Editorial

Inhibitors of Histone Deacetylase Are Potentially Effective Anticancer Agents

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During the past decade, a number of HDAC2 inhibitors have been identified that induce tumor cells in culture and in tumor-bearing animals to undergo growth arrest, differentiation, and/or apoptotic cell death (1). Acetylation and deacetylation of histones, part of the core proteins of nucleosomes, play an important role in the regulation of gene expression (2). There are two classes of enzymes involved in determining the degree of acetylation of histones, HATs, and HDACs. At least four groups of proteins with HAT activity and eight HDACs have been identified in mammalian cells (1–3). HDACs are generally found in association with large protein complexes that are involved in regulation of gene expression. HDACs may also regulate gene expression by deacetylating transcription factors, such as p53, and may participate in cell cycle regulation. It has been shown that RB (retinoblastoma protein) binding to the transcription factor E2F involves recruitment of HDAC1 or HDAC2. There are several reports that altered HAT or HDAC activity is associated with cancers.

HDAC Inhibitors

HDAC inhibitors that have been shown to arrest tumor cell growth belong to several chemical structural classes including: (a) hydroxamic acids, e.g., TSA, whose activity is reported by Vigushin et al. (4) and a series of hybrid polar hydroxamic acid compounds, of which SAHA is a prototype, described by investigators at our laboratory (5); (b) short-chain fatty acids, e.g., butyric acid; (c) cyclic tetrapeptides containing a AOE moiety, e.g., trapoxin; (d) cyclic peptides not containing the AOE moiety, e.g., FR901228 and apicidin; and (e) benzamides, e.g., MS-27–275 (reviewed in Ref. 1).

The series of hydroxamic acid-based hybrid polar compounds inhibit HDACs activity at or below micromolar concentra-

trations, both in vitro and in vivo. X-ray crystallographic analyses of a HDAC-like protein (HDLP), isolated from an anaerobic bacterium, showed that the catalytic site of the enzyme has a tubular pocket with a zinc-binding site at its base and two Asp-Histidine charge relay systems (6). The hydroxamic moiety of TSA and that of SAHA were shown to bind to the zinc at the base of the tubular pocket, and the carbon ring of these compounds projects out of the pocket onto the surface of the protein.

Antitumor Activity of HDAC Inhibitors in Vitro and in Vivo

HDAC inhibitors have been shown to cause growth arrest, differentiation, and or apoptotic cell death in a wide variety of transformed cells in culture, including neuroblastoma, melanoma, and leukemia, as well as cells from breast (Fig. 1), prostate, lung, ovarian, and colon cancers (reviewed in Ref. 1). Several HDAC inhibitors including the depsipeptide MS-27–275, oxamflatin, and the hydroxamic acid-based hybrid polar compounds, such as SAHA, have been shown to inhibit tumor growth in cancer-bearing animal models. These previous studies included the demonstration that the HDAC inhibitor, SAHA, inhibits methylnitrosourea-induced mammary breast carcinoma in rats (7), a finding similar to that reported with TSA by Vigushin et al. (4). Yoshida et al. (8) reported that TSA was a potent inhibitor of HDAC activity in both purified enzyme preparation and cells in culture. It is interesting to note that Qui et al. (9) reported that TSA did not inhibit the growth of human melanoma xenograft in nude mice, but the tumor growth was inhibited by azeloic bis-hydroxamide, structurally related to SAHA. In studies demonstrating that SAHA inhibits growth of xenograft human prostate tumors in nude mice, the HDAC inhibitor was shown to increase the accumulation of acetylated histone in tumor tissue, as well as, normal tissues (10). Furthermore, SAHA induced essentially complete inhibition of prostate cancer cell growth in these mice studies with little or no detectable toxicity. The accumulation of acetylated histones in peripheral mononuclear cells, as well as in tumor tissue, has been found in patients treated with as little as 75 mg/m2 SAHA as a 2-h infusion. Assay for the accumulation of acetylated histones (1, 5) is useful as a biological marker of activity of the administered HDAC inhibition, as shown with the studies with TSA (4). SAHA and a second hybrid polar hydroxamic acid-based HDAC inhibitor, pyroxamide, are in Phase I clinical trials.
References


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3 Figure was kindly provided by P. N. Munster, T. Torso-Sandoval, N. Rosen, R. A. Rifkind, P. A. Marks, and V. M. Richon. Suberoylanilide hydroxamic acid induces differentiation in mammary epithelial carcinoma cells, submitted for publication.