Published in final edited form as:
Epigenetics. 2008 November ; 3(6): 300–309.

The Role of Histone Deacetylases in Prostate Cancer

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Abstract

Epigenetic modifications play a key role in the patho-physiology of prostate cancer. Histone deacetylases (HDACs) play major roles in prostate cancer progression. HDACs are part of a transcriptional co-repressor complex that influences various tumor suppressor genes. Because of the significant roles played by HDACs in various human cancers, HDAC inhibitors are emerging as a new class of chemotherapeutic agents. HDAC inhibitors have been shown to induce cell growth arrest, differentiation and/or apoptosis in prostate cancer. The combined use of HDAC inhibitors with other chemotherapeutic agents or radiotherapy in cancer treatment has shown promising results. Various HDAC inhibitors are in different stages of clinical trials. In this review we discuss the molecular mechanism(s) through which HDACs influence prostate cancer progression, and the potential roles of HDAC inhibitors in prostate cancer prevention and therapy.

Keywords

prostate cancer; histone deacetylases; apoptosis; growth arrest; epigenetics; histone modification; acetylation

Introduction

Aberrant gene functions and altered patterns of gene expression play important roles in the biology of cancer. This deregulation is often governed at the epigenetic level i.e., heritable changes in gene expression that are not accompanied by changes in DNA sequences. Epigenetic silencing of the gene is very important in eukaryotic organisms, particularly in differentiation, development and imprinting. However, deregulation of this silencing can result in the development of various human diseases, including cancer. The key processes that are responsible for epigenetic gene silencing are DNA methylation, modification of chromatin (covalent modification of core histones), nucleosome positioning (physical alteration) and non-coding RNAs. It is well established that methylation of cytosine in CpG islands results in gene silencing, and there is no doubt that this methylation is intimately associated with the development of cancer. Further, it has been demonstrated and well established that promoter methylation at CpG island sites leads to gene silencing. However, since about 40% of human gene promoters do not contain CpG islands[1], other factors such as histone modification and nucleosome remodeling are also involved in establishing heritable epigenetic gene silencing.

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In 1998, it was shown that methylated DNA binding protein could bind methylated cytosine and makes a complex with histone deacetylase (HDAC) that lead to chromatin compactions and gene silencing.[2-3] Furthermore, it was demonstrated that nucleosome remodeling complex (NuRD) can methylate DNA by interacting with DNA methylation binding protein (MBD2), which directs the NuRD complex to methylate DNA.[4] These and other more recent findings have established that DNA cytosine methylation, covalent modification of histones and nucleosome remodeling are linked together and are the main components of epigenetic gene regulation. Several detailed and informative reviews of the associations between DNA methylation and prostate cancer are available.[5-9]

Histone modifications, particularly acetylation and deacetylation, are the major driving force for epigenetic gene regulation.[10] The reversible covalent modification of histone is heritable and is maintained from generation to generation. Histone deacetylase (HDAC) and histone acetyltransferase (HAT) are the key enzymes responsible for these reversible modifications. The histone deacetylases are a group of enzymes that primarily target histone proteins; however, more than 50 non-histone targets of HDACs have been discovered.[10-11] Many of these HDAC substrates are the regulatory proteins that are involved in cell adhesion, cell division and apoptosis. For example, HDACs 1, 2 and 3 are involved in the regulation of cell cycle by repressing cell cycle genes such as p21/Waf-1.[12-14] HDAC8, regulates smooth muscle contractility,[15] and participate in cellular proliferation.[16] HDAC4, HDAC5, HDAC7 and HDAC9 are transcriptional co-repressors and responsible for catalytic activity of various co-repressor complexes such as N-CoR, SMRT, BCoR and CtBP.[17] They also interact with various DNA-binding transcription factors including BCL6, MEF2, PLZF, TR2, and with the methyllysine-binding protein HP1 that regulates several physiological functions.[17-19] HDAC6 is a multifunctional protein that regulates several important biological processes, including cell migration, protein folding, mis-folded proteins degradation, cellular stress, immune synapse formation.[20-25] Furthermore, HDAC6 and HDAC10 play important roles in HSP-mediated vascular endothelial growth factor receptors VEGFR regulation.[26] Because a broad spectrum of histone and non-histone proteins are targets of HDACs, it follows that HDACs act as master regulators of many diseases, including cancer. Elevated HDACs level in cancers results in increased proliferation of cancer cells, associated with down regulation of apoptosis, altered cell cycle regulation, enhanced tumor angiogenesis, and induction of various oncogenes. In this review we discuss the role of HDACs in the progression of prostate cancer, and the role of HDAC inhibitors in prostate cancer treatment.

Histone deacetylases: Classification and biological function

Histone deacetylases (HDACs) comprise a group of enzymes that are responsible for the removal of acetyl groups from a ε-N-acetyl lysine amino acid. As the organization and packaging of eukaryotic DNA is achieved through the addition of core histones H2A, H2B, H3 and H4, which form a complex structure called chromatin, the modification of core histones is of fundamental importance to conformational changes in chromatin.[17, 18] The level of acetylation influences transcription activity: acetylation induces an open chromatin confirmation that allows the transcription machinery access to promoters. Chromatin acetylation correlates with transcriptional activity (euchromatin), whereas deacetylation correlates with gene silencing. HDACs are also involved in the reversible acetylation of non-histone proteins.

