Review Article

Histone Deacetylases and Histone Deacetylase Inhibitors: Molecular Mechanisms of Action in Various Cancers

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Abstract

Epigenetic modifications such as histone modification play an important role in tumorigenesis. There are several evidence that histone deacetylases (HDACs) play a key role in cancer induction and progression by histone deacetylation. Besides, histone acetylation is being accessed as a therapeutic target because of its role in regulating gene expression. HDAC inhibitors (HDACIs) are a family of synthetic and natural compounds that differ in their target specificities and activities. They affect markedly cancer cells, inducing cell differentiation, cell cycle arrest and cell death, reduction of angiogenesis, and modulation of the immune system. Here, we summarize the mechanisms of HDACs and the HDACIs in several cancers. An online search of different sources such as PubMed, ISI, and Scopus was performed to find available data on mechanisms and pathways of HDACs and HDACIs in different cancers. The result indicated that HDACs induce cancer through multiple mechanisms in various tissues. This effect can be inhibited by HDACIs which affect cancer cell by different pathways such as cell differentiation, cell cycle arrest, and cell death. In conclusion, these findings indicate that the HDACs play a major role in carcinogenesis through various pathways, and HDACIs can inhibit HDAC activity by multiple mechanisms resulting in cell cycle arrest, cell growth inhibition, and apoptosis induction.

Keywords: *Cancer, histone deacetylase, histone deacetylase inhibitors*

Introduction

Epigenetic modifications, such as histone acetylation and deoxyribonucleic acid (DNA) methylation, play an important role in the tumorigenesis and cancer progression. Among them, the importance of histone deacetylase (HDAC)-mediated epigenetic processes in the carcinogenesis has been highlighted. As a reversible posttranslational modification, histone acetylation plays a major and fundamental role in chromatin structure/function and regulating eukaryotic gene expression. Histone acetylation is regulated by opposing activities of HDACs and histone acetyltransferases (HATs) [Figure 1].[1] HDACs are enzymes that remove an acetyl group from histones and are divided into two major families, including zinc-dependent and NADD-dependent families.[2] Bacteria have HDAC- and HAT-like proteins, which may act as enzymes regulating acetylation of nonhistone proteins.[3] The mammalian HDACs can deacetylate histones and a variety of nonhistone cellular proteins.[4] HATs catalyze the transfer of an acetyl group from acetyl coenzyme A (acetyl-CoA) to lysine residues in proteins.[5] The balance between histone acetylation and deacetylation is often damaged in cancer, resulting in silenced expressions of tumor suppressor genes. HDACs can be divided into two distinct families depending on the pathway and molecular mechanisms of removing the acetyl group and also divided into four classes based on the homology to their yeast analogs.[6] HDAC inhibitors (HDACIs) are a family of synthetic and natural compounds that differ in their target specificities and activities. Based on their structure, they are classified into four main groups including cyclic peptides, hydroxamic acids, benzamides, and short-chain fatty acids.[7] Indeed, HDACIs affect markedly cancer cells, inducing cell differentiation, cell cycle arrest, cell death, reduction of angiogenesis, and modulation of the immune system.[8] Previously, we evaluated the effect of HDACIs and DNA demethylating agents on hepatocellular

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carcinoma (HCC) which encouraged us to write this article.[9-11] The current review mainly focuses on the action of HDAC and the effect of HDACIs in several cancers.

Histone Modification

Histone acetylation relaxes the chromatin structure by which facilitates gene transcription and expression. The overall level of histone acetylation is controlled by a balance between two opposing enzyme groups including HATs and HDACs. HATs catalyze the transfer of the acetyl group to the ε-amino group of lysine side chains utilizing acetyl-CoA as a common acetyl donor by which abolishes the positive charge of lysine resulting in eliminates the electrostatic bond between DNA and histone [Figure 2].[12,13] HATs, therefore, open the local region of chromatin structure, rendering it more accessible to transcription factors. HDACs remove the acetyl residues and restore the positive charge of lysine. Consequently, HDACs are associated with condensed chromatin structures and transcriptional repression [Figure 3].[14,15]

Histone Deacetylases

Histone deacetylases and cancer

According to recent studies, HDAC enzyme dysfunctions and altered acetylation levels are linked to numerous cancers.[16] It has been reported that the expression of HDACs is increased in solid and hematological cancers. HDACs play an important role in the epigenetic regulation of gene transcription and expression through their effects on the chromatin compaction state. Recently, HDACs have become promising therapeutic targets because of their potential to reverse the aberrant epigenetic states associated with carcinogenesis. The overexpression of HDACs have been reported in many cancers.[5]

Histone deacetylases classification

In human, 18 HDAC enzymes have been classified into four groups based on their homology with yeast HDACs. Classes I, II, and IV require a zinc molecule, as a cofactor, in their active site and are inhibited by Zn^{2+}-binding HDACIs. Class III HDACs have similar structural homologous to the yeast Sir2 protein and require NAD + as a cofactor instead of Zn^{2+}. Therefore, Zn^{2+}-binding HDACIs cannot inhibit them. The role of sirtuins in carcinogenesis is still debatable, because some SIRTs have dual roles as tumor suppressors and oncoproteins.[17]

Class I HDACs include HDACs 1, 2, 3, and 8 and are similar to yeast Rpd3. They are the most abundant HDACs localized in the nucleus. Class II HDACs can shuttle between the nucleus and the cytoplasm and are similar to yeast Hda1 and larger than the other two classes of HDACs, based on sequence and domain organization, Class II HDACs can be further subdivided. Class IIa (HDACs 4, 5, 7, and 9) contains a highly conserved C-terminal deacetylase catalytic domain homologous to Hda1. Class IIb (HDACs 6 and 8) is characterized by having two deacetylase domains.[18,19] HDAC11 is the sole member of class IV. The classification and structures of HDACs are indicated in Figure 4.[20]

