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Review Article

Overview of the Classical Histone Deacetylase Enzymes and Histone Deacetylase Inhibitors

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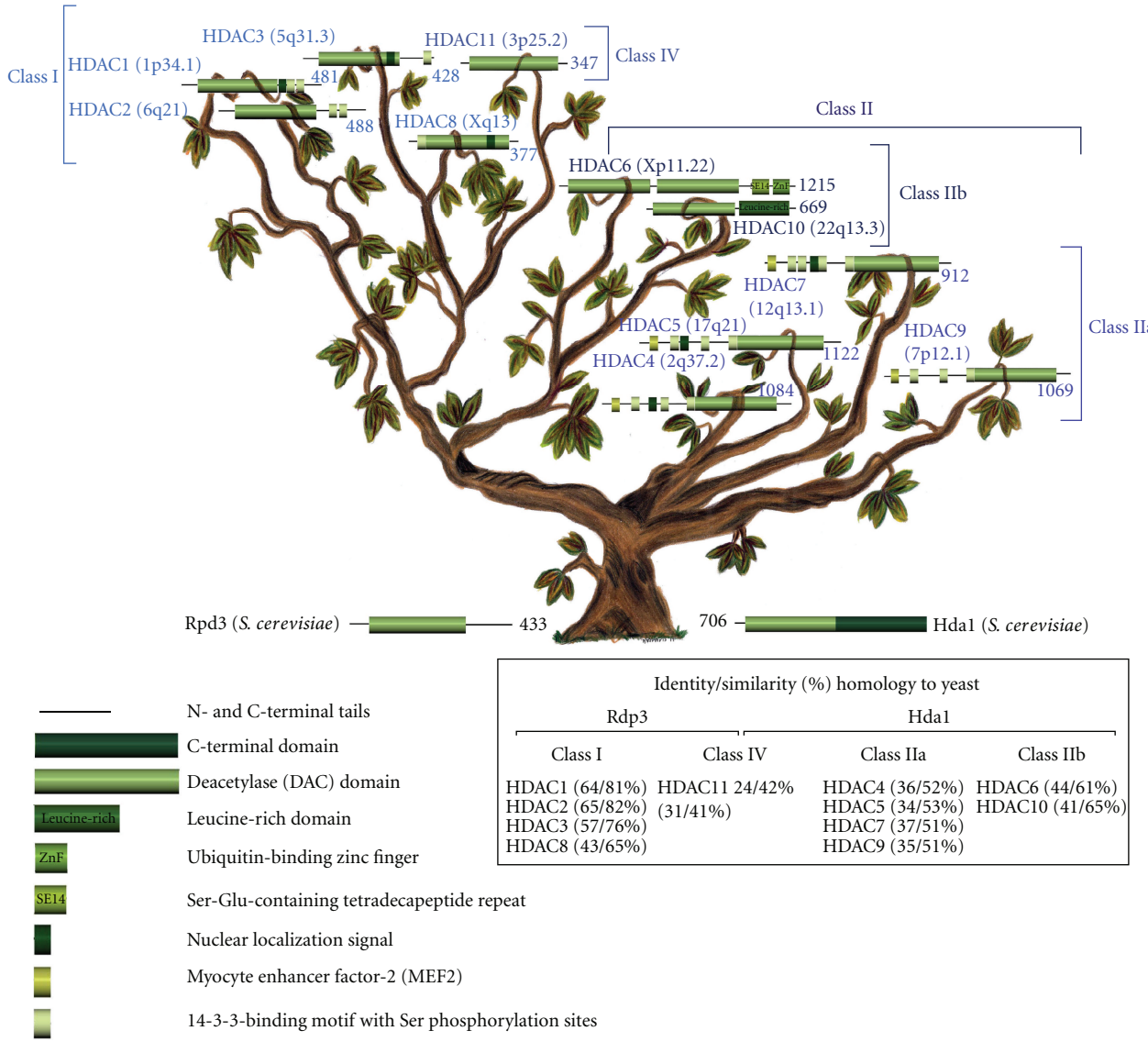
The important role of histone deacetylase enzymes in regulating gene expression, cellular proliferation, and survival has made them attractive targets for the development of histone deacetylase inhibitors as anticancer drugs. Suberoylanilide hydroxamic acid (Vorinostat, Zolinza), a structural analogue of the prototypical Trichostatin A, was approved by the US Food and Drug Administration for the treatment of advanced cutaneous T-cell lymphoma in 2006. This was followed by approval of the cyclic peptide, depsipeptide (Romidepsin, Istodax) for the same disease in 2009. Currently numerous histone deacetylase inhibitors are undergoing preclinical and clinical trials for the treatment of hematological and solid malignancies. Most of these studies are focused on combinations of histone deacetylase inhibitors with other therapeutic modalities, particularly conventional chemotherapeutics and radiotherapy. The aim of this paper is to provide an overview of the classical histone deacetylase enzymes and histone deacetylase inhibitors with an emphasis on potential combination therapies.