In mammals, total 18 HDACs have been identified and grouped into four classes i.e., class I (HDACs1-3 & 8), class II (HDACs 4-7 and HDACs 9-10), class III (Sirt1-Sirt7) and class IV (HDAC11). The members of class I HDACs (HDACs 1-3 & HDAC 8) contain a deacetylase domain and are the homologs of yeast RPD3. They exhibit 45% to 93% amino acid sequence identity and localize in the nucleus. Class II HDACs (HDACs 4-7 and HDACs 9-10) are

homologs of yeast Hda1 and are present in both the nucleus and cytoplasm. HDAC 6 is an exception which contains two deacetylase domains, at both the N and C-terminals. The molecular weights of class II HDACs are twofold higher than class I HDACs. The members of HDAC class III (Sirt1-Sirt7) are homologs of yeast Sir2 (silent mating type information regulation 2) and form a structurally distinct class of NAD-dependent enzymes found in both the nucleus and cytoplasm. HDAC 11 has properties of both class I and class II HDACs and represents class IV (Table-1).

HDAC classes I and II are highly conserved from yeast to humans, and have a zinc-binding motif. Both class -I and -II HDACs are inhibited by trichostatin A (TSA), an antifungal antibiotic. Despite the important roles played by both HDAC class -I and -II enzymes in the regulation of gene expression, the exact mechanisms of their catalytic activities are still not completely known. The zinc-coordinated active site activates an H_2O molecule for hydrolysis of the acetyl group to form acetate. The acetylation of lysine amino acids in core histones provides a balance of positive-negative charges that leads to chromatin relaxation. However, HDACs alter this balance; the resultant condensation of chromatin leads to gene silencing. HDAC class III members are Sir2-like proteins; they catalyze a unique reaction that requires the coenzyme NAD+. These enzymes deacetylase acetylated lysine *via* hydrolysis of NAD+ that liberates nicotinamide and a novel metabolite, O-acetyl-ADP ribose. Due to NAD+ dependency, Sir2 enzymes are linked directly to the energy status of the cells, and may play important roles in aging.

Histone deacetylases work in multi-subunit transcriptional co-repressor complexes that are recruited by sequence-specific transcription factors to promoter regions.[18] There are several co-repressor complexes for distinct promoters, which recruit specific HDAC isoforms for silencing of target genes.[27-28] For example, HDACs1, 2 and 3 are majorly responsible for catalytic core for different co-repressor complexes to achieve efficient transcriptional repression. HDAC1 and HDAC2 are present in the CoREST, Mi2/NuRD and Sin3 complexes, whereas HDAC3 is responsible for catalytic activity of the N-CoR and SMRT co-repressor complexes.[29-30] HDACs cooperate with various other transcriptional regulators; such as, HDAC1 and HDAC2 associate with DNA methyltransferases (DNMTs)[31-32] and histone methyltransferases (HMTs).[33] Furthermore, HDAC1 interacts with topoisomerase II enzyme that is responsible for chromosome condensation.[34] However, little is known about the specificity of a particular histone deacetylase enzyme for a specific lysine residue. Zhang *et al.* reported the preferential acetylation of H3K18 and H3K9 following knockdown of HDAC1 and HDAC3, respectively.[35] Non-histone deacetylation-based gene repression involves deacetylation of various transcription factors by HDACs. Deacetylation of sequence-specific transcription factors can decrease their DNA binding activity, and subsequently may repress transcription. The covalent modifications of several transcriptional factors, including E2F, sp3, p53, GATA1, TFIIF etc. have been reported. [36-41] Ito *et al.* described the specificity of HDAC1 for p53 deacetylation, resulting in degradation of de-acetylated p53.[42] It has also been found that HDAC2 deacetylates the glucocorticoid receptor and HDAC3 is needed for deacetylation of monocyte enhancer factor-2.[43-44] HDACs are also involved in deacetylation of non-nuclear proteins like tubulin45 and HSP90.[45-46]

HDAC and cancer

The targets of HDAC enzymes are the acetyl (CH_3CO) groups on histones. Histones are proteins that form a scaffold around which a cell's DNA is wrapped. Modification of these histone proteins by acetylation controls the tightness of the DNA around the histone proteins and, consequently, controls the expression of the genes. In cancer, increased HDAC expression results in deacetylation of histone proteins. Deacetylation causes the DNA to be wrapped too

tightly around the histones, thereby inhibiting gene expression. Cancer may result if the genes affected are tumor suppressor genes.

Over expression of HDACs in many cancer cells, results in repression of important growth suppressive genes, is an important mechanism to promote cancer cell proliferation. However, some cancer cells over expresses a particular HDAC enzyme, for example, HDAC1 is over expressed in prostate cancer cells[47] and HDAC2 is commonly over expressed colorectal carcinomas, cervical dysplasias, endometrial stromal sarcomas and by gastric carcinomas.[48] Both HDAC1 and HDAC2 over expression correlate with reduced cyclin-dependent kinase inhibitor p21 expression.[49, 50] HDAC2 knockdown increases apoptosis; however, sporadic colorectal carcinomas with a frame-shift mutation encoding truncated, non-functional HDAC2 are resistant to the HDAC inhibitor induced apoptosis.[51, 52] Colon cancer cells over express HDAC3 leads to the inhibition of p21 expression and HDAC3 silencing increases *p21* promoter activity and expression.[14] HDACs also modulate various genes involved in cancer progression *via* angiogenesis, adhesion, cell migration and invasion required for metastasis. Over expression of HDAC1 represses the p53 and von Hippel–Lindau (VHL) and induces the hypoxia-responsive HIF-1α and VEGF results in increased angiogenesis; however, HDAC inhibitors reverse the process and inhibits hypoxia-induced angiogenesis.[53, 54] HDAC1 represses cystatin, a peptidase inhibitor that suppresses tumor invasion. Knockdown of HDAC1 or overexpression of cystatin reduces cellular invasion.[55] The cell adhesion protein E-cadherin expression is also regulated by Snail mediated HDAC1/HDAC2/mSin3A co-repressor complex whose loss is responsible for tumor metastasis.

