Antitumor Effects of a Novel Phenylbutyrate-Based Histone Deacetylase Inhibitor, (S)-HDAC-42, in Prostate Cancer

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Abstract

Purpose: To assess the antitumor effects of a novel phenylbutyrate-derived histone deacetylase (HDAC) inhibitor, (S)-HDAC-42, vis-à-vis suberoylanilide hydroxamic acid (SAHA) in in vitro and in vivo models of human prostate cancer.

Experimental Design: The in vitro effects of (S)-HDAC-42 and SAHA were evaluated in PC-3, DU-145, or LNCaP human prostate cancer cell lines. Cell viability, apoptosis, and indicators of HDAC inhibition were assessed. Effects on Akt and inhibitor of apoptosis protein families were determined by immunoblotting. Immunocompromised mice bearing established s.c. PC-3 xenograft tumors were treated orally with (S)-HDAC-42 (50 mg/kg q.o.d. or 25 mg/kg q.d.) or SAHA (50 mg/kg q.d.) for 28 days. In vivo end points included tumor volumes and intratumoral changes in histone acetylation, phospho-Akt status, and protein levels of Bcl-xL and survivin.

Results: (S)-HDAC-42 was more potent than SAHA in suppressing the viability of all cell lines evaluated with submicromolar IC50 values. Relative to SAHA, (S)-HDAC-42 exhibited distinctly superior apoptogenic potency, and caused markedly greater decreases in phospho-Akt, Bcl-xL, and survivin in PC-3 cells. The growth of PC-3 tumor xenografts was suppressed by 52% and 67% after treatment with (S)-HDAC-42 at 25 and 50 mg/kg, respectively, whereas SAHA at 50 mg/kg suppressed growth by 31%. Intratumoral levels of phospho-Akt and Bcl-xL were markedly reduced in (S)-HDAC-42-treated mice, in contrast to mice treated with SAHA.

Conclusions: (S)-HDAC-42 is a potent orally bioavailable inhibitor of HDAC, as well as targets regulating multiple aspects of cancer cell survival, which might have clinical value in prostate cancer chemotherapy and warrants further investigation in this regard.

The aberrant regulation of core histone acetylation is among the epigenetic modifications that contribute to inappropriate gene expression in cancer cells. The histone deacetylases (HDAC), which participate in this mode of gene regulation, are recognized as promising targets for cancer therapy as they have been linked to the pathogenesis of both solid and hematologic malignancies (1, 2). Based on substantial preclinical evidence that HDAC Inhibitors can induce growth arrest, differentiation and apoptosis in cancer cells, and suppress tumor growth in mouse models, many structurally distinct, small-molecule HDAC inhibitors are currently undergoing phase I and II clinical evaluations (3–5). The mechanistic paradigm for the anticancer activities of these HDAC inhibitors has been that drug-induced hyperacetylation of core histones leads to chromatin remodeling and reactivated expression of a restricted set of genes regulating cell proliferation, cell cycle progression, and cell survival (3, 4, 6–9). However, emerging evidence suggests that, in addition to this histone acetylation–dependent modulation of transcription, the anticancer activities of some HDAC inhibitors may also comprise histone acetylation–independent mechanisms involving nonhistone HDAC substrates (5, 8, 10), such as nuclear factor-κB (11, 12), STAT3 (13), p53 (14, 15), and heat shock protein-90 (16, 17). More recently, we also showed that broad-spectrum HDAC inhibitors facilitated Akt dephosphorylation by causing the disruption of HDAC-protein phosphatase 1 complexes (18). Together, these findings indicate the complexity in the mechanism of HDAC inhibitors that underlies their high potency in suppressing tumor growth in vitro and in vivo (19).