1. Introduction

Chromatin is a dynamic structure that, via numerous mechanisms including DNA methylation and posttranslational histone modifications, undergoes remodeling to facilitate metabolic processes including transcription, replication, and repair [1]. One of the well-investigated posttranslational histone modifications is acetylation which was first defined in the 1960s [2, 3]. Histone acetylation is controlled by the opposing actions of two groups of enzymes, namely, histone acetyltransferases (HATs) and histone deacetylases (HDACs) [4–6]. HATs catalyze the transfer of the acetyl moiety of the substrate acetyl-coA to the ε-amino group of lysine residues on histones. This neutralizes the positive charge of histones, weakening their interaction with the negatively charged DNA. This results in a more relaxed, transcriptionally permissive chromatin conformation [7, 8]. HDAC enzymes remove acetyl groups from histones resulting in a more condensed, transcriptionally repressive chromatin state [4, 5].

The 18 mammalian HDAC enzymes identified to date are categorized into two distinct groups. The class III HDAC enzymes which include the sirtuins 1–7 require nicotinamide adenine dinucleotide (NAD^+) to deacetylate lysine residues [12, 13]. These have been implicated with numerous diseases and in the process of aging [14]. The remaining 11 enzymes are typically known as the classical HDAC enzymes and will be the focus of the remaining of this paper [9]. An intense interest in function and pharmacological manipulation of these enzymes rapidly followed the initial cloning and characterization of the first human HDACs in the 1990s [15–23]. The different isoforms of the classical HDAC enzymes have undergone extensive phylogenetic analysis and are grouped into three different classes (Figure 1) [10]. Class 1 enzymes consisting of HDAC1, 2, 3, and 8 which share similarity with the yeast transcriptional regulator RDP3 are primarily localized in the nucleus [9, 10]. They are expressed ubiquitously and have important functional roles in regulating cellular proliferation and survival [11, 24]. In



Identity/similarity (%) homology to yeast

Rdp3		Hda1	
Class I	Class IV	Class IIa	Class IIb
HDAC1 (64/81%)	HDAC11 24/42%	HDAC4 (36/52%)	HDAC6 (44/61%)
HDAC2 (65/82%)	(31/41%)	HDAC5 (34/53%)	HDAC10 (41/65%)
HDAC3 (57/76%)		HDAC7 (37/51%)	
HDAC8 (43/65%)		HDAC9 (35/51%)	

Figure 1: Evolutionary relationship between the classical histone deacetylase enzymes (HDACs). The HDAC superfamily form evolutionary distinct groups according to their sequence homology to yeast. Class I enzymes share similarity with the yeast, reduced potassium dependency-3 (Rpd3), and consist of HDAC1, 2, 3, and 8. Rpd3 is most homologous to HDAC1 and HDAC2. The class II HDACs share homology to the yeast, histone deacetylase-1 (Hda1), and enzymes in this class form two separate subclasses. Class IIa is comprised of HDAC4, 5, 7, and 9; class IIb consists of HDAC6 and 10. Hda1 is most closely related to HDAC6. The phylogenetic tree shows that HDAC11 does not share enough homology with class I or class II HDACs so forms class IV and shares some identity to both Rpd3 and Hda1. The percentage of HDAC amino acid sequence identity/similarity to that of Rpd3 or Hda1 is shown in brackets, for HDAC11 the sequence identity/similarity to Hda1 is shown and to Rpd3 is given in brackets. The HDACs have a conserved deacetylase (DAC) domain with the C- and N-terminal tails represented as black lines. Nuclear localization signals, the myocyte enhancer factor-2- (MEF2-) binding domains, and the 14-3-3 chaperone-binding motifs with serine phosphorylation sites are shown. The number of amino acid residues of the longest isoform of each HDAC is shown on the right, and the chromosomal site of each HDAC is shown in brackets. *H. sapiens*: *Homo sapiens*; *S. cerevisiae*: *Saccharomyces cerevisiae*; SE14: Ser-Glu-containing tetradecapeptide repeats; ZnF: ubiquitin-binding zinc finger domain. Adapted from [9–11].