Histone Acetylases Classification

HATs contain two major types including nuclear (A-type) and cytoplasmic (B-type). The type-A HATs contains various family classified into at least three separate groups based on functional similarities and structural homologies, including GCN5-related N-acetyltransferases family, Moz-Ybf2/Sas3-Sas2-Tip60 family, and the p300/CREB-binding protein (CBP/CREBBP) family.[21] Type-B HATs is highly conserved and share sequence homology with scHat1. This type acetylates newly synthesized histone H4 at K5 and K12 which is important for deposition of the histones, after which the marks are removed.[22,23]

Mechanism of the Action of Histone Deacetylase Inhibitors

HDACIs belong to a diverse family of both natural and synthetic compounds which can be divided into four groups including aliphatic fatty acids, hydroximic acid, benzamides, and cyclic peptides. Several agents are characterized for their potential as HDACIs, first of which identified was n-butyrate, responsible for the accumulation of hyper acetylated histone inside the nucleus. Subsequently, trapoxin A and trichostatin A (TSA) were found to be irreversible and reversible inhibitors of HDACs, respectively. HDACIs increase the level of histone acetylation and the molecular mechanism for this effect is associated with the inhibition of HDAC activity.[24] HDACs have multiple mechanisms and many different cellular and target proteins, including proteins that are involved in cancer progression, apoptosis, cell cycle control, angiogenesis, and cell invasion. Thus, HDACIs exert multiple mechanisms of action such as activation of the apoptotic pathway, cell

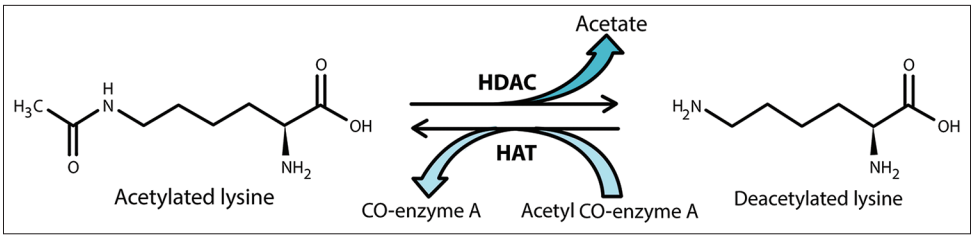

Figure 1: Acetylation and deacetylation reactions of lysine catalyzed by histone acetyltransferases and histone deacetylases

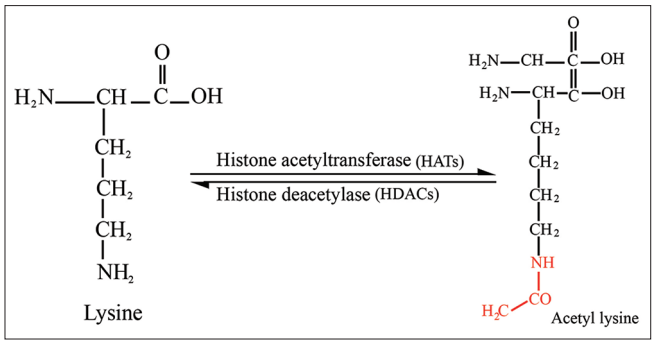

Figure 2: Histone acetylation at the N-terminus lysine by histone acetyltransferases and histone deacetylation by histone deacetylases

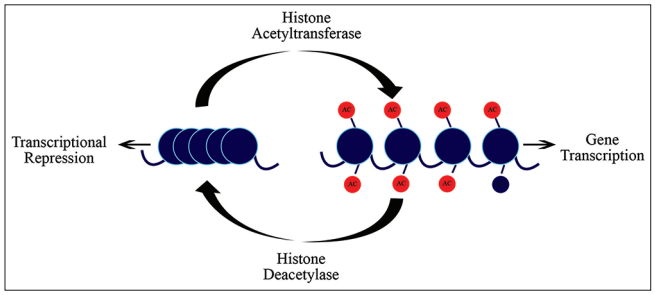

Figure 3: Histone acetylation converts chromatin to an open state, it is regulated by the histone acetyltransferase (HAC). Histone deacetylation is regulated by the histone deacetylase which converts chromatin structure to a condensed or transcriptionally repressive state

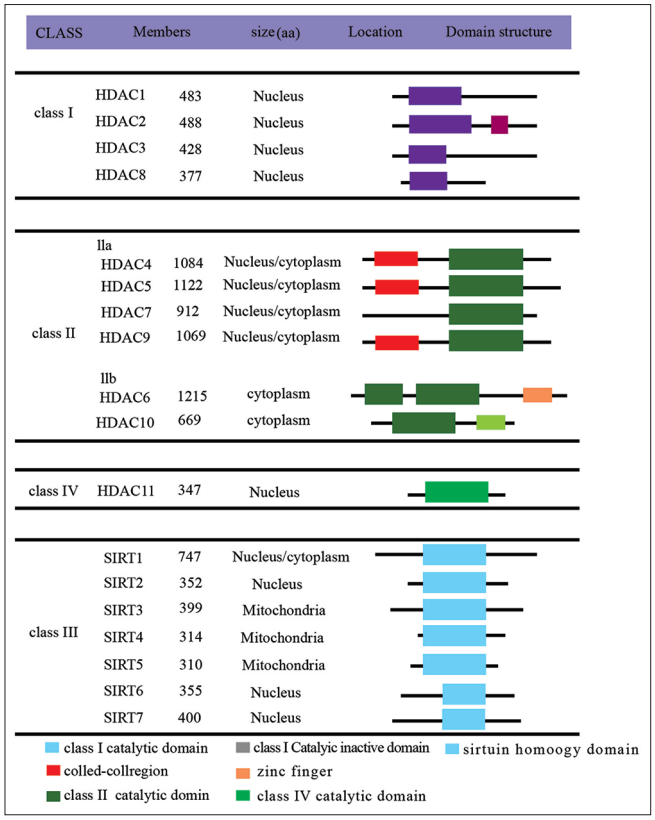

Figure 4: Classification, structures, and cellular localization of Zn^{2+}-dependent histone deacetylase isoforms

cycle arrest, apoptotic induction occurs via extrinsic (death receptor) or intrinsic (mitochondrial) pathways, both of which lead to caspase activation and cell death induction. HDACIs can induce cell cycle arrest at G1/S or G2/M transition, resulting in differentiation and/or apoptosis. They increase CDK inhibitor p21WAF1/CIP1 expression leads to cell cycle arrest at G1/S.[25] Together, multiple pathways, by which HDACIs act upon cancer cell are indicated in Figure 5.[26] Chemical structure of several HDACIs has been indicated in Figure 6.

