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REVIEW ARTICLE

Metabolism as a key to histone deacetylase inhibition

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Abstract

There is growing interest in the epigenetic mechanisms that are dysregulated in cancer and other human pathologies. Under this broad umbrella, modulators of histone deacetylase (HDAC) activity have gained interest as both cancer chemopreventive and therapeutic agents. Of the first generation, FDA-approved HDAC inhibitors to have progressed to clinical trials, vorinostat represents a "direct acting" compound with structural features suitable for docking into the HDAC pocket, whereas romidepsin can be considered a prodrug that undergoes reductive metabolism to generate the active intermediate (a zinc-binding thiol). It is now evident that other agents, including those in the human diet, can be converted by metabolism to intermediates that affect HDAC activity. Examples are cited of short-chain fatty acids, seleno-α-keto acids, small molecule thiols, mercapturic acid metabolites, indoles, and polyphenols. The findings are discussed in the context of putative endogenous HDAC inhibitors generated by intermediary metabolism (e.g. pyruvate), the yin–yang of HDAC inhibition versus HDAC activation, and the screening assays that might be most appropriate for discovery of novel HDAC inhibitors in the future.

Keywords: Epigenetics, chromatin remodeling, protein acetylation, HDAC, chemoprevention, chemoprotection, cancer

Introduction

Epigenetics has arrived front-and-center on the popular landscape. A widely read current affairs magazine recently showed a cover image of double-stranded DNA being unzipped next to the words: "Why your DNA isn't your destiny: the new science of epigenetics reveals how the choices you make can change your genes—and those of your kids." Just how "new" this science really is can be debated, since it has its roots in the earliest discussions on nature versus nurture. Although Darwin argued that incremental changes underlie the process of natural selection and survival of the fittest, Lamarck postulated that some traits were acquired within a lifetime due to environmental pressures. Handel and Ramagopalan (2010) adopted the middle ground in stating that epigenetics allows for the "peaceful co-existence" of Darwinian and Lamarckian evolution, while emphasizing that the underlying mechanisms are now clearly implicated in disease susceptibility.

The US National Institutes of Health developed the Roadmap Epigenetics Program with the goal of studying human health and disease in the context of "changes in the regulation of gene activity and expression that are not dependent on gene sequence ... both heritable changes in gene activity and expression, and long-term alterations in the transcriptional potential of a cell that are not necessarily heritable. Epigenetics refers to the study of single genes or sets of genes, whereas epigenomics refers to more global analyses of epigenetic changes across the entire genome" (http://nihroadmap.nih.gov/epigenomics/).

Articles related to this topic have appeared in the present journal, including a discussion on histone recognition by conserved structural folds (Yap and Zhou, 2010), decoding of the histone H4 lysine 20 methylation mark (Balakrishnan and Milavetz, 2010), and modifying chromatin architecture during the response to DNA breakage

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Abbreviations:

HATs, histone acetyltransferases;
HDACs, histone deacetylases;
N-Cor, nuclear repressor co-repressor;
SMRT, silencing mediator for retinoid and thyroid hormone receptors;
TSA, trichostatin A;
KDAC, lysine deacetylase;
FK228, depsipeptide;
KMSB, keto-methylselenobutyrate;
MSP, methylselenopyruvate;
MSC, methylselenocysteine;
SM, selenomethionine;
GTL, glutamine transaminase-liver;
GTK, glutamine transaminase-kidney;
SCMTs, sodium-coupled monocarboxylate transporters;
SAC, *S*-allylcysteine;
SAMC, *S*-allylmercaptocysteine;
DAS, diallyl sulfide;
DADS, diallyl disulfide;
DATS, diallyl trisulfide;
AMS, allyl methyl sulfide;
AM, allyl mercaptan;
SFN, sulforaphane;
Nrf2, nuclear factor erythroid 2-related factor 2;
Keap1, Kelch-like ECH-associated protein 1;
GST, glutathione *S*-transferase;
SFN-GSH, SFN–glutathione;
SFN-Cys, SFN–cysteine;
SFN-NAC, SFN–*N*-acetylcysteine;
SAHA, suberoylanilide hydroxamic acid;
BITC, benzyl isothiocyanate;
hTERT, human telomerase reverse transcriptase;
PHITC, phenylhexyl isothiocyanate;
PEITC, phenethyl isothiocyanate;
I3C, indole-3-carbinol;
DIM, 3,3′-diindolylmethane;
SIRT1, sirtuin 1;
COPD, chronic obstructive pulmonary disease;
GR, glucocorticoid receptor;
NF-κB, nuclear factor kappa B;
GI, gastrointestinal;
HMTs, histone methyltransferases;
DNMTs, DNA methyltransferases;
MeCP2, methyl CpG-binding protein 2.

(Venkitaraman, 2010). The latter subject also falls under the umbrella of epigenetic changes implicated in cancer development, along with aberrant DNA methylation, altered profiles of microRNAs, and miswritten or misinterpreted histone modifications (Iorio and Croce, 2009; Chi et al., 2010; Poke et al., 2010; Sharma et al., 2010).

Histone modifications, histone deacetylases, and associated human pathologies

Posttranslational modifications to histones such as acetylation, methylation, phosphorylation, and ubiquitination play a pivotal role in the regulation of gene expression (Myzak and Dashwood, 2006a; Delage and Dashwood, 2008, 2009a,b; Lee et al., 2010a). These modifications alter chromatin structure and influence the binding of remodeling factors, transcription factors, co-activators, and co-repressors (Figure 1). For example, acetylation and deacetylation of histones is mediated by the opposing activities of two classes of enzymes: histone acetyltransferases (HATs) and histone deacetylases (HDACs). HDACs include the zinc-dependent members of classes I, II, and IV, as well as the class III "sirtuins." Among the class I HDACs, HDAC1, HDAC2, and HDAC8 are present mainly in the nucleus, whereas HDAC3 can be found in either the nucleus or the cytoplasm. HDAC3 may be associated in nuclear co-repressor complexes with protein partners such as N-Cor/SMRT (nuclear receptor co-repressor/silencing mediator for retinoid and thyroid hormone receptors) and HDAC4. The latter is designated as a class II HDAC, along with HDAC5, HDAC6, HDAC7, HDAC9, and HDAC 10, all of which can shuttle between the nucleus and cytoplasm, and tend to exhibit a more restricted tissue expression pattern than class I HDACs. HDAC11, currently the sole member of HDAC class IV, was identified by DNA sequence similarity; little is known about its major function(s) and possible redundancy with other HDACs (Yang and Seto, 2008). Classes I, II, and IV HDACs are inhibited to some degree by compounds such as trichostatin A (TSA).

Class III HDACs are NAD^+-dependent enzymes that lack the catalytic zinc atom and are generally TSA-insensitive. Their dependence on NAD^+ links sirtuins to intermediary metabolism and to factors that affect NAD^+/NADH ratios in cells. This topic connects basic aspects of intermediary metabolism to the modulation of HDAC activity. The reader is referred elsewhere for articles on sirtuins and metabolic signaling (Denu, 2007; Calabrese et al., 2008; Dittenhafer-Reed et al., 2010; Imai, 2010; Imai and Guarente, 2010; Kyrylenko and BaniAhmad, 2010; Silva and Wahlestedt, 2010; Yu and Auwerx, 2010).

In addition to metabolic signaling and metabolic disorders, HDACs have been implicated in diabetes (Lawless et al., 2009; Imai and Guarente, 2010), the cardiorenal axis and cardiovascular diseases (Bush and McKinsey, 2010; Colussi et al., 2010), psychiatric disorders (Stahl, 2010), neurodegenerative diseases (Dietz and Casaccia, 2010; Krainc, 2010; Ramadori and Coppari, 2010), chronic obstructive pulmonary disease (Barnes, 2010a), aging (Donmez and Guarente, 2010), and cancer (Marks and Xu, 2009; Biancotto et al., 2010; Mercurio et al., 2010). There is growing appreciation, therefore, for the importance of reversible protein acetylation in human health and disease.