Among clinically relevant HDAC inhibitors, phenylbutyrate and other short-chain fatty acids are weak inhibitors of HDACs exhibiting millimolar potency in vitro. We recently reported our development of a novel class of potent phenylbutyrate-based HDAC inhibitors possessing submicromolar HDAC-inhibitory activity (20). Further structure-based lead optimization culminated in the generation of (S)-HDAC-42, a hydroxamate-tethered phenylbutyrate derivative with a low nanomolar IC50 for HDAC inhibition (Fig. 1A; ref. 21). In light of the apparent
role of HDACs in prostate carcinogenesis and progression (22–25), and the efficacy of HDAC inhibitors in preclinical models of prostate cancer (15, 17, 26–29), the antitumor potential of (S)-HDAC-42, in comparison with suberoylanilide hydroxamic acid (SAHA), a HDAC inhibitor currently in clinical trials, was evaluated in prostate cancer models in vitro and in vivo. We show here that (S)-HDAC-42 is a potent inhibitor of prostate cancer cell viability and induces a greater apoptotic response relative to SAHA. We also provide evidence that this potent apoptotic activity is associated with the greater ability of (S)-HDAC-42 to influence multiple regulators of cell survival including Akt, Bad, Bcl-xL, and members of the inhibitor of apoptosis protein (IAP) family. Finally, these in vitro results were extended to an in vivo prostate cancer xenograft model in which orally administered (S)-HDAC-42 potently inhibited tumor growth in association with intratumoral histone hyperacetylation and reductions in phospho-Akt and Bcl-xL levels. (S)-HDAC-42 is a novel orally bioavailable, phenylbutyrate-based HDAC inhibitor with anti-tumor activity at multiple cellular levels which, based on our results, may have value in prostate cancer chemotherapy and warrants further investigation in this regard.

Materials and Methods

Reagents. The HDAC inhibitors SAHA and (S)-(+)-N-hydroxy-4-(3-methyl-2-phenyl-butyrylamino)benzamide [(S)-HDAC-42] were synthesized in our laboratory with purities exceeding 99% as shown by nuclear magnetic resonance spectroscopy (300 MHz). (S)-HDAC-42 (NCS 736012) is a novel hydroxamate-tethered phenylbutyrate derivative (20, 21) and is currently undergoing preclinical evaluation through the Rapid Access to Intervention Development Program at the National Cancer Institute. For in vitro studies, stock solutions of inhibitors were prepared in DMSO and diluted in 10% serum-supplemented RPMI 1640 in 96-well plates for 24, 48, or 72 hours, and cell viability was assessed by MTT assay. Points, mean; bars, ±SD (n = 6). C. effect of (S)-HDAC-42 on the viability of PrECs in comparison to PC-3, LNCaP, and DU-145 prostate cancer cell lines. PrECs were treated with (S)-HDAC-42 at the indicated concentrations in 10% FBS-supplemented prostate epithelial growth medium in 96 well-plates for 72 hours, and cell viability was assessed by MTT assay. Corresponding dose-response data for the prostate cancer cell lines were extracted from (B) and presented for purposes of comparison. Points, mean; bars, ±SD (n = 6).
In vivo studies. Intact male NgR athymic nude mice (5-7 weeks of age) were obtained from the National Cancer Institute (Frederick, MD). The mice were group-housed under conditions of constant photoperiod (12 hours light/12 hours dark) with ad libitum access to sterilized food and water. All experimental procedures using these mice were done in accordance with protocols approved by the Institutional Laboratory Animal Care and Use Committee of The Ohio State University.

Each mouse was inoculated s.c. with $5 \times 10^5$ PC-3 cells in a total volume of 0.1 mL serum-free medium containing 50% Matrigel (BD Biosciences, Bedford, MA) under isoflurane anesthesia. As tumors became established (mean starting tumor volume, 145.1 $\pm$ 22.1 mm$^3$), mice were randomized to four groups ($n = 7$) that received the following treatments: (a) (S)-HDAC-42 at 25 mg/kg body weight q.d., (b) (S)-HDAC-42 at 50 mg/kg q.o.d., (c) SAHA at 50 mg/kg q.d., and (d) the methylcellulose/Tween 80 vehicle. Mice received treatments by gavage (10 $\mu$L/g body weight) for the duration of the study. Tumors were measured weekly using calipers and their volumes calculated using a standard formula: $v = \frac{1}{2} \times \text{length} \times \text{width}^2$. Body weights were measured weekly. At the conclusion of the study, tumors were harvested, snap-frozen in liquid nitrogen, and stored at $-80^\circ$C until needed for Western blot analysis of relevant biomarkers. The percentage of reductions in tumor growth were calculated using the formula: $\left[ 1 - \left( \frac{T_f - T_i}{C_f - C_i} \right) \right] \times 100$, where $T_f$ and $T_i$ are the final and initial mean tumor volumes, respectively, of the group receiving a specified treatment, and $C_f$ and $C_i$ are the final and initial mean tumor volumes, respectively, of the control group. One mouse from each treatment group was submitted to The Ohio State University Mouse Phenotyping Shared Resource for evaluation of gross and histologic pathology.