Ozdag and co-workers reported the expression patterns of HDAC1, HDAC2, HDAC4, HDAC5, HDAC7 and SIRT1 along with several histone acetyl transferases (HATs) and histone methyl transferases (HMATs) in 225 samples (135 primary tumors, 47 cancer cell lines, and 43 normal tissues) analyzed by QRT-PCR.[56] These genes are hot spots for neoplastic transformation, with expression patterns that are characteristic of different tissue types. These investigators discovered an insertion of a CAG triplet in the 5′-UTR of HDAC2 in 18% of 181 cancer samples and in 10% of 192 normal DNA controls ($P<0.01$, Fisher's exact test), however, further studies are needed with larger sample sizes to confirm this association with cancer. Overexpression of HDAC1 has been reported in prostate and gastric cancers.[57, 58]

Possible links between germ-line mutations in various HDACs and increased risk of lung and breast cancer have been investigated, but no associations have been observed. [59, 60] Ropero *et al.* screened six colorectal and four endometrial cancer cell lines with microsatellite instability for all the exonic mononucleotide repeats in the coding sequences of HDAC1 and HDAC2, along with various others selected histone modifier genes and found no mutations except for the A9 repeat of exon 1 of HDAC2.[61] This truncating mutation in HDAC2 was detected in colonic, gastric and endometrial primary tumors with microsatellite instability. The presence of a HDAC2 frame-shift mutation causes a loss of HDAC2 protein expression and enzymatic activity, making these cells more resistant to the pro-apoptotic and anti-proliferative effects of HDAC inhibitors.[61] In another study, HDAC1 and HDAC2 were screened for mutations in 181 cancer samples (116 primary tumors of breast, ovarian and colorectal origin and 65 cancer cell lines of breast, ovarian, lung, pancreatic and colorectal origin); a single nucleotide deletion was detected, resulting in a frame-shift mutation in exon 12 of HDAC2 in the HCT15 colorectal cell line.[56] In a large-scale sequencing study of breast and colorectal cancers, Sjoblom and co-workers identified a significant frequency of HDAC4 mutations in breast cancer.[62]

HDACs and prostate cancer

Prostate cancer is the second most frequently diagnosed cancer, and the third most common cause of cancer-related death in men in the United States and other developed nations.[63] Prostate cancer is a heterogeneous disease, the etiology of which appears to be related to a complex range of risk factors, including lifestyle patterns, genetic factors and epigenetic modifications. Hypermethylation of CpG islands and chromatin remodeling play important roles in repression of various tumor suppressor genes during malignant transformation of prostate epithelial cells. It has been demonstrated that DNMT1 and HDAC1 levels are up-regulated in prostate cancer compared to BPH, suggesting that they play roles in the inactivation of various critical genes by DNA-methylation-induced chromatin-remodeling.[64] In various prostate cancer cell lines, DNMT inhibitor 5′-aza-2′-deoxycytidine and HDAC inhibitor TSA reduce cell proliferation and induce caspase activation as well as re-expression of ER-beta.[65] Acetylation of the androgen receptor (AR) is induced by dihydrotestosterone, and HDAC inhibitors enhance the binding of p300 and reduce N-CoR/HDAC/Smad3 co-repressor binding, enhancing cell survival and growth of prostate cancer cells both *in vivo* and *in vitro*.[66]

Androgen deprivation, an important therapeutic strategy for patients with advanced stage prostate cancer, reduces clinical symptoms in about 70–80% of patients, but most patients suffer relapse within 2 years due to the development of an androgen-independent tumor. The molecular mechanisms by which androgen antagonists inhibit prostate cancer cell proliferation are not fully defined. The acetylation of AR is necessary for co-activator bonding to AR as well as reduced co-repressor binding that promotes aberrant cell growth.[66] Tip60 (Tat-interactive protein, 60 kDa) is an AR co-activator which regulates AR activity *via* HDAC1 as they form a trimeric complex upon the PSA promoter.[67] It has been demonstrated that AR is the direct target for Mdm-2 mediated ubiquitylation and proteolysis. In LNCaP cells, Mdm-2 associates with HDAC1 and AR at androgen-responsive PSA promoter and both Mdm-2 and HDAC1 cooperatively down regulate the AR target genes.[68] Logan *et al* reported that hPIRH2 (human p53-induced RING-H2 protein) is over-expressed in prostate cancers and significantly correlated with metastasis. They further showed that hPIRH2 interacts with AR lead to enhance AR target gene expression and also targets AR co-repressor HDAC1 and represses gene silencing.[69] It was shown recently that NAD-dependent sirtuin 1 (SIRT1) is required for androgen antagonist-mediated transcriptional repression and growth suppression. Androgen antagonist-bound androgen receptor (AR) recruits SIRT1 and nuclear receptor co-repressor to AR-responsive promoters and deacetylates histone H3 locally at the PSA promoter.[70] ARR19 is a novel AR co-repressor that recruits HDAC4, leading to repression of AR transactivation.[71] It has also been demonstrated that androgen is involved in nuclear localization of HDAC4 and is predominantly present in the nucleus in more aggressive prostate cancers.[72] These findings demonstrate that androgen, HDAC4 and ARR19 play important roles in prostate cancer progression.