Histone Deacetylases, Histone Deacetylase Inhibitors and Urogenital Cancer

Renal cancer

The high expression of class I HDAC isoforms 1 and 2 and low the expression of HDAC3 have been shown in renal cell carcinoma (RCC). These differences in the expression patterns suggest difference regulatory pathways.[27] Experimental studies have indicated that the HDACI MS-275 alone and in combination with interleukin-2 have an antitumor effect *in vivo* in RCC. The effect is associated with a decreased number of T regulatory cells and the increased antitumor cytotoxicity by splenocytes. The MS-275 has antitumor activity in a human RCC of T-cells (CD4+ CD25+ Foxp3+) that have been associated with self-reactive T-cells suppression.[28] The HDACI MS-275 can reactivate epigenetic silencing of retinoic acid receptor B2 (RARb2) in a human RCC model and has greater antitumor activity in combination with 13-cis-retinoic acid compared with single component.[29] *In vitro* and *in vivo* studies have shown that HDACI LBH589 has the potent anticancer effect on renal cancer cells. This agent induces G2-M arrest and cell apoptosis of renal cancer via degradation of Aurora A and B kinases by HDAC3 and HDAC6 inhibition.[30]

Bladder cancer

High expression levels of HDAC-1 and HDAC-2 have been reported in bladder cancer. Similarly, overexpression of HDAC-1 to HDAC-3 has been reported in this cancer.[31] Expression array data from another study has been shown the overexpression of HDAC-1 in bladder cancer compared to normal bladder tissue.[32] Clinical studies have indicated a high level of HDAC1 mRNA expression in human bladder cancer specimens. The immunohistochemical study has shown that HDAC1 is expressed in the cytoplasm and nucleus in the bladder specimens.[33]

The potential efficacy of HDACI TSA and sodium butyrate (NaB) against bladder cancer cells has been reported. Experimental studies have indicated that TSA inhibits the growth of BIU-87 bladder cancer cells through cell cycle arrest in G1 phase and induces apoptosis. This pathway is controlled by protein p21WAF1, since increased expression of this gene has been reported in TSA-treated cells. It should be noted that p21WAF1 is one of the most commonly induced genes by HDACIs such as

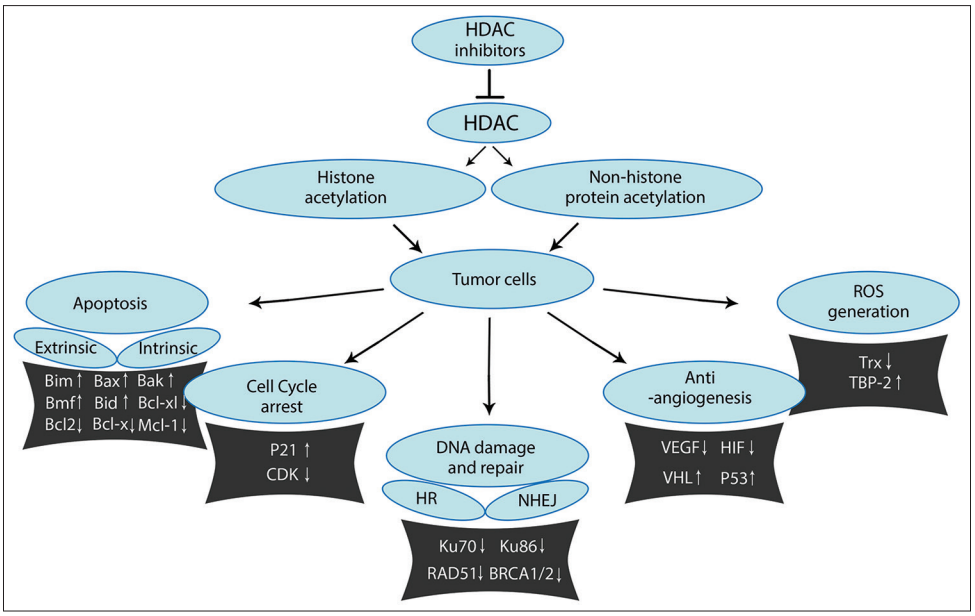

Figure 5: Multiple antitumor pathways activated by histone deacetylase inhibitors. Extrinsic and intrinsic refer to two apoptosis pathways, and homologous recombination and nonhomologous end joining refer to two double strand breaks (DBS) repair pathways

suberoylanilide hydroxamic acid (SAHA), TSA, and sodium butyrate.[34,35] Experimental studies have been demonstrated the potential preventive efficacy of valproic acid (VPA) on N-butyl-N-(4-hydroxybutyl) nitrosamine (BBN) in bladder cancer.[36,37] VPA-induced inhibition can be attributed to increased levels of the cyclin-dependent kinase inhibitor p21 WAF1, which can lead to the arrest of cells in the G1 phase.[38]

Prostate cancer

Prostate cancer has been reported as the second most frequently diagnosed cancer, and the third most common cause of cancer-related death in men. The cancer is a heterogeneous disease, the etiology of which appears to be related to a complex range of risk factors, such as genetic factors and epigenetic modifications. HDAC upregulation has been established in most human cancers.[39] The overexpression of various Class I and Class II HDACs in PC-3, DU145, and LNCaP human prostate cancer cell lines have been indicated. All HDAC isoforms are presented in prostate cancer at various levels. HDAC1 protein is abundantly presented in normal and malignant epithelial cell of the prostate tissue. HDAC5 and HDAC8 have not been detected in prostate tissues.[40] Expression of the Class I HDAC in the epithelial and stromal cells, and the prominent cytosolic distribution of HDAC8 in epithelial cells suggest that the various HDAC isoforms may play an important role in the prostate cancer induction and progression. The other studies have shown strong expression of HDAC1, HDAC2, and HDAC3 in the prostate cancer and the expression of HDAC2 as a highly significant prognostic value. HDAC1 expression is increased in premalignant and malignant lesions. HDAC4 is predominantly localized in the cytoplasm of benign prostate hyperplasia cells and primary prostate cancer cells.[41]

