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FORUM REVIEW ARTICLE

Influence of Natural and Synthetic Histone Deacetylase Inhibitors on Chromatin

Paul V. Licciardi,[1,2] Faith A.A. Kwa,[3] Katherine Ververis,[3,4] Natasha Di Costanzo,[1–3] Aneta Balcerczyk,[5] Mimi L. Tang,[1,2] Assam El-Osta,[4–7] and Tom C. Karagiannis[3,4]

Abstract

Significance: Histone deacetylase inhibitors (HDACIs) have emerged as a new class of anticancer therapeutics. The hydroxamic acid, suberoylanilide hydroxamic acid (Vorinostat, Zolinza™), and the cyclic peptide, depsipeptide (Romidepsin, Istodax™), were approved by the U.S. Food and Drug Administration (FDA) for the treatment of cutaneous T-cell lymphoma in 2006 and 2009, respectively. At least 15 HDACIs are currently undergoing clinical trials either alone or in combination with other therapeutic modalities for the treatment of numerous hematological and solid malignancies. ***Recent Advances:*** The potential utility of HDACIs has been extended to nononcologic applications, including autoimmune disorders, inflammation, diseases of the central nervous system, and malaria. ***Critical Issues:*** Given the promise of HDACIs, there is growing interest in the potential of dietary compounds that possess HDAC inhibition activity. This review is focused on the identification of and recent findings with HDACIs from dietary, medicinal plant, and microbial sources. We discuss the mechanisms of action and clinical potential of natural HDACIs. ***Future Directions:*** Apart from identification of further HDACI compounds from dietary sources, further research will be aimed at understanding the effects on gene regulation on lifetime exposure to these compounds. Another important issue that requires clarification. *Antioxid. Redox Signal*. 17, 340–354.

Introduction

Chromatin undergoes dynamic remodeling to facilitate DNA metabolic processes, including transcription, replication, and repair (88). Histone proteins organize the DNA into nucleosomes, the basic repeating units of chromatin. Nucleosomes consist of 146 base pairs of DNA tightly wrapped around a histone octamer consisting of two each of the core histones, H2A, H2B, H3, and H4 (88). It is now well established that post-translational modifications of core histones play a major role in modeling higher-order chromatin structure and controlling gene transcription. These include acetylation and deacetylation of lysine residues, methylation of lysine and arginine residues, phosphorylation of serines, and ubiquination and sumoylation of lysines (32). Combinations of these post-translational modifications represent a histone code that is recognized by nonhistone proteins that are involved in regulating gene expression (68).

Histone Acetylation

Acetylation and deacetylation of the amino-terminal tails of lysine residues are the most well-characterized post-translational histone modifications. The process has been the subject of excellent reviews (32, 92, 173). Briefly, the opposing actions of two classes of enzymes, histone acetyltransferases (HATs) and histone deacetylases (HDACs), regulate the acetylation status of the core histones (Fig. 1). The HATs belong in one of three major families, namely, the Gcn5-related N-acetyltransferase, MYST (which incorporates monocytic leukemia zinc finger protein [MOZ], Ybf2/sas3, sas2, and Tip60), and p300/CBP families (150). By abstracting a proton from the ε-amino group of lysine, they catalyze the acetylation of lysines in core histones. This results in neutralization of the positive charges on histones decreasing their interaction with the negatively charged DNA. The effect is a more open or relaxed, transcriptionally active, chromatin conformation

[1]Allergy and Immune Disorders, Murdoch Childrens Research Institute, Royal Children's Hospital, Parkville, Victoria, Australia.
[2]Department of Paediatrics, The University of Melbourne, Parkville, Victoria, Australia.
[3]Epigenomic Medicine, Baker IDI Heart and Diabetes Institute, The Alfred Medical Research and Education Precinct, Melbourne, Victoria, Australia.
[4]Department of Pathology, The University of Melbourne, Parkville, Victoria, Australia.
[5]Epigenetics in Human Health and Disease and [6]Epigenomic Profiling Facility, Baker IDI Heart and Diabetes Institute, The Alfred Medical Research and Education Precinct, Melbourne, Victoria, Australia.
[7]Department of Medicine, Monash University, Melbourne, Victoria, Australia.

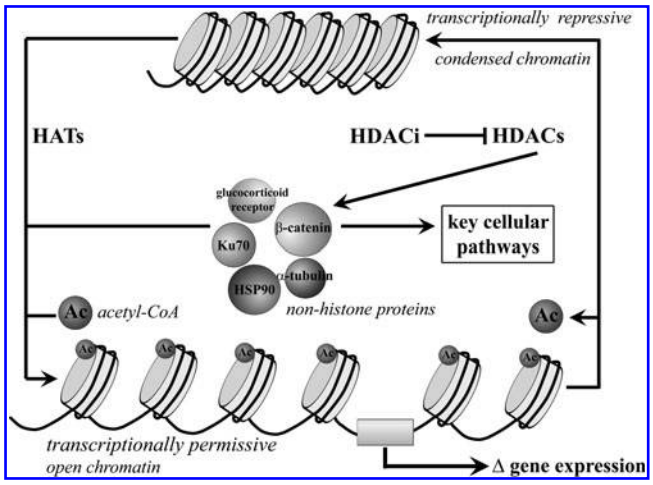

FIG. 1. Protein and histone acetylation status is regulated by the opposing actions of histone acetyltransferases (HATs) and histone deacetylases (HDACs). HATs catalyze the addition of the acetyl moiety of the substrate acetyl-coA leading to histone hyperacetylation. This results in a more open, transcriptionally permissive chromatin architecture. HDACs catalyze the removal of acetyl, resulting in a more condensed, transcriptionally repressive chromatin conformation. In addition, HDAC enzymes have numerous nonhistone protein substrates that are involved in key molecular pathways. HDAC activity can be attenuated by HDAC inhibitors (HDACIs). The overall effects of HDAC inhibition are decreased proliferation, induction of cell death and apoptosis, cell cycle arrest, differentiation and decreased migration, invasion, and angiogenesis in malignant and transformed cell lines. These effects of HDACIs are much more pronounced in cancer cells compared to normal cell lines, providing a therapeutic window for anticancer therapy.