Cellular targets of HDAC inhibitors include both histone and non-histone proteins. As a consequence, terms such as protein deacetylase, lysine (K) deacetylase (KDAC), and "KDAC inhibitor" have appeared in the

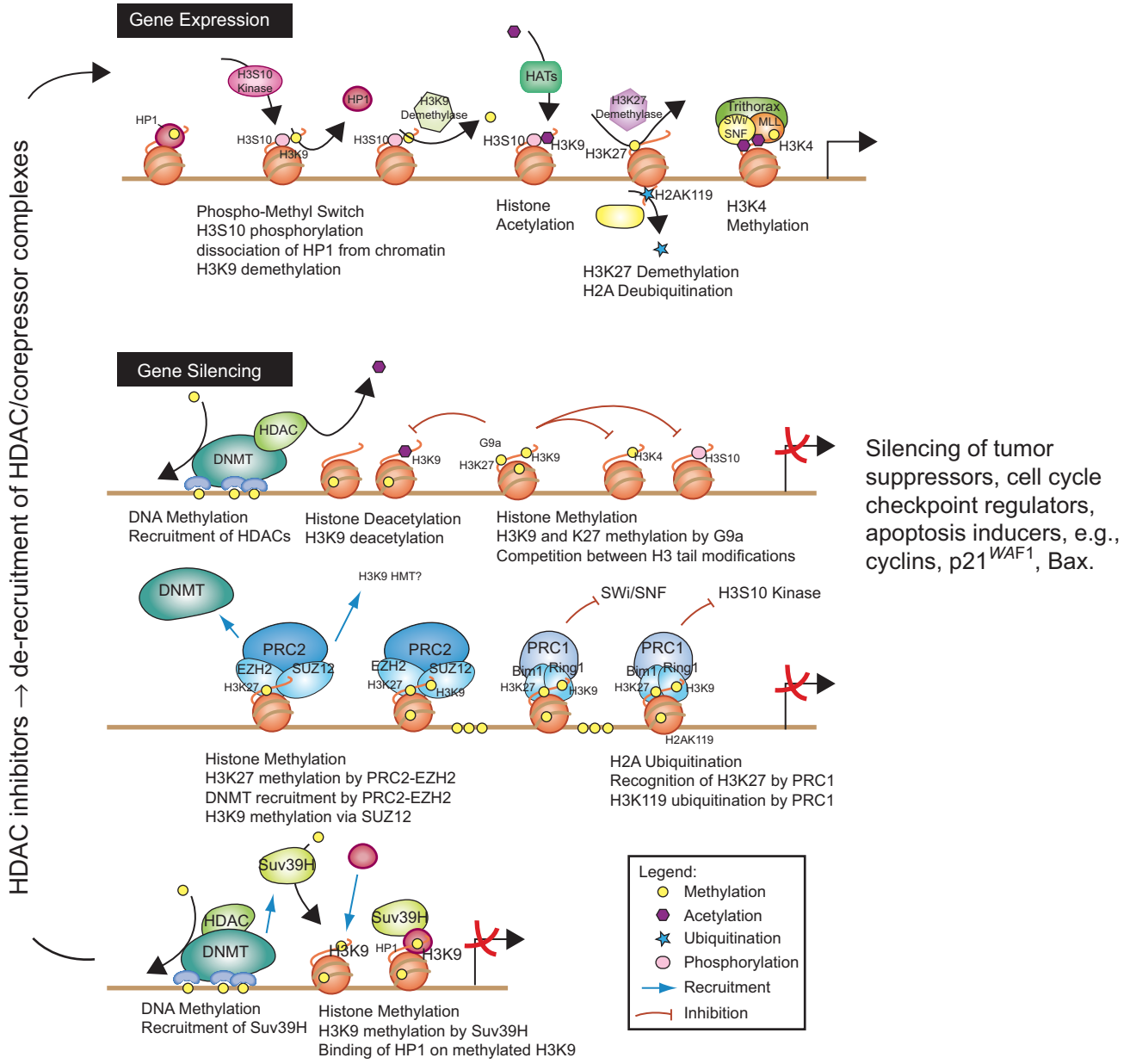


Figure 1. Interactions between histone-modifying enzymes and histone modifications associated with gene silencing and unsilencing. Gene activation (top) requires the recruitment of chromatin-remodeling complexes, histone acetyltransferases (HATs), and histone methyltransferases (HMTs, such as trithorax). During gene silencing, DNA methylation catalyzed by DNA methyltransferases (DNMTs) and methyl-binding domain proteins (e.g. methyl CpG binding protein 2, MeCP2) recruits histone deacetylases (HDACs) and HMTs to repress transcription. HDAC inhibitors trigger the release of HDACs and their co-repressor complexes, leading to an open chromatin state that is poised for gene activation. In cancer cells, epigenetic mechanisms affecting DNA methylation and histone marks silence tumor suppressors, cell cycle checkpoint regulators, and apoptosis inducers. For further details, see Delage and Dashwood (2008).

literature (Gurard-Levin et al., 2010; Lundh et al., 2010; Singh et al., 2010a). HDAC6, for example, is a "KDAC" with a nuclear role in regulating the *survivin* gene promoter (Ma et al., 2005), but it also modulates the chaperone functions of heat shock protein 90 (Bali et al., 2005; Park et al., 2008; Kekatpure et al., 2009). HDAC6 acts as a tubulin deacetylase and master regulator of cellular responses to cytotoxic insults (Hubbert et al., 2002; Matthias et al., 2008). Effects on tubulin acetylation and protein trafficking link HDAC6 to various neurodegenerative disorders (Pandey et al., 2007; Ding et al., 2008; Rivieccio et al., 2009; Lee et al., 2010b). Thus, HDAC6 and other HDACs appear to influence protein misfolding/trafficking in the brain, as well as affecting neuronal cell differentiation and apoptosis via gene repression/de-repression.

Gene de-repression also provides a mechanistic basis for the use of HDAC inhibitors in cancer therapy. When HDACs remove the acetyl groups from histone tails (Figure 1), the resulting chromatin condensation leads to transcriptional repression (reviewed by Delage and Dashwood, 2008; Lee et al., 2010a). In cancer cells, this represents an important mechanism of gene silencing,

shutting down the expression of critical players involved in cell survival, mitosis, nucleotide metabolism, and angiogenesis (Miyanaga et al., 2008; LaBonte et al., 2009). Since epigenetic modifications are potentially reversible, unlike the genetic changes that affect DNA sequence, they are desirable targets for therapeutic or chemopreventive strategies. Such an approach may be feasible in many different cancer types, and throughout the progression from early initiation to promotion and metastasis. By coaxing neoplastically transformed cells into re-expressing epigenetically silenced tumor suppressors, HDAC inhibitors trigger growth inhibition, cell cycle arrest, differentiation, and/or apoptosis. This can enhance the debulking of tumors by augmenting other cancer treatment modalities. Epigenetic modifications can also be early events in carcinogenesis; thus, prevention/reversal efforts might affect pre-neoplastic cells or early stages of tumorigenesis, before wholesale changes in histone posttranslational modifications and HDAC expression.

HDAC overexpression has been observed in a number of human primary cancers and cancer cell lines, including neuroblastoma (Oehme et al., 2009a,b), renal cancer (Fritzsche et al., 2008), prostate cancer (Patra et al., 2001; Abbas and Gupta, 2008), gastric cancer (Kim et al., 2003), and colorectal cancer (Mariadason, 2008; Ashktorab et al., 2009). In the latter case, for example, HDAC2 nuclear expression was detected at high levels in 82%, 62%, and 53% of human colorectal carcinomas, adenomas, and normal tissues, respectively (Ashktorab et al., 2009). Collectively, these and other studies provide evidence that perturbation of the balance between acetylation and deacetylation is an important factor in neoplastic transformation. Indirect evidence of the importance of acetylation status in tumorigenesis also comes from the observation that tumor cell growth can be halted or even reversed by HDAC inhibitors.

HDAC inhibitors and cancer therapeutics—role of metabolism

HDAC inhibitors were first identified and isolated from natural sources (reviewed by Yoshida et al., 2003). In the intervening two decades, the list of HDAC inhibitors has expanded to include hydroxamic acids, short-chain fatty acids, boronic acids, α-keto acids, cyclic tetrapeptides, benzamides, ketones, isothiocyanates, organosulfur compounds, selenium-based compounds and their metabolites, and other miscellaneous agents (Minucci and Pelicci, 2006; Delage and Dashwood, 2009a; Lane and Chabner, 2009; Nian et al., 2009a,b; Suzuki et al., 2009; Desai et al., 2010; Noureen et al., 2010). Based on the features of the active site pocket in the presence and absence of bound ligands (Finnin et al., 1999; Vannini et al., 2004, 2007; Somoza et al., 2004; Bottomley et al., 2008; Dowling et al., 2008; Schuetz et al., 2008; Ficner, 2009), and computational modeling *in silico* (Vannini et al., 2007; Nian et al., 2008, 2009b; Ortore et al., 2009; Suzuki et al., 2009; Wang, 2009; Oger et al., 2010), numerous HDAC inhibitor candidates have been identified. These compounds typically have a functional group that interacts with the zinc atom in the enzyme pocket, a spacer "arm" that fits into the channel near the active site, and in many (but not all cases) a cap group that associates with residues near the surface.