The ErbB3 binding protein, Ebp1 inhibits the proliferation and induces the differentiation of human ErbB-positive prostate cancer cell lines. Ebp1 binds the tumor suppressor retinoblastoma protein (Rb) both *in vivo* and *in vitro*, and Rb and Ebp1 cooperate to inhibit the transcription of the E2F1-regulated cyclin E promoter. Zhang and co-workers reported that Ebp1 can inhibit the transcription of other E2F-regulated reporter genes and of several endogenous E2F-regulated genes important in cell cycle progression in both Rb positive and negative cells. The C-terminal region of Ebp1 has a HDAC binding domain that can repress transcription of some E2F-regulated promoters *via* recruitment of HDAC.[73] Ebp1 interacts with Sin3A both *in vitro* and *in vivo* and Ebp1 participates in transcriptional regulation *via* its interaction with the Sin3-HDAC.[74] Blockage of the ErbB signaling pathway may be a useful strategy for cancer treatment. ErbB blockade in conjunction with HDAC inhibition inhibits cell proliferation and induces apoptosis in prostate cancer cells.[75]

Maspin, a tumor-suppressor, is associated with cancers that are better differentiated, more sensitive to drug therapy, and prognostically more favorable. Maspin interacts with HDAC1 in human prostate cancer cell lines and prostate tissues.[76] Studies have further shown that this direct molecular interaction in both the nucleus and cytoplasm inhibits HDAC1 *via* glutathione S-transferase (GST).[76] An inverse relationship has been observed between maspin expression and metastasis. It has been demonstrated that IKKα is the mediator that controls prostate cancer metastasis by repressing maspin.[77] RANK ligand (RANKL/TNFSF11) activates IKKα, leading to inhibition of maspin expression in prostate epithelial cells and producing a metastatic phenotype, whereas repression of maspin transcription requires nuclear translocation of active IKKα.[77] More recently, Hall and co-workers reported that maspin significantly reduces prostate cancer metastases to bone in an animal model.[78]

Human DAB2 interactive protein (hDAB2IP), a member of Ras GTPase-activating family, directly interacts with DAB2 (disabled 2 protein). DAB2 is also known as DOC-2 (differentially expressed in ovarian carcinoma 2). This protein complex negatively regulates Ras mediated signaling and exhibits growth inhibitory effects on prostate cancer.[79] The hDAB2IP gene is epigenetically suppressed in prostate cancer through both DNA methylation and chromatin alterations.[80] Downregulation of hDAB2IP is mediated by Ezh2, a histone lysine methyltransferase, and HDAC1.[81] The polycomb Ezh2 level is elevated during prostate cancer progression. The elevated Ezh2 along with Sirt1 and Eed2 forms a polycomb repressive complex 4 (PRC4).[82] Yang *et al.* demonstrated that SIRT1 interacts with FOXO1, a transcription factor that influences the cell cycle, apoptosis and stress response in prostate cancer cells. Another protein FHL2 (four and a half LIM2) enhances SIRT1/FOXO1 interaction, resulting in enhanced acetylation and inhibition of FOXO1 activity.[83]

Expression of histone deacetylases in prostate cancer

It has been established that histone deacetylases are upregulated in most human cancers.[84] However, the function of specific HDAC isoforms in human cancers remains elusive. Waltregny *et al.* screened the expression profiles of various class I and class II HDACs in DU145, PC-3 and LNCaP human prostate cancer cell lines as well as in matched malignant and non-malignant prostate tissues by use of real time RT-PCR, immunoblot and immunohistochemical analysis. All HDAC isoforms screened were present in prostate cancer cell lines at various levels. HDAC1 protein was abundantly present in normal and malignant epithelial nuclei in prostate tissue, with lower expression in the stromal cells. HDAC5 was absent in prostate tissues and HDAC8 was not detected in epithelial cells but was uniquely expressed in the cytoplasm of the stromal cells.[85] The differential class I HDAC expression profiles in epithelial and stromal cells, and the prominent cytosolic distribution of HDAC8 suggest that the various HDAC isoforms may play important roles in the progression of prostate cancer. However, more mechanistic studies are needed to explore the patho-physiology of histone deacetylases in prostate cancer.

Weichert and co-workers investigated the expression of class I histone deacetylases by immunohistochemistry in 192 prostate cancer samples.[86] They reported strong expression of HDAC1, HDAC2 and HDAC3 in the majority of cases, and found that the expression of HDAC2 is of highly significant prognostic value, and that the differential expression of HDAC1, HDAC2 and HDAC3 in prostate cancer may play some role during cancer progression. HDAC1 immunohistochemical expression in prostate neoplasms was shown to be increased in pre malignant and malignant lesions and in hormone-refractory cancers.[87] The expression of HDAC8 in benign and malignant prostatic tissue was found to be lower than in various non-prostatic malignancies.[84] HDAC4, a class II HDAC, is predominantly localized in the cytoplasm of benign prostate hyperplasia cells and primary prostate cancer cells; in

hormone-refractory cancers, HDAC4 is predominantly expressed in the nucleus.[72] The nuclear presence of HDAC4 may contribute to more aggressive biologic behavior.