HDACIs induce dose-dependent inhibition of Class I or Class II HDACs leading to G1 or G2 cell cycle. Some HDACIs increase Ku70 acetylation, a crucial agent of the DNA repair machinery, resulted in decreased DNA-binding affinity.[42] Some compounds are potentially effective for both chemoprevention and cancer therapy.[43] HDACIs selectively reactivate tumor suppressor genes, a therapeutic effect that is not induced by traditional chemotherapy. Five classes of HDACIs have been recognized. The response of prostate cancer cells to HDACIs is not uniform, as shown in Table 1.[44]

Histone Deacetylases, Histone Deacetylase Inhibitors, and Reproductive Cancer

Ovarian cancer

It has been reported that Class I HDACs (HDAC 1, 2, and 3) promote ovarian cancer induction and progression. The overexpression of this class play a critical role in ovarian cancer[45] and increases gradually from a benign state to borderline, and malignant ovarian tumors. The expression level of Class I HDAC is markedly different in various ovarian cancer subtypes and the most positive in mucinous subtypes, followed by high-grade serous, clear cell, and endometrioid subtypes. Strongly tumor cell proliferation exhibits increased Class I HDAC expression which is an independent risk factor for poor malignant ovarian tumor prognosis.[46] The specific mechanisms of Class I HDACs in the ovarian carcinogenesis is the suppression of the promoter region of RGS2.[47] RGS2 is a regulator of G-protein signaling 2 and an inhibitor

