REVIEW

Novel Chemotherapy using Histone Deacetylase Inhibitors in Cervical Cancer

Noriyuki Takai*, Naoko Kira, Terukazu Ishii, Masakazu Nishida, Kaei Nasu, Hisashi Narahara

Abstract

   Since epigenetic alterations are believed to be involved in the repression of tumor suppressor genes and promotion of tumorigenesis in cervical cancers, novel compounds endowed with a histone deacetylase (HDAC) inhibitory activity are an attractive therapeutic approach. In this review, we discuss the biologic and therapeutic effects of HDAC inhibitors (HDACIs) in treating cervical cancer. HDACIs were able to mediate inhibition of cell growth, cell cycle arrest, apoptosis, and the expression of genes related to the malignant phenotype in a variety of cervical cancer cell lines. Furthermore, HDACIs were able to induce the accumulation of acetylated histones in the chromatin of the p21WAF1 gene in human cervical carcinoma cells. In xenograft models, some HDACIs have demonstrated antitumor activity with only few side effects. Some clinical trials demonstrate that HDACI drugs provide an important class of new mechanism-based therapeutics for cervical cancer. In this review, we discuss the biologic and therapeutic effects of HDACIs in treating cervical cancer, especially focusing on preclinical studies and clinical trials.

Keywords: Histone deacetylase inhibitor - cervical cancer - cell cycle - apoptosis

Introduction

   Cervical cancer is the most common malignant disease of the female reproductive organs, with an approximate morbidity of 500,000 women per year, of whom 80% live in developing countries (Pisani et al., 2002). Due to non-existent or inadequate screening, disease is normally detected at late stage. Improved treatment options for this type of malignancy are highly needed.

   One of the most important mechanisms in chromatin remodeling is the post-translational modification of the N-terminal tails of histones by acetylation, which contributes to a "histone code" determining the activity of target genes (Strahl and Allis, 2000). Transcriptionally silent chromatin is composed of nucleosomes in which the histones have low levels of acetylation on the lysine residues of their amino-terminal tails. Acetylation of histone proteins neutralizes the positive charge on lysine residues and disrupts the nucleosome structure, allowing unfolding of the associated DNA with subsequent access by transcription factors, resulting in changes in gene expression. Acetylation of core nucleosomal histones is regulated by the opposing activities of histone acetyltransferases (HATs) and histone deacetylases (HDACs). HDACs catalyze the removal of acetyl groups on the amino-terminal lysine residues of core nucleosomal histones, and this activity is generally associated with transcriptional repression. HDACs remove the acetyl groups which then induce a positive charge on the histones, and this suppresses gene transcription, including tumor suppressor genes silenced in cancer. Moreover, acetylation of histones facilitates destabilization of DNAnucleosome interaction and renders DNA more accessible to transcription factors (Jenuwein and Allis, 2001). Aberrant recruitment of HDAC activity has been associated with the development of certain human cancers (Bolden et al., 2006). HDAC inhibitors (HDACIs) can inhibit cancer cell growth in vitro and in vivo, revert oncogene-transformed cell morphology, induce apoptosis, and enhance cell differentiation.

   The classes of HDACIs that have been identified are: (a) organic hydroxamic acids (e.g., Trichostatin A (TSA) and suberoylanilide bishydroxamine (SAHA)) (b) short-chain fatty acids (e.g., butyrates and valproic acid (VPA)), (c) benzamides (e.g., MS-275), (d) cyclic tetrapeptides (e.g., trapoxin), and (e) sulfonamide anilides (Takai and Narahara, 2007b) (see Table 1).

   In this review, we discuss the biologic and therapeutic effects of HDACIs in treating cervical cancer, with a special focus on preclinical studies.