Bakin & Jung demonstrated that HDAC7 localizes to the mitochondrial inner membrane space in prostate epithelial cells and delocalizes into the cytoplasm in response to initiation of the cell death cascade.[88] Since mitochondria are known to play an important role in programmed cell death, these findings suggest that HDACs, and HDAC7 in particular, may be responsible for initiation of apoptotic signaling. Further studies will be needed to explore the molecular link between mitochondria, HDAC and apoptosis.

Kojima *et al.* reported higher SIRT1 expression in androgen-refractory PC3 and DU145 cells compared with androgen-sensitive LNCaP cells that may play an important role in promoting cell growth and chemo-resistance.[89] Dai *et al.* demonstrated that SIRT1 is required for androgen antagonist-mediated growth suppression and that down-regulation or suppression of SIRT1 activity increases the sensitivity of prostate cancer cells to the transcriptional and proliferative activities of androgens.[90] Increased expression of SIRT1 protein has been demonstrated in human prostate cancer and in the prostates of TRAMP mouse, suggesting that SIRT1 may represent a molecular target for prostate cancer prevention and therapy.

Use of HDAC inhibitors in prostate cancer

HDAC activity is enhanced in various cancers including prostate cancer. Inhibitors of HDACs have emerged as potent anti-cancer agents. HDAC inhibitors induce dose-dependent inhibition of either class I or class II HDACs, or both, leading to G_1 or G_2 cell cycle arrest and/or cell death. HDAC inhibitors cause the accumulation of acetylated histones, leading to activation of transcription of selected genes whose expression causes inhibition of tumor cell growth and induction of apoptosis.[91-93] However, HDACs also have various non-histones targets. Some HDAC inhibitors increase Ku70 acetylation, a crucial component of the DNA repair machinery for double-strand breaks, resulted in reduced DNA-binding affinity.[94] This sensitizing effect of HDAC inhibitors is potentially useful in combination with DNA-damaging agents for the treatment of prostate cancer. Some newly synthesized compounds are potentially effective for both cancer chemoprevention and cancer therapy. Various HDAC inhibitors with putative radio-sensitization properties have been screened.[95, 96] HDAC inhibitors selectively turn on tumor suppressor genes, a therapeutic effect that is not induced by traditional chemotherapy. Relatively little is known about the molecular mechanisms of HDAC inhibitors and their modes of action. Five classes of HDAC inhibitors have been characterized:

1. Hydroxamic acids (e.g., TSA, SAHA)
2. Short-chain fatty acids (e.g., sodium butyrate)
3. Cyclic peptides with 2-amino-8-oxo-9,10-epoxy-decanoyl (e.g., trapoxin A)
4. Cyclic peptides without the 2-amino-8-oxo-9,10-epoxy-decanoyl moiety (e.g., FK228)
5. Benzamides (e.g., MS-275)

The response of prostate cancer cells to HDAC inhibitors is not uniform, but cell line, target and inhibitor specific[97] as shown in Table-2. There are a number of reports pertaining to the utility of various HDAC inhibitors in the management of prostate cancer. The detail description of HDAC inhibitors in context to prostate cancer is described below.

Suberoylanilide hydroxamic acid (SAHA) or Vorinostat

SAHA or vorinostat is a member of a family of hybrid polar compounds that induce growth arrest via inhibition of HDAC. SAHA is marketed under the name Vorinostat (brand name

Zolinza) for the treatment of a skin cancer called cutaneous T cell lymphoma. Vorinostat is based on hydroxamic acid, can inhibit the HDAC class -I, -II, and -IV, but not class-III. Dokmanovic *et al.* demonstrated that vorinostat selectively down-regulates HDAC7 in various cancerous cell lines including prostate cancer cell lines.[98] SAHA can also enhance radiation-induced cytotoxicity in DU145 human prostate cell line.[99] Sonnemann *et al.* reported that SAHA in combination of zoledronic acid (ZOL) synergistically induce cell death in the prostate cancer cell lines LNCaP and PC-3. Further they induce dissipation of the mitochondrial transmembrane potential, to activate caspase-3, and to trigger DNA fragmentation.[100] SAHA decreases androgen receptor (AR) expression and PSA in LNCaP cells and acts synergistically with an androgen receptor antagonist to inhibit prostate cancer cell proliferation.[101]

Trichostatin A (TSA)

Trichostatin A is an antifungal antibiotic that selectively inhibits the class I and II mammalian histone deacetylase enzymes, but do not inhibits class III (Sirtuins). TSA inhibits the eukaryotic cell cycle during the beginning of the growth stage. In prostate cancer cell lines TSA can lead to TRAIL-induced cell death.[102] TSA up-regulates fibroblast growth factor 8 (FGF8) via activation of NF-kappaB.[103] Hernandez *et al.* demonstrated that TSA restores the connexin 43 (cx43) gene expression in prostate cancer.[104] The cx43 is responsible for gap junctional intercellular communication (GJIC) important for regulation of tissue homeostasis. TSA causes Akt dephosphorylation in PC-3 prostate cancer cells by disrupting HDAC-protein phosphatase 1 (PP1) complexes. This down-regulation of phospho-Akt is not mediated through deactivation of upstream kinases or activation of downstream phosphatases. However, TSA blocks specific interactions of PP1 with HDACs 1 and 6, resulting in increased PP1-Akt association.[105] Suenaga *et al.* reported a novel mechanism of anti-proliferative effects of HDAC inhibitors TSA by down-regulating the telomerase activity *via* suppression of hTERT mRNA expression in prostate cancer PC-3 and LNCaP cells.[106]