contrast, class II HDAC enzymes, which share homology with yeast Hda1, shuttle between the cytoplasm and nucleus, and they have more restricted tissue-specific expression patterns and regulatory functions [25, 26]. Class II enzymes are further subdivided into class IIa (HDAC4, 5, 7, and 9; shuttle between nucleus and cytoplasm) and class IIb (HDAC6 and 10; mainly cytoplasmic) [25, 26]. The functions of the different isoforms of HDAC enzymes have been reviewed recently [25, 26]. Of particular interest is HDAC6, a major cytoplasmic deacetylase which has been relatively well characterized, at least in part, because of work with tubacin, a specific inhibitor [27]. Numerous nonhistone protein

targets for HDAC6 have been identified including α-tubulin, cortactin, other chaperones, and peroxiredoxins [28–30]. An important role in cellular proliferation and survival has made HDAC6 an important target for cancer therapy. Recent findings have indicated the combined cytotoxic and apoptotic effects of the specific HDAC6 inhibitor tubacin with conventional chemotherapeutic agents in cancer but not normal cells [27]. Further, it has been shown that HDAC6 is an important target for protection and regeneration following central nervous system injury [29]. HDAC11 is the only member of class IV sharing similarity with both class I and class II enzymes [9]. Recent evidence indicates that HDAC11 has immunomodulatory roles [31].

2. Histone Deacetylase Inhibitors

Several different structural groups of compounds are known to possess HDAC inhibition activity. The most widely investigated HDAC inhibitor is the prototypical hydroxamic acid, Trichostatin A [32]. Trichostatin A is a potent antifungal antibiotic that was isolated from a metabolite of *Streptomyces hygroscopicus* [32]. It is a potent broad-spectrum HDAC inhibitor with cell-free assays indicating a relatively high affinity for all of the class I, II, and IV enzymes [4, 33]. Another example of a hydroxamic is the clinically available suberoylanilide hydroxamic acid (SAHA, Vorinostat, Zolinza) [34]. Like Trichostatin A, SAHA is a potent broad-spectrum HDAC inhibitor. Given its potent anticancer effects and favorable therapeutic window, SAHA was approved by the US Food and Drug Administration (FDA) for the treatment of advanced cutaneous T-cell lymphoma (CTCL) in 2006 [34]. Other hydroxamic acids currently in clinical trials include belinostat (PXD101), panobinostat (LBH589), and givinostat (ITF-2357) [26, 35]. This class of compounds possesses HDAC inhibition activity in the nanomolar to low micromolar range [26, 35].

The cyclic peptides which include trapoxin and depsipeptide are also potent HDAC inhibitors. Depsipeptide (Romidepsin, Istodax) has also been approved by the FDA for the treatment of CTCL in 2009 [36]. Similarly, the benzamides which include entinostat (MS-275, SNDX 275) and MGCD0103 are potent HDAC inhibitors with activity in the low micromolar range [25, 34, 35]. The least potent class of HDAC inhibitors is the aliphatic acids which possess activity in the millimolar range [37]. This group includes valproic acid, a compound that has been used extensively in the clinic as an antiepileptic drug [38–40]. We have used another example of an aliphatic acid, sodium butyrate, to highlight the anticancer effects of histone deacetylase inhibitors (Figure 2).

Briefly, HDAC inhibitors result in the accumulation of hyperacetylated histones and have been shown to alter the expression of approximately 2–20% of genes in malignant cell lines [4, 33, 41, 42]. Overall, HDAC inhibitors have been shown to decrease cellular proliferation, induce cell death, apoptosis, and differentiation, cause cell cycle arrest (G1 at lower concentrations and both G1 and G2/M at relatively high concentrations), and decrease migration, invasion, and angiogenesis in malignant and transformed cell lines [4, 33, 41, 42]. The effects of HDAC inhibitors are much less pronounced, by at least a factor 10, in normal cells providing the basis of their clinical utility in cancer [43]. To potentially improve the therapeutic index of HDAC inhibitors in cancer therapy, class-selective or isoform-specific compounds have been suggested. In this context, isoform-specific tubacin and PC-34051 which selectively inhibit HDAC6 and HDA8, respectively, are examples. Both compounds have recently been shown to possess anticancer effects [27, 28, 44]. However, the issue of selectivity remains controversial with arguments suggesting that the pleiotropic effects of broad-spectrum HDAC inhibitors, which are generally well tolerated, may be advantageous for cancer therapy given the heterogeneity and adaptability of malignant cells. However, it is generally accepted that selective compounds will most likely be more beneficial for nononcological applications of HDAC inhibitors which potentially include treatment cardiac hypertrophy, asthma, and various neurodegenerative disorders [45–52].

3. Combinatorial Therapies with Histone Deacetylase Inhibitors

Although they possess intrinsic anticancer effects, it is widely accepted that HDAC inhibitors will be most effective when used in combination with other cancer modalities. There are numerous combinations that are currently undergoing preclinical and clinical evaluation. These include combinations with methyltransferase inhibitors such as azacitidine, receptor-mediated cytotoxics such as retinoic acid, and phototherapy [53–57]. To highlight the advantages and potential complexities, here we will focus on combinations of HDAC inhibitors with the conventional anthracycline chemotherapeutics and radiotherapy (Figure 3).

