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Review

The Role of Histone Deacetylase Inhibitors in Uveal Melanoma: Current Evidence

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Abstract. *Uveal melanoma is the most common intraocular malignancy in adults, representing approximately 3% of all melanoma cases. Despite progress in chemotherapy, radiation and surgical treatment options, the prognosis and survival rates remain poor. Acetylation of histone proteins causes transcription of genes involved in cell growth, DNA replication and progression of cell cycle. Overexpression of histone deacetylases occurs in a wide spectrum of malignancies. Histone deacetylase inhibitors block the action of histone deacetylases, leading to inhibition of tumor cell proliferation. This article reviewed the potential therapeutic effects of histone deacetylase inhibitors on uveal melanoma. MEDLINE database was used under the key words/phrases: histone deacetylase, inhibitors, uveal melanoma and targeted therapies for uveal melanoma. A total of 47, English articles, not only referring to uveal melanoma, published up to February 2018 were used. Valproic acid, trichostatin A, tenovin-6, depsipeptide, panobinostat (LBH-589), vorinostat (suberanilohydroxamic acid) entinostat (MS-275), quisinostat, NaB, JSL-1, MC1568 and MC1575 are histone deacetylase inhibitors that have demonstrated promising antitumor effects against uveal melanoma. Histone deacetylase inhibitors represent a promising therapeutic approach for the treatment of uveal melanoma.*

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Uveal melanoma (UM) is the most common primary intraocular malignancy in adults, representing approximately 3% of all melanoma cases. (1) UM arises from melanocytes along the uveal tract, including the iris, ciliary body and choroid, with the majority of cases (approximately 85%) originating in the choroid. The annual incidence of UM is 6-7 cases per million people and remains stable across decades (2-4). The median age at diagnosis is about 62 years. Risk factors for the development of UM include fair skin color, light eye color, ultraviolet light exposure, cutaneous dysplastic nevi, ocular melanocytosis and the presence of mutations, such as guanine nucleotide-binding protein subunit alpha 11 (*GNA11*), *GNAQ* and breast cancer 1 (BRCA1)-associated protein 1 (*BAP1*) (5-9).

Approximately half of all patients with primary UM ultimately develop metastasis with spread of tumor cells to the liver (89%), lung (29%), bone (17%), skin and subcutaneous tissue (12%), and lymph nodes (11%) (10). Metastasis may occur despite successful treatment of the primary tumor indicating subclinical micrometastases at initial presentation. Prognosis after metastatic disease remains poor with a reported death rate of 80% at 1 year and 92% at 2 years (11).

The most accurate method for identifying patients with UM who are at high risk of metastasis is by gene-expression profiling of the primary tumor, which is performed on tissue obtained by fine-needle biopsy, using a validated 15-gene assay (12). UM is separated into two classes. Class 1 tumors have a very low metastatic risk and contain well-differentiated tumor cells with a gene-expression profile similar to that of normal differentiated melanocytes. On the contrary, class 2 tumors have a high risk of metastasis and are composed of cells that lack the morphological features of melanocytic differentiation with a gene-expression profile enriched in genes expressed in primitive neuroectodermal cells (13).

Given that UM represents an aggressive type of cancer that exhibits a strong tendency for lethal metastasis, the development of dedicated management and treatment approaches is necessary. Local treatment for UM consists of enucleation, photodynamic therapy, radiotherapy and chemotherapy (14). Currently, however, there is no effective treatment for metastatic UM.

In recent years, UM has been studied intensively at the genetic and molecular levels in an attempt to develop new therapeutic approaches (9, 15). In the past decade, a family of enzymes that alter epigenetic expression, namely histone deacetylase inhibitors (HDACIs), has generated increased interest due to their possible therapeutic role in uveal cancer. HDACIs interfere with the deacetylation process mediated by HDAC, resulting in a global increase of histone acetylation. HDACs are able to regulate expression of tumor-suppressor genes and activity of transcriptional factors involved in both tumor initiation and progression through alteration of either DNA or the structural components of chromatin (16). In UM, HDACIs induce morphological differentiation, and inhibit the growth of tumor *in vivo* and *in vitro* (17).