Before their mechanisms of action were elucidated, small molecule hydroxamic acids and cyclic tetrapeptides were observed to alter the differentiation status of cancer cells in culture (reviewed by Myzak and Dashwood, 2006b; Santini et al., 2007; Jones and Steinkühler, 2008). Yoshida et al. (1990) were the first to report on the potent HDAC inhibitory activity of TSA, a natural compound isolated from *Streptomyces platensis*. Subsequent studies showed that TSA reversed the morphological transformation of oncogenic *ras*-transformed NIH3T3 cells (Futamura et al., 1995). In addition, TSA increased global histone H3 and H4 acetylation, enhanced the expression of hepatocyte-specific genes, and induced hepatocyte differentiation in human hepatoma cells (Yamashita et al., 2003). In human embryonic kidney 293 (HEK293) cells, the glutathione *S*-transferase (GST) inhibitor ethacrynic acid potentiated the effects of TSA (Myzak et al., 2004), implicating the mercapturic acid pathway in the metabolism of this prototype HDAC inhibitor. The mercapturic acid pathway is a glutathione-dependent pathway that plays a critical role in the detoxification of a large number of foreign compounds (also known as xenobiotics). This pathway is modulated by many factors, including dietary constituents (Higdon et al., 2007; see also sulforaphane text below). In principle, therefore, nutrient interactions that induce the mercapturic acid pathway might lower the efficacy of TSA and structurally related HDAC inhibitors *in vivo*. This might account for the fact that TSA shows no effect in animal models due to its "metabolic instability" (Masuoka et al., 2008).

Due to these concerns, alternative hydroxamate-based HDAC inhibitors have been developed. Vorinostat (suberoylanilide hydroxamic acid, SAHA) has been described as hitting "the happy medium ... potent enough to be useful and tolerated in patients" (Marks and Breslow, 2007). Early Phase I studies in humans suggested that vorinostat was well-tolerated (Kelly et al., 2003), had linear pharmacokinetics and good bioavailability (Kelly et al., 2005), and was effective in hematologic malignancies, including Hodgkin's disease and subtypes of non-Hodgkin's lymphoma (O'Connor et al., 2006). Phase 2 trials of vorinostat demonstrated activity in patients with cutaneous T-cell lymphoma (Duvic et al., 2007) and modest single-agent responses in patients with glioblastoma multiforme (Galanis et al., 2009). Other clinical trials have been conducted with vorinostat, alone and in combination with cancer therapeutic agents (Fouladi et al., 2010; Kadia et al., 2010; Ramalingam et al., 2010; Wilson et al., 2010). Marked interindividual pharmacokinetic variability has been observed with vorinostat, possibly related to pharmacogenetic influences on glucuronidation (Kang

et al., 2010), or to dietary factors that modulate the mercapturic acid pathway (Higdon et al., 2007).

Like TSA, trapoxin was shown to induce morphological reversion in transformed NIH3T3 fibroblasts (Itazaki et al., 1990; Yoshida and Sugita, 1992). Subsequent work demonstrated that trapoxin was an irreversible HDAC inhibitor, and that chemical reduction of the epoxide group abolished the inhibitory activity (Kijima et al., 1993). The latter observation hinted at the possibility that reductive metabolism might play a role in lowering the efficacy of trapoxin and structurally related HDAC inhibitors *in vivo*. Trapoxin resembles TSA in lacking efficacy in animal models due to the "metabolic instability" of the parent compound (Masuoka et al., 2008).

On the other hand, cellular reduction of the disulfide bond in depsipeptide (FK228) generates a more active compound, most likely a mercaptobutenyl intermediate that fits into the HDAC pocket (Desai et al., 2010). This HDAC inhibitor was first isolated as a fermentation product from *Chromobacterium violaceum* (reviewed by Masuoka et al., 2008). FK228 has progressed to clinical trials under the name romidepsin, with evidence for "significant and sustainable single-agent activity and an acceptable safety profile" (Whittaker et al., 2010). Depsipeptide thus provided one of the earliest examples of metabolism generating an HDAC inhibitor, but other examples are now known, including the various compounds from dietary sources (see below).

HDAC inhibitors were discovered based on their ability to induce differentiation in cancer cells, and this continues to be an active area of research. For example, neuroblastoma cells differentiate in response to HDAC8-selective inhibitors or targeted knockdown of HDAC8 (Oehme et al., 2009b), and human leukemia differentiate after treatment with HDAC inhibitors FK228 and sodium phenylbutyrate (Savickiene et al., 2010). Sodium phenylbutyrate has been used clinically in the treatment of disorders such as maple syrup urine disease (Brunetti-Pierri et al., 2010), and there is growing interest in the neuroprotective properties of this compound and its metabolites (Gardian et al., 2005; Ryu et al., 2005; Petri et al., 2006; Hogarth et al., 2007; Ebbel et al., 2010). A recently completed Phase 2 study in patients with amyotrophic lateral sclerosis (Lou Gehrig's disease) concluded that blood levels of phenylbutyrate, and of its primary metabolite phenylacetate, increased with dosage, and that 9 g/day was effective for improving histone acetylation status (Cudkowicz et al., 2009). Phenylbutyrate shares structural features with the antiepileptic agent valproic acid (Göttlicher, 2004), and with the oldest known dietary HDAC inhibitor, butyrate.

Dietary HDAC inhibitors—role of metabolism

Short-chain fatty acids: HDAC inhibitors generated via gut fermentation of dietary fiber

Butyrate serves as the primary metabolic fuel for the colonocyte, where it can be present at up to millimolar concentrations in the gut (reviewed by Myzak and Dashwood, 2006b). This short-chain fatty acid is generated via the gut fermentation of dietary fiber, and it can be considered an early example of the role of metabolism in generating HDAC inhibitors. As in the case of TSA, butyrate was first reported to increase cell differentiation (Leder and Leder, 1975), and subsequently was shown to affect histone acetylation status (Riggs et al., 1977; Boffa et al., 1978). Like TSA, butyrate acts as a competitive HDAC inhibitor (Sekhavat et al., 2007). A K_i of 46 μM was reported for HDAC inhibition by butyrate in whole cell lysates of human MCF-7 breast cancer cells, compared with a K_i of 1 nM for TSA under the same conditions (Sekhavat et al., 2007). The difference in K_i values highlights an important point, namely that dietary factors are much weaker HDAC ligands than the agents developed for cancer therapy. The possible relevance of this observation in the context of cancer prevention and treatment has been discussed elsewhere (Dashwood et al., 2006).

In erythroleukemia cells, 4-phenylbutyrate was a more effective HDAC inhibitor and a more potent inducer of histone acetylation than other structural analogs of butyrate, including 2- and 3-phenylbutyrate, 2-phenoxybutyrate, phenoxyacetate, cinnamate, and methoxycinnamate (Lea et al., 1999a). A prodrug form of butyrate, tributyrin, suppressed hepatocarcinogenesis in the rat and increased hepatic nuclear histone H3K9 acetylation levels (Kuroiwa-Trzmielina et al., 2009). Butyrate also was reported as the most relevant HDAC inhibitor formed in fermentations of human fecal slurry with apple pectin, and apple juice extracts produced butyrate and other unidentified HDAC inhibitors (Waldecker et al., 2008a,b).

Despite one case of remission in a child with acute myelogenous leukemia (Novogrodsky et al., 1983), therapeutic interventions with butyrate have been disappointing (Oki and Issa, 2006). Optimization of the route and length of administration of butyrate may increase its therapeutic effects. For example, in a randomized, double-blind cross-over study, daily rectal administration of butyrate was found to improve biomarkers of oxidative stress in the healthy human colon (Hamer et al., 2009). Combining butyrate with mesalazine produced a marked improvement in the symptoms and endoscopic appearance of the gut mucosa in ulcerative colitis patients (Assisi et al., 2008).