The anthracyclines, typified by daunomycin and its structural analogue doxorubicin, are front-line cancer chemotherapeutic agents with a clinical history spanning more than 50 years [58]. They are well-known DNA intercalators and topoisomerase II enzyme inhibitors. The mechanisms of action of anthracyclines involve inhibition of RNA synthesis, generation of reactive oxygen species, and accumulation of DNA lesions including the particularly lethal, DNA double-strand breaks [58, 59]. A plethora of studies have shown that HDAC inhibitors can potentiate the cytotoxic effects of anthracyclines. For example, Trichostatin A has been shown to augment doxorubicin-induced apoptosis and cell death in human erythroleukemic K562 cells, anaplastic thyroid carcinoma, and A549 alveolar adenocarcinoma cells [60, 61]. Similarly, SAHA and valproic acid have been shown to enhance the sensitivity of malignant cells to the effects of doxorubicin [62, 63]. HDAC inhibitors induce histone hyperacetylation, resulting in a more open transcriptionally permissive chromatin conformation, a phenomenon that has been verified by MNase digestion assays [64]. In addition, it has been shown that HDAC inhibitors increase the number of binding sites and also the affinity of those sites for anthracyclines in acetylated chromatin [65]. Therefore, it

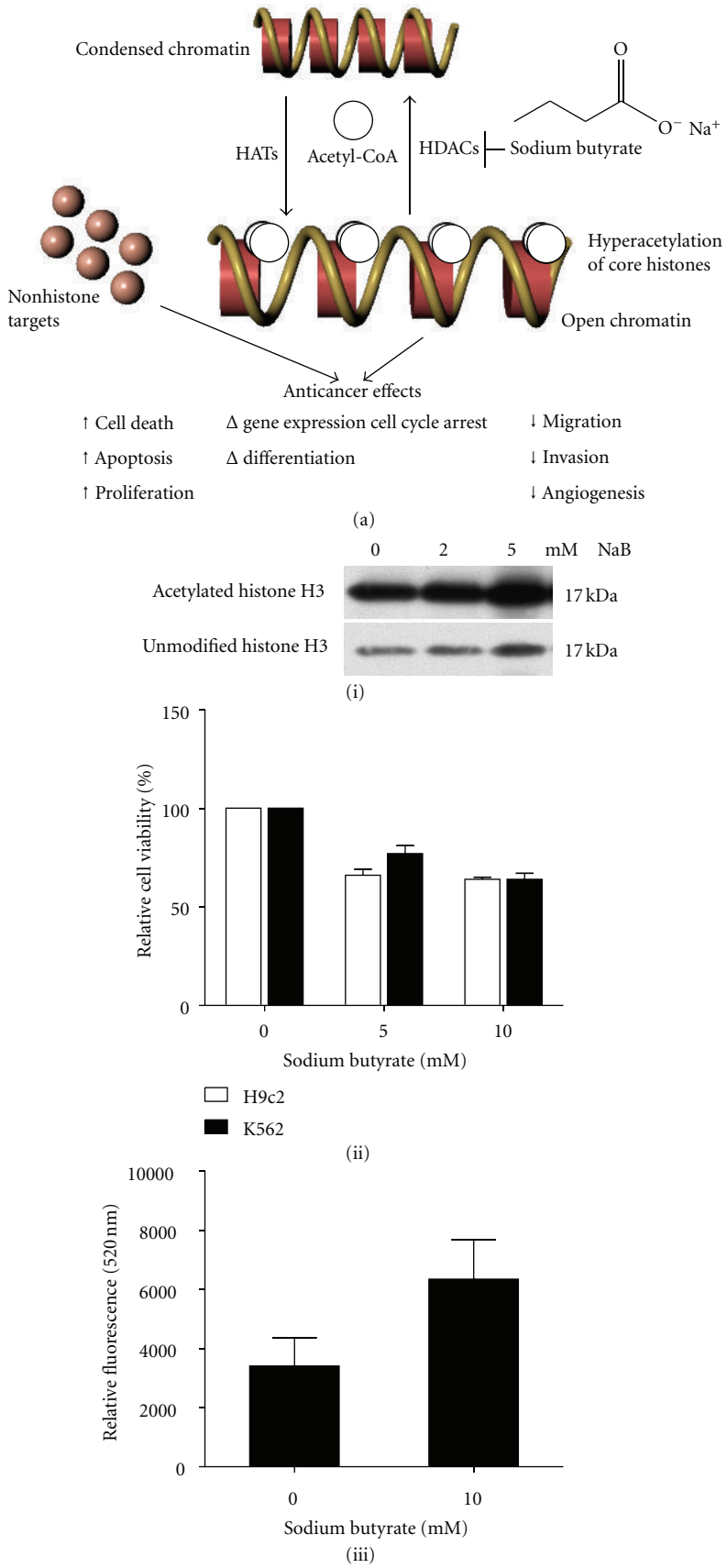
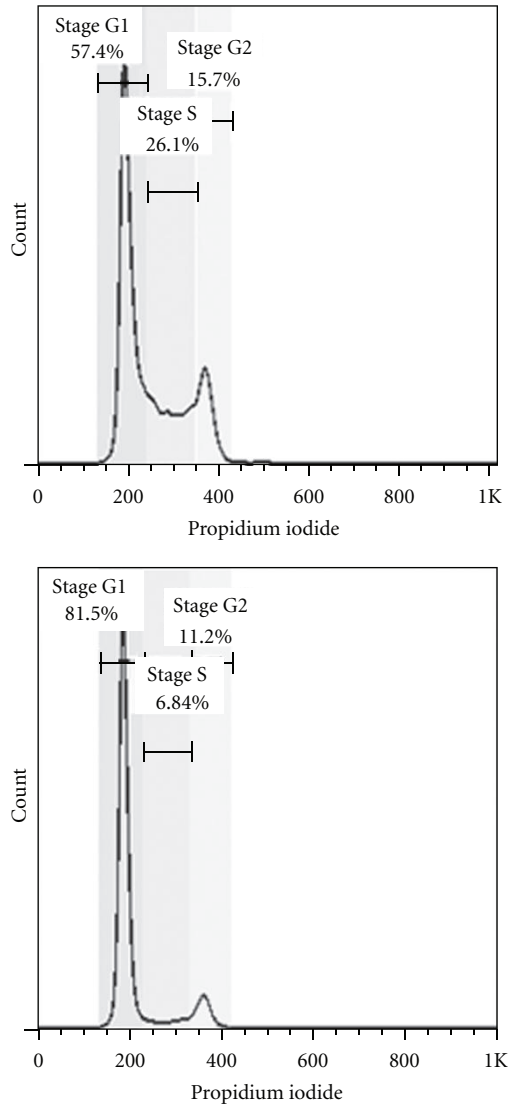