Mechanism of Action

   Cervical cancer is the most common malignant disease

Department of Obstetrics and Gynecology, Oita University Faculty of Medicine, Oita, Japan *For correspondence: takai@oita-u.ac.jp

Table 1. Overview of frequently used histone deacetylase inhibitors that are available for clinical and research purposes. (Modified the references of Takai et al., 2010a; Takai et al., 2010b)

Substance group	Derivatives	Isotype
Hydroxamates	Trichostatin A (TSA)	I, II
	Suberoylanilide hydroxamic acid (SAHA, vorinostat)	I, II, IV
	LBH589 (panobinostat)	I, II, IV
	PCI24781 (CRA-024781)	I, IIb
	LAQ824	I, II
	PXD101 (belinostat)	I, II, IV
	ITF2357	I, II
	SB939	Unknown
	JNJ-16241199 (R306465)	I
	m-carboxycinnamic acid bishydroxamide (CBHA)	
	Scriptaid	
	Oxamflatin	
	Pyroxamide	
	CHAPs	
Short chain fatty acids	Butyrate	I, IIa
	Valproate	I, IIa
	AN-9	
	OSU-HDAC42	
Benzamides	MS-275 (entinostat)	1, 2, 3, 9
	MGCD0103	1, 2, 3, 11
	Pimelic diphenylamide	1, 2, 3
	M344	
	N-acetyldinaline (CI-994)	
Cyclic tetrapeptides	Apicidine	I, II
	Trapoxins	
	HC-toxin	
	Chlamydocin	
	Depsipeptide (FR901228 or FK228) (romidepsin)	1, 2, 4, 6
Sulfonamide anilides	2-aminophenyl-3-[4-(4-methyl N-benzenesulfonylamino)-phenyl]-2-propenamide	
Others	BML-210	
	Depudecin	
	NDH-51	
	KD5150	
	Pan-HDACI	

CHAPs, Cyclic hydroxamic acid containing peptides; Class I: HDAC1, -2, -3 and -8; class IIa: HDAC4, -5, -7, and -9; class IIb: HDAC 6, and -10; class III: SIRT1-7; class IV: HDAC11

Histone deacetylases (HDACs) comprise a family of 18 genes that are subdivided into four classes (Haberland et al., 2009). Classes I, II, and IV are referred to as "classical" HDACs and are generally simultaneously targeted by most HDACIs (Table 1). HDACIs were initially discovered on the basis of their ability to reverse the malignant phenotype of transformed cells in culture. It has been shown that HDACIs carry the potential to activate differentiation programs on one hand, while on the other hand they were also shown to inhibit cell proliferation by cell cycle arrest in the G1 and/or G2 phases of the cell cycle and to induce apoptosis in cultured transformed cells. p21WAF1 and p27KIP1 are cyclin-dependent kinase inhibitors (CDKIs) that bind to cyclin-dependent kinase complexes and decrease kinase activity, and may act as key regulators of the G0/G1 accumulation (reviewed in Takai et al., 2004). The p21WAF1 expression in particular is induced by HDACIs in various cell lines. Additionally, this event is associated with both an increase in histone acetylation in the promoter region of the p21WAF1 gene and a selective loss of a specific HDAC enzyme, HDAC1, in the same region (Gui et al., 2004). Therefore, the upregulation of p21WAF1 is a direct consequence of HDACIs on p21WAF1 transcription. In the future, testing should be conducted using p21WAF1-negative cell lines to see if p21WAF1 is absolutely required for HDACI-induced growth arrest. Takai et al. examined the effect of HDACIs on the expression of p21WAF1 and p27KIP1 in cervical cancer cells by Western blot analysis. HDACIs markedly upregulated the level of p21WAF1 and p27KIP1 proteins, which were expressed at negligible levels in the untreated cell lines. Conversely, HDACIs decreased the levels of cyclin A. HDACIs decreased the bcl-2 levels. E-cadherin binds to β-catenin and can act as a tumor suppressor gene; its promoter has CpG islands which are frequently methylated in selected cancers. HDACIs markedly increased the expression level of E-cadherin in cervical cancer cells and exhibited antiproliferative activity in these cells (Takai et al., 2007a). HDACIs have also been shown to generate reactive oxygen species (ROS) in solid tumor and leukemia cells (Ruefli et al., 2001; Rosato et al., 2003; Xu et al., 2006), which may contribute to the mechanism. HDACIs have been shown to inhibit angiogenesis. HDACIs repress the expression of proangiogenic factors such as HIF1α, VEGF, VEGF receptor, endothelial nitric oxide synthase, IL-2 and IL-8 and the induction of antiangiogenic factors, such as p53 and von Hippel-Lindau (reviewed in Marchion and Münster, 2007). HDACIs should not be considered to act solely as enzyme inhibitors of HDACs. A large variety of nonhistone transcription factors and transcriptional co-regulators are known to be modified by acetylation. HDACIs can alter the degree of acetylation nonhistone effector molecules and thereby increase or repress the transcription of genes by this mechanism. Examples include: ACTR, cMyb, E2F1, EKLF, FEN 1, GATA, HNF-4, HSP90, Ku70, NFκB, PCNA, p53, RB, Runx, SF1 Sp3, STAT, TFIIE, TCF, YY1, and so forth, (reviewed in Marchion and Münster, 2007).