(150, 157). HDAC enzymes catalyze the removal of acetyl groups from lysine residues resulting in a more compacted, transcriptionally repressed, chromatin structure (92). Overall, it is proposed that acetylation levels regulate gene transcription by controlling the accessibility of transcription factors to DNA (88). Further, HDAC enzymes have over 50 nonhistone protein substrates, including gene transcription factors and coregulators (*e.g.,* p53, c-myc, and BCL-2), chaperones (*e.g.,* heat-shock protein [HSP] 70 and HSP90), signaling mediators (*e.g.,* SAT3, Smad7, and β-catenin), DNA repair proteins (Ku70 and Ku86), and proteins involved in cell motility (α-tubulin) (38, 120, 149, 182).

Histone Deacetylases

Eighteen HDAC enzymes have been identified and these are grouped into four classes on the basis of their homology to yeast proteins (36, 37, 109, 111). First, class III HDACs include sirtuins 1–7, which have homology with the yeast enzyme silent information regulator 2 (59, 95, 96). These are nicotinamide adenine dinucleotide (NAD^+)-dependent enzymes that deacetylate lysine residues by consuming NAD and releasing the metabolites nicotinamide and 1-O-acetyl-ADP-ribose (164). This review will focus on the other 11 enzymes, which are grouped into class I, II, and IV and are typically referred to as zinc-dependent (54). They require coordination of a divalent metal ion, which initial studies indicated was zinc. However, recent findings have demonstrated that iron may have a more significant catalytic role (47). Class I enzymes consists of HDAC1, 2, 3, and 8; these have homology to the yeast (*Saccharomyces cerevisiae*) transcriptional regulator RDP3 (11, 108). Class I enzymes contain a nuclear localization signal and are predominantly localized in the nucleus (36, 70). They have a ubiquitous tissue distribution. HDAC1–3 are part of nuclear repressor complexes including CoREST, NURD, SIN3, N-COR, and SMRT (3, 65, 178). These have important roles in regulating gene transcription, and overall class I enzymes have critical roles in cell survival and proliferation (184). Although HDAC8 is phylogenetically linked with class I, it has overlapping features of both class I and class II enzymes (42). Its function is largely unknown, and to date it has not been associated with any nuclear complexes.

Class II enzymes are further classified into IIa and IIb subgroups. Class IIa (HDACs 4, 5, 7, and 9) are structurally related to yeast HDA1 (112, 179). These enzymes can shuttle between the cytoplasm and nucleus and are thought to have tissue-specific roles (11, 36, 37, 107, 109, 111, 120, 182). HDAC6 and 10 make up class IIb enzymes. HDAC6 is a key cytoplasmic protein and numerous specific substrates have been indentified, including α-tubulin and HSP90 (57, 89). It has diverse roles, including aggresome formation and epidermal growth factor signaling (48, 66, 78). The function of HDAC10 remains largely unknown. Similarly, little is known about the class IV enzyme HDAC11, which shares conserved residues in the catalytic domain with both class I and II enzymes. Recent findings suggest a role for HDAC11 in immunomodulation and glial cell biology (103, 171).

Histone Deacetylase Inhibitors

Aberrant HDAC activity due to altered expression or recruitment has been observed in numerous malignancies (22, 50, 111, 126, 177, 193). Further, various mutations of HDAC enzymes have been reported in cancer. For example, a mutation in HDAC2 has been identified in colon and endometrial cancer cells and HDAC4 mutations have been reported in breast and colorectal cancers (147, 156). Apart from regulating gene expression, HDAC substrates are either directly or indirectly involved in modulating numerous critical cellular pathways, including proliferation, apoptosis, migration, and differentiation (37, 108, 109). These provide the basis for the clinical potential of histone deacetylase inhibitors (HDACIs) in cancer therapy.

HDACIs have emerged as a new class of anticancer therapeutics with suberoylanilide hydroxamic acid (SAHA; Vorinostat; brand name Zolinza) and depsipeptide (codenamed FK228 and FR901228; Romidepsin; brand name, Istodax) having been approved by the U.S. Food and Drug Administration (FDA) for the treatment of cutaneous T-cell lymphoma in 2006 and 2009, respectively (Fig. 2) (19, 40, 53, 110). The potential utility of HDACIs has been extended to nononcologic applications, including autoimmune disorders, inflammation, diseases of the central nervous system, and malaria (1, 6, 17, 63, 79, 82, 107, 134, 172). Apart from SAHA and romidepsin that have been approved by the FDA for clinical use, there are at least 15 other currently in clinical trials either as stand-alone therapeutics or in combination with other modalities (93, 109, 111).

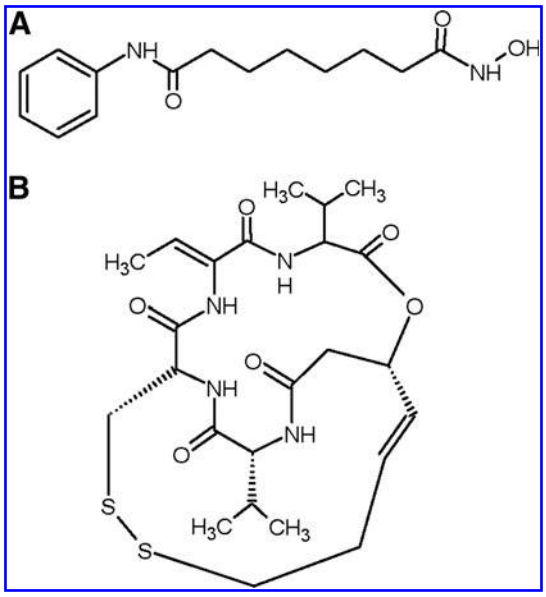

FIG. 2. Chemical structures of Food and Drug Administration (FDA)–approved HDACIs. (A) Suberoylanilide hydroxamic acid (Vorinostat, Zolinza) and **(B)** depsipeptide (Romidepsin, Istodax) were approved by the U.S. FDA for the treatment of cutaneous T-cell lymphoma in 2006 and 2009, respectively.

