European Review for Medical and Pharmacological Sciences 2018; 22: 950-960

Targeting histone deacetylases in endometrial cancer: a paradigm-shifting therapeutic strategy?

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Abstract. – OBJECTIVE: Endometrial cancer is increasingly prevalent in western societies and affects mainly postmenopausal women; notably incidence rates have been rising by 1.9% per year on average since 2005. Although the early-stage endometrial cancer can be effectively managed with surgery, more advanced stages of the disease require multimodality treatment with varying results. In recent years, endometrial cancer has been extensively studied at the molecular level in an attempt to develop effective therapies. Recently, a family of compounds that alter epigenetic expression, namely histone deacetylase inhibitors, have shown promise as possible therapeutic agents in endometrial cancer. The present review aims to discuss the therapeutic potential of these agents.

MATERIALS AND METHODS: This literature review was performed using the MEDLINE database; the search terms histone, deacetylase, inhibitors, endometrial, targeted therapies for endometrial cancer were employed to identify relevant studies. We only reviewed English language publications and also considered studies that were not entirely focused on endometrial cancer. Ultimately, sixty-four articles published until January 2018 were incorporated into our review.

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RESULTS: Studies in cell cultures have demonstrated that histone deacetylase inhibitors exert their antineoplastic activity by promoting expression of $p21^{WAF1}$ and $p27^{KIP1}$, cyclin-dependent kinase inhibitors, that have important roles in cell cycle regulation; importantly, the transcription of specific genes (e.g., E-cadherin, PTEN) that are commonly silenced in endometrial cancer is also enhanced. In addition to these abstracts effects, novel compounds with histone deacetylase inhibitor activity (e.g., scriptaid, trichostatin, entinostat) have also demonstrated significant antineoplastic activity both *in vitro* and in vivo, by liming tumor growth, inducing apoptosis, inhibiting angiogenesis and potentiating the effects of chemotherapy.

CONCLUSIONS: The applications of histone deacetylase inhibitors in endometrial cancer appear promising; nonetheless, additional trials are necessary to establish the therapeutic role, clinical utility, and safety of these promising compounds.

Key Words

Histone, Deacetylase, Inhibitors, HDAC, HDACI, Endometrial, Cancer; Targeted, Therapy, Epigenetics.

Introduction

In the Western world, endometrial carcinoma (EC) is currently the most commonly diagnosed neoplasm of the female genital tract[1,2]. Furthermore, EC has a significant epidemiologic impact worldwide and is the seventh most common malignant tumor among women globally[3]. In the United States of America, EC is currently the fourth most common cancer in women, with an estimated 54,870 new cases and 10,170 deaths in 2015 alone[4,5]. Most EC cases are diagnosed after menopause. However, 14% of ECs are diagnosed in pre-menopausal women, below the age of 40 years[4]. Depending on the stage, disease-free five-year survival rates vary from 20% to 95%[6]. Although the majority of women with EC present at an early stage and have a favorable prognosis[1], a steady increase in EC-specific mortality has been noted over the past two decades[3,7].

Treatment for the early-stage disease is primarily surgical, with total abdominal hysterectomy, bilateral salpingo-oophorectomy, peritoneal washings and pelvic lymphadenectomy; in turn, surgery provides localized therapy and assists with determining the stage of the disease[8]. Subsequently, the need for adjuvant treatment is determined by prognostic factors such as tumor grade, depth of myometrial invasion, lymph node involvement and peritoneal cytology. Moreover, tumor histopathological characteristics also play a critical role in adjuvant treatment determination. Specifically, endometrial malignancies are currently categorized into two distinct histopathologic subgroups with different clinical and molecular characteristics: Type I (endometrioid carcinomas) and Type II (non-endometrioid, i.e., papillary serous and clear-cell carcinomas)[9,10]. Surgical treatment remains the gold standard for Stages I-III, irrespective of cancer histopathologic type[11]. However, women with high-risk endometrial malignancies [i.e., females with Stage I_B (>50% myometrium invasion) and grade 3 tumors, Stage II, III or IV endometrioid cancers, as well as serous or clear cell carcinomas regardless of Stage should be offered adjuvant chemotherapy[12]. Several chemotherapeutic agents – either alone or in combination – have been used for the treatment of advanced or relapsed EC, such as carboplatin, paclitaxel, cisplatin, doxorubicin, docetaxel, ifosfamide, topotecan, bevacizumab and temsirolimus[13-26], but without conclusive evidence of benefit[27]; in turn, this dearth of effective therapies may contribute to the increase in disease-specific mortality[2]. Consequently, the development of novel agents is urgently needed. To this end, recent data suggest that histone deacetylase inhibitors (HDACIs) are extremely promising anti-neoplastic compounds, with the capacity to inhibit cancer growth, induce apoptosis and reverse changes in cellular differentiation that are observed with neoplastic transformation[3]. Given the paradigm shifting potential of HDACIs in EC, the objective of this review is to summarize the existing literature on these novel agents.