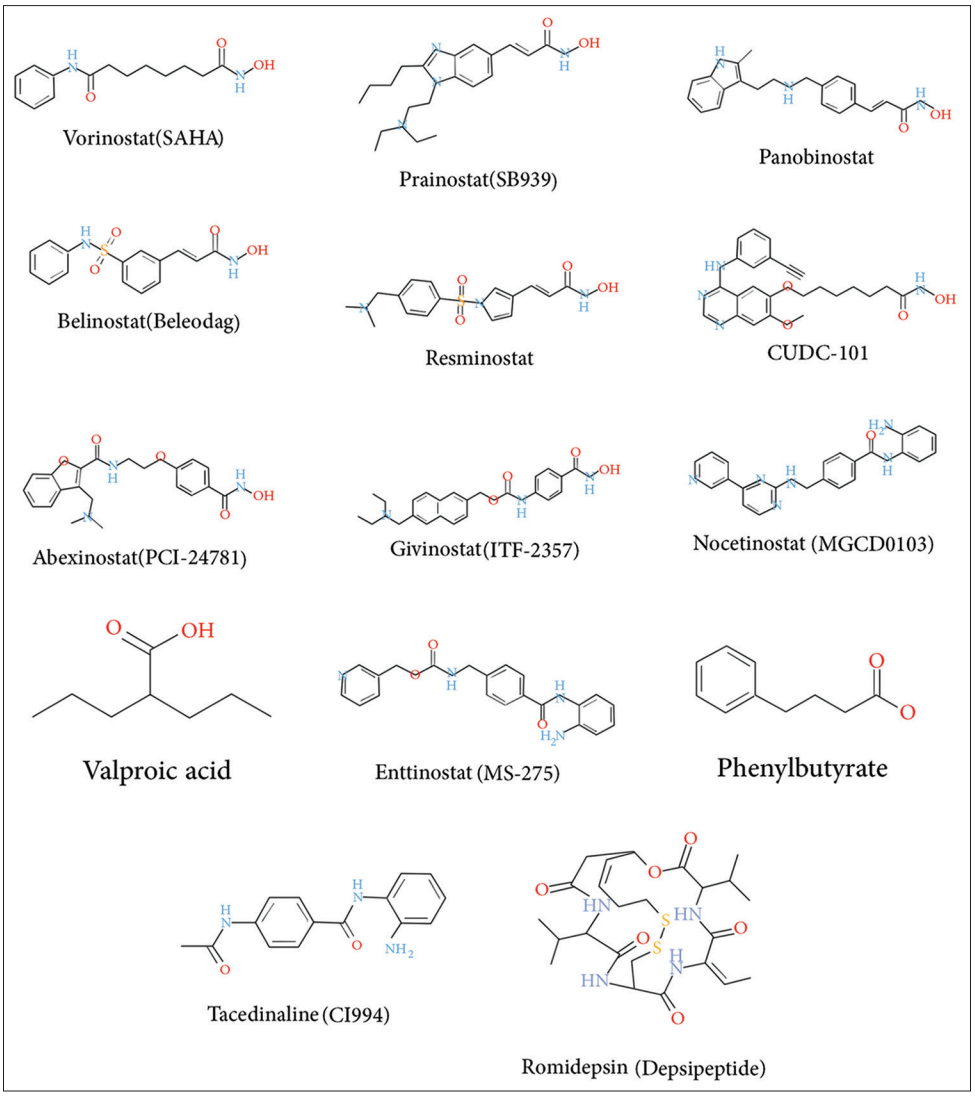

Figure 6: Chemical structure of several histone deacetylase inhibitors

of G-protein coupled receptors through accelerating the deactivation of heterotrimeric G-proteins. It has been reported that HDAC1 enhances cell proliferation via Cyclin A promotion. In ovarian epithelial cancer cells, HDAC2 remodels chromatin structure in response to platinum-based chemical therapies. HDAC3 facilitates cell migration by suppressing the E-cadherin expression.[48] HDACIs have been reported to decrease cancer cell proliferation, induce apoptosis, and promote cell differentiation. A wide variety of agents that can function as HDACIs include organic hydroxamic acids, short-chain fatty acids, benzamides, cyclic tetrapeptides, and sulfonamides.[49] Of the current HDACIs, three have been tested in ovarian cancer including VPA, SAHA, and romidepsin. The other HDACIs have also recently indicated for the potential treatment of ovarian cancer including M344 and TSA. The M344 is specific for HDAC6 and promotes cell growth inhibition, cell cycle arrest, and cellular apoptosis[50] and also TSA specifically inhibits Class I and II mammalian HDAC families, resulting in increases p73 gene expression and promote Bax-dependent apoptosis in cisplatin-resistant ovarian cancer cells.[51] The other investigators have reported the effects of a wide array of HDACIs (VPA, SAHA, TSA, and NaB) on OVCAR-3, SK-OV-3, TOV-21G, TOV-112D, OV-90, OVCA429, OVCA420, OVCA432, and OVCA433, nine ovarian cell lines.[52] The mechanism of HDACIs has been depicted in Figure 7.[53]

Endometrial cancer

Endometrial cancer is the seventh most common carcinoma among women worldwide. Strong HDAC1 protein expression has been reported with poor prognosis of endometrial carcinoma.[46] Overexpression of HDAC2 has been shown in this cancer too.[54] Several studies have indicated the proapoptotic or the antiproliferative effects of HDACIs on endometrial cancer cells. In endometrial cancer cells, HDACIs markedly increase the expression level of E-cadherin exhibit antiproliferative activity in these cancer cells. They can alter the degree of the acetylation of nonhistone effector molecules by which increase or

Table 1: Several histone deacetylase inhibitors studied in prostate cancer

Name	Cell lines/animal models	Fate of cancerous cells
KD5170	PC3 (*in vivo* and *in vitro*)	Inhibition of cell proliferation, tumor growth inhibition, and apoptosis
Sodium butyrate	LNCaP, PC-3	Apoptosis, cell growth inhibition, cell cycle arrest, and cell differentiation
R306465	DU145, PC-3	cell growth inhibition
OSU-HDAC42	PC3 xenograft and TRAMP mice	Tumor growth inhibition, cell differentiation
Valproic acid	PC3, LNCaP, DU145, xenograft	Cell and tumor growth inhibition, apoptosis
LBH589	PC3, mice model	Inhibition of tumor angiogenesis
Trichostatin A	LNCaP, PC-3	Apoptosis, cell growth inhibition
(S)-HDAC-42	PC-3	Apoptosis, tumor xenografts' growth suppression
MS-275	DU145, PC-3, LNCaP, TRAMP	Inhibition of xenografts' growth, cell death
SAHA or vorinostat	DU145, LNCaP, PC-3	Apoptosis, growth arrest
Phenylhexyl isothiocyanate	LNCaP	Cell cycle arrest, cell apoptosis
FK228	PC-3, DU145 xenograft	Inhibition of cell proliferation, tumor growth inhibition
SFN	PC-3, xenograft	Cell cycle arrest, apoptosis
Pyroxamide	CWR22 xenograft	Cell growth inhibition
Apicidin	PC-3-M	Cell growth and cell proliferation inhibition
Phenyl butyrate	PC-3, DU145, LNCaP	Cell apoptosis
LAQ824	LNCaP	Cell apoptosis and cell growth inhibition

SAHA: Suberoylanilide hydroxamic acid, SFN: Sulforaphane, HDAC: Histone deacetylase, TRAMP: Transgenic adenocarcinoma of mouse prostate (TRAMP), LNCaP: Prostate cancer cell line LNCaP

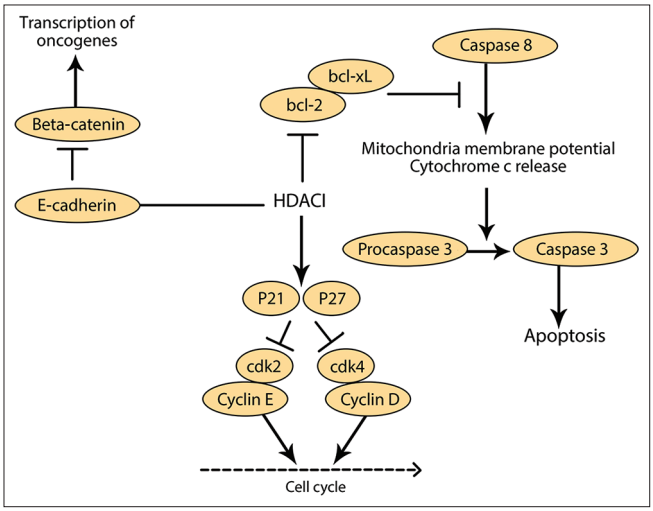

Figure 7: The mechanism of histone deacetylase inhibitorsHDACIs against ovarian cancer

decrease the transcription of genes such E2F1, EKLF, FEN 1, ACTR, cMyb, GATA, NFκB, PCNA, HNF-4, HSP90, Runx, SF1 Sp3, Ku70, p53, RB, STAT, TFIIE, TCF, YY1, and so forth.[55] Different classes of HDACIs studied in endometrial cancer have been shown in Table 2.[56]

Cervical cancer

The expression of HDAC6 has been demonstrated in different cell lines of cervical cancer such as HeLa, A549, HCT11, K562, and MDAMB 231. There is no significant change in the expression of HDAC6 in between HeLa, HEK 293 T, and HCT11 cell lines, when compared to K562, A549, and MDA-MB 231. Whereas, the overexpression of HDAC8 has been reported in HeLa, HCT11, A549, and MDA-MB 231.[57] A positive correlation between histone H3 acetylation and the tumor suppressor expression RARb2 and E-cadherin has been reported in cervical squamous cell carcinoma specimens. Recently, the studies have indicated that the combination of local histone deacetylation and CpG island methylation results in the strong epigenetic silence of E-cadherin and RARb2. Besides, a direct correlation between RARb2 and E-cadherin expression has been shown in cervical cancer.[58] Other investigators have demonstrated that HDAC1 and 2 are overexpressed in cervical cancer. The suppression of HDAC2 resulting in apoptosis induction is associated with an increased p53-independent expression of p21Cip1/WAF1.[59]