LBH589

LBH589 is hydroxamic acid derivative and has potent HDAC inhibition activity. Very recently it was reported that HDAC inhibitor LBH589 decreases the hypoxia-inducible factor-1alpha (HIF-1α) expression in PC3 prostate cancer cell line.[107] Hypoxia-inducible factor is not only responsible for oxygen homeostasis but it act as a master regulator responsible for controlling intracellular pH, regulation of apoptosis and cell migration, balancing energy metabolism and off-course responsible for formation of new blood vessels.[108] The HIF-1α regulates specific genes that result in tumor induced angiogenesis. However, the role of LBH589 in the inhibition of tumor angiogenesis has already been reported in mice model.[109]

R306465

R306465 is a novel broad spectrum hydroxamate based HDAC inhibitor. R306465 selectively inhibits class-I HDAC, HDAC1 and HDAC8 but not very much effective for HDAC6 in a variety of hematological and solid tumors including prostate cancer.[110]

KD5170

The KD5170 is a non-hydroxamate-based broad spectrum HDAC inhibitor. Recently Hassig *et al.* reported a high anti-proliferative activity of KD5170 in various cancerous cell lines including PC-3 prostate adenocarcinoma cell line *in-vivo* as well as *in-vitro*.[111]

Sodium Butyrate

Sodium butyrate is a four-carbon chain volatile fatty acid induces apoptosis in prostate cancer cells.[112] Sodium butyrate can alter the expression of androgen receptors and various cell cycle regulators at epigenetic level in androgen dependent LNCaP cells that lead to induction of

apoptosis and inhibition of cell proliferation.[113] Sodium butyrate can trigger the TRAIL-induced apoptosis in prostate cancer cell lines.[102] In prostate cancer preclinical model, millimolar concentration of sodium butyrate inhibits the telomerase activity via inhibition of hTERT mRNA expression, may lead to cell cycle arrest, apoptosis, or cell differentiation.[106]

FK228

FK228 is a bicyclic peptide containing a non-cysteine disulfide bridge, isolated from *Chromobacterium violaceum* Strain WB968. It has potential anticancer activity in vitro and showed significant inhibitory effects on the growth of human solid tumors xenografts. In prostate cancer pre-clinical model, FK228 down regulate the expression of angiogenesis factors VEGF and basic fibroblast growth factor (bFGF) in PC-3 cells.[114-115]

Valproic acid

Valproic acid is a potent HDAC inhibitor that is able to check cell proliferation, upregulates the androgen receptor levels and E-cadherin expression in human prostate cancer cells. However the effect of valproic acid is cell line specific as the effects are more pronounced in androgen independent PC-3 cells than androgen dependent LNCaP.[116] The derivatives of valproic acid ACS2 and ACS33 are having more potential anti-tumoral activities as compared to the original compound.[117] Very recently Angelucci *et al.* showed that VPA induces the neuro-endocrine transdifferentiation (NET) in androgen independent PC3 cells at the both in vitro and in vivo level.[118] The prostate glands contain a small population of neuroendocrine (NE) cells in the epithelial compartment.[119] In case of prostate cancer progression, the cells showing NE phenotypes with NE markers are increased, and correlated with poor prognosis and androgen-independency. Various *in-vitro*, *in-vivo* and clinical data suggest that cancerous cells undergo a transdifferentiation process to become NE-like cells.[120] Because of the dual effect of VPA as a HDAC inhibitor as well as inducer of NET, the NE transdifferentiation pathway need to be blocked while using VPA for therapy of prostate cancer. Furthermore, VPA can modulate the expression of different androgen metabolism genes and may enhance dihydrotestosterone (DHT) catabolism.[121]

(S)-HDAC-42

It is a phenylbutyrate-derived histone deacetylase inhibitor induces apoptosis and down regulates phospho-Akt, Bcl-xL, and survivin level as well as suppresses the growth of PC-3 tumor xenografts.[122]

MS-275

MS-275 is a benzamide-based HDAC inhibitor. MS-275 exerts growth arrest and induces cell death in prostate cancer cell lines as well as inhibits the growth of subcutaneous xenografts.[123] HDAC inhibitor MS-275 restores the retinoid sensitivity in prostate cancer cells.[124] Further, it enhances the histone hyperacetylation and radiosensitivity of DU145 xenografts.[125] The exposure to MS-275 before and after irradiation resulted in an increase in radiosensitivity in DU145 cell and may affect DNA repair.[126]

OSU-HDAC42

OSU-HDAC42 is a novel HDAC inhibitor showing broad spectrum inhibition of HDAC activity lead to increased apoptosis and cell differentiation and decreased proliferation of cancerous cells. A recent study based on TRAMP model showed that dietary administration of OSU-HDAC42 causes a suppression of PC-3 xenograft tumor growth, block the tumor progression and shifted tumorigenesis to a more differentiated phenotype.[127]