Figure 2: Continued.



(iv)

(b)

Figure 2: Overview of the biological effects of histone deacetylase (HDAC) inhibitors in malignant and transformed cells, using sodium butyrate (NaB) as an example. (a) Simplified schematic representation of the molecular pathways accounting for the clinical potential of HDAC inhibitors in cancer therapy. The acetylation status of histones is regulated by the opposing actions of histone acetyltransferases (HATs) and HDACs. HDAC inhibitors mediate anticancer effects through histone-hyperacetylation-mediated changes (Δ) in the expression of certain genes and by directly interacting with numerous key intracellular nonhistone proteins including α-tubulin, heat-shock protein 90, and Ku70. HDAC inhibitors result in transcriptional activation and repression of 2–20% of genes; some of which are associated with differentiation, cell cycle arrest, apoptosis, growth inhibition, and cell death as well as inhibition of cancer cell migration, invasion, and angiogenesis. (b) Biological effects of sodium butyrate (NaB) in cancer and normal cells. (i) Sodium butyrate causes hyperacetylation of histones in H9c2 cardiac myocytes. Cells were differentiated with 10 nM all-*trans*-retinoic acid for 7 days in low serum media, before 24-hour incubation with 2 and 5 mM sodium butyrate. Total cell lysates were immunoblotted for acetylated histone H3, and unmodified histone H3 was used as a loading control. (ii) Sodium butyrate causes reduced cell viability in K562 human erythroleukemic cells and H9c2 cardiac myocytes. Cells were treated with the indicated concentrations of sodium butyrate for 24 hours, and relative cell viability was measured using the Cell Titer blue (Promega) assay kit. (iii) Sodium butyrate induces apoptosis in K562 cells. Cells were treated with 10 mM sodium butyrate for 24 hours, and caspase 3/7 activity was measured using the Apo-ONE Homogeneous (Promega) assay kit. (iv) Sodium butyrate causes K562 cells to arrest in the G1 phase of the cell cycle. Untreated cells (top) and cells treated with 5 mM sodium butyrate (bottom) for 24 hours were stained with propidium iodide, and the cell cycle distribution was examined by flow cytometry.