The role of histone acetylation in the regulation of cellular growth

Although it is conceptually attractive to think of DNA as a long uncoiled double-helix, as classically described by Watson and Creek, in reality a fully uncoiled DNA strand is not encountered in nature; the length of an uncoiled DNA strand is considerably longer than the radius of the eukaryotic nucleus, thus necessitating the 'packaging' of DNA in a denser structural form[28]. In turn, pioneering crystallographic studies determined that the basis of DNA structural organization is the nucleosome, namely a DNA strand of relatively constant length (146 base pairs) wrapped around a protein core. Four proteins of the histone family (H2A, H2B, H3, H4) have been identified as the central elements of this protein core; interestingly, each of the aforementioned histones is present in two identical

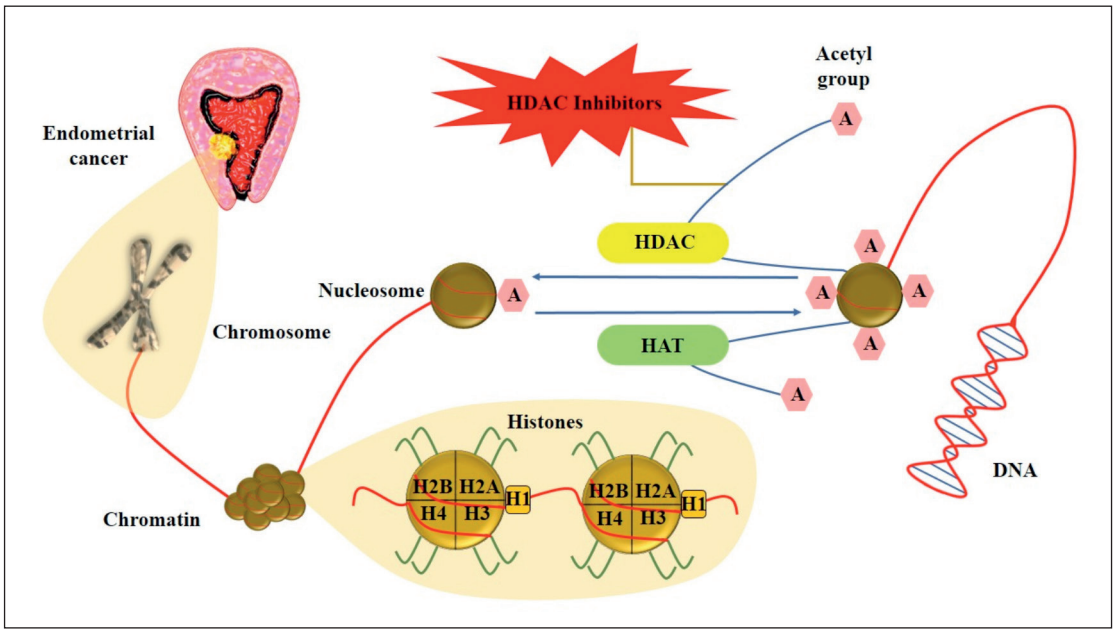

Figure 1. Therapeutic strategy against endometrial cancer targeting histone deacetylases. The nucleosome is the basis of DNA structural organization and it consists of histone proteins (H2A, H2B, H3, H4) presented in two identical copies. This structure is called histone octamer. Histone acetylation leads to DNA 'unpackaging' which is necessary for transcription to occur; conversely, deacetylation leads to the formation of condensed chromatin and suppresses genetic expression. The balance between histone acetylation and deacetylation is maintained by two antagonistic enzymes: histone deacetylases (HDACs) and histone acetyltransferases (HATs). Given that dysfunctional histone acetylation can promote carcinogenesis, histone deacetylase inhibitors consists a promising therapeutic antineoplastic strategy.

copies, giving rise to a structure that is referred to as a histone octamer[29,30].

