

Histone Deacetylase Inhibitors

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What does histone deacetylase do?

The nucleosome is a subunit of chromatin that is composed of approximately 150 base pairs of 2 superhelical turns of DNA wrapped around 8 core histone proteins. This octamer is composed of a tetramer of histone H3-H4 and 2 dimers of H2A and H2B. When DNA is replicated, it unwinds, splits, replicates, and then winds back up around these core histones. In this process, it is the terminal lysine-rich tail of the histones that can be modified by deacetylation or acetylation that will regulate the transcriptional activity of the specific genes. The histone deacetylase (HDAC) removes the terminal acetyl group from the lysine tail and restores the positive charge to the lysine residue and condenses the nucleosome structure. Histone acetylase (HAT) adds the terminal acetyl group back on, changing the charge of the terminal lysine so that the DNA uncoils around the core histones.

How is this process involved in cancer development or progression?

HATs and HDACs are involved in acetylation and deacetylation of chromatin, which can lead to altered regulation of transcription of genes and other proteins that control the cell cycle, terminal differentiation, and apoptosis. Disruption of HAT and HDAC activity has been found in many human cancers. For instance, HDAC 1 modifies breast cancer progression by altering cell proliferation through the interaction with the estrogen receptor α , causing a loss in its expression. In acute myeloid leukemia (AML), the *AML-1* gene is commonly found fused to the *ETO* gene. This protein is formed from the fused genes and will inhibit *AML-1*-dependent transcription. This process requires the recruitment of HDACs in order to occur. In addition, other non-histone proteins can be deacetylated by HDACs, including p53, E2F, α -tubulin, and Myo D.

What is the basic principle behind HDAC inhibitors?

Inhibiting HDAC alters the gene expression either by affecting the chromatin structure by causing an accumulation of acetylated histones or by affecting the activity of transcription factors by altering the acetylation status of the transcription factors (Figure 1). Gene expression arrays in transformed

HDAC inhibitors remodel chromatin by increasing histone acetylation

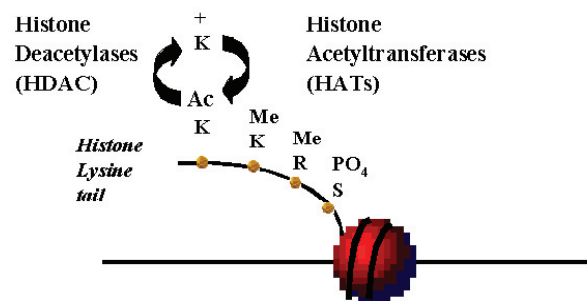


Figure 1. The mechanism of action of histone deacetylase inhibitors.

cell lines treated with HDAC inhibitors have shown that only a very small subset—approximately 2%—of all genes are altered by HDAC inhibitors. Yet, this effect is powerful enough to inhibit tumor cell growth, differentiation, and/or apoptosis. HDAC inhibitors have been shown to induce growth arrest in a wide range of transformed tumor cells and inhibit tumor growth in animal models.

What are the different types of HDAC inhibitors being developed?

There are several classes of HDAC inhibitors that are being developed, including short-chain fatty acids (butyrate derivatives and valproic acid); hydroxamic acids (suberoylanilide hydroxamic acid [SAHA], pyroxamide, trichostatin A, oxamflatin, scriptaid); cyclic tripeptides (trapoxin, decapeptide, apicidin); and benzamides (MS-275).

What differentiates these various agents from one another?

In general, HDAC inhibitors cause cell cycle arrest in the G1 and/or G2 phase, apoptosis and/or terminal differentiation in cell cultures. These agents have also been shown to inhibit tumor growth in a wide range of solid tumor cell lines (bladder, breast, ovarian, colon, lung, prostate, neuroblastoma,

and gliomas) and hematologic transformed cell lines (multiple myeloma, leukemias, and lymphomas). Currently, there are 2 classes that contain 12 characterized HDACs that are sensitive to the inhibition of trichostatin A, SAHA, and related compounds. The potency of HDAC inhibitors varies between the classes of agents. However, no compound to date has been selective for one or another specific HDAC. It is too early to know how these agents are going to differentiate themselves in the clinic. However, early trials have shown there are differences in the toxicity profiles in these agents. In trials with the butyrates, central nervous system depression has been shown to be a dose-limiting toxicity, while in trials with the hydroxamic acids and cyclic tripeptides, asthenia and marrow suppression were seen as dose-limiting events. Future clinical trials will further define the activity of these agents in particular diseases.