Chronic exposure to butyrate through the daily consumption of dietary fiber as "whole food" may also have significant chemopreventive effects over a lifetime (Pool-Zobel and Sauer, 2007). Consumption of whole grain foods made from high-amylose barley resulted in a 57% increase in fecal total short-chain fatty acids and a 91% higher excretion of butyrate (Bird et al., 2008). Soy oligosaccharide intake (3 g/day) increased the levels of short-chain fatty acids in women, such as propionate and butyrate, compared with women who had not consumed soy oligosaccharide (Bang et al., 2007). A cereal-based evening meal rich in indigestible carbohydrates

was shown to increase plasma butyrate the next morning; the authors concluded that short-chain fatty acids, in particular butyrate, might account for the protection afforded by whole grains against cardiovascular disease and type 2 diabetes (Nilsson et al., 2010). An ongoing study in human volunteers seeks to examine the relationships between colonic cell turnover and early biomarkers of carcinogenesis, dietary fiber intake/fermentation, and global protein acetylation (Corfe et al., 2009). It will be of great interest if these findings can be related to altered HDAC activities and to the role of metabolism generating intermediates such as butyrate.

Organoselenium compounds: α-keto acid metabolites as HDAC inhibitors

Butyrate is the oldest known dietary HDAC inhibitor, but an interesting structural analog was recently discovered that pointed to a new class of selenium-based HDAC inhibitors. Thus, keto-methylselenobutyrate (KMSB) and its structural analog methylselenopyruvate (MSP) were identified as novel competitive HDAC inhibitors. Enzyme kinetic studies supported a competitive mechanism, with a K_i of 35 μM MSP with human HDAC8 (Lee et al., 2009; Nian et al., 2009b).

Seleno-α-keto acids are generated as metabolites of natural organoselenium compounds, including the major dietary forms methylselenocysteine (MSC) and selenomethionine (SM). The transamination of SM to KMSB, and of MSC to MSP, competes with a lyase-catalyzed pathway that produces methylselenol (Figure 2). The latter metabolite has been considered an important mediator of the anticancer effects of selenium compounds, acting on redox-sensitive signaling proteins and transcription factors to reduce the risk of cancer development and progression (Lü and Jiang, 2005; Jackson and Combs, 2008; Ohta and Suzuki, 2008; Tsuji et al., 2009; Pinto et al., 2010; Zeng et al., 2010).

Hepatic enzymes such as L-amino acid oxidase and glutamine transaminase-liver (GTL) produce the seleno-α-keto acid metabolites from the corresponding parent compounds in liver (Pinto et al., 2010), but in other tissues this reaction is catalyzed by glutamine transaminase-kidney (GTK). Interestingly, human colon and prostate cancer cells contain the enzyme GTK, which has high affinity for MSC but negligible activity toward SM as a substrate (Lee et al., 2009). As a consequence, in colon and prostate cancer cells SM is not readily converted to KMSB, whereas MSP is readily formed from MSC. Inhibitors of the pyridoxal phosphate group in GTK indicated that transamination is an important and necessary step for HDAC inhibition and histone hyperacetylation by MSC. From molecular docking studies, the carbonyl group generated by the transamination reaction was predicted to interact in the HDAC pocket with a critical tyrosine residue and with the zinc atom (Figure 3, arrows). An amine group in the substrate interfered with docking and zinc-binding, thus explaining the lack of inhibition by MSC and SM parent compounds when added directly to HDAC activity assays *in vitro*.

Further work is needed to corroborate whether these seleno-α-keto acid metabolites are generated *in vivo*, under conditions of normal dietary intake in foods such as Brazil nuts, garlic, seafood, and cruciferous vegetables, and below the threshold for selenium toxicity (http://lpi.oregonstate.edu/infocenter/minerals/selenium/). PubMed lists over 400 separate reviews on selenium and human health, including the conflicting evidence from various clinical trials (reviewed by Muecke et al., 2010). It is noteworthy that a large trial that was halted recently (Lippman et al., 2009) used SM, a form of selenium that is anticipated to generate methylselenol, but not KMSB, in tissues such as prostate and colon. MSC might have been a better candidate for the clinical trials, based on the new paradigm of HDAC inhibition.

MSP has a pyruvate moiety, which raises an interesting question—does pyruvate itself act as an HDAC inhibitor, and do other α-keto acids generated as part of normal intermediary metabolism serve the role of endogenous HDAC inhibitors? There is evidence, in fact, to support such a possibility. Interestingly, the findings connect with the Warburg hypothesis (Warburg, 1956) and the divergent roles of nutrient transporters in normal cells and cancer cells. Thus, SLC5A8 and SLC5A12 are sodium-coupled monocarboxylate transporters (SCMTs) with important physiological functions in the gastrointestinal (GI) tract and other tissues (Ganapathy et al., 2009). These transporters exert a tumor suppressor function by regulating the intracellular concentrations of pyruvate, butyrate, and propionate. In cancer cells, silencing of SCMTs coupled with the conversion of pyruvate to lactate correlates with increased HDAC activity and reduced apoptosis (Ganapathy et al., 2009). When MCF-7 breast cancer cells were transfected with SLC5A8 cDNA, pyruvate-mediated apoptosis was triggered, a response also seen with butyrate and propionate, but not lactate. Lactate is produced in cancer cells as a result of the increased rate of glycolysis and the relatively low oxidation of pyruvate in mitochondria (Hockenbery, 2010; Israelsen and Vander Heiden, 2010; Sattler et al., 2010). Interestingly, pyruvate, butyrate, and propionate were identified as inhibitors of HDAC1 and HDAC3, whereas lactate had no effect on HDAC activity (Thangaraju et al., 2009a). Pyruvate and butyrate inhibited HDAC1 with IC_{50} values of 24 and 20 μM, and inhibited HDAC3 with IC_{50} values 80 and 75 μM, respectively. 3-Bromopyruvate, an alkylating agent with antitumor activity, also inhibited HDAC1 and HDAC3 in human breast cancer cells (Thangaraju et al., 2009b). This led to the intriguing hypothesis that cancer cells silence monocarboxylate transporters, and convert pyruvate to lactate, as a cooperative approach to circumventing pyruvate-mediated HDAC inhibition and apoptosis induction (Ganapathy et al., 2008).

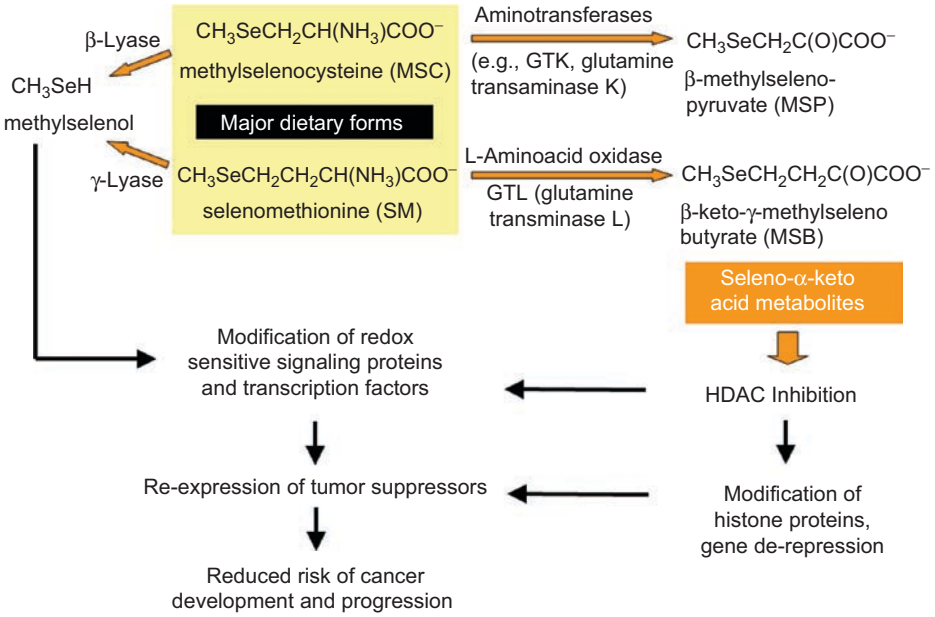


Figure 2. Working model for chemoprotection by organoselenium compounds. The production of methylselenol competes with a transamination reaction that generates seleno-α-keto acid metabolites as histone deacetylase (HDAC) inhibitors. For further details, see text and Lee et al. (2009) and Nian et al. (2009b).