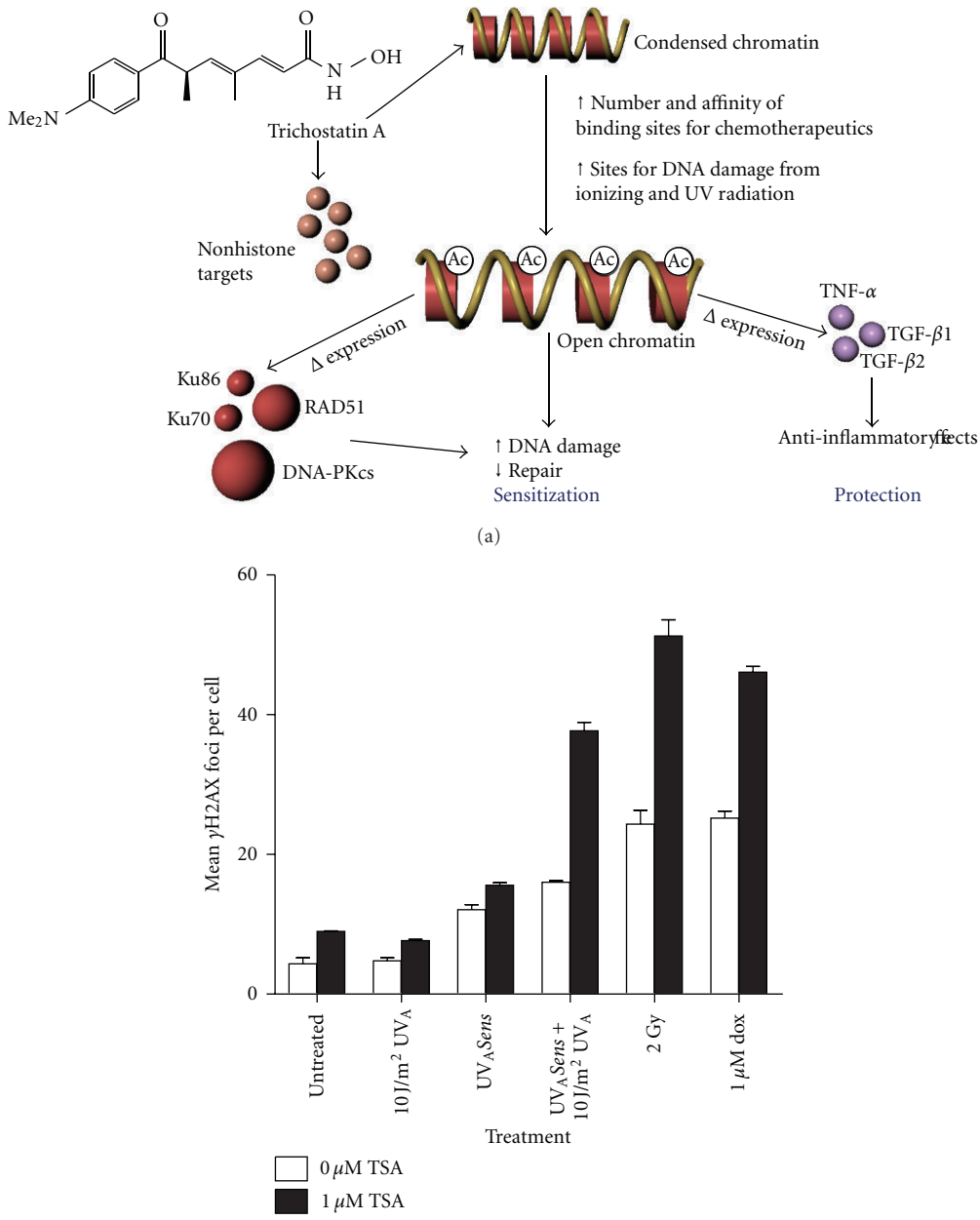


Figure 3: Molecular pathways accounting for the additive and/or synergistic effects of combinations of HDAC inhibitors with chemotherapeutics or radiation. (a) Simplified schematic representation. Additive and/or synergistic cytotoxic effects with the use of combinations of HDAC inhibitors and chemotherapeutics may be the result of histone-acetylation-mediated changes in chromatin conformation *per se* (particularly in the cases where combinations with DNA targeting drugs such as anthracyclines, which require accessibility to DNA, are used). Similarly, HDAC inhibitors may enhance the cytotoxic effects of ionizing and ultraviolet (UV) radiation by increasing the accessibility of DNA to damage. A further mechanism involves HDACi-mediated regulation of gene transcription—in particular decreased expression of genes for Ku70, Ku86, DNA-PKcs, and Rad51 which are key components of double-strand break repair pathways. Paradoxically, HDAC inhibitors have been shown to protect from the effects of ionizing radiation *in vivo* by decreasing the expression of inflammatory cytokines such as tumor necrosis factor, TNF-α, and fibrogenic growth factors such as TGF-β1 and TGF-β2. (b) Trichostatin A (TSA) augments DNA damage induced by DNA-targeted phototherapeutics (UV_A*Sens*), ionizing radiation, and chemotherapeutic agents. In the example shown, DNA double-strand break formation was as assessed by staining for γH2AX foci. Cells were treated with 1 μM TSA for 24 hours prior to one-hour incubation with 0.1 μM UV_A*Sens*. Cells were then irradiated with 10 J/m^2 UV_A and incubated for a further one hour before staining for γH2AX. Appropriate 10 J/m^2 and UV_A*Sens* only controls are also depicted. In separate experiments, cells were treated with 1 μM TSA for 24 hours prior to irradiation with 2 Gy (^{137}Cs). Cells were stained for γH2AX foci one hour after irradiation. In other experiments, cells were treated with 1 μM TSA for 24 hours prior to one-hour incubation with 1 μM doxorubicin. Cells were washed and incubated for a further 24 hours prior to staining for γH2AX.