Statistical analysis. Tumor volume data met the assumptions of normality and homogeneity of variance for parametric analysis; thus, group means at 28 days of treatment were compared using one-way ANOVA followed by Fisher’s least significant difference method for multiple comparisons. Tumor growth data are expressed as mean tumor volumes ± SE. In vitro data are expressed as mean ± SD and were assessed by one-way ANOVA and Fisher’s least significant difference method for post hoc comparisons. Differences were considered significant at $P < 0.05$. Statistical analysis was done using SPSS (SPSS, Inc., Chicago, IL).

Results

(S)-HDAC-42 induces apoptosis in prostate cancer cells. The antitumor effects of (S)-HDAC-42 vis-à-vis SAHA were assessed in three different human prostate cancer cell lines, PC-3, DU-145, and LNCaP. These cells were exposed to individual agents over the dose range of 0.1 to 2.5 $\mu$mol/L, and the cell viability was determined by the MTT assay at 24, 48, and 72 hours. Both agents showed a time-dependent reduction in cell viability. Neither (S)-HDAC-42 nor SAHA showed significant antiproliferative effect until 48 hours, and (S)-HDAC-42 was clearly more potent than SAHA in suppressing cell viability in all cell lines evaluated (Fig. 1B). All cell lines were comparably susceptible to the antiproliferative effect of (S)-HDAC-42 with submicromolar IC$_{50}$ values after 72 hours of treatment (PC-3, 0.48 $\pm$ 0.02; LNCaP, 0.30 $\pm$ 0.07; DU-145, 0.43 $\pm$ 0.05 $\mu$mol/L; $P > 0.8$, ANOVA), irrespective of the differences in androgen responsiveness, the functional status of p53 and PTEN, and the Bcl-xL expression levels that distinguish these cell lines. On the other hand, SAHA exhibited a statistically significant differential effect on growth inhibition among all the cell lines tested, with DU-145 cells being the most sensitive (IC$_{50}$ 1.62 $\pm$ 0.16 $\mu$mol/L), followed by LNCaP and PC-3 cells for which IC$_{50}$ values were extrapolated to be 2.20 $\pm$ 0.32 and 3.10 $\pm$ 0.16 $\mu$mol/L, respectively ($P < 0.05$, ANOVA).
This discrepancy in cellular sensitivity might reflect the differences in mechanisms underlying the antiproliferative effects of these two agents as described below. Assessment of effects on nonmalignant cells revealed that PrECs exhibited a 7.5- to 9.5-fold lower sensitivity to the antiproliferative effects of (S)-HDAC-42 than the prostate cancer cells (IC\textsubscript{50} 3.69 ± 0.96 \textmu M; P < 0.001, ANOVA; Fig. 1C).

It is noteworthy that although neither agent showed a sizeable inhibition of cell proliferation at 24 hours of treatment, particularly in PC-3 cells, morphologic changes were evident. As shown in Fig. 2, 24 hours’ exposure of PC-3 cells to 1 \textmu M (S)-HDAC-42 transformed the typical epithelial morphology to a more spindle-shaped morphology (top left and middle). These drug-treated cells seemed to be severely contracted with diminished cell-to-cell contacts and long spine-like processes. Similar morphologic changes were also observed in PC-3 cells treated with 2.5 \textmu M of SAHA, although to a lesser extent (top right). These changes were also apparent in DU-145 (middle) and LNCaP cells (bottom), although the typical spindle-like morphology of untreated LNCaP cells made such changes in them more difficult to discern. Although the driving force underlying these morphologic changes remain unclear, these findings indicate a clear effect of drug treatment on prostate cancer cells, which preceded the observable effects on cell viability and/or apoptosis.

Western blot analysis of the status of p21 expression and histone H3 acetylation in drug-treated cells revealed dose-dependent up-regulation of these HDAC-associated biomarkers (Fig. 3A), which paralleled the drugs’ activities in inhibiting cell proliferation. Of these two HDAC inhibitors, (S)-HDAC-42 exhibited higher potency in stimulating p21 up-regulation and histone H3 hyperacetylation (right). In addition, as evidenced by mitochondrial cytochrome c release, activation of caspase 9, cleavage of PARP (Fig. 3A, left), and DNA fragmentation (Fig. 3B), the antiproliferative activity of (S)-HDAC-42 was, at least in part, attributable to apoptosis. Moreover, these changes in apoptotic markers were markedly higher than those observed in the SAHA-treated PC-3 cells, consistent with the greater potency of (S)-HDAC-42.