Briefly, the main HDACI structural groups include hydroxamic acids (Trichostatin A [TSA], SAHA, and LBH589 [Panobinostat]), cyclic peptides (depsipeptide and trapoxin), short-chain fatty acids (SCFA and valproic acid), benzamides (MS275 [Entinostat]), and electrophilic ketones (α-ketomide) (37, 38, 108–111). The potency of HDACIs extends from the nanomolar range typically for hydroxamic acids and cyclic peptides to the millimolar range for SCFA. These may be termed broad-spectrum HDACIs, as they inhibit multiple class I, II, and IV enzymes although some isoform specificity has been identified for all HDACIs using cell-free assay systems. Indeed, there is intense effort in the development of isoform-specific HDACIs, and tubacin and PC-34051, which selectively inhibit HDAC6 and HDAC8, respectively, are prime examples (58, 127, 137, 163). However, it remains controversial whether isoform selective inhibitors would offer a therapeutic advantage compared to broad-spectrum HDACIs, which are expected to have more pleiotropic effects.

Mechanisms of Action of HDACIs

Although the mechanisms of action have not been completely elucidated, multiple biological effects have been defined for HDACIs and these have been reviewed recently (93, 109, 111). The main consequence of hyperacetylation of histones and other protein substrates by HDACIs is modulation of gene expression. HDACIs have been shown to alter the expression of a finite number of genes (2%–20%) with an approximately equal number of genes up and down regulated (11, 37, 38, 139). In general, HDACIs induce cell death, perturbations in the cell cycle with G1 arrest and both G1 and G2 arrest at higher doses, altered migration, and angiogenesis in transformed and cancer cell lines (37, 38, 109, 111). HDACIs are also known to induce apoptosis in malignant cells *via* both the extrinsic and intrinsic pathways. A relatively well-characterized mechanism of HDACIs involves the induction of p21 in a p53-independent manner or *via* the generation of reactive oxygen species (44, 98, 120, 167, 187). The exact mechanism by which HDACIs regulate p21 expression remains unclear, but it is speculated to involve c-myc, a vital protein that controls cell proliferation, differentiation, and survival (25). The inhibition of CDKs (*e.g.,* CDK2) by p21 leads to hypophosphorylation of the Rb gene product, which is then free to bind to and therefore inactivate the transcription factor E2F (46). Inactivation of E2F prevents transcription of genes involved in cell cycle progression such as c-myc. Hence, subsequent events that are essential for cells to enter S phase are halted, leading to cell differentiation or apoptosis (34). Histone acetylation has also been linked to HDACI-induced p21 expression (194). The inhibition of HDAC activity by HDACIs, TSA and sodium butyrate, permits the HAT activity of p300 to increase hyperacetylation at the promoter and nearby regions, thereby opening the chromatin structure in the region of the p21 gene, inducing cell cycle arrest and apoptosis (34, 194). Alternatively, increased p21 expression alone may stimulate apoptosis (132, 148). Importantly, normal cells are relatively resistant to HDACIs, providing a favorable therapeutic window.

Combination Therapies

In addition to their intrinsic anticancer properties, findings have indicated that at least additive effects are achievable when HDACIs are combined with conventional chemotherapeutic drugs such as retinoic acid, anthracyclines, and tumor-necrosis-factor-related apoptosis-inducing ligand (TRAIL), as well as with UV radiation (16, 39, 74, 81, 84, 85, 120, 186). Further, research has indicated that numerous HDACIs possess radiosensitizing properties, including TSA, SAHA, depsipeptide, valproic acid, phenylbutyrate, sodium butyrate, and MS-275 (20, 26, 60, 71, 75–77, 123, 130, 190, 191). Currently, the SCFA, valproic acid is undergoing clinical evaluation in phase II trials, in combination with temozolomide and radiation therapy for the treatment of glioblastoma multiforme (153). Indeed, it is widely accepted that combinatorial strategies will provide the most useful therapeutic outcomes.

Potential Nononcological Applications of HDACIs

HDACIs have also been investigated for their clinical potential in numerous nononcological applications. A particularly interesting example is the finding that the HDACIs TSA and apicidin inhibit the major malarial protozoan, *Plasmodium falciparum* (30, 31, 33). Given the need for potent antimalarial drugs, further research is aimed at developing analogs with HDAC inhibition activity that more specific for protozoan enzymes compared to the mammalian HDACs (5, 6). HDACIs have also been widely investigated for their potential as therapeutics for various heart conditions, particularly cardiac hypertrophy (7, 10, 52, 80, 86, 87). Although beneficial responses have been observed in relevant animal model systems of cardiac hypertrophy, the use of HDACIs for cardiac diseases remains controversial (7, 10, 52, 80, 86, 87). It has been shown that class I and class II HDAC enzymes have disparate actions in cardiac hypertrophy, with class I enzymes thought to potentiate cardiac hypertrophy and class II HDACs thought to suppress pro-hypertrophic responses (8, 57, 118,

131, 189). Therefore, it is widely anticipated that class I HDACIs may be more efficacious in this disease. HDACIs have also shown beneficial effects in a wide range of models of neurodegenerative conditions. Neurodegenerative diseases that have shown improvement with the use of HDACIs, particularly TSA and butyrates, include Rubinstein-Taybi syndrome and Parkinson's, Huntington's, and Alzheimer's diseases (28, 79, 170). Much research has focused on Alzheimer's disease in which it has been shown that HDACIs result in histone acetylation and decrease β-amyloid levels and phosphorylation of Tau, in relevant models of disease (45, 141, 145). In addition, HDACIs have been shown to improve synaptic plasticity, learning, and spatial memory defects (45, 141, 145). HDACIs may also have therapeutic potential in inflammatory lung diseases, particularly asthma. Recent findings indicate that TSA reduces airway hyper-responsiveness and agonist-induced contraction in a mouse model of allergic airways disease (9). These findings extend previous observations which indicated that TSA has anti-inflammatory effects in an analogous mouse model of asthma (27).

