism, is demonstrated to be regulated by HDAC1. HDAC1 interacts and deacetylates AMPK to increase its interaction with liver kinase B1 (LKB1), resulting in AMPK phosphorylation and activation [123]. HDAC2 transgenic mice shows increased hypertrophy associated with glycogen synthase kinase 3β (Gsk3β) inactivation, while chemical inhibition of Gsk3β activity renders HDAC2-deficient cells more sensitive to hypertrophic stimuli, suggesting a role cof HDAC2 in metabolism [124]. Genetic deletion of HDAC3 is associated with alteration of genes involved in fatty acid metabolism, glucose utilization and oxidative phosphorylation possibly through the activation of peroxisome proliferator-activated receptor-γ (PPARγ) or mTOR signaling [125-127].

Searching of the GenAge Database reveals an amount of 288 genes analyzed for the possible association with human longevity, including HDAC1, 2, 3 and SIRT1, 3, 6 and 7. Researches show that deletion of Rpd3, homologous to class I HDAC, leads to life-span extension in yeast and calorie restriction in Drosophila, while deletion of Hda1, homologous to class II HDAC, does not [128, 129]. Butyrate and TSA treatment reduce life span of human diploid fibroblasts [130]. Whether class I HDAC is involved in human ageing, however, is still unknown. Sirtuins have been demonstrated to be a master regulator in senescence [122, 131, 132]. Sir2 mutant impairs life span extension, while an increased level of Sir2 gives rise to it in *S. cerevisiae* [133]. Moderate overexpression of SIRT1 suppresses the expression of senescence markers and retards ageing [134]. Increased SIRT1 level also attenuates age-dependent transcriptional changes [134, 135]. Sirtinol, a SIRT1-specific inhibitor, augments the activity of senescence-associated β-galactosidase to induce senescence-like growth arrest [136]. SIRT6-deficient mice show age-related degenerative phenotypes [137]. Other studies reveal a possible role of SIRT3 and SIRT7 in the regulation of senescence [29, 30]. The regulatory role of HDACs are largely explained by their interaction with other regulators of metabolism and senescence, while HDAC inhibitors impede this interaction.