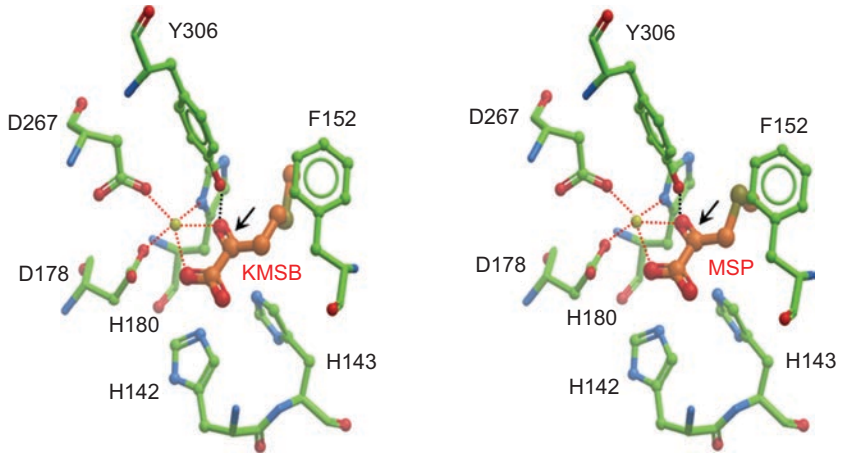


Figure 3. Molecular docking of seleno-α-keto acid metabolites in the histone deacetylase (HDAC) pocket. β-Keto-methyl-γ-selenobutyrate (KMSB) and β-methylselenopyruvate (MSP) contain a carbonyl group generated in the transamination reaction, see Figure 2. This carbonyl group is predicted to interact in the human HDAC8 pocket with a critical tyrosine 306 residue and the zinc atom. For details on the modeling procedure, see Nian et al. (2009b).

Organosulfur compounds: small molecule thiols as HDAC inhibitors

Garlic, onions, shallots, and other members of the *Allium* family contain an interesting and complex range of water-soluble and fat-soluble organosulfur compounds, some of which have been implicated as cancer chemopreventive agents (Powolny and Singh, 2008; Iciek et al., 2009; Nian et al., 2009a; Gullett et al., 2010). Alliin (allylcysteine sulfoxide), allicin (allyl 2-propenethiosulfinate), *S*-allylcysteine (SAC), *S*-allylmercaptocysteine (SAMC), diallyl sulfide (DAS), diallyl disulfide (DADS), and diallyl trisulfide (DATS), as well as their metabolites allyl methyl sulfide (AMS), methyl mercaptan, and allyl mercaptan (AM) have been examined in the context of inhibition of carcinogen activation, induction of phase 2 detoxification pathways, and changes in cell differentiation and apoptosis pathways.

Over a decade ago, Lea and colleagues reported on the increased acetylation of histones in mouse erythroleukemia cells treated with DADS. Acetylation was also induced in rat hepatoma and human breast cancer cells by DADS and its metabolite, AM (Lea et al., 1999b). These observations were extended to other organosulfur compounds, including allyl isothiocyanate (Lea and Randolph, 2001; Lea et al., 2001) and SAMC (Lea et al., 2002). Increased histone acetylation in liver and Morris hepatoma 7777

was induced by treatment of rats with DADS, AM, and butanethiol (Lea and Randolph, 2001). In human colon cancer cells incubated with DADS, HDAC activity was inhibited and there was increased histone acetylation and $p21^{WAF1}$ expression (Druesne et al., 2004a). Repetitive treatment of colon cancer cells with DADS induced prolonged hyperacetylation of histone H3 K14 (Druesne et al., 2004b). In rats given DADS by gavage or intracecal perfusion, increased histone acetylation was evident in normal colonocytes (Druesne-Pecollo et al., 2007, 2008).

Using HeLa nuclear extracts or purified human HDAC8 as source of enzyme, only AM inhibited HDAC activity in a concentration-dependent manner among several garlic-derived organosulfur compounds and their metabolites, including SAMC, SAC, DAS, DADS, DATS, AMS, and AM. Enzyme kinetics experiments coupled with computational modeling supported a competitive mechanism, with a K_i of 24 μM for AM with human HDAC8 (Nian et al., 2008). In the docked structure, the–SH group of AM was optimally positioned to interact with the zinc atom in the HDAC pocket (Figure 4). This paralleled the findings with other thiol-based HDAC inhibitors and their prodrug candidates (Suzuki et al., 2004, 2005; Sanda et al., 2007). Collectively, the studies with dietary organosulfur compounds support the hypothesis that a complex profile of water-soluble and lipid-soluble compounds is funneled by metabolism toward a small number of reactive thiols, with AM being the most effective HDAC inhibitor (Lea et al., 1999b; Nian et al., 2008). These findings do not preclude other mechanisms or molecular targets of dietary organosulfur compounds (Powolny and Singh, 2008; Iciek et al., 2009; Gullett et al., 2010).

Isothiocyanates: mercapturic acid metabolites and HDAC inhibition

Brassica or cruciferous vegetables are a rich source of glucosinolates (Higdon et al., 2007). The hydrolysis of these glucosinolates by the plant enzyme myrosinase generates biologically active isothiocyanates and indoles. For example, broccoli and broccoli sprouts are a rich source of glucoraphanin, the precursor of sulforaphane (SFN). SFN is widely reported to exert anticancer effects *in vitro* and *in vivo* (Higdon et al., 2007; Juge et al., 2007; Clarke et al., 2008; Dinkova-Kostova and Talalay, 2008; Nian et al., 2009a; Valgimigli and Iori, 2009; Cheung and Kong, 2010; Gullett et al., 2010; Kwak and Kensler, 2010).

SFN was first discovered as a potent Phase 2 enzyme inducer (Zhang et al., 1992), acting via the Kelch-like ECH-associated protein 1/nuclear factor erythroid 2-related factor 2 (Keap1/Nrf2) pathway and other anticancer mechanisms (reviewed in Clarke et al., 2008; Cheung and Kong, 2010; Gullett et al., 2010; Kwak and Kensler, 2010). A "one–two" chemoprotection paradigm has been proposed for SFN in which the electrophilic parent compound targets Keap1 to release Nrf2 into the nucleus, and the metabolites inhibit HDAC activity, leading to unsilencing of tumor suppressor genes that trigger cell cycle arrest and apoptosis (Dashwood et al., 2006; Dashwood and Ho, 2007).

Support for the latter hypothesis first came from experiments in HEK293 cells and human HCT116 colon cancer cells (Myzak et al., 2004), and subsequently in human prostate and breast cancer cells (Myzak et al., 2006; Pledgie-Tracy et al., 2007). Rather than the parent compound, SFN metabolites generated via the mercapturic acid pathway were implicated in the mechanism of HDAC inhibition (Figure 5). GST catalyzes formation of the SFN–glutathione (SFN-GSH) conjugate, which is then converted to other intermediates such as SFN–cysteine (SFN-Cys) and SFN–*N*-acetylcysteine (SFN-NAC). When cells were incubated with SFN and the cell-free media was added to the *in vitro* HDAC activity assay, concentration-dependent inhibition was evident (Myzak et al., 2004). This was attenuated when cells were