The aim of this review was to summarize the existing literature on these promising anti-neoplastic agents for UM therapy. MEDLINE database was used under the key words/phrases: histone deacetylase, inhibitors, uveal melanoma and targeted therapies for uveal melanoma. A total of 47, English articles, not only referring to uveal melanoma, published up to February 2018 were used. References of the selected articles were also reviewed. References were included if they discussed the role of HDACIs in UM. Studies conducted both in patients and animals were included. Case reports and articles studied less than 10 patients were excluded

HDAC Classification

HDACs have been extensively studied in human and other eukaryotic cells. HDACs are enzymes that remove the acetyl group from histone. Human HDACs include 18 different substances grouped into four classes based on function and similarity of DNA sequence. Class I includes HDAC1, -2, -3 and-8, which are located in the cell nucleus. Class II is subdivided into class IIa, which includes HDAC4, -5 and-7, and class IIb, which consists of HDAC6 and-10, with exonuclear and nuclear localization. Class III consists of sirtuins (SRT1, -2, -3, -4, -5, -6 and-7) and class IV includes only HDAC11, which has characteristics of both class I and II HDAC. Classes I, II and IV require zinc (Zn) to transfer an acetyl group from their substrates (Zn-dependent), whereas class III require nicotinamide adenine dinucleotide (NAD^+) for their catalytic activity (NAD^+-dependent) (18, 19) (Table I).

Table I. *Classification of histone deacetylases.*

Class I	Class II	Class III	Class IV
HDAC1	IIa HDAC4	SIRT1	HDAC11
HDAC2	HDAC5	SIRT2	
HDAC3	HDAC7	SIRT3	
HDAC8	HDAC9	SIRT4	
	IIb HDAC6	SIRT5	
	HDAC10	SIRT6	
		SIRT7	
Zn-dependent		NAD-dependent	Zn-dependent

HDAC: Histone deacetylases; NAD: nicotinamide adenine dinucleotide; SIRT: sirtuins.

HDAC Mechanism of Action

The balance of histone acetylation and deacetylation plays a critical role in the regulation of gene expression (20). Histone acetylation, induced by histone acetyltransferases (HAT), is associated with gene transcription, whereas histone deacetylation, induced by HDAC activity, is associated with gene silencing. HDACs catalyze the removal of the acetyl group of histone lysine residues (deacetylation), allowing the histones to wrap DNA more tightly, thus reducing access to transcription factors and leading to transcriptional repression. On the contrary, acetylation of lysine residues of histone leads to a less condensed chromatin structure by increasing the distance between the nucleosome and the DNA wrapped around it (Figure 1). As a consequence, transcription factors can combine with the DNA, resulting in activation of transcription of many genes involved in the control of cell-cycle progression, differentiation and proliferation (18). Apart from histones, other acetylated proteins have been reported to constitute substrates of HDACs, including nuclear transcription factor Y subunit A (NFYA), p53 and erythroid transcription factor also known as GATA-binding factor 1 (GATA1) (21).

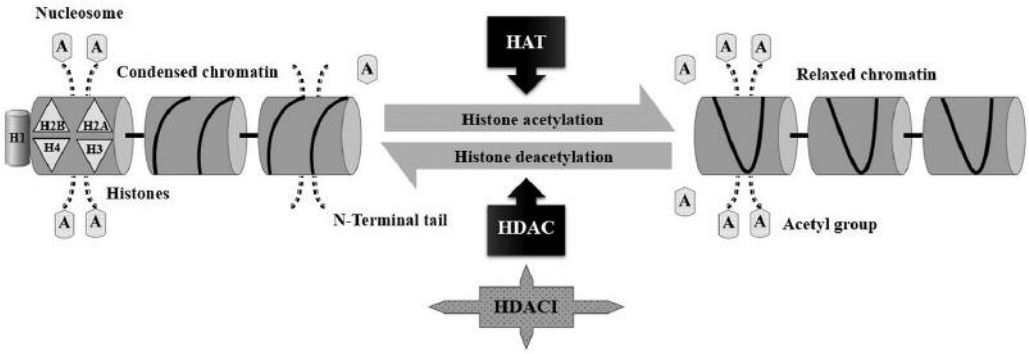

Figure 1. *Histone acetylation is a dynamic process, catalyzed by histone acetyltransferases and histone deacetylases. Histone acetylation reduces the interaction between histones and DNA. Histone deacetylation removes acetyl groups. H: Histone; A: Acetyl group; HAT: histone acetyltransferases; HDAC: histone deacetylase; HDACI: histone deacetylase inhibitor.*

Increasing evidence suggests that alterations in HAT and HDAC activity occur in cancer. HAT activity can be disrupted by translocation, over-or under expression or mutation in different types of cancer, including both hematological and solid malignancies (21-23). Several studies have demonstrated that HDACs are overexpressed in a wide spectrum of tumors. For example, HDAC1 and HDAC2 are overexpressed in endometrial cancer, HDAC2 is highly expressed also in breast and lung cancer and HDAC6 is overexpressed in liver cancer (19, 24-26). Moreover, the expression of *HDAC7* gene is significantly increased in pancreatic adenocarcinoma and HDAC6 has been found to be overexpressed in cutaneous T-cell lymphoma (21).