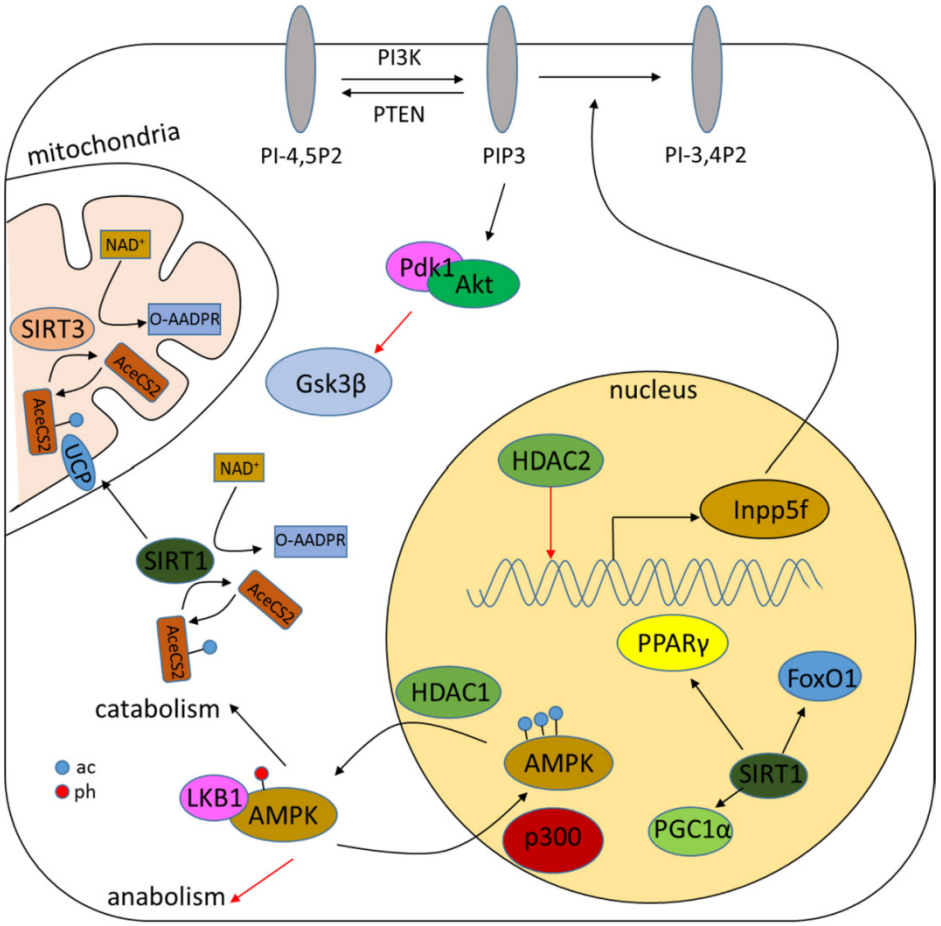

Figure 4. Role of HDACs in regulating metabolism. HDACs regulate metabolism mainly through modulation of the acetylation level of metabolic proteins such as AMPK. Sirtuins can also regulate the NAD^+/NADH ratio.

Chaperone function

The molecular chaperone heat shock protein 90 (HSP90) facilitates structural maturation of its client proteins, which is critical for their functions and activities. HDAC6 deacetylates HSP90, while inactivation of HDAC6 results in HSP90 hyperacetylation and loss of activity in tumor cell lines [138, 139]. Inhibition or silencing of HDAC6 and HDAC10 reduces the binding of HSP90 to vascular endothelial growth factor receptor (VEGFR)1 and VEGFR2 with an increasing binding of HSP70, leading to a reduction of VEGFR1 and VEGFR2 in a pro-

teasome-dependent pathway [140]. Depsipeptide inactivates HSP90 and disassociate RUNX1-ETO fusion oncoprotein with HSP90 to induce its proteasomal degradation [141]. The binding of mutant p53 and acetylated HSP90 is also reduced when treated with depsipeptide, leading to accelerated p53 depletion [67]. LBH589 promotes the extracellular export of HSP90α in a deacetylation-dependent manner. Extracellular HSP90α interacts with matrix metalloproteinase-2 (MMP-2) and promotes tumor cell invasion [142]. MS-275 induces HSP90 acetylation and blocks its interaction with fms-like tyrosine kinase 3 (FLT3) in leukemia cells, resulting in ubiquitination and subsequent proteasomal degradation of FLT3 [143]. Another HSP family chaperone, HSP70, is also modulated by HDAC inhibitors. Valproic acid (VPA) induces HSP70 through promoter hyperacetylation [144]. Chaperone function is critical in the stability of numerous proteins, including some important oncoproteins and tumor suppressors. HDAC inhibitors inactivate and interfere the binding of HSP90 to these client proteins, leading to their instability and degradation.

Angiogenesis

Angiogenesis is a fundamental step in the metastasis of tumors to provide nutrients for cancer overgrowth. Overexpression of HDAC1 stimulates angiogenesis, while HDAC inhibitors block angiogenesis by downregulating angiogenesis-stimulating factor hypoxia inducible factor 1α (HIF-1α) and vascular endothelial growth [145, 146]. HDAC4 and HDAC6 interact with HIF-1α directly. Inhibition or knockdown of HDAC4 and HDAC6 reduces HIF-1α level [147]. TSA and SAHA potently inhibit VEGF-induced angiogenesis by repressing VEGF-induced expression of VEGFRs or upregulating VEGF competitor [148]. Nitric oxide (NO) is a key second messenger in angiogenesis signaling. TSA also reduces NO level through downregulation of endothelial nitric oxide synthase (eNOS) [149]. HDAC7 forms a complex with HIF-1α and translocates to the nucleus to enhance the transcriptional activity of HIF-1α upon hypoxia insults, resulting in an increased level of HIF-1α target genes, including VEGF [150]. Another study shows cardiovascular abnormalities in HDAC7 mutant mice and HDAC7 represses the expression of MMP10 by interacting and repressing the activity of MEF2 [151]. Genetic silencing of HDAC7 decreases endothelial cell migration and alters the formation of capillary-like structures partly by induction of platelet-derived growth factor-B (PDGF-B) and its β receptor [152]. Depsipeptide also inhibits tumor neovascularization, possibly by suppressing pro-angiogenic factors such as EGFR or inducing anti-angiogenic factors such as von Hippel Lindau [153]. LBH589 reduces angiogenesis through inhibition of endothelial tube formation and the expression of VEGF-signaling factors, such as angiopoietin-2, survivin and CXCR4 [154]. In general, HDAC inhibitors repress neovascularization by inhibiting positive factors of angiogenesis or altering angiogenesis signaling pathway.