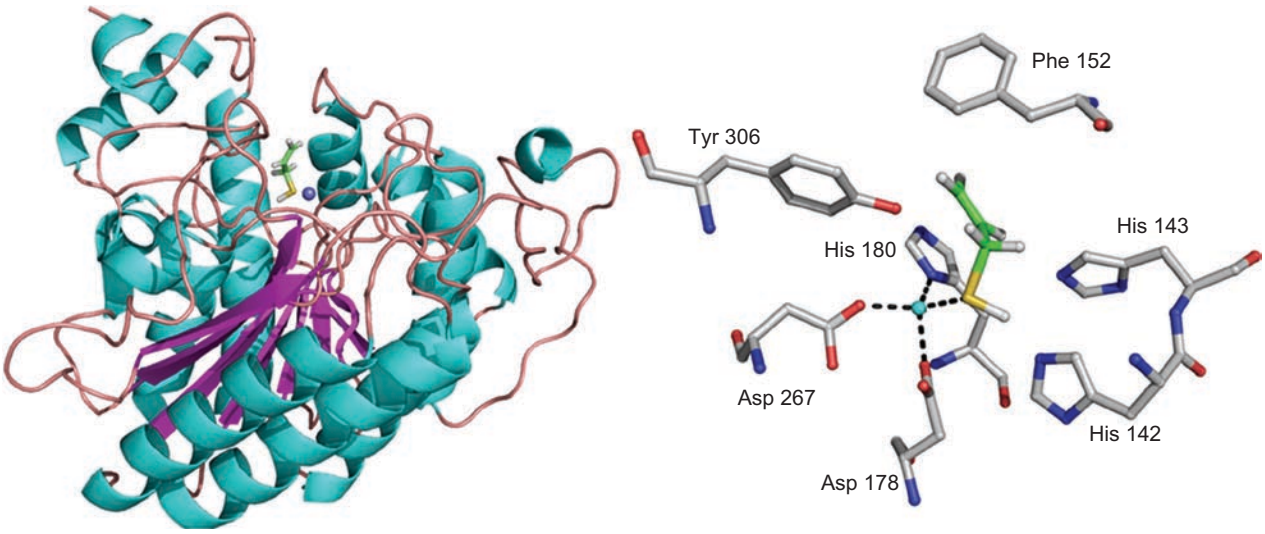


Figure 4. Molecular modeling of histone deacetylase (HDAC) 8-allyl mercaptan (AM) complex. AM is a small molecule thiol generated via the metabolism of organosulfur compounds in garlic, see Nian et al. (2008).

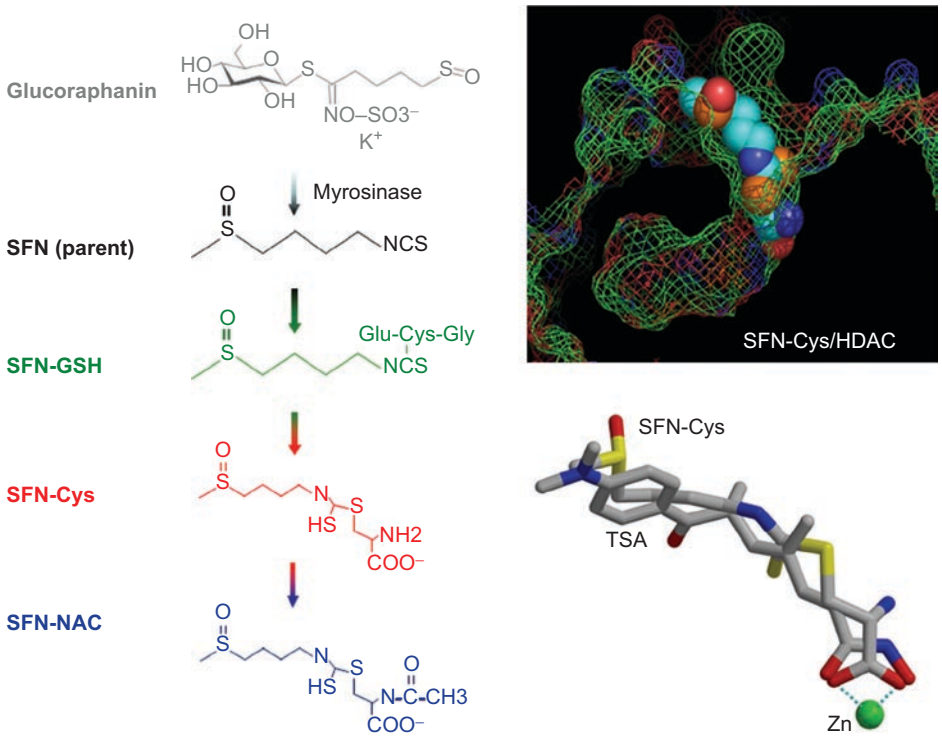


Figure 5. Metabolism of sulforaphane (SFN) via the mercapturic acid pathway generates intermediates such as SFN–glutathione (SFN-GSH), SFN–cysteine (SFN-Cys), and SFN–*N*-acetylcysteine (SFN-NAC). SFN-Cys was modeled to fit into the histone deacetylase (HDAC) pocket in a similar orientation as trichostatin A (TSA). A bidentate interaction is shown for SFN-Cys with the zinc atom, as occurs in the crystal structure containing TSA. See text and Myzak et al. (2004).

pretreated with a GST inhibitor, ethacrynic acid, which blocks the first step in the mercapturic acid pathway. Notably, direct addition of SFN parent compound to the *in vitro* HDAC activity assay, with HeLa nuclear extracts as source of enzyme, had no inhibitory effect. Subsequent experiments provided evidence for the following order of HDAC inhibition *in vitro*: SFN-Cys > SFN-NAC > SFN-GSH >> SFN. By computational modeling, SFN-Cys fit the HDAC pocket and adopted a similar orientation as SAHA and TSA (Figure 5). The carboxylate group in SFN-Cys was predicted to form a bidentate ligand with the zinc atom, analogous to that seen for SAHA and TSA in the crystal structure (Finnin et al., 1999; Somoza et al., 2004).

Since the–Cys group was predicted to enter into the HDAC pocket, other isothiocyanates that are metabolized via the mercapturic pathway were considered candidate HDAC inhibitors, including those found in pungent foods such as mustard, radish, horseradish, wasabi, and daikon (Higdon et al., 2007; Nian et al., 2009a; Verkerk et al., 2009; Yamasaki et al., 2009; Ernst et al., 2010). The mustard oil compound allyl isothiocyanate was reported earlier to induce histone acetylation in mouse erythroleukemia cells, but with no apparent inhibition of HDAC activity (Lea et al., 2001). We confirmed the latter observation, while showing that longer-chain isothiocyanates inhibited HDAC activity in human colon cancer cells (Dashwood et al., 2006). The inhibition of HDAC activity increased with length of the spacer "arm" in the parent molecule, and was associated with H4K12 hyperacetylation, $p21^{WAF}$ induction, cell cycle arrest, and apoptosis (Rajendran et al., manuscript in preparation). As with SFN *in vitro*, none of the isothiocyanates were inhibitory when added directly to the HDAC assay in the presence of HeLa nuclear extracts, supporting the need for metabolites to be formed as the "ultimate" HDAC inhibitors.

The cap group in HDAC inhibitors lies close to the surface and can dictate specificity toward individual HDACs (Vannini et al., 2007; Nian et al., 2008, 2009b; Ortore et al., 2009; Suzuki et al., 2009; Wang, 2009; Oger et al., 2010). Interestingly, benzyl isothiocyanate (BITC) was reported to inhibit HDAC activity in human pancreatic carcinoma cells, and this was rescued by overexpression of HDAC1 or HDAC3 (Batra et al., 2010). Immunohistochemical staining of tumors from mice treated with BITC showed significantly reduced staining of HDAC1 and HDAC3 compared with controls (Batra et al., 2010).

In addition to HDAC expression and histone acetylation, other epigenetic marks may be involved. In human breast cancer cells, analyses of the human telomerase reverse transcriptase (hTERT) promoter revealed that SFN increased the levels of active chromatin marks, such as acetyl-H3, acetyl-H3K9, and acetyl-H4, while lowering repressive marks such as H3K9Me3 and H327Me3 (Meeran et al., 2010). Ma et al. also reported that phenylhexyl isothiocyanate (PHITC) inhibited HDAC activity in human leukemia cells, with evidence for increased histone acetylation, elevated H3K4 "active" methylation,

and loss of H3K9 "repressive" methylation marks (Ma et al., 2006). PHITC reactivated aberrantly hypermethylated *P15* gene expression in acute leukemia cells through changes in both DNA methylation and histone acetylation (Jiang et al., 2010). Moreover, in patients with acute leukemia, histone acetylation was virtually undetectable, but was reversed in the presence of PHITC (Xiao et al., 2010). Phenethyl isothiocyanate (PEITC), found in watercress, de-repressed the *P21WAF1* promoter in prostate cancer cells via inhibition of HDAC activity, enhanced histone acetylation, and changes in histone methylation (Wang et al., 2008). Interestingly, PEITC was reported to overcome resistance to vorinostat in human leukemia cells (Hu et al., 2010), hinting at drug/diet interactions that augment HDAC inhibition and gene re-expression.