Cervical cancer is the second most frequent cancer in women. Recently, significant interest in epigenetic modifications of tumor suppressor genes has catalyzed the investigation of novel treatment methods using histone HDACIs. HDACs remove the acetyl groups resulting in chromatin compaction and tumor suppressor genes silenced in various malignancies. In cervical cancer, VPA acts as a specific inhibitor of class I HDACs and induces proteaosomal degradation of HDAC2, leading to cell growth arrest *in vitro* and *in vivo*.[60]

Breast cancer

The initiation and progression of breast cancer are secondary to the accumulation of genetic and epigenetic alternations which lead to aberrant cellular function. The more recent studies have reported reversible alterations in histone proteins and DNA which leads to carcinogenesis. Epigenetic alterations including histone deacetylation are prevalent in breast cancers. In this cancer, HDAC1

Table 2: Histone deacetylase inhibitors used in endometrial cancer

HDACI	Cell line
TSA	Ishikawa, HEC-1b, HEC59, KLE, AN3CA, Ark2
SAHA	Ishikawa, HEC-1b, HEC59, KLE, AN3CA
CBHA	Ishikawa, HHUA, HEC-1B
NaB	Ishikawa, HEC-1b, HEC59, KLE, AN3CA
VPA	Ishikawa, HEC-1b, HEC59, KLE, AN3CA, RL95-2
MS-275	Ishikawa, HEC-1b, HHUA, RL95-2, AN3CA, Ark2
M344	Ishikawa
Apicidine	Ishikawa

HDACI: Histone deacetylase inhibitor, TSA: Trichostatin A, SAHA: Suberoylanilide hydroxamic acid, VPA: Valproic acid, CBHA: m-carboxycinnamic acid bis-hydroxamide (CBHA), NaB: Sodium butyrate (NaB)

expression is associated with estrogen receptor (ER) and progesterone receptor (PR) expression, an earlier stage of disease at diagnosis.[61] HDAC6 is more frequently expressed in breast cancer ER and PR-positive.[62] The HDAC family is divided into two groups including zinc-dependent enzymes (Classes I, IIa, IIb, and IV) and zinc-independent enzymes (class III also called sirtuins).[63] Based on their chemical structures, they are divided into four groups, including hydroxamic acids, short-chain fatty acids, cyclic tetrapeptides, and benzamides.[64] Most of the HDACIs have been designed to target primarily the zinc cofactor at the active site of the HDACs and to exhibit their inhibitory effects in the nanomolar or micromolar range. HDACIs inhibit HDAC activity result in ER alpha and PR gene reactivation in ER-negative breast cancer cells.[65] It has been indicated that inhibition of Class III HDAC SIRT1 using a splitomicin or siRNA reactivates silenced SFRP1, SFRP2, CRBP1 genes, and E-cadherin in human breast cancer cells.[66]

Another HDACI vorinostat has been evaluated in several Phase II trials in breast cancer cells, including combination therapy of vorinostat with standard components (for example, paclitaxel), novel targeted therapy (trastuzumab, bevacizumab), and endocrine therapy (tamoxifen). Other HDACIs such as LBH-589 (panobinostat) and MS-275 (entinostat) are in Phase I/II study in combination with other components, such as trastuzumab, in women with metastatic HER2-positive breast cancer.[67]

Histone Deacetylases, Histone Deacetylase Inhibitors, and Gastrointestinal and Associated Glands Cancer

Colon cancer

HDACs alterations are found in many cancers including colorectal cancer (CRC). In colon cancer, the expression of HDAC1, HDAC2, HDAC3, and HDAC8 has been reported.[68] A tumor suppressor gene Rb represses gene expression by modulating the chromatin architecture. This gene recruits HDAC to E2F and cooperates with HDAC1 to suppress E2F regulated promoter of genes encoding cyclin E as a cell cycle protein. HDAC1 removes the highly charged acetyl groups from core histones, preventing transcription factor from accessing to DNA.[69] The role of HDAC1, HDAC2, HDAC3, HDAC5, and HDAC7 upregulation has been demonstrated by other investigators in human CRC.

Furthermore, HDAC2 upregulation has been reported as the earliest events in CRC.

The universality of HDAC2 upregulation suggests that HDAC2 upregulation may serve as a CRC biomarker.[70] HDACI SAHA can reduce the expression of active glucose transporter (SGLT1), and thereby suppressed the glucose uptake of colon cancer cells. Besides, it can induce the dissociation of SP1/CBP/HDAC3 from the regions around epidermal growth factor receptor (EGFR) transcription start site, the region in which the histones became hypoacetylated. Furthermore, SAHA can serve as a single agent to block EGFR and HDAC, two important factors in CRC.[71] Experimental studies have indicated that vorinostat and LBH589 can rapidly induce histone acetylation, cell growth inhibition, and cell cycle arrest in both HCT116 and HT29 colon cancer cells.[72]

Hepatocellular carcinoma

Recent investigations have shown that HDAC1 and HDAC2 play different roles during HCC progression. These enzymes are expressed in HCC, and the expression of both is associated with mortality from HCC. HDAC1 expression is correlated with moderately and poorly differentiated tumors. Another research has demonstrated that high HDAC2 expression is correlated with poor survival in early-stage HCC.[73]

HDAC3 plays an important role in HCC formation. It is expressed in liver cancer stem cells and is required for the self-renewal of these cells. HDAC3 downregulation decreases the expression of stem cell markers, including OCT4, Nanog, and SOX2.[74]