What side effects are associated with HDAC inhibitors?

The side effects that have been observed in association with HDAC inhibitors are different than those seen with traditional cytotoxic agents. In general, these agents are well tolerated, toxicities are rapidly reversible, and patients can be maintained on chronic dosing schedules for prolonged periods without developing end-organ damage. The most common toxicities that have been seen with these agents include fatigue, diarrhea, leukopenia, thrombocytopenia, anemia, dysgeusia, decreased appetite, diarrhea, and nausea.

Are HDAC inhibitors being studied in combination with other classes of anticancer therapy?

HDAC inhibitors can affect the transcription of multiple genes that include p21^{WAF1}, BCL6, p53, gelsolin, cyclin D1, ErbB2, thymidylate synthase, and vascular endothelial growth factor (VEGF). In addition, these agents can affect the acetylation of the microtubules resulting in aberrant mitosis or affect acetylation of heat shock proteins leading to downregulation of growth factors receptors. These discoveries have led to a strong rationale to evaluate HDAC inhibitors with other biologic and chemotherapeutic agents. In APL, combinations of HDAC inhibitors with all-trans retinoic acid (ATRA) have shown synergistic effects in cell cultures and reports in patients with AML refractory to ATRA have shown clinical responses to the combination of phenylbutyrate and ATRA. These results suggested that the phenylbutyrate inhibited the corepressor complex that contains the HDAC for the oncoprotein that is encoded by one of the translocation-generated fusions of APL, *PML-RAR α* . Other preclinical studies in cell cultures and animals have shown additive or synergistic activity of a HDAC inhibitor in combination with a variety of agents that include: epirubicin, 5-fluorouracil, flavopiridol, imatinib (Gleevec, Novartis), or retinoic acid. Clinical trials with the newer and more potent HDAC inhibitors in combination with biologic and chemotherapeutic agents are now ongoing.

What has led to the sudden explosion in HDAC inhibitor drug development?

A better understanding of the role of chromatin structure, the function of the HATs and HDACs in cells, and the development of novel, more potent inhibitors of HDAC have moved these drugs forward quickly. More importantly, these drugs had a favorable toxicity profile in patients and demonstrated clinical activity in early clinical trials. A phase I trial by Piekarz and colleagues from the National Cancer Institute first showed that the novel HDAC inhibitor depsipeptide could be given safely with partial and complete responses being observed in several patients with cutaneous T-cell lymphoma. Trials with oral and intravenous SAHA at Memorial Sloan-Kettering Cancer Center also showed these drugs could be given safely, had biologic activity, and produced clinical responses with tumor regression in a wide range of solid and hematologic tumors. Currently, there are at least a dozen HDAC inhibitors in clinical trials and multiple novel agents that are being developed in the laboratory designed to inhibit specific HDACs.

Are HDAC inhibitors being evaluated in diseases other than cancer?

Since transcriptional dysregulation may occur in multiple chronic diseases, inhibitors of HDAC may be applicable to a wide range of disorders. For example, Huntington's disease is an inherited fatal neurologic disorder that is caused by an expanded CAG/polyglutamine repeat in a gene coding for the Huntington protein. It is hypothesized that this protein or others are toxic to neurons which lead to neuronal degeneration. This process is thought to be due to the transcriptional dysregulation of histone acetyltransferase, Sp1, and TATA-binding-protein-associated factor (TAF) II130 activity. Early preclinical studies with HDAC inhibitors in mouse models of Huntington's disease have shown improved transcriptional regulation and improvement of motor impairment. Human trials have not been performed but these early results are encouraging for this fatal disease. The role of the HDAC inhibitors may be expanded as we better understand the transcriptional regulation or dysregulation associated with other chronic diseases.

Suggested Reading

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