Indoles: acid condensation products that alter HDAC expression

As noted above, cruciferous vegetables contain glucosinolates such as glucoraphanin, the precursor of SFN, and glucobrassicin, the precursor of indole-3-carbinol (I3C). The latter compound and its acid condensation products, such as 3,3′-diindolylmethane (DIM), have been examined extensively for their cancer chemoprotective properties (Aggarwal and Ichikawa, 2005; Higdon et al., 2007; Weng et al., 2008; Ahmad et al., 2010). A recent report found that DIM selectively induced the proteasome-mediated degradation of class I HDACs in human colon cancer cells, without affecting class II HDACs (Li et al., 2010a). This distinguishes DIM, a dimer of I3C formed *in vivo*, from synthetic HDAC inhibitors centered around a 3-piperidin-3-ylindole moiety (Cho et al., 2010), and the 3-arylindeneindolin-2-one-based compounds that specifically target class III HDACs (Huber et al., 2010). Given that I3C generates a diverse array of oligomers in addition to DIM (Higdon et al., 2007), further studies appear to be warranted on dietary indoles and their effects on HDAC activity and turnover.

Polyphenols: pros and cons of HDAC modulation

Dietary polyphenols such as resveratrol, quercetin, curcumin, and tea catechins have been examined as HDAC activators as well as HDAC inhibitors (Wood et al., 2004; Han, 2009; Imai, 2009, 2010; Chung et al., 2010; Imai and Guarente, 2010). A recent review summarized the debate surrounding "purported activators" of class III HDACs, such as SIRT1, in the context of therapeutic strategies related to aging, type II diabetes, and neurodegeneration (Dittenhafer-Reed et al., 2010).

In a rat liver cancer model, black tea polyphenols were reported to reduce significantly the expression levels of HDAC1 protein in liver and lung (Murugan et al., 2009). It was not clear whether other HDACs were affected, and whether alternative epigenetic mechanisms were involved, such as the inhibition of DNA methylation that has been reported for green tea catechins (Lee et al., 2005; Fang et al., 2007; Gilbert and Liu, 2010; Li and Tollefsbol, 2010). Polyphenols, including those in tea, undergo extensive metabolism *in vivo* to methylated and glucuronidated intermediates, as well as to novel breakdown products formed in the GI tract (Lee et al., 2002; Schantz et al., 2010; Sies, 2010; Stalmach et al., 2010a,b). Little if anything is known at present about how these intermediates affect HDAC activity.

Curcumin, and other curcuminoid polyphenols in Indian spices such as turmeric, have cancer chemoprotective properties (Aggarwal, 2010; Bar-Sela et al., 2010; Epstein et al., 2010; Padhye et al., 2010). There is growing interest in these compounds and their potential epigenetic mechanisms (Rahman, 2008; Chung et al., 2010; Fu and Kurzrock, 2010; Li et al., 2010b).

For example, selective loss of HDAC2 protein expression occurs in the pathogenesis of chronic obstructive pulmonary disease (COPD) (Barnes, 2009, 2010b; RajendrasozHan et al., 2009; Marwick et al., 2010), a situation exacerbated by cigarette smoke (Adenuga et al., 2009). In lung, HDAC2 deacetylates the glucocorticoid receptor (GR), an "off" mechanism that permits proinflammatory genes to be silenced (Figure 6). Curcumin treatment can help to maintain HDAC2 expression and activity, restoring corticosteroid function in monocytes exposed to oxidants (Meja et al., 2008). It is presently unclear whether this mechanism applies to curcumin metabolites such as di-, tetra-, and hexahydrocurcumin, the glucuronide and sulfate conjugates (Sharma et al., 2004; Hoehle et al., 2007; Dempe et al., 2008), and structural analogs such as dimethylcurcumin, 1,5-bis(3-pyridyl)-1,4-pentadien-3-one, and 3,5-bis-(2-fluorobenzylidene)-piperidinium-4-oneacetate (Steward and Gescher, 2008).

As noted above, curcumin maintains rather than attenuates HDAC2 activity in lung and is beneficial in cases such as COPD, but this runs counter to the general paradigm of dietary HDAC inhibitors triggering gene derepression as a beneficial outcome in cancer cells. There also exist dietary compounds that purportedly activate HDACs or inhibit HATs, such as resveratrol and theophylline (Delage and Dashwood, 2009b), which could theoretically up-regulate proinflammatory genes under conditions of oxidative stress. In the case of inflammatory bowel disease, curcumin has been described as having "bright prospects" due to it beneficial effects on cyclooxygenase, lipoxygenase, tumor necrosis factor, interferon, and nuclear factor kappa B (NF-κB) pathways (Hanai and Sugimoto, 2009). In GI tissues, mechanisms might exist to maintain HDAC2 (and other HDACs), which are not active under conditions of oxidative stress and chronic inflammation in the lung. The yin–yang of HDAC inhibition versus HDAC activation under conditions of oxidative stress, as well as normal conditions, warrants further investigation.

Miscellaneous agents: whole foods and HDAC inhibition

In addition to studying the HDAC inhibitory effects of isolated dietary constituents, such as SFN, the corresponding

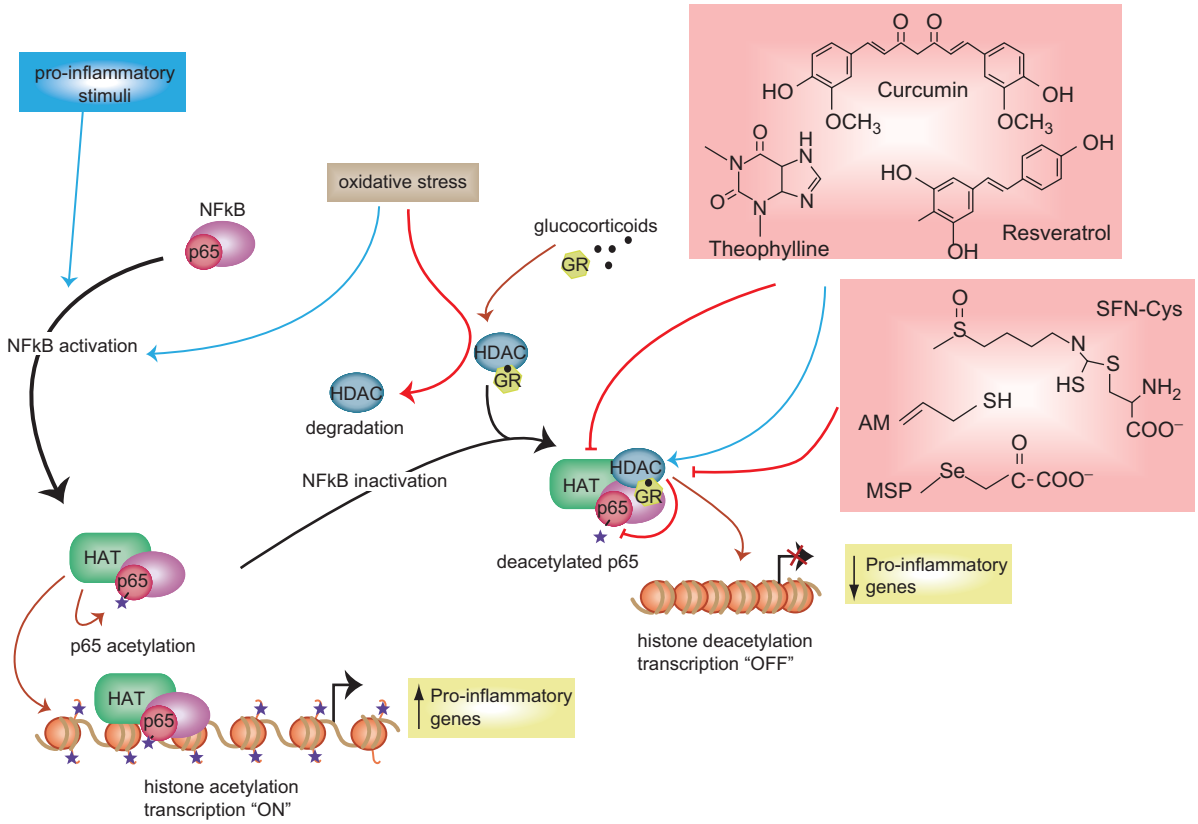


Figure 6. Regulation of chromatin structure influences the expression of proinflammatory genes. In response to oxidative stress and proinflammatory conditions, signaling molecules such as NF-κB–p65 become activated and enter the nucleus, thereby recruiting HATs and their coactivator complexes to enhance gene activity. Corticosteroids and natural modulators of HAT and HDAC activities regulate the acetylation status of the glucocorticoid receptor (GR) and its ability to bind to the promoters of proinflammatory genes. For further details, see Delage and Dashwood (2009b).