Other functions

In addition to the mechanisms listed above that may lead to cancer cell lethality, other pathways also contribute to the anti-tumor capacities of HDAC inhibitors. Accumulation of ROS in malignant cells is an important mechanism of HDAC inhibitor-mediated cell death [155, 156]. HDAC inhibitors alter the expression of ROS-modulated proteins such as thioredoxin-binding protein 2 and thioredoxin, the latter of which is a principal antioxidant scavenger of ROS [157]. HDAC6 is a regulatory component of aggresome, which is an intracellular storage unit of misfolded proteins [158]. Targeted inhibition of HDAC6 leads to repression of the aggresome pathway and causes autophagic cell death in tumor cells [159]. HDACs function as regulators of cytoskeletal proteins, such as tubulin and actin to modulate cell motility and migration. HDAC6 interacts and deacetylates tubulin [160, 161]. Overexpression of HDAC6 promotes cell mobility, but deletion of HDAC6 has no effect on normal development and disease progression in mice model [162, 163]. Inhibition of HDAC activity by TSA suppresses TGF-β1-induced renal tubular epithelial-to-mesenchymal transition (EMT) through upregulation of E-cadherin and downregulation of collagen type I [164], suggesting a role of HDACs in the regulation of EMT process, which is critical in the development of various diseases including cancer. Later studies confirm the role of HDACs in EMT regulation of tumor cells [165, 166]. The function spectrum of HDACs and HDAC inhibitors are rapidly expanding. In-depth studies are proceeding to explore functions and activities beyond our knowledge. Anyway, treatment of HDAC inhibitors results in an anti-tumor profile.

Clinical implications of HDAC inhibitors in cancer treatment

HDAC inhibitors are under intensive investigation for cancer therapy. Tens of structurally disparate HDAC inhibitors are under different stages of clinical trials while some of them have shown promising effects for various cancers, especially in hematological malignancies (Table 2). Depsipeptide, first identified as a natural produrg, induces a complete or partial

clinical response in cutaneous T cell lymphoma (CTCL) patients [167]. SAHA can induce growth arrest and kill various types of cancer cells with little cytotoxicity to normal cells [168]. Both depsipeptide and SAHA have now been approved to manage advanced CTCL [40]. LBH589, another potent hydroxamic acid-based HDAC inhibitor, shows clinical effects in CTCL patients with a rapid change of the expression of genes involved in apoptosis, immune regulation and angiogenesis [169]. HDAC inhibitors have also been implicated in the treatment of solid tumors such as VPA [170]. VPA used as a single agent or in combination with other cytotoxic drugs may have positive effects across several different types of cancer including lung, breast, pancreas and prostate cancer [170, 171].

A major barrier for the development of HDAC inhibitors is that most of them have side effects because of their cytotoxicity to normal host cells although they are much more favorable than many other traditional cancer chemotherapeutics [40]. Common adverse effects including nausea, vomiting, anorexia, and fatigue are mostly manageable. However, some specific HDAC inhibitors may cause serious adverse events. For example, depsipeptide has been proved to be associated with life-threatening cardiac arrhythmia in cancer patients [172]. The different cytotoxicity profiles of HDAC inhibitors compared to conventional chemotherapeutic agents have led to the abortion of a large number of clinical trials [39]. This arouses considerable doubts about the clinical safety of HDAC inhibitors. Combination with other therapies or development of more specific inhibitors may be a way out as many combination trials are being pursued [173]. Second-generation HDAC inhibitors with more specific inhibitory selectivity and greater potency are under clinical development. Although HDAC inhibitors have shown potent anti-tumor activities when used alone, experimental studies and clinical trials support the synergistic combination of HDAC inhibitors and other anti-cancer therapies [173]. For example, doxorubicin (DAC), a DNA demethylating drug and cancer chemotherapeutic agent, enhances HDAC inhibitor-induced tumor cell apoptosis [68]. Later studies demonstrate that DAC also cooperates with depsipeptide to inhibit tumor cell proliferation in a methylation-independent way [174].