HDACIs from Natural Sources

While a significant proportion of research and development by laboratories and pharmaceutical companies worldwide have focused on synthetic drug discovery programs, the contribution of nature to drug discovery is well known. The overwhelming success of the National Cancer Institute's extensive natural product screening programs last century—leading to the discovery and ultimately FDA approval of now common anticancer drugs paclitaxel, vincristine, and vinblastine—has offered promise for the identification of new-generation epigenomic-modifying drugs from nature. Indeed, a number of structurally diverse natural compounds with such activity have been identified from both plant and microbial sources. This includes the FDA-approved depsipeptide, which is a natural product obtained from the bacteria *Chromobacterium violaceum* (168). Another example of the success using this approach was the discovery of the novel HDACI, NVP-LAQ824 (cinnamic acid hydroxamate) following high-throughput screening of Novartis' chemical compound archive, which is now in phase I clinical trials in the United States for multiple myeloma (21, 144).

Another pertinent example of a naturally occurring HDACI is the prototypical broad-spectrum hydroxamic acid, TSA (Fig. 3). TSA is a potent antifungal antibiotic isolated from a metabolite from *Streptomyces hygroscopicus* and is one of the most widely investigated HDACI (136, 185). Cell-free assays indicate that TSA has high affinity for all of the class I, II, and IV enzymes. When TSA enters the cell, it mimics the natural substrate of HDACs and interacts directly with the catalytic site, resulting in hyperacetylation of core histones and multiple other nonhistone substrates (72). Although not suitable for clinical application, the cell-death-inducing and apoptotic effects of TSA in cancer cells, as highlighted in Figure 3, typify responses of HDACIs. Similarly, the enhancement of doxorubicin and ischemia-reperfusion-induced cell death observed with TSA is typical (Fig. 3).

HDACIs from dietary plants

Plants are a rich source of biologically active substances. The scientific literature is replete with documented evidence on the ability of plant compounds to modulate a variety of host-effector functions, including immunity, metabolism, cognitive function, and hormonal balance. Further, plants and their derivatives have been shown to be beneficial in the treatment of certain cancers either as an adjunct to conventional therapy or as an alternative approach to reduce malignancy. The ability of plants to modulate epigenetic events that in turn regulate biological function is a new and exciting area of research. Some examples of dietary compounds with known HDAC inhibition activity are shown in Table 1.

A relatively well-investigated HDACI is the dietary isothiocyanate, sulforaphane (SFN), derived from cruciferous vegetables such as broccoli, cauliflower, and cabbage (62). Consumption of cruciferous vegetables leads to the conversion of the precursor, glucoraphanin, to SFN by the myrosinase enzyme, which is released from the plant cell wall upon chewing or cooking of the vegetable (43, 192). It is thought that isothiocyanate compounds such as SFN act as HDACIs based on structural analyses identifying a spacer arm that could fit into the HDAC active site (38). SFN has been reported to have HDACIs and cell death-promoting properties in cultured human cancer cells by induction of G_2/M phase cell cycle arrest, autophagy, and apoptosis *via* generation of mitochondrion-derived reactive oxygen species (61, 140, 181). In addition, the anticarcinogenic effects of SFN became apparent when it was found to inhibit lung metastases and decrease polyp formation after *in vivo* treatment, and induce phase II detoxification enzymes (*e.g.*, glutathione-S-transferase) levels in prostate cancer cells (55, 124, 166). Moreover, while limited clinical evidence is available in humans on the anticancer effects of SFN, one study reported reduced HDAC activity in peripheral blood mononuclear cells from healthy humans 3–6 h after ingestion (125), suggesting a potentially useful compound for cancer treatment.

Other dietary compounds have been investigated for HDACIs potential. Epidemiological evidence suggests that diets rich in *Allium* vegetables such as chive, leek, garlic, and onion reduce the risk of stomach and colorectal cancer (119). Organosulfur compounds such as diallyl disulfide found in garlic induce histone acetylation in cancer cells, resulting in the activation of DNA repair genes and suppression of genes involved in cell proliferation (128). Diallyl disulfide is metabolized to allyl mercaptan, which was found to be a potent HDACI on purified human HDAC8 *in vitro* (129). On the basis of these observations, synthetic phenylhexyl (PHI) or phenethyl isothiocyanates (PEITC) have been constructed for investigation of novel HDACI properties. Previous reports demonstrate that PHI prevents carcinogen-induced lung cancer in mice (69), inhibits HDAC1 and HDAC2 activity, as well as upregulates histone acetylation (106). Both PHI and PEITC have also been shown to increase p21 expression (176).

Broccoli, garlic, and onion also contain organoselenium compounds such as *Se*-methyl-L-selenocysteine (MSC) and are thought to inhibit the growth of various tumors after *in situ* generation of methylselenol by β-lysases (100). Using an *in vitro* system to mimic the production of α-keto metabolites from MSC, reduction in HDAC activity was shown for β-methylselenopyruvate and α-keto-γ-methylselenobutyrate with increased histone H3 acetylation in human prostate cancer cell lines (99). Taken together, dietary HDACIs therefore represent a novel class of cancer therapeutics that requires further investigation for clinical efficacy.