HDAC2 has been reported as an independent predictor of survival in HCC. Overexpression of HDACs 1, 2, 3, and 7 have been reported in primary HCC by Several studies. HDACs 1, 2, and 3 upregulation are highly related to the growth of tumor grades. A high level of HDAC2 is also associated with poor survival in low-grade and early-stage tumors.[73] HDAC activity is suppressed by TSA and sodium butyrate in HCC lead to the inhibition of invasion and metastasis by upregulation of early growth response claudin-3 and gene-1.[75] HDACI sodium butyrate performs its anticancer effect by HDAC4 inhibition on HCC SMMC-7721 and HepG2 cells. The high concentrations of sodium butyrate significantly inhibit the HCC cell growth in various states including apoptosis, cell cycle arrest, and inhibition of cell migration/invasion. Other HDACIs

SAHA and OSU-HDAC42 induce autophagy through downregulation of Akt/mTOR signaling and ER stress response induction in HCC HepG2, Hep3B, and Huh7 cell lines.[76] Preclinical studies have shown that treatment with HDACI belinostat can induce apoptosis in HCC cell lines.[77]

Cholangiocarcinoma

Several HDACIs targeting chromatin remodeling has been approved by the FDA such as vorinostat and romidepsin. These inhibitors have increased therapeutic utility in cholangiocarcinoma (CCA). MS-275 treatment potently inhibits the cell proliferation of EGI-1 and TFK-1 CCA cells by inducing cell cycle arrest and apoptosis.[78] The apoptotic pathway is characterized by activation of caspase-3, downregulation of Bcl-2, and upregulation of Bax. The cell cycle is predominantly arrested at the G_1/S checkpoint, which is associated with the cyclin-dependent kinase inhibitor $p21^{Waf/CIP1}$ induction.[79] It has been shown that HDAC3-specific inhibitor MI192 can inhibit the deacetylase activity of HDAC3 in CCA. Immunochemistry study has been indicated that HDAC3 is upregulated in CCA tissues compared with adjacent normal tissues. Taken together, MI192 targets HDAC3 and induces cell apoptosis in human CCA cells.[80] Several experimental studies have demonstrated that administration of the cisplatin in combination with HDACIs TSA, and SAHA resulted in cell growth inhibition and apoptosis induction in the CCA KKU-100 and KKU-M214 cell lines.[81] The expression of HDAC isoforms HDAC 1 and 2 is upregulated in the CCA HuCCT-1 and TFK-1 cell lines. HDACIs SAHA treatment causes significant cell number decline in three cell lines.[82]

Gallbladder carcinoma

Gallbladder carcinoma is an aggressive disease affecting older people. Unfortunately, it is difficult to detect this cancer in the early stage, because of lacking characteristic signs or symptoms. Another study has indicated that HDAC 1 / 2 is expressed in the nuclei of gallbladder carcinoma cells.[82]

Among HDACIs, SAHA is one of the most advanced in clinical fields as an anticancer drug.[83] SAHA treatment inhibits gallbladder carcinoma cell proliferation. It activates tumor suppressor genes p21 in gallbladder carcinoma cells. Other works have shown that SAHA and TSA reduce gallbladder carcinoma SGC-996 cells viability and arrest the cell cycle at the G1 phase. Furthermore, they promote apoptosis of these cells, downregulate the expression of c-Myc, cyclin D1, and Bmi1, and decrease the phosphorylation of mTOR p70S6K1, AKT, S6, and 4E-BP1.[82] Besides, SAHA treatment induces a significant inhibition of cell viability in gallbladder carcinoma TGBC2TKB cells.[84] Clinical and experimental studies have shown that HDACI PCI-24781 has an inhibitory effect on human gallbladder carcinoma and BK5.erbB2 in mice. This effect is associated with downregulation of erbB2 mRNA and erbB2 protein/activity and upregulation of acetylated tubulin and acetylated histone. Treatment with this agent results in decreased expression of Muc4, an intramembrane ligand for erbB2, in human gallbladder carcinoma cells.[85]

Pancreatic cancer

Pancreatic ductal adenocarcinoma (PDAC) is ranked fourth and fifth to the sixth leading cause of cancer death. It has been demonstrated that HDAC gene expression, particularly HDAC7, could be a possible marker of pancreatic cancer.[86]

Overexpression of class I HDACs, HDAC2, and HDAC7 has been reported in PDAC. The function and expression of individual HDACs in PDAC are shown in Table 3.[86]

TSA and SAHA have been demonstrated to induce apoptosis in human pancreatic adenocarcinoma cell. Other studies have indicated that TSA can synergize with the proteasome inhibitor PS-341 or gemcitabine[87] to induce cell apoptosis in human pancreatic cancer cell lines. Furthermore, HDAC Class I and II inhibitors such as TSA can induce apoptosis in tumor cell lines.[88] Other investigators have reported that Class III HDACis, such as sirtinol and nicotinamide, can induce apoptosis in the pancreatic cancer cells.[89] TSA and SAHA, as HDACIs, can induce apoptosis in pancreatic cancer cell lines IMIM-PC-2, IMIM-PC-1, and RWP-1. TSA and SK-7041both induce apoptosis and G2-M cell cycle arrest in the pancreatic cancer cell lines. They increase H4 histone acetylation and also suppress the expression of the anti-apoptotic proteins Bcl-XL, and Mcl-1 but do not affect either Bcl-2 or the pro-apoptotic Bak and Bax proteins.[90] Apoptotic effect of TSA in PDAC cell lines correlates with overexpression of mRNA expression of the pro-apoptotic BH3-only protein BIM together with

Table 3: Function and expression of individual histone deacetylases in pancreatic ductal adenocarcinoma

HDAC	Function/expression
HDAC1	Coexpression of HDAC1 and HIF-1α correlates with poor prognosis
	Contains a SNAIL recruited repressor complex that controls EMT, E-cadherin expression, and metastasis
HDAC2	Overexpressed, especially in G2 and G3 differentiated PDAC
	Mediates resistance toward DNA-damage induced apoptosis by controlling expression of the pro-apoptotic BH3-only protein NOXA
HDAC3	Contains a SNAIL recruited repressor complex that controls EMT, E-cadherin expression, and metastasis
HDAC6	Reduces efficiency of proteasome inhibitors
HDAC7	Overexpressed in PDAC