The ability of histones to function as the nidus of nucleosome formation by interacting with DNA rests on their chemical properties; specifically, histones are positively charged proteins with a high affinity for negatively charged DNA strands. However, the role of histones is not merely structural, but functional as well. Specifically, it is widely accepted that gene transcription is partly regulated by the acetylation of nucleosome histones. In chemical terms, histone acetylation counterbalances the positive charge provided to the histone octamer by lysine residues[31,32]; consequently, the propensity of histones to bind negatively charged DNA is reduced, thus allowing DNA strands to uncoil. As such, histone acetylation leads to DNA 'unpackaging' which is necessary for transcription to occur; conversely, deacetylation leads to the formation of condensed chromatin (heterochromatin) and suppresses genetic expression. Of note, the equilibrium between histone acetylation and deacetylation is maintained by two antagonistic classes of enzymes, namely histone deacetylases (HDACs) and histone acetyltransferases (HATs)[33-35] (Figure 1). Of these two enzyme classes, HDACs have been studied extensively in both human and other eukaryotic cells. Specifically, 18 distinct members of the human HDAC superfamily have been identified, giving rise to four HDAC classes: Class I (HDAC-1, -2, -3 and -8), class II [class IIa (HDAC-4, -5, -7 and -9) and class IIb (HDAC-6 and -10)], class III [also termed sirtuins, as they are homologous with HDACs identified in *Saccharomyces cerevisia* (SIRT-1, -2, -3, -4, -5, -6 and -7)] and class IV (HDAC-11). Importantly, Classes I, II and IV are

Table I. Classification of histone deacetylases (HDACs).

Class I	Class II	Class III	Class IV
HDAC-1	a HDAC-4	SIRT-1	HDAC-11
HDAC-2	HDAC-5	SIRT-2	
HDAC-3	HDAC-7	SIRT-3	
HDAC-8	HDAC-9	SIRT-4	
	b HDAC-6	SIRT-5	
	HDAC-10	SIRT-6	
		SIRT-7	
Zn^{2+}-dependent		**NAD-dependent**	**Zn^{2+}-dependent**

Zn^{2+}-dependent whereas Class III is NAD-dependent[36] (Table I).

Given its ability to promote or suppress genetic expression, histone acetylation is important in the regulation of the cell cycle. In turn, dysfunctional histone acetylation can promote carcinogenesis by either reducing the expression of tumor suppressor genes (hypoacetylation) or promoting the expression of oncogenes (hyperacetylation)[35]. Consequently, a more detailed investigation of histone-mediated epigenetic alterations in both EC and other cancers (e.g., malignancies of the pancreas, tongue, lung, skin, thyroid, colon, rectum, liver, breast and blood)[35,37-47] may lead to an enhanced understanding of the neoplastic process and development of new targeted therapies.

Histone-mediated epigenetics and the molecular biology of EC

A great variety of molecular prognostic factors has been described in EC, such as p53 and p16 overexpression, PTEN mutations, microsatellite instability, tumor expression of estrogen and/or progesterone receptors and/or proteins involved in the PI3K/AKT/mTOR pathway[48-54]. Interestingly, the molecular profiles of Type I *vs.* Type II ECs are distinct, with type I EC characterized by PTEN inactivation, K-ras, β-catenin or hMLH1/MSH2[3,10] mutations, as well as microsatellite instability. On the contrary, type II EC is characterized by p53 mutations, E-cadherin and p16 inactivation, amplification of HER2/neu and down-regulation of hormone receptors[1,3]. In turn, these genetic differences underscore the distinct molecular origins of the two tumor types. Specifically Type I EC frequently develops in a background of adenomatous hyperplasia, while most Type II tumors develop from atrophic endometrium in older women, are hormonally independent and have a more aggressive clinical course than Type I neoplasms[10].