whole foods also have been examined. Consumption of a single cup of broccoli sprouts in human volunteers was shown to inhibit HDAC activity in circulating peripheral blood mononuclear cells (Myzak et al., 2007). Bitter melon (*Momordica charantia*), a plant that is both eaten and used medicinally, contains a protein MCP30 that inhibited HDAC1 activity and promoted histone acetylation in prostate cancer cells (Xiong et al., 2009). MCP30 was identified as a Type I ribosome-inactivating protein, which suppressed the growth of PC3 cells *in vivo* in a fashion similar to SFN (Myzak et al., 2007), with no effect on normal prostate cells. There is a major gap in the literature related to whole foods and their effects on HDAC activity, histone acetylation, and other epigenetic endpoints.

Concluding remarks

There is accumulating evidence to support the role of metabolism in generating modulators of HDAC activity (Table 1). HDAC inhibitor drugs developed to date are typically potent agents, some being "direct acting" and others requiring metabolism to be active. For compounds such as vorinostat, metabolism tends to lower the overall efficacy *in vivo*. However, there is a growing list of compounds, many from the human diet, that are converted by metabolism to the presumed "ultimate" HDAC inhibitor. The pharmacokinetic/pharmacodynamic distribution of HDAC inhibitors is also likely to be influenced by diet and nutritional status. A better understanding of this issue might clarify the interindividual variability observed with HDAC inhibitors in human subjects, and the potential for drug–diet interactions. For example, in patients treated with agents such as vorinostat, phenylbutyrate, or valproic acid, might additional benefit derive from HDAC inhibitor intake in the form of broccoli sprouts or other foods? Might the toxicity and drug resistance associated with some clinically used HDAC inhibitors be circumvented by lowering the dose, while supplementing with dietary HDAC inhibitors that must be metabolized to their active forms? The latter typically provides for a more sustained level of HDAC inhibition than the "fast-on/fast-off" agents currently used in the clinic (Chou et al., 2008). There is still much to learn about the epigenetic mechanisms that influence human health and disease susceptibility, and how these mechanisms are affected by diet and other lifestyle factors. Mainstream smoke, for example, in known to alter microRNA expression patterns in mouse lung, whereas PEITC and *N*-acetylcysteine given during pregnancy or weaning can normalize these microRNA profiles (Izzotti

Table 1. Summary of the role of metabolism in generating histone deacetylase (HDAC) inhibitors.

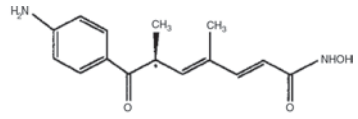
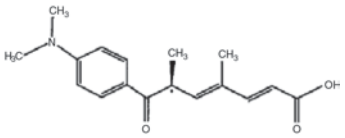
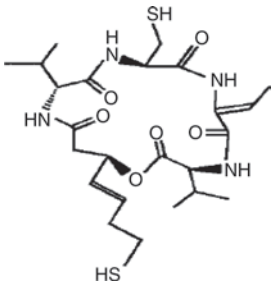
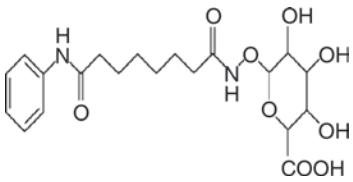
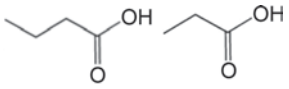
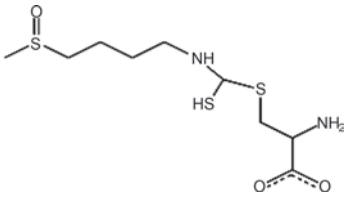
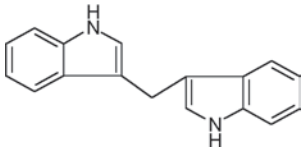
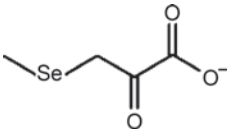
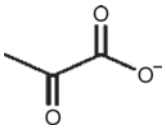
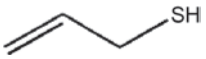
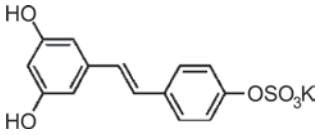
Parent compound (non-dietary)	Metabolite(s)	HDAC-related mechanism(s)	Structure(s) of key intermediates/ metabolites	References
Trichostatin A (TSA)	N-Demethylated trichostatin, trichostatic acid	N-Demethylated metabolite retained HDAC inhibitory activity while the acid did not. Mercapturic acid pathway lowers activity/efficacy *in vivo*?	 Active  Inactive	Elaut et al. (2002), Sanderson et al. (2004), Myzak et al. (2004)
Romidepsin	Reduced dithiol (4-reduced)	Class I HDAC inhibitor, FDA approved for CTCL. A prodrug converted to active metabolite HDAC inhibitor		Furumai et al. (2002)
Vorinostat (SAHA)	SAHA-glucuronide	FDA-approved HDAC inhibitor, for CTCL. Phase II conjugation leads to PK variability; mercapturic acid pathway lowers activity *in vivo*?		Kang et al. (2010)
Parent compound (dietary)	Metabolite(s)	HDAC-related mechanism(s)	Structures of key intermediates/ metabolites	References
Dietary fiber, fat, alcohol	Short-chain fatty acids (butyrate, propionate) from gut fermentation	Competitive HDAC inhibition; butyrate $K_i = 46$ μM in MCF-7 whole cell lysate	 Butyrate Propionate	Boffa et al., (1978), Choudhury and Shukla (2008), Singh et al. (2010b), Sekhavat et al. (2007)
Sulforaphane (SFN), other diet-derived isothiocyanates	SFN–cysteine, mercapturic acid pathway intermediates	Reduces HDAC activity via direct and/or indirect mechanisms		Myzak et al. (2004)
Indole-3-carbinol	Oligomers (3,3′-diindolylmethane and others)	Inhibits the expression of class I HDACs		Li et al. (2010a), Higdon et al. (2007)
Organoselenium compounds (methyl selenocysteine)	Methyl selenopyruvate	Inhibits HDAC activity, K_i 35 μM hHDAC8		Nian et al. (2009b), Lee et al. (2009)
Glucose, other intermediates of intermediary metabolism	Pyruvate	HDAC1 (IC_{50} 24 μM) and HDAC3 (IC_{50} 80 μM) inhibition		Thangaraju et al. (2009a)

Table 1. continued on next page

Table 1. Continued.

Parent compound (dietary)	Metabolite(s)	HDAC-related mechanism(s)	Structure(s) of key intermediates/ metabolites	References
Organosulfur compounds (diallyl disulfide, other garlic compounds)	Allyl mercaptan, endogenous small molecule thiols?	Competitive inhibitor, K_i 25 μM for hHDAC8; Sp3 increased on *P21WAF1* promoter		Nian et al. (2008), Lea et al. (1999b)
Resveratrol (and other dietary polyphenols)	4′-*O*-Sulfate-resveratrol	Purported inducer of SIRT1, class III HDACs		Calamini et al. (2010)

Both dietary and non-dietary sources provide constituents which, through metabolism, can lead to intermediates with the ability to affect HDAC activity, chromatin silencing/unsilencing, and gene expression. See text and the references listed for further details.
CTCL, cutaneous T-cell lymphoma; hHDAC8, human HDAC8.

et al., 2010). Thus, microRNAs, DNA methylation, and histone status collectively comprise a cadre of epigenetic elements that can be modulated by dietary factors and their metabolites (Davis and Ross, 2007, 2008; Ross and Milner, 2007). In the future, an improved understanding of epigenetic mechanisms and their impact on human health and disease will depend on several avenues of research, including metabolism as a key to HDAC inhibition.

Declaration of interest

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