PDAC: Pancreatic ductal adenocarcinoma, HDAC: Histone deacetylase, EMT: Epithelial-to-mesenchymal transition, NOXA: NADPH oxidases (Nox) A, SNAIL: a zinc-finger transcription factor

attenuation of the anti-apoptotic BCL2 family members BCLW and BCLXL [Figure 8].[91]

Histone Deacetylases, Histone Deacetylase Inhibitors, and Respiratory System Cancer

Lung cancer

Increased HDAC1 mRNA levels are more common in advanced stages of lung cancer, suggesting a role of HDAC in more aggressive tumors. The patients with lung cancer with high level of HDAC3 have significantly shorter survivals than the patients with low HDAC3 expression.[92] Similarly, it has been reported that overexpression of HDAC1 mRNA or protein expression is closely associated with the differentiation grade of lung cancer.[93] Compared to normal lung cells, lung cancer cells display aberrant histone H4 modification patterns with hypoacetylation of H4K12/H4K16, hyperacetylation of H4K5/H4K8, and loss of H4K20 trimethylation. The modifications of histone H4 is known as a potential biomarker for the detection and therapeutic approaches of lung cancer.[94] Overexpression of HDAC1 appears to be correlated with lung cancer progression and also overexpression of HDAC1 and HDAC3 correlates with a poor prognosis in pulmonary AdC patients. The histological evaluation has been shown the elevation of HDAC3 in SqCC.[95] Epigenetic aberrations involving lung cancer has been shown by many studies. HDACIs TSA and vorinostat both display antitumor activities in nonsmall cell lung cancer (NSCLC).[96] LBH589 is a novel inhibitor of Class I and II HDACs in two human NSCLC cell lines (H23 and H460) by several pathways including Bax, Bak, p53, caspase-3, caspase-8, caspase-9, Bid, and Bad. They repress anti-apoptotic genes such as survivin, Bcl-2, C-FLIP, and NF-jB.[97] It has been reported that HDACI FR901228 effectively inhibits lung cancer cells. In this cancer, FR901228 induce caspase-dependent apoptosis via the mitochondrial pathway rather than the death receptor pathway.[98] Experimental studies have shown that HDACI SAHA alone and in combination with BAY-11-7085 induce significant apoptosis and cell death in five tumorigenic NSCLC cell lines including H157, A549, H358, H460, and H1299.[99] The main classes of HDAIs have been shown in Table 4.

Conclusions

In the past decade, it has been an increasing report in the field of HDACs inhibition by HDACI. Right now, we have extensive studies that have reported the mechanism of HDACs and HDACIs. In the current review, we summarized recent studies on the classification and molecular mechanisms of action of HDACs and HDACIs in several cancers. These findings indicate that the HDACs play a major role in carcinogenesis through various pathways and HDACIs can inhibit HDAC activity by multiple mechanisms resulting in cell cycle arrest, cell growth inhibition, and apoptosis induction. These compounds can upregulate global histone acetylation levels, by which regulate the expression of genes that are involved in diverse biological pathways. The changes in histone acetylation levels at gene promoters tend to correlate with the changes

Table 4: The main classes of epigenetic therapies in lung cancer

Group	Class	Drug
HDAC inhibitors	Alphatic acid	Valproic acid
	Hydroxamic acid	Vorinostat
		Belinostat
		Panobinostat
	Benzamides	Entinostat
	Cyclic peptides	Romidepsin

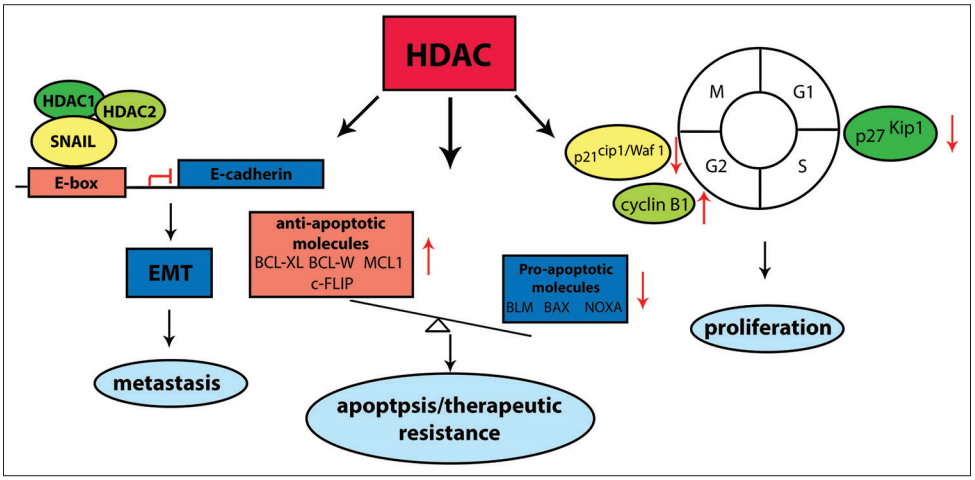

Figure 8: Characterized mechanisms of histone deacetylasesHDACs in pancreatic ductal adenocarcinomaPDAC. Three histone deacetylasesHDAC pathways are demonstrated. Right part: histone deacetylasesHDACs control expression of the CDKI p21Cip1/Waf1 and cyclin B1 to control the G1/S-phase or G2/M-phase or the cell cycle. Middle part: histone deacetylasesHDACs contribute to the imbalanced expression of the anti-apoptotic (BCLw, MCL1, BCLXL, and c-Flip) and pro-apoptotic (BIM, BAX, and NOXA) genes. Left part: histone deacetylases HDAC1 and 2 containing repressor complex is recruited to the E-box of the E-cadherin promoter by the transcription factor SNAIL

in gene expression levels in most cases. Together, a better understanding of the molecular mechanism and pathway of HDACs and HDACIs leads a new window toward treating patients who have cancer.

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Conflicts of interest

There are no conflicts of interest.

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