HDACI and Their Effects in UM

HDACIs are compounds that inhibit the action of HDAC and alter the balance of histone acetylation and deacetylation. HDACI may block tumor cell proliferation by inducing hyperacetylation of histones and, consequently, affect gene expression. Studies have shown that these compounds can induce growth arrest of transformed cells, terminal differentiation, cell death and inhibition of angiogenesis (20, 27). Normal cells are relatively resistant to HDACI-induced cell death. The cell-death pathways identified in mediating HDACI-induced death of transformed cells include apoptosis by the intrinsic and extrinsic pathways, mitotic catastrophe/ cell death, autophagic cell death, senescence, and reactive oxygen species (ROS)-facilitated cell death. The response to HDACIs seems to depend on the nature of the HDACI, its concentration, duration of exposure and the cell context (27).

HDACIs are divided into four main classes based on their structure (hydroxamic acid, cyclic tetrapeptide, benzamide and aliphatic acid). HDACIs are structurally heterogeneous but share a common ability to recognize and bind to the catalytic zinc-pocket on class 1 and II HDACs (28).

Four HDACIs are currently approved by the US Food and Drug Administration (FDA) and the European Medicines Agency for anticancer therapy: vorinostat (suberanilohydroxamic acid, Zolinza) and romodepsin (FK228, Istodax) for T-cell lymphoma;belinostat (Beleodaq) for peripheral T-cell lymphoma;and panobinstat (Farydak) for multiple melanoma.

Clinical trials of other HDACIs are underway, while several studies have demonstrated their important anticancer effects, highlighting their action against malignancies such as pancreatic, breast, medullary thyroid, and non-small cell lung cancer (21, 29-33).

HDACI such as valproic acid (VPA), trichostatin A (TSA), tenovin-6, depsipeptide, panobinostat, vorinostat, entinostat, quisinostat, NaB, JSL-1, MC1568 and MC1575 are being studied in UM with promising results. Table II summarizes the anticancer action of HDACIs in UM.

Valproic acid. VPA is a well-characterized compound that has been used in the treatment of epilepsy for almost 40 years and more recently as an anticancer agent for the treatment of cutaneous T-cell lymphoma (16). VPA increases histone H3 acetylation in UM cell lines and inhibits proliferation without reducing the fraction of viable cells. VPA induces G_1 cell-cycle arrest and significantly reduces the clonogenicity of UM cells. Furthermore, VPA inhibits the growth and reduces the final volume of UM *in vivo* (17). Knock-down of *BAP1* causes an increase in histone H2A ubiquitination, consistent with its H2A ubiquitin carboxy-terminal hydrolase activity, which is critical for its tumor-suppressor function (34). VPA reverses H2A hyper-ubiquitination in BAP1-depleted UM cells without affecting the total histone H2A level (17). Studies have shown that BAP1 loss in UM cells is associated with morphological and transcriptional changes consistent with a loss of melanocytic differentiation and a shift from a class 1 to class 2 gene-expression profile, therefore with an increased metastatic

Table II. *The anticancer effects of histone deacetylase inhibitors (HDACI) in uveal melanoma (UM).*