may be speculated that HDAC inhibitors may augment anthracycline-induced cell death, at least in part, by changing the chromatin architecture. However, HDAC-inhibitor mediated changes in gene expression and alteration of the function of nonhistone substrates is also involved as highlighted by studies with isoform-selective inhibitors [4, 25–27].

The additive and/or synergistic cytotoxic effect provides the basis for the clinical trials using combinations of histo-ne deacetylase inhibitors and anthracyclines for various malignancies [35]. However, potential complications have been identified. For example, depsipeptide has been shown to upregulate the MDR1 gene in leukemia cells resulting in resistance to doxorubicin [66]. Expression of the MDR1-encoded, P-glycoprotein pump, is well known to result in multidrug resistance, a major clinical problem in oncology, and the potential for reversal of repression of the MDR1 gene in malignant cells by a variety of HDAC inhibitors has been indicated by further studies [67]. In contrast, other more recent studies have indicated that HDAC inhibitors may suppress the expression of ABC transporters highlighting that this issue requires further clarification [68].

Another potential complication with the use of HDAC inhibitors is cardiac toxicity. Studies have shown that broad-spectrum HDAC inhibitors may possess cardiotoxic activity *per se* [69, 70]. Further studies have shown that pretreatment with HDAC inhibitors potentiates the DNA damaging and cytotoxic effects of doxorubicin in cell culture systems [71, 72]. It is well known that the dose-limiting side effect of anthracyclines is irreversible cardiac toxicity due to the generation of reactive oxygen species including the damaging hydroxyl radicals and hydrogen peroxide [73]. Cardiomyocytes are particularly susceptible given that they have relatively low levels of superoxide anion and hydrogen peroxide detoxifying enzymes compared to other cell types [73]. Studies using hypertrophic responses and induction of DNA double-strand breaks as endpoints have indicated that the broad-spectrum HDAC inhibitors, Trichostatin A, valproic acid, and sodium butyrate, augment the effects of doxorubicin [71, 72]. Similarly, *in vivo* studies highlight the controversies regarding the biology of HDAC inhibitors in the heart. For example, recent findings demonstrate that Trichostatin A and valproic acid protect from load- and agonist-induced cardiac hypertrophy *in vivo* [74, 75]. However, contrasting findings indicate that Trichostatin A worsens right ventricular dysfunction induced by pulmonary artery banding in rats [76]. Given these potential complications, combinatorial effects of more selective or isoform-specific HDAC inhibitors with conventional therapeutics may provide a therapeutic advantage. In this context, a recent study identified that the HDAC6-selective compound, tubacin, potentiates the effects of doxorubicin and etoposide in transformed cell lines [27]. Further evaluations in this direction are anticipated.