Preclinical and Clinical studies of HDACIs

A variety of structurally distinct classes of compounds that inhibit deacetylation of both histone and non-histone proteins have gradually been identified (Table 1) (Takai and Narahara, 2010a; Takai and Narahara, 2010b). Despite the shared capacity of each class of HDACIs to promote histone acetylation, individual HDACIs exert different actions on signal transduction and the induction of differentiation and/or apoptosis. Table 2 shows data from different reports investigating cervical cancer cell lines treated with different classes of HDACIs.

Trichostatin A (TSA)

The trichostatins were initially isolated from Streptomyces hygroscopicus as antifungal antibiotics in 1976 (Tsuji et al., 1976; Tsuji and Kobayashi, 1978).

About 10 years later, TSA and its analogues were discovered to induce cell differentiation of murine erythroleukemia cells and to induce hyperacetylation of histone proteins at nanomolar concentrations. TSA has been extensively studied; it has antitumor activity and can induce differentiation of some cancer cell lines, but its clinical utility has been restricted because of toxic side effects in vivo (Sandor et al., 2000). TSA causes mitotic arrest through the formation of aberrant mitotic spindles, probably by interfering with chromosome attachment, but does not affect mitotic microtubules (Sandor et al., 2000). This effect may account for the higher cytotoxicity of TSA in comparison to other HDACIs (i.e., suberoylanilide bishydroxamine). HDAC inhibition is not believed to have a generalized effect on the genome, but only on the transcription of a small subset of the genome. Differential display analysis of transformed lymphoid cell lines revealed that the expression of only 2%–5% of transcribed genes is changed significantly after treatment with TSA (Van Lint et al., 1996). The effective dose of TSA that inhibited 50% clonal growth (ED50) of the cervical cancer cell lines (CaSki, ME180 and SiHa) was calculated, and ranged between 4.3×10^{-8}M and 9.8×10^{-8}M (Takai et al., 2007a) (Table 2). Furthermore, HeLa, HT3, and C33A cervical cancer cells were treated by combination with TSA and other cytotoxic agent (Finzer et al., 2001; Lin et al., 2009; Darvas et al., 2010). In addition, it is very noteworthy that TSA is able to reduce cutaneous radiation toxicity following radiotherapy (Chung et al., 2004).