Notably, all of the aforementioned genetic alterations in both EC tumor types are heavily influenced by histone-mediated epigenetics. Specifically, DNA hypermethylation and/or histone deacetylation mechanisms are directly involved in the silencing of hMLH1/MSH2, PTEN, and progesterone receptor (PR) genes, all of which are central to EC development and progression. In turn, the disordered hMLH1/MSH2 expression is thought to drive early carcinogenesis (as it is present in pre-neoplastic atypical hyperplasia), PTEN suppression is associated with worse outcomes and the loss of PR expression may contribute to the development of hormone-resistant EC[10]. Importantly, the expression of HDAC has been shown to parallel neoplastic development, providing further evidence of the importance of histone acetylation in neoplastic growth. For example, Weichert et al[55] demonstrated that most ECs are characterized by elevated expression of class I HDAC isoforms in the nuclei of tumor cells, in the following order: HDAC-2 (95%) > HDAC-3 (83%) > HDAC-1 (61%). Subsequently, the authors correlated the expression of HDAC-1, -2 and -3 within individual cells and between cells of varying proliferative capacity. Notably, clear cell and serous subtypes showed significantly higher expression rates of all three HDACs when compared with endometrioid carcinomas, attesting to their distinct genetic profiles and biologic behavior; interestingly, increased HDAC-1 protein expression was associated with poor prognosis in endometrioid carcinoma. These findings were further confirmed by Hrzenjak et al[56], who studied the expression of HDAC-1 and -2 in endometrioid and endometrial cell lines using TaqMan® gene expression assays. The authors reported that the expression of both HDAC-1 and HDAC-2 genes was significantly higher in neoplastic cells, compared with normal endometrial cells. Of note, steroid hormone treatment was demonstrated to induce up-regulation of HDAC-1 and HDAC-2 in endometrial stromal cells; specifically, HDAC-1 expression was increased by progesterone, whereas HDAC-2 expression was increased by both estrogen and progesterone, highlighting the complex interplay between hormonal and molecular factors. The aforementioned findings support the etiologic role of increased HDAC expression in EC; as such, inhibition of these enzymes would be expected to limit neoplastic proliferation.

Targeting histone deacetylation: mechanisms of action and impact of HDACI use in EC

HDACIs are known to derive their antineoplastic properties from two main mechanisms: 1) a generalized effect on cell-cycle control mechanisms that inhibits cellular proliferation and 2) an ability to promote the expression of specific tumor suppressor genes at the transcriptional level[3]. Concerning the first mechanism, HDACIs are known to promote expression of $p21^{WAF1}$ and $p27^{KIP1}$, cyclin-dependent kinase inhibitors

that have important roles in blocking the cell cycle in the G1 phase, thus arresting neoplastic cell growth. This general mechanism of action has been demonstrated to be effective in EC and may account for some of the antineoplastic properties of HDACIs[2]. The impact of HDACI use on the transcriptional expression of important tumor-suppressor genes probably serves to augment this general mechanism, by producing specific effects in different tumor types.

For example, the E-cadherin gene, which is involved in cell-cell adhesion, has been associated with the enhanced metastatic growth of tumor cells[57]; importantly, hypermethylation of this gene is associated with poor tumor differentiation and myometrial invasion in EC[27]. In turn, the use of HDACIs can restore E-cadherin expression, reversing these effects[2]. Moreover, silencing of hMLH1 and/or MSH2 by epigenetic mechanisms, such as histone deacetylation, has been associated with microsatellite instability, invasive growth and acquired resistance to cisplatin in EC. Consequently, epigenetic reactivation of MLH1 gene expression can be achieved with the use of HDACIs, thus restoring normal DNA repair function. Similarly, histone deacetylation-mediated progesterone receptor-B silencing is also common in high-grade EC, rendering these tumors resistant to hormonal therapy. As such, treatment with HDACIs may not only result in re-expression of progesterone receptor-B, but in sensitization of EC to hormonal therapy[58].

An assessment of currently available agents with HDACI activity

Research into histone-mediated epigenetic regulation has produced many candidate agents with the capacity to inhibit histone deacetylation. Each of these agents is highly effective in suppressing the growth of human EC cells; the existing literature on each agent is summarized below (Table II).