HDACI	Effect (Ref)
Valproic acid;	Inhibition of proliferation (17)
	Induction of G_1 cell-cycle arrest (17)
	Reduction of clonogenicity (17)
	Inhibition of UM growth *in vivo* (17)
	Reduction of UM final volume *in vivo* (17)
	Reversion of H2A hyperubiquitination (17)
	Shift of gene expression profile of class 2 cells to a class 1 profile (17)
Trichostatin A	Inhibition of proliferation (17, 35)
	Induction of G1 cell-cycle arrest (17)
	Reduction of clonogenicity (17)
	Up-regulation of miR-137 and miR-124a (36, 37)
	Synergistic action with the drug 5-aza-deoxycytidine (36, 37)
Tenovin-6	Inhibition of cell growth (39)
	Induction of apoptosis (39)
	Activation of p53 expression (39)
	Synergistic action with vinblastin (39)
	Decrease of XIAP and survivin (39)
	Induction of mitochondrial damage (39)
	Increase of intracellular reactive oxygen species (39)
	Decrease of cancer stem cells (39)
	Decrease of intracellular active-β-catenin (39)
	Blockage of WNT/β-catenin signaling (39)
Depsipeptide	Inhibition of cell growth (35)
	Induction of apoptosis (35)
	Decrease of migration (40)
	Decrease of MMP2, MMP9 and MMP1 levels and activity (40)
	Up-regulation of TIMP1 and TIMP2 (40)
	Increase of caspase-3, Fas/FasL, $p21^{Waf/Cip1}$ and $p27^{Kip1}$ (35)
Panobinostat	Induction of G_1 cell-cycle arrest (17)
	Shift of gene expression profile of class 2 cells to a class 1 profile (13)
Vorinostat	Increase of $p14^{ARF}$ expression (41)
	Shift of gene expression profile of class 2 cells to a class 1 profile (17)
MS-275	Induction of apoptosis (42)
	Increase of DR4, DR5 and procaspase 8 expression (42)
	Synergistic action with TRAIL (42)
	Down-regulation of c-FLIP (42)
	Up-regulation of c-MYC (43)
	Decrease of *miR-92a-3p* (44)
	Decrease of MYCBP2 (44)
Quisinostat	Inhibition of proliferation (45)
	Decrease of migration (45)
NaB	Decrease of proliferation (35)
	Induction of apoptosis (35)
JSL-1	Activation of p53 (46)
	Inhibition of proliferation (46)
	Induction of apoptosis (46)
	Synergistic action with the chemotherapeutic agent vinblastine (46)
	Increase of pro-apoptotic BH3-only protein BIM expression (46)
	Reduction of MMP2 (46)
	Blockage of WNT/β-catenin pathway (46)
	Reduction of $ALDH^+$ cells (46)
	Inhibition of UM growth *in vivo* (46)
	Decrease of UM height *in vivo* (46)
MC1568 and MC1575	Decrease of cell proliferation (47)
	Decrease of IL8 level (47)
	Suppression of c-JUN expression (47)
	Suppression of c-JUN binding to IL8 promoter (47)
	Suppression of H3, H4, RNA Pol II and TFIIB recruitment to *c-JUN* promoter (47)

UM: Uveal melanoma; XIAP: X-linked inhibitor of apoptosis protein; MMP: matrix metalloproteinases; TIMP: tissue inhibitors of matrix metalloproteinases; DR4: death receptor 4; TRAIL: tumor necrosis factor-related apoptosis-inducing ligand; c-FLIP: cellular Fas-associated death domain (FADD)-like interleukin-1beta-converting enzyme-inhibitory protein; MYCBP2: myc-binding protein 2; BIM: BCL-2-like protein 11; ALDH: aldehyde dehydrogenase; IL8: interleukin-8.

potential (8, 34). Interestingly, VPA has been reported to induce morphological changes consistent with melanocytic differentiation and shifts the gene-expression profile of class 2 cells towards a class 1 profile (17).

Trichostatin A. TSA is an organic compound that serves as an antifungal antibiotic and selectively inhibits class I and II but not class III HDACs. TSA inhibits proliferation of UM cells, induces G1 cell-cycle arrest and markedly reduces the clonogenicity of UM cells (17, 35). However, apart from inhibiting proliferation, TSA also significantly reduces the fraction of viable cells and increases the proportion of cells undergoing apoptosis, which is consistent with increased cytotoxicity (17). TSA has been reported to up-regulate the expression of *miR-137* and *miR-124a* in UM cells and the combination of TSA with a DNA hypomethylating drug (5-aza-deoxycytidine) seemed to have additive effect on the expression of these microRNAs (36, 37). Studies have shown that *miR-137* expression is lower in UM cells than in uveal melanocytes and ectopic transfection of *miR-137* into UM cells induces G_1 cell-cycle arrest, leading to a significant decrease in cell growth (36). Moreover, overexpression of *miR-137* down-regulates microphthalmia-associated transcription factor (*MITF*), a transcription factor with oncogenic activity, and cyclin-dependent kinase 6 (*CDK6*), an important kinase that plays an essential role in cell-cycle G_1 phase progression and cell differentiation. Therefore, TSA represents an avenue to increasing the expression level of tumor-suppressor *miR-137* through down-regulation of the targets *MITF* and *CDK6*. Similarly, *miR-124a* is down-regulated in UM cells and transient transfection of miR-124a into UM cells inhibits cell growth, migration and invasion, with CDK4, CDK6, cyclin D2 and enhancer of zeste homolog 2 (EZH2) representing the potential targets of *miR-124a* (37).