(S)-HDAC-42 dephosphorylates Akt and alters the dynamics of Bcl-xl expression. Previously, we reported that (S)-HDAC-42 and, to a lesser extent, SAHA caused Akt dephosphorylation in PC-3 cells through the disruption of HDAC-protein phosphatase (PP1) complexes, leading to increased PP1-Akt association (18). This finding indicates the complexity in the mechanism of (S)-HDAC-42’s antitumor effects and suggests a basis for the difference in the apoptogenic potencies of these two compounds. Moreover, the modulation of the expression of Bcl-2 family members by several HDAC inhibitors has been reported in a variety of cancer cell lines including mesothelioma, prostate cancer, melanoma, leukemia, and lung cancer (32–36). To shed light into the mechanism underlying the differential antiproliferative activities of (S)-HDAC-42 and SAHA, the effects of these agents on the status of Akt signaling and expression levels of Bcl-2 family members in PC-3 cells were compared.

Western blot analysis revealed that (S)-HDAC-42, even at 1 \textmu M, caused substantial reductions in the levels of p-Ser\textsuperscript{17} and p-Thr\textsuperscript{308} Akt (64.4 ± 11.9% and 61.4 ± 14.8% reductions, respectively, compared with DMSO-treated controls) in PC-3 cells after 72 hours of exposure. Therefore, SAHA required at least 5 \textmu M to attain similar levels of Akt dephosphorylation (48.9 ± 12.7% and 58.0 ± 15.6%, respectively; Fig. 4B). To validate the functional consequence of diminished phospho-Akt, we examined the phosphorylation status of Bad, an apoptosis-relevant substrate of Akt. In parallel with phospho-Akt levels, the amount of phospho-Bad was significantly reduced by (S)-HDAC-42 without changes in the activity of Akt.

\[ \text{Akt} \rightarrow \text{Bad} \]

**Fig. 3.** Effects of (S)-HDAC-42 versus SAHA on various biomarkers associated with HDAC inhibition or apoptosis in PC-3 cells. A, Western blot analysis of the dose–dependent effects of (S)-HDAC-42 and SAHA on p21 expression, histone H3 acetylation, cytochrome c release, caspase 9 activation, and PARP cleavage in PC-3 cells after 72 hours’ exposure in 10% FBS-supplemented RPMI 1640. A representative immunoblot (left). Signals for p21 and acetylated histone H3 were quantitated by densitometry and normalized against that of \textit{\textalpha}-actin (right). Columns, mean; bars, ±SD (n = 3). AcH3, acetylated histone H3; S, formation of cytoplasmic nucleosomal DNA in PC-3 cells treated with (S)-HDAC-42 or SAHA at the indicated concentrations for 72 hours in 10% FBS-supplemented RPMI 1640. DNA fragmentation was quantitatively measured by a cell death detection ELISA kit as described in Materials and Methods. Columns, mean; bars, ±SD (n = 3).
expression of total Bad protein (Fig. 4A and B). Furthermore, (S)-HDAC-42 caused a pronounced, dose-dependent attenuation in Bcl-xl expression, achieving a 75.4 ± 2.5% reduction at 2.5 μmol/L. In contrast, SAHA failed to reduce Bcl-xl protein levels below 82.8 ± 2.6% of the control level at the highest concentration tested (Fig. 4C, top). This clear difference in the abilities of SAHA and (S)-HDAC-42 to suppress Bcl-xl protein expression was mirrored by their respective effects on steady state levels of Bcl-xl mRNA. Semiquantitative reverse transcription-PCR revealed that SAHA reduced Bcl-xl mRNA levels by 9.5 ± 1.7%, 9.3 ± 1.3%, and 10.2 ± 6.0% at 0.5, 2.5, and 5.0 μmol/L, respectively, compared with vehicle-treated controls, whereas (S)-HDAC-42 more potently suppressed mRNA levels by 16.7 ± 9.0%, 38.9 ± 3.3%, and 46.4 ± 4.4% at 0.25, 1.0, and 2.5 μmol/L, respectively. (S)-HDAC-42 also caused a nearly 2-fold increase in Bax expression level, whereas no detectable increase occurred in SAHA-treated PC-3 cells (Fig. 4A). These proapoptotic changes in Bcl-2 family members were accompanied by increases in the expression levels of antiapoptotic Bcl-2 protein in cells treated with either agent. (S)-HDAC-42 treatment induced a 1.6- to 4.9-fold increase in the amount of Bcl-2 protein over the concentration range tested, whereas SAHA caused a 2.2-fold increase at 5 μmol/L (Fig. 4C, bottom).