Scriptaid/Oxamflatin

These synthetic analogs, isolated from screening libraries, were discovered to have a common structure with Trichostatin (TSA) and Suberoylanilide Hydroxamic Acid (SAHA); specifically, a hydroxamic acid zinc-binding group linked via a spacer (5 or 6 CH_2), an aliphatic chain and an aromatic cap at the other end. Scriptaid is a potent HDACI that produces a >100-fold increase in histone acetylation, with relatively low toxicity. It has also been demonstrated to be highly effective in suppressing the growth of human EC cell lines. These effects are mediated by induction of $p21^{WAF1}$ and $p27^{KIP1}$ and down-regulation of several anti-apoptotic and cell cycle-related proteins, such as Bcl-2, cyclin A and E-cadherin[59]. It has also been suggested that scriptaid can increase signal transduction in the TGF-β pathway, thus promoting the expression of several tumor suppressor genes, such as SMAD4[3].

Trichostatin

TSA is a naturally-derived organic hydroxamic acid[3], isolated from *Streptomyces hygroscopicus* and was initially used as an antifungal antibiotic[2,3]. TSA causes hyperacetylation of histones H3 and H4[60], is active against all class I and II HDACs and can also inhibit DNMT3B activity, thus facilitating DNA hypomethylation by DNA methyltransferase (DNMT) inhibitors[58]. The latter mechanism may contribute to the antineoplastic synergy observed between HDAC and DNMT inhibitors[60]. Moreover, TSA and SAHA activate several gene promoters, including p21/wild-type p53-activated fragment 1/cyclin-dependent kinase interacting protein 1, human telomerase reverse transcriptase, mitochondrial 3-hydroxy-3-methyl-glutaryl-coenzyme A synthase and inhibitor of cyclin-dependent kinase 4d through the Sp1 site(s), as well as stimulate LIF expression[61].

Importantly, combined treatment with TSA and paclitaxel is known to cause synergistic inhibition of cell growth in the Ark2 and KLE EC cell lines[3]. Interestingly, a TSA/paclitaxel regimen also produced a significant increase in tubulin acetylation, thus promoting microtubule stabilization; in turn, these results suggest that non-histone protein acetylation may also play a minor role in the antineoplastic effects of HDACIs[3]. A more recent study showed that TSA-mediated tumor growth suppression was also associated with the up-regulation of p21 expression, consistent with previous studies. Furthermore, TSA has been demonstrated to down-regulate cyclin D1 and cyclin A expression and promote apoptosis, possibly through p21 up-regulation and modulation of the mitochondrial apoptotic pathway[62]. Finally, TSA can inhibit the VEGF-induced expression of VEGF receptors (VEGFR1, VEGFR2, Nrp1), the VEGF family member D (VEGFD) and Bfgf, thus blocking angiogenesis[58]. Nonetheless, in spite of all these beneficial *in vitro* effects, the high *in vivo* toxicity of TSA will probably limit its clinical use[2].

Table II. Major actions of histone deacetylase inhibitors (HDACIs) against endometrial cancer (EC).

Histone deacetylase inhibitors (HDACI)	Increases expression of:	Decreases expression of:	Notes
Scriptaid/ oxamflatin	$p21^{WAF1}$ $p27^{KIP1}$ SMAD4	Bcl-2 cyclin A E-cadherin	Synthetic molecules
Trichostatin (TSA)	p21/wild-type p53-activated fragment 1/ cyclin-dependent kinase interacting protein 1, human telomerase reverse transcriptase, mitochondrial 3-hydroxy-3-methyl-glutaryl-coenzyme A synthase inhibitor of cyclin-dependent kinase 4d LIF expression	cyclin D1 cyclin A VEGFR1 VEGFR2 Nrp1 VEGFD Bfgf	Class I and Class II HDAC inhibitor DNA Methyltransferase inhibitor High toxicity
Voronostat (SAHA, MK0683)	SEMA3	n/a	Low toxicity
Entinostat (MS-275)	$p21^{WAF1}$ $p27^{KIP1}$ E-cadherin	Bcl-2	n/a
Psammaplin (PsA)	$p21^{WAF1}$	cyclin D1 cyclin E CDK4 p53 hyperphospho-rylated pRb	Topoisomerase II inhibitor, farnesyl protein transferase inhibitor, leucine aminopeptidase inhibitor chitinase inhibitor DNA methyltransferase inhibitor Promotes p53 independent apoptosis
Sodium Butyrate (NaB)	n/a	n/a	Short half-life
Valproic acid (VPA)	ERα	eNOS	Class I and Class II HDAC inhibitor Long half-life Well-established toxicity profile
Apicidin/Depsipeptide	p21 p16	HDAC3 HDAC4 cyclin A VEGF	Antineoplastic efficacy in cell lines remains controversial
Romidepsin (FK288)	PARP and caspase-7	n/a	Promotes p53 independent apoptosis