Tenovin-6. Tenovin-6 is a potent class III-specific HDAC inhibitor as well as a p53 activator (38). Tenovin-6 has been found to inhibit deacetylating activity of SIRT1 and SIRT2 in UM cells and suppresses the growth of UM cells *in vitro* (39). Furthermore, Tenovin-6 induces apoptosis in UM cells by activating the expression of p53 and its combination with the conventional chemotherapeutic agent vinblastine, used for systemic therapy of UM patients, synergistically inhibited the viability of UM cells. Tenovin-6 reduces expression of X-linked inhibitor of apoptosis protein (XIAP) and survivin, but does not affect B-cell lymphoma 2 (BCL2) and BCL2 associated X (BAX), proteins and leads to mitochondrial damage, indicating that tenovin-6 triggers the intrinsic apoptosis pathway. Notably, tenovin-6 increases the level of intracellular ROS, which may partially contribute to UM cells apoptosis. Moreover, tenovin-6 reduces cancer stem cells in UM cells, lowers the level of intracellular active β-catenin and blocks WNT/β-catenin signaling (39).

Depsipeptide. Depsipeptide is a natural tetrapeptide that was isolated from Chromobacterium violaceum. Depsipeptide is a very potent HDACI; inhibiting cell growth, inducing apoptosis and reducing migration of viable UM cells in both primary and metastatic cell lines (35, 40). Furthermore, depsipeptide reduces the protein levels and activity of matrix metalloproteinases MMP2, MMP9 and MMP, and up-regulates the protein levels of tissue inhibitors of matrix metalloproteinases 1 and 2 (35).It alsoincreases the amount of caspase-3, Fas/FasL, $p21^{WAF/CIP1}$ and $p27^{KIP1}$ proteins but does not affect *BCL2*/*BAX* gene expression (35).

Panobinostat (LBH-589). Panobinostat is a hydroxamic acid and acts as a non-selective HDACI. It has received FDA-accelerated approval for use in patients with multiple myeloma. In cultured UM cells, similarly to VPA, panobinostat has been demonstrated to induce morphological differentiation, G_1 cell-cycle arrest and a shift to a differentiated, melanocytic gene-expression profile. Panobinostat not only inhibits proliferation of UM cells but also significantly reduces the fraction of viable cells (17).

Vorinostat. Also known as suberanilohydroxamic acid, vorinostat acts on class I, II and IV HDACs by binding to their active site and acting as a chelator for zinc ions. Vorinostat represents the first HDACI approved by the FDA for the treatment of cutaneous T-cell lymphoma for patients with progressive, persistent or recurrent disease. Vorinostat induces H3 and H4 hyperacetylation at the $p14^{ARF}$ promoter, leading to an increase in p14ARF expression in UM cells, which significantly reduces UM cell growth, migration and invasion (41). Additionally, similarly to VPA and panobinostat, vorinostat has been shown to reverse the phenotypic effects of BAP1 loss by inducing morphological differentiation and transition from a high-risk to a low-risk gene expression profile in cultured UM cells (17).

Entinostat. Entinostat (also known as MS-275) is a class I-specific HDACI. It can synergize with tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), a powerful anticancer agent, to induce apoptosis in TRAIL-resistant UM cell lines and enhance susceptibility of sensitive cells (42). In addition, entinostat increases expression of death receptor 4 (DR4), DR5 and procaspase 8 expression in both TRAIL-sensitive and TRAIL-resistant cell lines. It has also been demonstrated that the overriding of TRAIL resistance by entinostat involves *c-MYC* up-regulation and subsequent transcriptional repression of cellular Fas-associated death domain (FADD)-like interleukin-1beta-converting enzyme-inhibitory protein (*c-FLIP*), a key regulator of extrinsic apoptotic signaling, through inhibition of HDAC1, -2 and-3 (43). Following entinostat treatment, a decrease in the expression oncogenic *miR-92a-3p* was observed both in

TRAIL-resistant and L-sensitive UM cells, suggesting that *miR-92a-3p* down-regulation is an additional component of the pathway triggered by entinostat and leads to increased sensitivity to apoptosis. The same study also revealed a significant decrease in myc-binding protein 2 (MYCBP2), which is greatly involved in entinostat-induced apoptosis in UM, being a cofactor interacting with the c-MYC *N*-terminal domain (44).