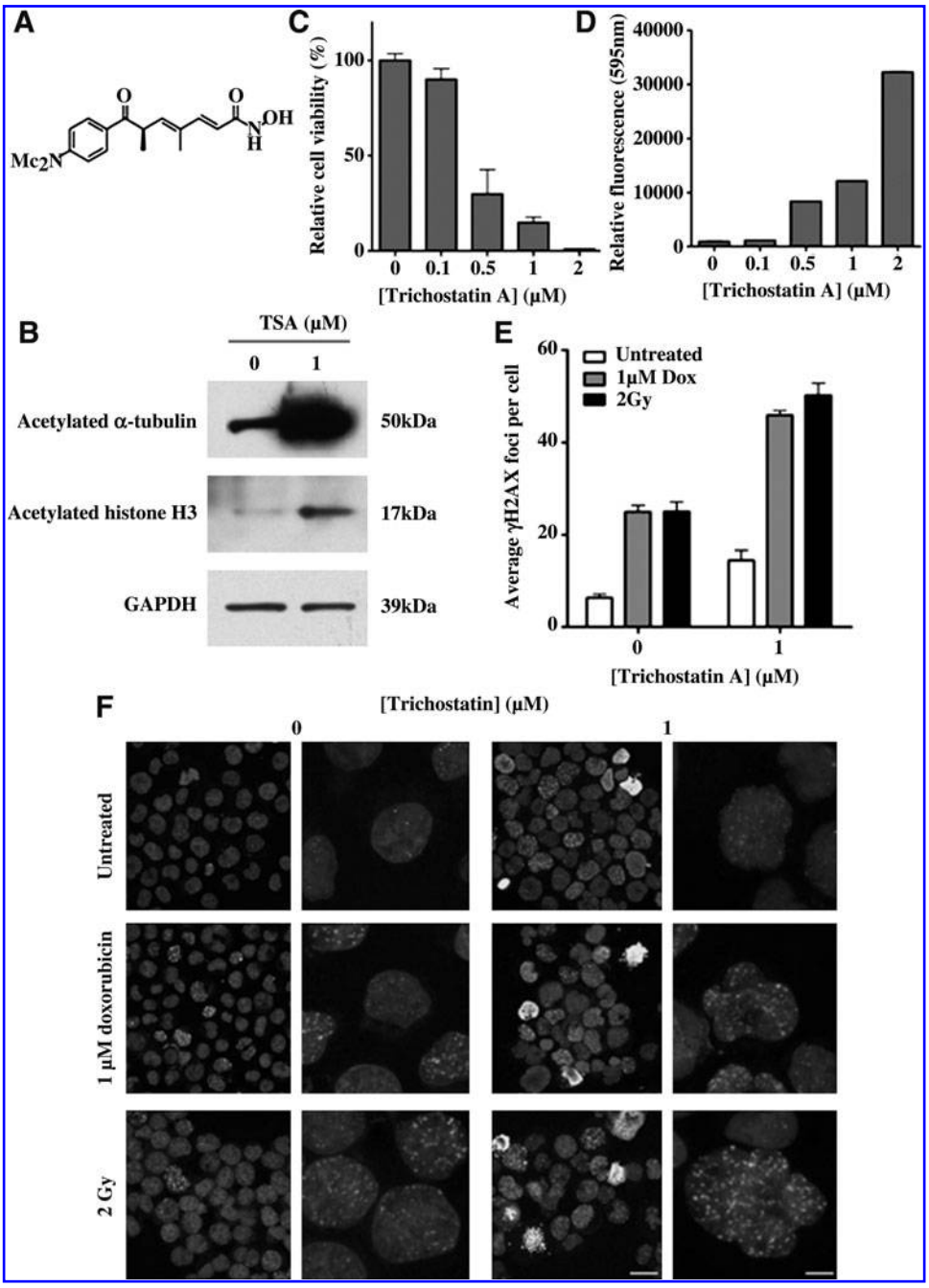

FIG. 3. Biological effects of the prototypical HDACI Trichostatin A (TSA). The cell death- and apoptosis-inducing effects of the HDACIs in human erythroleukemic K562 cells are shown. **(A)** Chemical structure. **(B)** TSA is a broad-spectrum HDACI-inhibiting class I, II, and IV HDAC enzymes resulting in hyperacetylation of histones (histone H3 shown) and other nonhistone substrates (α-tubulin shown). Immunoblot using whole-cell lysates from K562 cells treated with 1 *μM* TSA. **(C)** TSA induces a dose-dependent decrease in cell viability of K562 cells. Cells were treated with TSA at the indicated concentrations for 24 h, and viability was measured using the Cell Titer-Blue® assay (Promega). **(D)** TSA induces dose-dependent apoptosis in K562 cells. Cells were treated with TSA at the indicated concentrations for 24 h, and apoptosis, using caspase 3/7, was measured using the APO-one® assay kit (Promega). Apart from possessing intrinsic cytotoxic and apoptotic activity, HDAIs have been shown to enhance the effects of conventional cancer therapeutics. We show the augmentation of doxorubicin and radiation-induced DNA damage by TSA in K562 cells. Phosphorylated histone H2AX (γH2AX) was used as a molecular marker of DNA double-strand breaks. **(E)** TSA augments the number of doxorubicin and radiation-induced γH2AX foci. Cells were treated with or without 1 *μM* TSA for 24 h, before 1 h incubation with 1 *μM* doxorubicin, washed, and incubated in fresh media for a following 24 h. In separate experiments, cells were incubated with 1 *μM* TSA before irradiation with 2 Gy (^{137}Cs). Cells were stained for γH2AX and images were analyzed using ImageJ to determine the average number of γH2AX foci per nucleus. (**F**) Fluorescence photomicrographs showing enhancement of doxorubicin and radiation-induced γH2AX foci by TSA in K562 cells. Scale bar = 20 μm (*left*); 5 μm (*right*).