(S)-HDAC-42 attenuates protein levels of IAP family members. Members of the IAP family of proteins have been implicated in oncogenesis, cancer progression, and therapeutic resistance, at least in part, through their well-known antiapoptotic function of inhibiting caspase activity (37, 38). Several reports have described the suppression of IAP family members by treatment with HDAC inhibitors in cancer cells (35, 36, 39–43), as well as tumor endothelium (41). Accordingly, we sought to determine the effects of (S)-HDAC-42 and SAHA on the suppression of IAP members, including survivin, cIAP-1, cIAP-2, and ILP, in PC-3 cells. As shown in Fig. 5A and B, (S)-HDAC-42 induced a profound, dose-dependent loss of survivin that ranged from a 64.6 ± 6.2% reduction at 0.25 μmol/L up to 93.6 ± 2.5% at 2.5 μmol/L. SAHA caused a similar, although less potent, effect on survivin expression, diminishing it at all concentrations tested up to a 64.1 ± 7.6% reduction after treatment with 5.0 μmol/L. Although less robust, decrements in survivin were also observed at the level of mRNA. The highest concentrations of (S)-HDAC-42 and SAHA tested (2.5 and 5.0 μmol/L, respectively) reduced steady-state levels of survivin mRNA to 67.1 ± 1.7% and 81.9 ± 1.1% of that of the vehicle-treated controls. Of the other IAPs evaluated (Fig. 5A), cIAP-2 was the most responsive to either drug exhibiting 1.7- and 2.5-fold reductions after treatment with 5.0 and 2.5 μmol/L of SAHA and (S)-HDAC-42, respectively. (S)-HDAC-42 also induced a 2-fold inhibition of cIAP-1 at 2.5 μmol/L; however, neither agent altered the expression of ILP.
(S)-HDAC-42 suppresses prostate tumor xenograft growth in vivo. Collectively, the in vitro data described above indicate that (S)-HDAC-42 is a potent inhibitor of prostate cancer cell proliferation and survival, and owes this antitumor efficacy to the modulation of apoptotic machinery at multiple levels, including Akt signaling, mitochondrial integrity, and caspase activation. To further evaluate the antitumor potential of (S)-HDAC-42, athymic nude mice bearing established s.c. PC-3 tumor xenografts (mean tumor volume, 145.1 ± 22.1 mm³) were treated orally for 28 days with (S)-HDAC-42 at 25 mg/kg daily or 50 mg/kg every other day, with SAHA at 50 mg/kg daily, or with vehicle as described under Materials and Methods. A. Tumor volumes were evaluated by immunoblotting of PC-3 tumor homogenates collected after 28 days of treatment. As shown in Fig. 6A, treatment of mice with SAHA, 25 mg/kg of (S)-HDAC-42 daily and 50 mg/kg of (S)-HDAC-42 every other day significantly inhibited PC-3 tumor growth by 31%, 52%, and 67%, respectively, relative to vehicle-treated controls (P < 0.01). Moreover, at 50 mg/kg every other day, the antitumor effect of (S)-HDAC-42 was significantly greater than that of SAHA at 50 mg/kg daily (P < 0.001). This in vivo efficacy after oral administration confirmed (S)-HDAC-42’s oral bioavailability, which was previously determined to be 26%.³ Importantly, mice seemed to tolerate all of the agents without overt signs of toxicity, without significant changes in body weight compared with the vehicle-treated group, and without abnormalities in serum chemistry variables. The sole gross and histopathologic findings associated with (S)-HDAC-42 treatment were testicular atrophy and a marked diffuse testicular degeneration with associated epididymal hypospermia or aspermia. These testicular changes were not observed in the SAHA-treated mice.