Suberoylanilide Bishydroxamine (SAHA, Vorinostat)

Hydroxamic acid type inhibitors make up the largest and broadest group of HDACIs described to date. The inhibition of HDACs by SAHA occurs through a direct interaction with the catalytic site of the enzyme, as shown by X-ray crystallography studies (Finnin et al., 1999). Among the synthetic HDACIs, SAHA is the most advanced candidate as a cancer therapeutic drug, and is under phase I and II clinical trials (Camacho et al., 2007; Modesitt et al., 2008). SAHA has significant antitumor activity against many tumor types at dosages that can be tolerated by patients when administered intravenally and orally (Piekarz and Bates, 2004). Some HDACIs (e.g., TSA and trapoxin) are of limited therapeutic use due to poor bioavailability in vivo and have toxic side effects at high doses. SAHA, however, is relatively safe and non-toxic in vivo. The effective dose of SAHA that inhibited 50% clonal growth (ED50) of the cervical cancer cell lines (CaSki, ME180 and SiHa) was calculated and ranged between 1.0×10^{-6}M and 5.1×10^{-6}M (Takai et al., 2007a) (Table 2). The combination of proteasome inhibitor bortezomib and SAHA shows synergistic killing of HeLa, HT3, and C33A cervical cancer cell lines (Lin et al., 2009). It is remarkable that SAHA as well as M344 and depsipeptide are radiosensitizers in human squamous cell carcinoma cells (Zhang et al., 2004).

PCI24781

PCI-24781is a novel broad spectrum histone deacetylase inhibitor that is currently in phase I clinical trials. Human SiHa cervical carcinoma cells were

Table 2. Data for Endometrial Cancer Cell Lines Treated with Different Classes of HDACIs

HDACI	Cell line	ED50 (M)	Reference
TSA	CaSki	4.3×10^{-8}	Takai et al (2007a)
	ME180	5.1×10^{-8}	Takai et al (2007a)
	SiHa	7.0×10^{-8}	Takai et al (2007a)
	HeLa	3.3×10^{-7}	Darvas et al (2010)
			Finzer et al (2001)
			Lin et al (2009)
	HT3	3.3×10^{-7}	Lin et al (2009)
	C33A	3.3×10^{-7}	Lin et al (2009)
SAHA	CaSki	1.0×10^{-6}	Takai et al (2007a)
	ME180	4.5×10^{-6}	Takai et al (2007a)
	SiHa	5.1×10^{-6}	Takai et al (2007a)
	HeLa	5.0×10^{-5}	Lin et al (2009)
	HT3	5.0×10^{-5}	Lin et al (2009)
	C33A	5.0×10^{-5}	Lin et al (2009)
PCI24781	SiHa	1.0×10^{-5}	Banuelos et al (2007)
NaB	CaSki	2.7×10^{-4}	Takai et al (2007a)
			Decrion-Barthod etal (2010)
	ME180	4.8×10^{-4}	Takai et al (2007a)
	SiHa	9.3×10^{-4}	Takai et al (2007a)
	HeLa	5.0×10^{-3}	Takai et al (2007a)
			Darvas et al (2010)
			Finzer et al (2001)
			Decrion-Barthod etal (2010)
			Park et al (2006)
PB	HeLa	$2{\sim}10 \times 10^{-3}$	Finzer et al (2003)
	CaSki	$2{\sim}10 \times 10^{-3}$	Finzer et al (2003)
	SW756	$2{\sim}10 \times 10^{-3}$	Finzer et al (2003)
VPA	CaSki	3.2×10^{-4}	Takai et al (2007a)
			Sami et al (2008)
	ME180	6.3×10^{-4}	Takai et al (2007a)
	SiHa	7.8×10^{-4}	Takai et al (2007a)
			Sami et al (2008)
	HeLa	5.0×10^{-3}	Sami et al (2008)
			Chávez-Blanco et al (2006)
Apicidine	SiHa	1.0×10^{-6}	Luczak et al (2008)
BML-210	HeLa	1.0×10^{-5}	Borutinskaite et al (2006)

exposed to 0.1 to10 $\times 10^{-6}$M PCI-24781 in vitro for 2 to 20 h before irradiation and 0 to 4 h after irradiation. PCI-24781treatment for 24 h resulted in up to 80% cell kill and depletion of cells in S phase. Toxicity reached maximum levels at a drug concentration of about 1 $\times 10^{-6}$M, and cells in G1 phase at the end of treatment were preferentially spared. A similar dose-modifying factor was observed for SiHa cells exposed for 24 h at 0.1to 3 $\times 10^{-6}$M. Therefore, PCI-24781 acts as a radiation sensitizer (Banuelos et al., 2007).