Phenylhexyl isothiocyanate (PHI)

The isothiocyanates are the constituents of cruciferous vegetables and have anticancer properties. PHI inhibited the activity of HDAC and remodeled chromatins to activate p21 for G1 cell cycle arrest and apoptosis.[128]

Sulforaphane (SFN)

SFN is an isothiocyanate from broccoli having chemopreventive properties. SFN induces cell cycle arrest and activation of apoptosis in benign prostate hyperplasia, androgen-dependent prostate cancer and androgen-independent prostate cancer cells.[129] *In vivo* experiment with PC-3 xenografts also showed that SFN acts as a chemopreventive agent through inhibition of HDAC activity.[130] Furthermore, they reported that in human BroccoSprouts consumption significantly inhibits HDAC activity in peripheral blood mononuclear cells.[130] HDAC activity in peripheral blood mononuclear cells after exposure of HDAC inhibitors can be use as a biomarker for the assessment of chemotherapy.

HDAC Inhibitors in clinical trials

Several clinical trials with HDAC inhibitors are currently undergoing in combination with retinoids, taxol, gemcitabine and with radiation therapy in patients with hematologic malignancies and solid tumors including those of lungs, breast, bladder, breast and pancreas.[91-93] More than 100 clinical trials are ongoing with HDAC inhibitors as monotherapy or in various combination therapies. However there are no reports available on clinical trials with prostate cancer.

Conclusion and future prospective

Histones deacetylases are among the key regulators in the development and progression of prostate cancer. The functions of HDACs are diverse: they covalently modify histone core proteins and also deacetylate various other non-histone cytosolic and nuclear proteins. At least 18 HDACs have been characterized and categorized into four different groups on the basis of domain organization and sequence identity. Various studies have shown that HDACs have specific targets, but the exact role of specific HDACs in the patho-physiology of prostate cancer are still not well understood and need further clarification. Furthermore, HDAC inhibitors are emerging as promising drugs for cancer therapy and various inhibitors are undergoing clinical trials. The molecular mechanisms and targets of most HDAC inhibitors have not been elucidated. Preclinical studies of combination therapies, using HDAC inhibitors with other anti-cancer agents, have shown promising results that justify further investigation for potential use in the therapy of prostate cancer.

Although normal cells appear to be relatively resistant to the effects of HDAC inhibitors as compared to transformed cells, the pharmacological safety profiles of various HDAC inhibitors are not currently established. The efficacy and usefulness of isoform-specific *versus* broad spectrum HDAC inhibitors are under debate. HDAC inhibitors cause extensive histone deacetylation and usually affect less than 10% of the gene[131-132] but it has been shown in another study that at least 22% of genes are affected.[133] Broad-spectrum HDAC inhibitors may be more toxic than specific inhibitors. In various *in-vitro* studies of HDAC inhibitors, untreated cancerous cell lines have been used as controls, but ideally their corresponding normal cell lines should also be evaluated in such experiments.

The potential utility of HDAC inhibitors in prostate cancer prevention has not been demonstrated, but current information suggests that they may have a role in this arena. Various dietary agents with putative anticancer activities, such as butyrate, garlic organo-sulfur compounds, and sulforaphane, exhibit HDAC inhibitory activity, and this may provide a

rationale for their use in chemoprevention of prostate cancer which may account for their possible importance in this disease. However, extensive studies will be needed to clarify their molecular mechanisms and to further screen other dietary agents for their possible use in cancer prevention and therapy of prostate cancer.

Acknowledgements

Supported by United States Public Health Service Grants RO1 CA115491 and R21 109424