4. Combination of Histone Deacetylase Inhibitors with Radiotherapy

Early studies indicated that the short-chain fatty acid, sodium butyrate, potentiates colon and nasopharyngeal cancer cells to the cytotoxic effects of ionizing radiation [77–80]. Although an unusual mechanism was used to describe the effect, a further study indicated that the prototypical HDAC inhibitor, Trichostatin A, also enhances the radiosensitivity of malignant cells [81]. Further studies have corroborated these findings indicating that virtually all broad-spectrum HDAC inhibitors including Trichostatin A, SAHA, depsipeptide, sodium butyrate, phenylbutyrate, tributyrin, and valproic acid potentiate radiation-induced cell death in malignant cells [82–90]. At relatively high concentrations of HDAC inhibitor, dose modification factors (ratio of radiation doses in HDAC-inhibitor-treated and -untreated cells that yield the same level of survival) of ~2 have been observed [88]. At these higher concentrations, cell cycle arrest (G1 and G2), inhibition of DNA synthesis, and induction of apoptosis by the HDAC inhibitors has been speculated to account for the radiation sensitizing effect [85–88]. At relatively lower HDAC inhibitor concentrations, a radiation sensitizing effect is also observed. A number of studies have established an association between HDAC inhibition and proteins involved in signal cascades in response to DNA damage [83, 84, 87, 91–93]. In summary, the radiation sensitizing effects of HDAC inhibitors may involve the following mechanisms. Firstly, histone hyperacetylation changes chromatin architecture resulting in a more open chromatin confirmation, which may be more susceptible to initial radiation-induced DNA damage. Further, HDAC inhibitors may interact with key signal transduction proteins involved in DNA damage response pathways. Finally, HDAC inhibitors have been shown to regulate transcription of genes involved in the DNA double-strand break repair pathway. For example, it has been shown that pretreatment with SAHA attenuates the radiation-induced increase in the DNA repair proteins Rad51 and DNA-PKcs [90]. Similarly, sodium butyrate has been shown to decrease the expression of the DNA repair proteins Ku70, Ku86, and DNA-PKcs in melanoma cell lines [83]. In addition, using bleomycin, doxorubicin, and etoposide to induce DNA double-strand breaks as assessed by accumulation of γH2AX foci, it has been shown that histone deacetylase inhibitors target Ku70 acetylation resulting in sensitization [94].

In the context of combinations with radiotherapy, valproic acid which has long clinical history in the treatment of epilepsy is important [89]. Preclinical studies have indicated that the HDAC inhibitor sensitizes human glioma cell lines to the effects of ionizing radiation (X-rays) both *in vitro* and *in vivo* [89]. As reviewed recently, valproic acid has been combined with the alkylating agent temozolomide and radiation for the potential treatment of glioblastoma multiforme. The strategy is currently undergoing evaluation in a phase II clinical trial [95].

5. Radioprotective Effects of Histone Deacetylase Inhibitors

Paradoxically, emerging evidence is indicating that HDAC inhibitors possess radioprotective activities. Early studies indicated that pretreatment with phenylbutyrate offers a modest radioprotective effect in human normal and cancer cells [96]. Further studies indicated that phenylbutyrate protects from cutaneous radiation syndrome *in vivo* [97, 98]. The radioprotective properties of HDAC inhibitors is thought to involve repression of inflammatory cytokines (e.g., interleukin- (IL-) 1, IL-8, tumor necrosis factor- (TNF-)α) and fibrogenic growth factors (e.g., transforming growth factor- (TGF-)β) [97, 99–101]. These are known to be involved in the inflammatory response to radiation and particular, prolonged secretion of TNF-α and TGF-β from epithelial, endothelial, and connective tissue cells is implicated in cutaneous radiation syndrome [102]. In addition to phenylbutyrate, the broad-spectrum HDAC inhibitors Trichostatin A and valproic acid have been shown to protect from radiation-induced skin injury and from radiation-induced lethality in mice [103]. These effects were also correlated with decreased TNF-α, TGF-β1, and TGF-β2 expression [97]. Further research in this direction with phenylbutyrate has indicated that the HDAC inhibitor can protect mice from acute γ-radiation-induced lethality. The effects were correlated with an attenuation of DNA damage and apoptosis [104]. Interestingly prophylactic and postirradiation administrations of phenylbutyrate afforded radioprotection presenting interesting potential clinical applications. Prophylaxis would be appropriate for radiotherapy prior to exposure to irradiation, and postirradiation administrations would appropriate in cases of inadvertent radiation exposure.

6. Conclusions

HDAC inhibitors have emerged as an important new class of anticancer therapeutics. Although they possess potent cytotoxic and apoptotic effects alone, it is anticipated that they will be most useful when used in combination with other cancer modalities. This is reflected by the majority of current clinical trials which predominantly involve combinations of HDAC inhibitors with conventional chemotherapeutics and radiotherapy. An important question in the field remains on whether class-selective or isoform-specific compounds will have a greater therapeutic efficacy than the classical broad-spectrum HDAC inhibitors. Broad-spectrum HDAC inhibitors have pleiotropic anticancer effects, and this may be advantageous given the heterogeneity and adaptability of malignant cells. On the other hand, class- or isoform-selective compounds may offer a greater therapeutic window with decreased off-target effects. There is currently an intense research effort aimed at further understanding the function of HDAC enzymes, and there is an increasing availability of more specific compounds. Therefore, it is anticipated that the issue of selectivity will be clarified, perhaps opening further opportunities for clinical translation of this class of compounds.

Conflict of Interests

Both K. Ververis and T. C. Karagiannis declare that they have no direct financial relation with the commercial identities mentioned in this paper that might lead to a conflict of interests.

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