Table 1. Various Compounds with Histone Deacetylase Inhibition Activity from Dietary Sources

Source	*Compound*
Cruciferous vegetables	Sulforaphane
Allium vegetables	Organosulfur compounds (diallyl disulfide and allyl mercaptan)
Broccoli, garlic, and onion	β-methylselenopyruvate and α-keto-γ-methylselenobutyrate

HDACIs from medicinal plants

Plants have been used to maintain health since the beginning of civilization. Today, plants and plant-derived products are popular as an alternative to Western medicine, justifying the need for their rigorous scientific investigation. While dietary plants have received much attention as novel cancer drugs, the importance of medicinal plants has become increasingly realized. In particular, the capacity for medicinal plants to modulate epigenetic markers may have a significant impact of human health and disease. Although the safety and efficacy of most medicinal botanicals have not been established on a scientific basis, there has been a widespread use of herbal medicine in many countries all over the world. For many decades, "prevention rather than cure" has been the preferred option relative to chemotherapy. Therefore, dietary consumption of foods and herbal remedies has been considered a convenient and cost-effective way to prevent and treat diseases. Some of the known compounds with HDAC inhibition activity from medicinal plants are shown in Table 2.

Similar to the organosulfur compounds examined from dietary plants, the sulfur compound bis(4-hydroxybenzyl)sulfide isolated from the root extract of *Pleuropterus ciliinervis*, a traditional Chinese herbal medicine used for inflammation and bacterial infections, was shown to inhibit HDAC enzyme activity in HeLa cells (160). This sulfur compound was also able to inhibit the growth of several cancer cells lines, particularly the prostate PC-3 and breast MDA-MB-231 cell lines. Several compounds isolated from the rhizomes of *Zingiber zerumbet* (Asian ginseng) were also able to inhibit HDAC activity and induce activation of the estrogen-sensitive gene, presenelin-2, in breast cancer cell lines, including MDA-MB-231 and its subclone, S30 (29). Extracts from *Ayurveda,* otherwise known as "Indian Ginseng," were found to contain withanolides that exert anticancer effects by promoting apoptosis of tumor cells *via* suppression of nuclear factor kappa B (NF-κB) activation and protecting against skin cancer caused by UVB radiation (67, 115, 116). Withanolides have been reported to decrease histone H3 phosphoacetylation levels and increase DNA methylation of the promoter region of the interleukin (IL)-6 gene, thereby decreasing NF-κB and Fra 1 activity and silencing the *IL-6* gene (73). Analogous to these effects were those demonstrated by pomiferin, the active constituent of *Maclura pomifera*, eliciting HDACI effects while abrogating the growth of several cancer cell lines *in vitro* (4, 159).

Table 2. Various Compounds with Histone Deacetylase Inhibition Activity from Medicinal Plants

Source	*Compound*
Pleuropterus ciliinervis	Bis(4-hydroxybenzyl)sulfide
Zingiber zerumbet	Sesquiterpenoids (6-methoxy-2E,9E-humuladien-8-one)
Ayurveda	Withanolides
Maclura pomifera	Pomiferin
Feijoa sellowiana	Flavones
Microtropis japonica	Triterpenoid (ursolic acid)
Curcuma longa	Curcumin

The anticancer properties of extracts derived from *Feijoa sellowiana* (Guavasteen) were reported for both solid and hematological tumors. Both an acetonic extract as well as the purified fraction, Flavone, was found to elicit pro-apoptotic effects on human myeloid leukemia cells accompanied by increased caspase activation and p16, p21, and TRAIL overexpression (13). It was suggested that this was due to purified flavone exhibiting comparable HDAC1 inhibition to SAHA although the dose used was much higher (170 μM compared to 5 μM) accompanied by increased histone and nonhistone acetylation. Treatment of Ca9-22 (gingival cancer) and HL-60 (human leukemia) cells with ursolic acid, a triterpenoid compound purified from the stems of *Microtropis japonica*, resulted in cytotoxicity with IC_{50} values of 5.9 and 8.7 μg/ml, respectively (23). The biological activity of ursolic acid was related to increased H3 acetylation and inhibition of HDAC 1, 3, 4, 5, and 6 at a dose of 20 μg/ml when used in combination with TSA. Similarly, when the cellular effects of curcumin, a natural polyphenol from the turmeric plant (*Curcuma longa*), was investigated, antiproliferative activity was observed in human epidermoid A431 cancer cells and mesothelioma STO cells *in vitro* at subtoxic doses (0.5 and 1.5 μM) in combination with the known pan-HDACIs, vorinostat and panobinostat, and was thought to be attributed by increased Hsp90 acetylation (49). These effects were associated with a down-regulation of Hsp90 client proteins such as survivin, EGFR, Raf-1, and Cd4k and were achieved at very low drug concentrations that would be achievable *in vivo*, suggesting that this may be a novel combination therapy. Curcumin, a potent inhibitor of HDAC1 and HDAC3, has also been reported to covalently bind to and block the catalytic component of DNMT1 resulting in DNA hypomethylation and subsequent tumor cell death (24, 104). This natural compound also plays a role in regulating miRNA expression. For example, it can upregulate miRNA-15A and miRNA-16 in the breast cancer cell line, MCF-7, leading to inhibition of the expression of the antiapoptotic gene, *BCL-2* (183). The above epigenetic effects of curcumin on cancer cells promote it as a potential cancer therapeutic agent. The use of curcumin as an anticancer agent has been tested in clinical trials on colorectal cancer patients and were found to exhibit low toxicity at doses as high as 12 g/day (97, 154). In a recent study, an interesting approach to the development of novel HDACIs was explored, with the use of osthole, a prenylated coumarin derivative from the Chinese herb *Cnidium monnieri*, as the surface recognition cap for hydroxamate-based compounds (64). A variety of structures were synthesized, with some achieving HDAC1 and 6 inhibition similar to SAHA or selective HDAC1 inhibition and that the osthole moiety interacted with the same hydrophobic pocket that SAHA uses. This approach may provide a source

of novel HDACI structures that exhibit improved class-specific selectivity.