To correlate this in vivo tumor-suppressive response to mechanisms identified in vitro, the effects of treatment with HDAC inhibitors on intratumoral biomarkers of drug activity were evaluated by immunoblotting of PC-3 tumor homogenates collected after 28 days of treatment. As shown in Fig. 6B and C, treatment of mice with (S)-HDAC-42 or SAHA increased levels of acetylated histone H3. Amounts of immunoblotted proteins from all available tumor lysates were quantitated by densitometry and normalized to that of β-actin. Columns, mean; bars, ± SD (n = 6). D, relative expression levels of phospho-Akt, Bcl-xL, and survivin. Amounts of immunoblotted proteins from all available tumor lysates were quantitated by densitometry and normalized to that of total Akt or β-actin. Columns, mean; bars, ± SD (n = 6).
Antitumor Effect of a Novel HDAC Inhibitor

Discussion

HDAC is recognized as one of the promising targets for cancer treatment because many HDAC inhibitors have entered clinical trials for both solid and liquid tumors. In this report, we describe the in vitro and in vivo efficacy of a novel phenylbutyrate-derived HDAC inhibitor, (S)-HDAC-42, in prostate cancer. Our findings show that (S)-HDAC-42 exhibits a broad spectrum of antitumor activities at low micromolar concentrations that involve not only histone acetylation, but also the modulation of apoptotic regulators at multiple levels, including Akt signaling, mitochondrial integrity, and caspase activation.

In comparison with SAHA, a HDAC inhibitor currently in clinical trials, (S)-HDAC-42 exhibited greater antiproliferative activity in multiple prostate cancer cell lines in vitro. The greater potency of (S)-HDAC-42 to induce apoptosis, as evidenced by cytochrome c release, activation of caspase 9, PARP cleavage, and DNA fragmentation seemed to underlie this higher antitumor efficacy. Moreover, the marked differences in apoptosis induction between these two agents were paralleled by similar differences in their relative abilities to decrease Akt phosphorylation, to stimulate Bax expression, and to suppress expression levels of survivin and particularly Bcl-xL. This ability of (S)-HDAC-42 to affect multiple regulators of cancer cell survival is reflected in its equipotent antiproliferative effects against three prostate cancer cell lines that differ with respect to the functional status of p53, PTEN, and Bcl-xL expression levels, and suggests its potential clinical efficacy against molecularly heterogeneous tumors.

Evidence indicates that whereas histones still represent a primary target for the physiologic function of HDACs, the antitumor effects of some HDAC inhibitors, including (S)-HDAC-42, might also be attributed to histone acetylation–independent mechanisms by interfering with the activation or expression status of a number of signaling targets (19). Previously, we have shown that (S)-HDAC-42 mediates Akt dephosphorylation through the disruption of PP1-HDAC complexes, resulting in increased PP1-Akt association (18). Whether the observed (S)-HDAC-42-induced repression of Bcl-xL and survivin also occurred independently of histone acetylation cannot be concluded definitively from our study. Moreover, because levels of phospho-Akt and survivin were also reduced, although to a lesser degree, by SAHA treatment, it is likewise unclear whether the differential effects of these agents on apoptotic regulators are merely a function of their different potencies and/or result from true differences in the spectrum of their respective pharmacologic targets.

The correlation between the differential modulation of apoptotic signaling targets and in vitro antitumor activities of (S)-HDAC-42 and SAHA was mirrored in our in vivo study, in which (S)-HDAC-42 exhibited higher potency than SAHA in suppressing established PC-3 xenograft tumor growth. Western blot analysis of the tumor lysates revealed that the greater tumor growth inhibition of (S)-HDAC-42 paralleled its greater ability to inhibit putative histone acetylation-independent biomarkers, particularly Akt phosphorylation and Bcl-xL expression. With the exception of the observed testicular pathology, tumor growth suppression by (S)-HDAC-42 occurred in the absence of limiting toxicity. Although testicular toxicities are common adverse side effects of cancer therapy (44), to our knowledge, investigators have not previously reported testicular pathology as a consequence of HDAC inhibitor treatment in preclinical models of human cancer. A single study examining the antifertility effect of trichostatin A in mice reported a completely reversible impairment of spermatogenesis resulting from increased apoptosis of spermatoctyes (45). Although we do not know the cellular target mediating this toxicity of (S)-HDAC-42, the lack of pathologic changes in the pituitary and accessory sex organs suggests a primary testicular toxicity. Supporting this supposition is the absence of histopathologic changes in the gut and bone marrow, which are also common sites of adverse chemotherapeutic consequences.

In conclusion, our results show that the novel orally bioavailable, phenylbutyrate-derived HDAC inhibitor, (S)-HDAC-42, is a potent inhibitor of HDAC, as well as targets regulating multiple aspects of cancer cell survival including Akt signaling, mitochondrial integrity, and caspase activity. This broad spectrum of activity underlies the more potent apoptogenic and antitumor activities of (S)-HDAC-42 in vitro and in vivo relative to SAHA, and suggests its viability as part of a therapeutic strategy for prostate cancer.

References

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