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Abbreviations

AR

androgen receptor

BCoR

BCL6 co-repressor

CtBP

C-terminal binding protein

DNA
deoxyribonucleic acid

DHT
dihydrotestosterone

DOC-2
differentially expressed in ovarian carcinoma 2

FOXO
forkhead transcription factor

FHL2
four and a half LIM2

GJIC
gap junctional intercellular communication

GST
glutathione S-transferase

HDAC
histone deacetylase

HIF-1α
hypoxia-inducible factor-1alpha

HSP90
heat shock protein 90

hDAB2IP
Human DAB2 interactive protein

MEF-2
myocyte-enhancing factor-2

PRC4
polycomb repressive complex 4

NE
neuroendocrine

NuRD
nucleosome remodeling complex

MBD
methylation binding protein

NAD
Nicotinamide adenine dinucleotide

N-CoR
Nuclear receptor co-repressor

HAT
acetyltransferase

HMAT
histone methyl transferases

PLFZ
promyelocytic leukemia zinc finger

Rb
retinoblastoma

RNA
ribonucleic acid

SAHA
Suberoylanilide hydroxamic acid

SIRT
silent mating type information regulation

SMRT
silencing mediator for retinoic acid and thyroid hormone receptor

TRAMP
transgenic adenocarcinoma of the mouse prostate

TSA
trichostatin A

TFIIF
transcription Factor II F, Tip, Tat-interactive protein

VEGFR
vascular endothelial growth factor receptor

VHL
von Hippel–Lindau

Table 1

HDAC classification depending on sequence identity and domain organization

Histone Classes	Members	Localization	Target Proteins (partial list)
Class I	HDAC1	Nucleus	AR, p53, E2F-1, SHP, STAT3, MyoD
	HDAC2	Nucleus	STAT3, Bcl6, glucocorticoid receptor GATA-1, STAT-3,SHP, RelA, YY-1
	HDAC3	Nucleus	
	HDAC8	Nucleus	-
Class II	HDAC4	Nucleus/Cytoplasm	GCMa, GATA-1, HP-1
	HDAC5	Nucleus/Cytoplasm	GCMa, Smad7, HP-1
	HDAC6	Mostly Cytoplasm	HSP70, Smad7, SHP, α-tubulin
	HDAC7A	Nucleus/Cytoplasm	PLAG1, PLAG2
	HDAC9	Nucleus/Cytoplasm	-
	HDAC10	Mostly Cytoplasm	-
Class III	SIRT1	Nucleus	NF-κB, p53, FOXO
	SIRT2	Cytoplasm	α-tubulin, H4
	SIRT3	Nucleus/Mitochondria	Acetyl-CoA synthetases
	SIRT4	Mitochondria	Glutamate dehydrogenate
	SIRT5	Mitochondria	-
	SIRT6	Nucleus	DNA polymerase B
	SIRT7	Nucleus	RNA polymerase 1
Class IV	HDAC11	Nucleus/Cytoplasm	-

Table 2

HDAC inhibitors studied in reference to prostate cancer

S. No.	Name of HDAC inhibitors	Cell lines / animal models	Reported mechanisms of action	Fate of cancerous cells	References
1.	LBH589	PC3, mice model	Down regulation the HIF1- α	Inhibition of tumor angiogenesis	107, 109
2.	Valproic acid (derivatives ACS2 and ACS33)	PC3, LNCaP, DU145, xenograft	Up regulation of AR and E-cadherin expression, induction of neuro-endocrine transdifferentiation (NET), modulation of androgen metabolism gene expression	Blockade of cell proliferation and tumor growth, prevent cell attachment to endothelium, apoptosis	116-118, 121
3.	KD5170	PC3 (in-vivo and in vitro)	alteration in mitochondrial membrane potential and DNA fragmentation	Inhibition of cell proliferation, tumor growth inhibition and apoptosis	111
4.	OSU-HDAC42	PC3 xenograft, and TRAMP mice	modulation of intraprostatic biomarkers	Blockade of tumor growth, cell differentiation	127
5.	R306465	DU145, PC-3	Inhibition of class-I HDAC1 and HDAC8	Inhibition of cell proliferation	110
6.	Sodium Butyrate	LNCaP, PC-3	Alteration in the expression of AR and various cell cycle regulators, induction of TRAIL pathway, inhibition of telomerase activity via hTERT, terminal differentiation via induction of carboxypeptidase A3 (CPA3), increased expression of IGF binding protein-3	Apoptosis, inhibition of cell proliferation, cell differentiation, cell cycle arrest	102, 106, 112, 113, 134, 135
7.	MS-275	DU145, PC-3, LNCaP, TRAMP, mouse xenograft	Increase of hyperacetylation and radiosensitivity, restoration of retinoid sensitivity	Growth arrest, cell death, inhibition of xenografts' growth	123-126
8.	(S)-HDAC-42	PC-3	Down regulation of phospho-Akt, Bcl-xL, and survivin level	Apoptosis, tumor xenografts' growth suppression	122
9.	Trichostatin A (TSA)	LNCaP, PC-3	Up-regulation of tumor suppressor hDAB2IP gene, TRAIL-induced cell death, up-regulation of fibroblast growth factor 8 (FGF8) via activation of NF-κB, restores the connexin 43 expression, blocks interaction of PP1 with HDAC1 and 6 resulting in increased PP1-Akt association, down-regulation of telomerase activity *via* suppression of hTERT	Apoptosis, growth arrest	80, 102-106
10.	Suberoylanilide hydroxamic acid (SAHA) or Vorinostat	DU145, LNCaP, PC-3	Modulation of ErbB signaling, G2/M phase cell cycle arrest, up-regulation of HLA class I antigens, selectively down-regulates HDAC7; increased radiation-induced cytotoxicity, decreases AR expression and PSA level, in combination of zoledronic acid induce dissipation of the mitochondrial transmembrane potential, activate caspase-3, and trigger DNA fragmentation	Apoptosis, growth arrest	99-101, 136, 137
11.	FK228	PC-3, DU145 xenograft	Down regulation of VEGF and basic fibroblast growth factor (bFGF)	Inhibition of cell proliferation, tumor growth inhibition	114, 115

S. No.	Name of HDAC inhibitors	Cell lines / animal models	Reported mechanisms of action	Fate of cancerous cells	References
12.	Phenylhexyl isothiocyanate	LNCaP	Activation of p21 and G1 phase cell cycle arrest	Cell cycle arrest, apoptosis	128
13.	Sulforaphane (SFN)	PC-3, xenograft	Upregulation of p21/Cip1/Waf1	Cell cycle arrest, apoptosis	129, 130
15.	Apicidin	PC-3-M	Activation of p21	Inhibition of cell proliferation	138
16.	Pyroxamide	CWR22 xenograft	Increased acetylation and p21/WAF1 expression	Inhibition of tumor growth	139
17.	Phenyl butyrate	PC-3, DU145, LNCaP	Increased radio-sensitivity and down regulation of Bcl-X(L), DNA-PK, caveolin-1 and VEGF	Apoptosis	140
18.	LAQ824	LNCaP	Depletion of AR *via* Hsp90 inactivation	Inhibition of cell proliferation and apoptosis	105