Quisinostat. Quisinostat is an experimental inhibitor of HDAC enzymatic activity and highly potent against class I and II HDACs. The antitumor effects of quisinostat on UM have been studied with the use of a xenograft model in zebrafish embryos. Quisinostat was found to completely block proliferation of primary cell lines and markedly inhibit growth of metastatic cell lines *in vitro* and significantly reduce the migration of UM cells *in vivo*. In the same study, quisinostat toxicity was tested by determining which concentrations would be well tolerated with minimal effects on development and survival of embryos and it was reported that the compound was not toxic to embryos even at the highest concentration tested (45).

Sodium butyrate. Sodium butyrate is a low-potency HDACI that inhibits activity of class I HDACs. It has been shown that sodium butyrate reduces proliferation and induces apoptosis of primary and metastatic UM cell lines (35).

JSL-1. JSL-1 is a novel HDACI whose anti-UM activity was recently studied *in vitro* and *in vivo*. JSL-1 increases acetylation of histone proteins H3 and H4 and activates tumor suppressor p53 in UM cells. Moreover, it has been demonstrated that JSL-1 has potent antiproliferative effects on UM cells. JSL-1 exhibits synergistic effect in UM cells when combined with vinblastine, a chemotherapeutic agent used for systemic therapy in patients with UM. The combination of the two agents inhibits the proliferation of UM cells and induces more substantial apoptosis than the single agents, as evidenced by increased levels of cleaved poly-adenosine diphosphate (ADP) ribose polymerase. JSL-1 induces apoptosis with increased expression of proapoptotic BH3-only protein BCL-2-like protein 11 (BIM) in UM cells. JSL-1 reduces the protein level of MMP2, an enzyme critically involved in the degradation of collagen IV (an important component of basement membrane), indicating that JSL-1 can effectively inhibit migration and invasion of UM cells. In addition, JSL-1 blocks the canonical WNT/β-catenin pathway, impairs self-renewal capacity and reduces the percentage of aldehyde dehydrogenase-positive cells, hence reflecting elimination of UM cancer stem-like cells, which are believed to be the main cause of metastasis, drug resistance and disease recurrence. Furthermore, in mice, JSL-1 potently inhibited the growth of UM xenograft and significantly reduced the height of tumors (46).

MC1568 and MC1575. MC1568 and MC1575, two novel class II-specific HDACIs, inhibit expression of interleukin-8 (IL8), a cytokine recognized to have functional implications in tumors (47). It has been found that phorbol 12-myristate 13-acetate (PMA) up-regulates *IL8* transcription *via* the AP-1 binding site and c-JUN has been identified as the transcription factor involved in this event (47). The same study revealed that HDACIs inhibit IL8 expression in unstimulated and in PMA-stimulated melanoma cells through the suppression of (a) c-JUN expression; (b) c-JUN binding to the *IL8* promoter; and (c) recruitment of H3 and H4, RNA polymerase II and TFIIB to the *c-JUN* promoter. Furthermore, both HDACI reduce cell proliferation in untreated and PMA-treated UM cells (47).

Conclusion

The present review highlighted the potential therapeutic role of HDACI in UM. HDACIs have emerged as promising chemotherapeutic agents and the findings of numerous studies indicate their wide range of anticancer activities in various malignancies, including UM. Inhibition of proliferation, cell-cycle arrest, induction of apoptosis, inhibition of migration, induction of morphologic differentiation and transition from a high-risk to a low-risk gene-expression profile are some of the antitumor effects of HDACIs on UM cells. Unlike conventional chemotherapeutic agents that often induce DNA damage in tumor and normal tissues, HDACIs display strong selectivity and, consequently, exhibit less toxicity to normal tissues. Moreover, combining an HDACI with other therapeutic agents seems to have synergistic or additive effect on the expression of target genes, suggesting that this combination may be an attractive therapeutic strategy for using these compounds. The study of HDACIs in various types of cancer is rapidly evolving, however, the exact mechanism(s) of action of these agents against tumor cells is not yet fully understood. The fact that four HDACIs have already approved by the FDA for the treatment of cancer (vorinostat, romidepsin, and belinostat for T-cell lymphoma and panobinostat for multiple myeloma) and clinical trials of other HDACIs are underway, increase hope for their further use in therapy of other types of tumor. Concerning UM, however, additional studies offering a deeper understanding of the mechanisms involved in the antitumor activity of HDACIs would provide important insights into the treatment of this aggressive and life-threatening type of cancer.

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