Vorinostat (SAHA, MK0683)

Vorinostat (suberoylanilide hydroxamic acid)[61] has a similar chemical structure with TSA, but has been demonstrated to be relatively non-toxic *in vivo*[2,61]. Interestingly, SAHA causes HDAC inhibition through a direct reaction with the catalytic side of the enzyme[2]. Notably, SAHA has also been shown to promote the expression of SEMA3, a VEGF protein competitor, at both the mRNA and protein levels[58].

Entinostat (MS-275)

Entinostat (also known as MS-275), a derivative of 2-aminophenyl benzamides, is highly effective at suppressing the growth of human EC cells, without affecting normal endometrial epithelial cells. These effects were associated with H3 and H4 histone protein acetylation, confirming that MS-275 acts as a HDACI in human cancer cell lines. Importantly, the expression of $p21^{WAF1}$ and $p27^{KIP1}$ increased following treatment

of EC cells with MS-275, suggesting that cell cycle arrest at the G0/G1 checkpoint may mediate the agent's effects. It has also been demonstrated that treatment with MS-275 stimulates apoptosis in EC cell lines, possibly mediated by a decrease in the levels of the anti-apoptotic protein Bcl-2[63]. Increased transcription of E-cadherin has also been noted in cells treated with MS-275, suggesting a gain of tumor suppressor function in response to the inhibition of HDAC[59].

Psammaplin

Psammaplin A (PsA) is a natural bromotyrosine derivative; interestingly, it is produced by a two-sponge association, *Poecillastra sp.* and *Jaspis sp.* and was first isolated from the Psammaplysilla sponge in 1987. PsA has antibacterial and antitumor properties and inhibits various enzymes including topoisomerase II, farnesyl protein transferase, leucine aminopeptidase, and chitinase. PsA inhibits both HDAC-1 and DNMT, thus promoting the expression of tumor suppressor genes. In a recent study, PsA inhibited cell proliferation in the Ishikawa cell line through cell cycle arrest at the G1 or G2/M phases and induced apoptotic cell death, This was achieved through similar mechanisms with other HDACIs, ultimately resulting in a decreased proportion of cells in the S phase and an increased proportion of cells in the G0/G1 and/or G2/M phases, concurrently with increased $p21^{WAF1}$ expression. PsA also decreased the levels of cyclin D1, cyclin E, and CDK4, all of which are involved in G1 phase progression, but without affecting CDK6 expression. In addition, PsA treatment also resulted in a significant decrease in the level of hyperphosphorylated pRb, an important molecular 'switch' that determines cell cycle progression from the G1 to the S phase. Importantly, PsA treatment of Ishikawa cells increased $p21^{WAF1}$ expression, while decreasing p53 expression. This is noteworthy, as p53 is known to exert a central role in cell cycle regulation and apoptosis; as such, the effects of PsA appear to be mediated by a p53-independent pathway[64].

Sodium Butyrate

Sodium Butyrate (NaB) is a low-potency HDACI that has been shown to promote differentiation of cancer cell-lines through hyperacetylation of histones H3 and H4[60]. NaB also has significant antiproliferative activity on human endometrial cells, an effect that appears to be independent of p53 gene status, as in the case of PsA[58]. Nonetheless, the possible clinical utility of NaB is restricted by its short half-life (5 min)[2].

Valproic acid

Valproic acid (VPA) is a potent HDACI that has been used in the treatment of epilepsy for more than 40 years. Interestingly, VPA has been proven to inhibit cell proliferation, induce cell cycle arrest and stimulate apoptosis in HEC-1B EC cells. VPA also has convenient pharmacokinetic properties with a significantly longer biological half-life than the other HDACIs and a relatively well-established toxicity profile[2]. The ability of VPA to inhibit class I & II HDACs stems from a reduction of HDAC-1 protein expression[65] and an increase in proteasomal degradation of HDAC-2[66]. Of note, VPA may also induce ERα expression and has been shown to inhibit angiogenesis (both *in vitro* and *in vivo*) via diminished expression of eNOS[58].