Butyrates

It was first reported in 1978 that millimolar concentrations of sodium butyrate (NaB) inhibited HDACs in vitro (Candido et al., 1978). NaB is normally present in the human colon as a product of the metabolic degradation of complex carbohydrates by colonic bacteria and regulates the physiological differentiation of colonocytes, suggesting its possible use in the prevention of colorectal cancer and the treatment of premalignant and neoplastic lesions. Butyrate and its derivatives have a long history of safe clinical use in the treatment of inherited and acquired metabolic disorders. Some studies suggest that many of the cellular activities of phenylbutyrate are

more dependent on its butyric acid component than its phenyl group. A recent study by Terao et al. indicated that NaB had a significant growthsuppressing effect on human endometrial and ovarian cancer cells irrespective of their p53 gene status (Terao et al., 2001). NaB, a low-potency HDACI, has been extensively studied; it has antitumor activity and can induce differentiation of some cancer cell lines, but its clinical utility has been restricted by its short half-life (5 minutes), limiting the ability to achieve a therapeutic plasma level. NaB and phenylbutyrate are degraded rapidly after i.v. administration and therefore require high doses exceeding 400 mg/kg/day (Warrell Jr et al., 1998). Furthermore, these compounds are not specific for HDACs as they also inhibit phosphorylation and methylation of proteins as well as DNA methylation (Warrell Jr et al., 1998). The effective dose of Butyrates that inhibited 50% clonal growth (ED50) of the cervical cancer cell lines (CaSki, ME180 and SiHa) has been calculated and ranged between 2.7×10^{-4}M and 5.0×10^{-3} M (Takai et al., 2007a) (Table 2). Many investigators reported NaB and phenylbutyrate block proliferation of human papilloma 18-positive HeLa cervical carcinoma cells by inhibiting the G1 to S transition, which is paralleled by an up-regulation of the cyclin-dependent kinase inhibitors p21 and p27 as well as complete loss of cdk2 activity (Finzer et al., 2001; Finzer et al., 2003; Park et al., 2006; Darvas et al., 2010; Decrion-Barthod et al., 2010).

Valproic Acid (VPA)

Valproic acid, a shortchain fatty acid, has been approved for clinical use in the treatment of epilepsy and is frequently used in clinical trials and for in vitro research based on its HDAC inhibitory effect at comparatively high (millimolar) concentrations (Blaheta et al., 2002). Valproic acid has also been identified as an antiproliferative agent and HDACI (Phiel et al., 2001). Some HDACIs (e.g., TSA and trapoxin) are of limited therapeutic use due to poor bioavailability in vivo as well as toxic side effects at high doses, but VPA is relatively safe and non-toxic in vivo (Takai et al., 2007b). The effective dose of VPA that inhibited 50% clonal growth (ED50) of the cervical cancer cell lines (CaSki, ME180, SiHa and HeLa) has been calculated and ranged between 3.2×10^{-4}M and 7.8×10^{-4} M (Chavez-Blanco et al., 2006; Takai et al., 2007a; Sami et al., 2008) (Table 2).

Encouraging are recent data from a phase I study for metastatic solid tumors in which valproic acid was administered as an IV loading dose followed by five oral doses were administered every 12 hours followed by a dose of epirubicin at day 3. Major responses were observed in all tumor types including in anthracycline failures and in anthracycline-resistant cancers such as melanoma and cervical carcinoma, suggesting that inhibition of HDAC activity may chemosensitize tumor cells (Munster et al., 2005). Use of valproic acid in the form of magnesium valproate was recently reported in a phase I study where 12 newly diagnosed patients with cervical cancer were treated (Chávez-Blanco et al., 2005).