HDACIs from microbes

Microbes have a critical role in the prevention of disease. For example, the gastrointestinal tract contains the highest abundance of commensal micro-organisms important for digestion and regulation of immunity. The presence and diversity of microbial species in the gastrointestinal tract—more than 1000 species and 10^{12} organisms—is vital for the prevention of serious conditions such as chronic inflammatory disorders and allergy (56, 151). Microbes can elicit beneficial effects *via* direct interactions with the mucosal epithelium and immune system or can modulate host responses through the generation of biologically active metabolites after the digestion of food and other foreign substrates. Historically, natural drug screening programs have revealed important drugs originating from microbial sources. An emerging class of drugs are epigenome modulators, with HDACIs the most well-studied. Compounds with known HDAC inhibition activity from microbes are shown in Table 3.

The cyclotetrapeptide, azumamide E, isolated from the sponge *Mycale izuensis*, is the most potent carboxylic acid-containing HDACI currently known (117). This was shown to be a powerful selective inhibitor of class I HDACs 1–3 while exhibiting weaker activity on HDAC8 and very little activity on class II HDACs 4–7 and HDAC9 in HeLa nuclear extracts. The natural HDACI, Psammaplin A—derived from a two-sponge association between *Poecillastra* sp. and *Jaspis* sp.—exhibits cytotoxic activity toward lung, ovarian, and colon cancer cell lines as well as inhibiting class I HDACs (83). This compound was recently shown to inhibit the proliferation of Ishikawa endometrial cancer cells dose dependently, increase the expression of acetylated H3 and H4 histone proteins, and upregulate apoptosis through p21 (2).

Bacterial-derived HDACIs have also been discovered. One such compound, designated as YM753, is a novel cyclic peptide-based HDACI isolated from the culture broth of *Pseudomonas fluorescens*. This compound exhibited potent HDACI activity in K562 leukemic cells *in vitro* that was greater than several hydroxamic HDACIs such as TSA and SAHA (155). Moreover, YM753 induced the accumulation of acetylated H3 and H4 histones, p21 expression, and cell cycle arrest associated with selective cancer cell cytotoxicity. A similar effect was also observed in a mouse tumor xenograft model suggesting that YM753 may be a potential antitumor agent. Largazole, a cyanobacteria-derived class I-specific HDACI, is another microbial compound with cytotoxicity to a number of chemoresistant cancer cell lines (15). In a recent study, the HDACI effects of largazole were exploited in combination with symplostatin 4, a natural antimitotic compound that produced a synergistic reduction in cancer cell viability, although the exact mechanism of this combinatorial strategy was not fully elucidated (165).

Table 3. Various Compounds with Histone Deacetylase Inhibition Activity from Microbial Sources

Source	*Compound*
Chromobacterium violaceum	Depsipeptide
Streptomyces hygroscopicus	Trichostatin A
Mycale izuensis	Azumamide E
Poecillastra sp. *and Jaspis* sp.	Psammaplin A
Pseudomonas fluorescens	YM753
Cyanobacteria	Largazole
Commensal bacteria	Butyrate

SCFAs: butyrate

The SCFAs are a well-known class of HDACIs. Principal among these is butyrate, which is demonstrated to inhibit most HDAC except class III and class II HDACs 6 and 10 (34). Other SCFAs exist, including acetate and propionate, but are associated with weaker HDACI activity. Indeed, these SCFAs have potent anti-inflammatory activities and have been shown to ameliorate the pathology observed in mouse models of colitis and asthma (113, 114). Butyrate, a by-product of colonic bacterial fermentation, was the first identified HDACI (143). Butyrate is a competitive inhibitor of HDAC and mimics the normal substrate, the acetyl group of acetyl coenzyme A (120). This results in the accumulation of highly acetylated histones that switch on gene expression, cell differentiation, and mitochondrial-dependent apoptosis. In humans, butyrate is produced in large quantities following anaerobic bacterial fermentation of dietary fibers during digestion. Consequently, butyrate has an important role as an energy source for the mucosa in anaerobic-rich environments such as the gastrointestinal tract as well as having other critical biological functions such as immune regulation (14). Butyrate was found to be one of the most potent HDACIs in human colon cancer cell lines (174) and could therefore have an integral role as chemopreventive derivatives of microbial fermentation. Fermentation supernatants after incubation of human fecal slurries with apple pectin were rich in butyrate and exhibited strong HDAC inhibitory properties in several colon cancer cell lines (175). Butyrate also functions to inhibit phosphorylation and methylation of DNA (143). One disadvantage of using butyrate *in vivo* is the high concentrations (m*M*) required to kill CLL cells, which, in turn, have the potential to produce high toxicity and death of normal cells (122). Despite this, phase I and II clinical trials using butyrate derivatives for leukemia, lung cancer, and melanoma were generally well tolerated with neurological toxicity only at extremely high doses (51, 138). Other clinical dose-limiting toxicities of butyrate derivatives, including thrombocytopenia, nausea, and fatigue, have been reported in prostate and breast cancer patients (11).

Given the role of bacterial species in the production of SCFAs such as butyrate, the role of probiotic bacteria may also be considered as an alternative therapeutic approach for cancer and other chronic inflammatory disorders (18, 180). Moreover, probiotics are increasingly recognized as an important source of nutrition. Metabolic effects of probiotic-induced SCFAs include modulation of metabolism and apoptosis and can counteract the generation of free radicals and phenolic metabolites leading to DNA damage and cancer (142). The effects of SCFA on free radical production is important as this is a critical process in the development of many health problems, including heart disease, neurodegeneration, cancer, and other inflammatory conditions.