Another issue concerning cancer treatment is resistance to HDAC inhibitors. The underlying mechanisms are not well elucidated and a better understanding will surely improve their clinical efficacy [175]. Previous studies have proposed the mechanisms of drug efflux, altered expression and mutations of HDACs, protection from oxidative stress by antioxidants and altered expression of apoptosis-related proteins as determinants of resistance [175].

Concluding remarks and perspective

Over the past few decades, the growing understanding of epigenetics has led to a rapid expansion of our knowledge on its role in cancer. The execution of HDAC functions depends largely on the modifications of non-histone substrates although it has been widely accepted that histone modifications play an important role in this process. However, this also raises the question whether the modification of non-histone proteins is epigenetic or not. Epigenetics has been defined as the study of inheritable phenotypic changes that do not involve the alteration of DNA sequences. While protein is the effector of the genetic information flow, its role in epigenetic regulation cannot be ignored. By this token, the modifications of non-histone proteins can be at least considered as part of the epigenetic regulatory network. The contrary roles of HATs and HDACs in regulating the acetylation levels of histones and non-histone proteins make it possible that acetyl groups can be added or erased whenever necessary. The consistence of epigenome including acetylation patterns indicates that the acetylation of non-histone proteins may be inheritable along generations. This motivates scientists to find and characterize the determinants of the transmission of acetylation patterns. The roles of HDACs, especially sirtuins, in regulating non-histone proteins have arouse intense interests and should be explored more deeply. Further elucidation of this network would provide insights into the mechanisms of a great number of cellular processes.

The established network of HDACs in the regulation of cellular behaviors under physiological conditions or upon external insults makes HDACs critical modulators of disorders such as cancer and inflammatory diseases. The development of HDAC inhibitors as anti-tumor drugs opens a completely new window for cancer therapeutics. While the underlying mechanisms are under intensive investigation, there are quite a few questions that need to be answered regarding to the clinical application of HDAC inhibitors. How come that HDAC inhibitors specifically target tumor cells, while normal non-malignant cells remained largely unaltered? Although there has been some clues to explain this selectivity, further research is still required to elucidate this issue. Meanwhile, the specificity of HDAC inhibitors in cancer therapy should also be questioned. Clinical responses diversify between different HDAC inhibitors which target the same HDACs. To address this problem, more isoform-specific HDAC inhibitors may be needed. Along with the selectivity and specificity is the re-

sistance to HDAC inhibitors. How and why does the tumor cells respond to HDAC inhibitors differently remain poorly understood, and the mechanistic basis of the resistance needs to be illuminated for the development of better HDAC inhibitors.

Epigenetic therapy has emerged as a hot issue in cancer research. Inhibitors of deregulated chromatin modifiers are now under different stages of investigation [1]. Inhibitors of HDACs, DNA-methyltransferases (DNMTs), and JAK2 have shown great therapeutic benefits while a large number of epigenetic drugs are in development. Although there is still a long way to go in fighting cancer, epigenetic therapy may provide a bright future for us to follow.

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Abbreviation

AMPK, AMP-activated protein kinase; EMT, epithelial-to-mesenchymal transition; eNOS, endothelial nitric oxide synthase; FK228, depsipeptide; FoxO, forkhead box protein O; HAT, histone acetyltransferase; HDAC, histone deacetylase; HIF-1α, hypoxia inducible factor-1α; HR, homologous recombination; HSP, heat shock protein; KMT, histone methyltransferase; KDM, histone demethylase; MS-275, entinostat; NAD^+, nicotinamide adenine dinucleotide; NF-κB, nuclear factor-κB; NHEJ, non-homologous end joining; NO, nitric oxide; Rb, retinoblastoma protein; ROS, reactive oxygen species; SIRT, sirtuin; TSA, trichostatin A; SAHA, suberoylanilide hydroxamic acid; TGF-β1, transforming growth factor-β1; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; VPA, valproic acid

Competing Interests

No competing interest exists.

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