MS-275 (Entinostat)

MS-275 (MS-27-275) is a synthetic novel benzamide which exerts HDAC inhibitory activity and also induces the expression of the cyclin-dependent kinase inhibitor p21WAF1 and gelsolin, and changes the cell cycle distribution (Chapman et al., 1982; Suzuki et al., 1999). MS-275 has shown antiproliferative activity in various in vitro and in vivo human tumor models (Saito et al., 1999; Lee et al., 2001; Takai et al., 2006a). A phase I study of MS-275 revealed that a patient with cervical cancer had a sustained period of 10 months of stable disease (Ryan et al., 2005), supporting the potential activity of this class of drugs for this tumor type.

M344

Synthetic amide analogs were discovered to have a common structure with TSA (Jung et al., 1999). Using an in vitro enzyme inhibition assay of histone deacetylation, Jung et al. demonstrated that M344 is a potent HDACI and an inducer of terminal cell differentiation (Jung et al., 1999). M344 has shown antiproliferative activity in various human cancer cell lines (Takai et al., 2006b). Zhang et al. found that M344 is a radiosensitizer in human squamous cell carcinoma cells (2004).

Apicidin

Cyclic peptide HDACIs can be further divided into two classes: those with an epoxyketone group such as HC-toxin and trapoxin, and those without such a group (apicidin, depsipeptide or FK228). Apicidin is a novel cyclic tetrapeptide with a potent broad spectrum of antiprotozoal activity against Apicomplexan parasites (Darkin-Rattray et al., 1996). Its structure is related to trapoxin, a potent HDACI, and some biological activity, including antiproliferative and toxic effects, have been shown in some cancer cell lines (Han et al., 2000; Ueda et al., 2007).

Employing quantitative real-time PCR and Western blot analysis, apicidin significantly reduced HPV16-E6 and -E7 transcripts and protein levels in SiHa cervical cancer cells. Moreover, apicidin lowered HPV16-E6 and -E7 transcript stability and significantly decreased these transcripts' half-life from approximately 5 h to 2 h and from 6 h to 3 h, respectively. These results from experiments with protein biosynthesis inhibitor suggest the involvement of an RNase and/or mRNA stabilization protein in HPV16-E6 and -E7 transcript stabilization (Luczak and Jagodzinski, 2008).

BML-210

BML-210 is a novel histone deacetylase inhibitor. BML-210 alone or in combination with retinoic acid leads to cell growth inhibition with subsequent apoptosis of HeLa cervical carcinoma cells in a treatment time-dependent manner, and causes a marked increase in the level of p21, anti-apoptotic protein Bcl-2 and phosphorylated p38 MAP kinase (Borutinskaite et al., 2006).

Conclusions

In this review, we summarize recent preclinical and clinical studies on the use of HDACIs, especially in human

cervical cancer cells. Many questions are currently still unanswered with respect to HDACI specificities for definite tumor subtypes and the molecular mechanisms underlying HDACI-induced differentiation, cell cycle arrest and apoptosis. In addition, the regulation mechanisms of the specific gene expression and recruitment of HDAC complex to the specific promoter sites remain still to be determined. Also, it is still unclear to what extent different HDACs exhibit different and potentially overlapping functions, and it is important to distinguish the HDAC specificity of HDACIs for the development of selective therapy on the molecular level. Further work is needed to improve our understanding of why transformed cells are more susceptible to the effect of HDACIs than normal cells. Also, combinations of HDACIs with differentiation-inducing agents, with cytotoxic agents, and even with gene therapy may represent novel therapeutic strategies and new hope for the treatment of cervical cancer.

Acknowledgements

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