The butyric acid producing anaerobic bacterium, *Faecalibacterium prausnitzii*, is one such probiotic that has been used for

the treatment of inflammatory bowel disease (IBD). The levels of this bacterium was found to be lower in cases of IBD and mice fed *F. prausnitzii* led to a shift in the microbiota composition, reduced inflammatory cytokine levels such as IL-2, increased the anti-inflammatory cytokine IL-10, and reduced colitis and mortality, suggesting that butyrate and other related derivatives may be critical in host protection against gut and bowel diseases (158, 169). It may also be possible that SCFAs such as butyrate produce HDACI effects that have multiple downstream effector functions on many target cells, including those of the immune system. The role of SCFA-producing probiotic bacterium as chemoprotectives was further illustrated with *Propionibacterium freudenrichii*, with destruction of colorectal adenocarcinoma cells mediated *via* apoptosis through other SCFA such as acetate and propionate (94).

Probiotics are a heterogeneous group of bacteria that elicit diverse biological activities. The novel probiotic, *Bacillus polyfermenticus*, was suggested to protect rats against colon carcinogenesis by reducing DNA damage due to 1,2-dimethylhydrazine as well as reducing lipid peroxidation and increasing total plasma antioxidant activity (135). Studies involving probiotics belonging to the *Lactobacillus* species have been reported to reduce free radical levels through specific modulation of the redox state. *Lactobacillus rhamnosus* GG (LGG) was found to reduce hydroxyl radical formation in an *in vitro* colonic fermentation model, which correlated with increased superoxide dismutase (SOD) activity (162). Similar effects on lipid peroxidation and SOD activity using other *Lactobacillus* species have also been reported (146, 152, 161). Paradoxically, it was shown that butyrate, the major SCFA produced by probiotic bacteria, regulated the inflammatory response by inhibiting NF-κB *via* a transient and reversible influx of reactive oxygen species (90, 91). Such activity of LGG was also shown to downregulate pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) by a similar mechanism (102). This highlights the complexity of the interactions between commensal microbes and the host in the regulation of the inflammatory response.

Bifidobacteria also have the capacity to modulate antioxidant activity. In a rat model of colitis, *B. infantis* was able to attenuate disease severity through a reduced inflammatory response, including lower IL-1β and lipid peroxidation, compared to controls (133). Comparisons of total antioxidant activity revealed that *Bifidobacteria* produced significantly elevated glutathione concentrations compared to *Lactobacilli* but had a lower lipid peroxidation capacity (188). Rats that were fed a high-fat diet and treated with the probiotic mix VSL#3 containing *Bifidobacteria, Lactobacilli,* and *Streptococcus* probiotic strains were also observed to have reduced TNF-α and cyclo-oxygenase 2 enzyme activity that was associated with reduced NF-κB pathway activity (41, 101). Similarly, pretreatment of rats with another probiotic combination formula prevented intestinal barrier dysfunction in acute pancreatitis through upregulated glutathione biosynthesis and tight junction protein expression (105).

Future Directions and Conclusions

HDACIs have emerged as a new class of anticancer therapeutics for the treatment of cutaneous T-cell lymphoma. Numerous compounds are showing promise in advanced clinical trials for a range of hematological and solid malignancies. Given the synergistic and additive effects of HDACIs with conventional therapies such as chemotherapeutics and radiotherapy, it is widely accepted that HDACIs will be of most therapeutic benefit when used in combination with other anticancer modalities. An issue that does require clarification is whether selective or isoform-specific compounds will offer a therapeutic advantage compared to the more pleiotropic pan-HDACIs such as SAHA and depsipeptide. Although their anticancer effects are relatively well investigated, the mechanisms accounting for the greater cell death- and apoptosis-inducing activity of HDACIs in cancer and transformed cells compared to normal cells requires further clarification. This is particularly important given the clinical potential of HDACIs in nononcological applications.

The importance of chromatin modification by dietary HDACIs is becoming increasingly recognized. Apart from identification of further HDACI compounds from dietary sources, research will be aimed at understanding the effects on gene regulation on lifetime exposure to these compounds. In this context the effects of probiotic metabolites are important. These reported activities for probiotic metabolites such as butyrate offer a promising intervention approach for the treatment of specific cancers affecting the gastrointestinal system. The exact mechanisms of action for probiotic bacteria have yet to fully understood; therefore, epigenomic-modifying capacity of probiotics will be important in understanding how they mediate their health-promoting effects.

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Address correspondence to:
Dr. Tom C. Karagiannis
Epigenomic Medicine
Baker IDI Heart and Diabetes Institute
The Alfred Medical Research and Education Precinct
75 Commercial Road
Melbourne 3004
Victoria
Australia

E-mail: tom.karagiannis@bakeridi.edu.au

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Abbreviations Used

^{137}Cs = caesium-137
FDA = Food and Drug Administration
HAT = histone acetyltransferase
HDAC = histone deacetylase
HDACI = histone deacetylase inhibitor
HSP = heat-shock protein
IBD = inflammatory bowel disease
IL = interleukin
LGG = *Lactobacillus rhamnosus* GG
MOZ = monocytic leukemia zinc finger protein
MSC = *Se*-methyl-L-selenocysteine
NAD = nicotinamide adenine dinucleotide
NF-κB = nuclear factor kappa B
PEITC = phenethyl isothiocyanates
PHI = phenylhexyl
SAHA = suberoylanilide hydroxamic acid
sas2 = something about silencing 2
sas3 = something about silencing 3
SCFA = short-chain fatty acids
SFN = sulforaphane
SOD = superoxide dismutase
TIP60 = human immunodeficiency virus Tat-interacting 60-kDa protein
TNF-α = tumor necrosis factor-alpha
TRAIL = tumor-necrosis-factor-related apoptosis-inducing ligand
TSA = Trichostatin A

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