Apicidin/Depsipeptide

Apicidin, a natural fugal metabolite isolated from *Fusarium sp*, has demonstrated anti-tumor properties on EC cells by promoting the expression of genes related to cell cycle arrest and apoptosis *in vitro*. These effects are partly mediated by the up-regulation of acetylated H3, p21 and p16 and the down-regulation of HDAC-3, HDAC-4 and cyclin A in apicidin-treated cells. Noteworthy, apicidin may also reduce the levels of VEGF, thus inhibiting angiogenesis[67]. However, apicidin's efficacy has been more controversial than that of other HDACIs. Specifically, although some studies report that apicidin is effective at suppressing the Ishikawa EC cell line, other studies report that the Ishikawa and Hec-1B cell lines displayed resistance to apicidin even at high concentrations, casting doubt on the possible clinical utility of this agent[62].

Romidepsin (FK288)

Romidepsin (FK228) is a natural product isolated from *Chromobacterium violaceum*[62] and is known to significantly promote the acetylation of H3 and H4, thus testifying to its potency as a HDACI. Noticeably, FK228 administration to cancer cell lines has been demonstrated to result in increased levels of active chromatin markers such as acetyl-H3, acetyl-H3K9, and acetyl-H4 and decreased levels of inactive chromatin markers such as trimethyl-H3K9 and trimethyl-H3K27, thus demonstrating the agent's effects on epigenetic regulation. Aside from its effects on genetic expression, FK228 was also successful in inhibiting the proliferation of the Ishikawa and HEC-1-A EC cell lines and inducing cell death in

a dose and time-dependent manner. In turn, the effects of FK228 on the cell cycle, including the regulation of apoptosis, appear to be mediated by the p53-p21 pathway which leads to activation of PARP and caspase-7. Importantly, FK228 can also promote cellular apoptosis independently of p53, as in the case of other HDACIs; in turn, this suggests the possibility that FK228 may also be effective against p53 mutant tumors[4].

Limitations of HDACI use

Despite these promising early results, it should be noted that the effectiveness of HDACIs is ultimately dependent on HDAC expression by EC cells. Although the majority of EC cells do express HDACs, a significant minority (possibly as high as 35% of EC) may show a massive decrease or a complete loss of epithelial HDAC-1 protein expression; interestingly, this loss of HDAC expression may also extend to endometrial stroma cells. In turn, the variability of HDAC-1 expression leads to different sensitivity and responsiveness of tumors to HDACIs[65]. As such, it should always be kept in mind that epigenetic regulation is a complex process and HDACIs constitute a targeted therapy, not a panacea; consequently, testing for HDAC expression should certainly be incorporated in the design of future clinical trials assessing the clinical utility of these agents.

Conclusions

Histone acetylation represents a crucial and reversible step in the complex process of epigenetic regulation; importantly, dysfunction in this pathway contributes to cancer development and progression. The present review highlighted the important pathophysiologic role of HDAC in reducing the expression of tumor suppressor genes and, consequently, the potential therapeutic role of HDACIs. Indeed, early experiments in EC cell lines suggest that HDACIs may fulfill their theoretical potential by restoring physiologic gene expression, limiting tumor growth, facilitating the efficacy of systemic therapy and inducing apoptosis of cancer cells. In particular, the applications of HDACIs in EC appear particularly promising, given the limited effectiveness of available treatments and the substantial evidence of HDAC expression and HDACI efficacy in EC cell lines.

Nonetheless, further evidence is required before the widespread application of HDACIs in EC is considered. Though sound from a theoretical perspective, targeted therapies like HDACIs often do not function as anticipated when administered to patients, given the unfathomable complexity of interlocking regulatory pathways in human tissues. Furthermore, the relevance of histone acetylation for several "housekeeping" functions in normal cells, suggests that HDACI use may be associated with serious adverse events, a possibility that should be fully explored. Although some HDACIs, such as Romidepsin and Vorinostat, have already received FDA approval for use in other malignancies, additional clinical trials will be indispensable in establishing the clinical utility and safety of these promising compounds in EC.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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