Review

The Molecular Mechanism of HDAC Inhibitors in Anticancer Effects

Gaofeng Bi[1] and Guosheng Jiang[1, 2]

HDACs and HATs are two kinds of enzymes which catalyse deacetylation and acetylation of histone in eukaryotes, whose dynamic balance has accurate regulation for gene transcription and gene expression of eukaryotes at DNA level. Disbalance of them can bring the disorder of proliferation and differentiation in normal cells, and then lead to the initiation of tumor. Their aberrant functions were directly related to the initiation and progression of various tumors, such as promyelocytic leukemia, Hodgkin lymphoma, colonic cancer and gastral cancer. The inhibitors of HDACs are used for treatment of tumor. They can restrain the activity of HDACs and block the inhibition of gene expression caused by the disorder of deacetylation. Its major biological effects lie in inducing differentiation of tumor cells, arresting cell circle at G0/G1, activating cell apoptosis gene, enhancing the sensitivity of chemical therapy and radioactive therapy. So far HDAC has been an important target enzyme in anticancer drug research. *Cellular & Molecular Immunology*. 2006;3(4):285-290.

Key Words: HDAC inhibitor, HATs, leukemia, differentiation, apoptosis

Introduction

Most of anticancer drugs have side effects on human normal cells when they were used to treat tumor cells, for example, bone marrow depression and myocardium damage even can lead to death. All-trans retinoic acid (ATRA) was successfully used to treat acute promyelocytic leukemia (APL) by ways of inducing differentiation and apoptosis (1). Then some effective differentiation inducers were taken to treat other types of leukemia and solid tumors because of high remission rate and few side effects (2). Histone deacetylase (HDAC) inhibitors are a new class of targeted anticancer agents, which are potent inducers of growth arrest, differentiation, and/or apoptotic cell death of transformed cells *in vitro* and *in vivo*. Several HDAC inhibitors are in clinical trials and have shown significant activity against a spectrum of both haematological and solid tumors at doses that are well tolerated by patients. HDACs and histone acetyltransferases can, by reversible acetylation, modify the structure and function of histones and proteins in transcription factor complexes, which are involved in the regulation of gene expression, as well as many non-histone proteins that are involved in regulating cell proliferation and cell death. HDAC inhibitors are a group of structurally diverse molecules, which selectively altered the expression of genes. HDAC inhibitors can induce cancer cell death, whereas normal cells are relatively resistant to HDAC inhibitor-induced cell death (3). It has been confirmed that HDAC inhibitors could be used to induce differentiation of leukemia cells or solid tumor cells, for example sodium butyrate and trichostatin A (TSA) could increase the remission rate of many kinds of tumors obviously by cooperation with other anticancer drugs (4). Thereby we reviewed the progress of histone deacetylase inhibitors used in treatment of tumor cells, with analysis of its mechanism.

Classification of HDAC and HDAC inhibitors

HDACs almost exist in all creatures, and can be classified into three main families depending on the homology of transcriptional control factor sequence in yeast. At least 18 kinds of HDACs have been found, including HDAC1 to 11 and SIRT1 to 7 (Table 1).

Inhibitors of these enzymes can induce arrest of growth, differentiation and apoptosis of many cultural transformed cells. Pristine HDAC inhibitor was usually found from natural product of microorganism. Sodium butyrate is the first confirmed HDAC inhibitor and it belongs to the natural short-chain fatty acid which is fermental production of bacterium in colon. Another frequent HDAC inhibitor is TSA,

[1]Department of Hemato-oncology, Institute of Basic Medicine, Shandong Academy of Medical Science, Jinan 250062, Shandong Province, China;

[2]Corresponding to: Dr. Guosheng Jiang, Department of Hemato-oncology, Institute of Basic Medicine, Shandong Academy of Medical Science, Jingshi Road 89, Jinan 250062, Shandong Province, China. Tel & Fax: +86-531-8291-9505, E-mail: Jianggsh@hotmail.com.

Received Jul 7, 2006. Accepted Aug 15, 2006.

Table 1. Classification of histone deacetylases

Class	HDAC	Homology with yeast	Molecular weight
Class I	HDAC1, 2, 3, 8	RPD3 deacetylase	22-25 kD
Class II	HDAC4, 5, 6, 7, 9, 10, 11*	HDA1 deacetylase	120-135 kD
Class III**	SIRT1~7	SIRT2 family	40-50 kD

*HDAC11 has conserved residues in the catalytic core region that are shared by both class I and class II enzymes.
**Class III HDACs are NAD+-dependent enzymes.

Derived from metabolic product of streptomycete, it is one of the classic and representative drugs of HDAC inhibitors (5). Several natural and synthetic HDAC inhibitors have been shown to affect the growth and survival of tumor cells *in vitro* and *in vivo*. Interestingly, three dietary chemo-preventive agents, butyrate, diallyl disulfide, and sulforaphane, also have HDAC inhibitory activity (6). There are ranges of structurally diverse HDAC inhibitors which are either product isolated and purified from natural sources or synthetically produced compounds. These compounds can be divided into six groups based on their structure (Table 2). Hydroxamic acid-derived compounds including TSA and suberoylanilide hydroxamic acid (SAHA), et al.; Cyclic tetrapeptides: Depsipeptide (FK228, FR901228), Apicidine, Trapoxin et al; Short-chain fatty acides: Valproic acid (VA), Phenyl butyrate (PB), Sodium butyrate (SB), et al.; Synthetic pyridyl carbamate derivative: MS-275; Synthetic benzamide derivatives: CI-994 (N-acetyldinaline); Ketones: Trifluoromethyl ketone (7).

These compounds have polar end which binds zinc ion of HDAC catalytic pocket structure, other part produce effect through block passage of active site. Mechanism of action of hydroxamic acid groups were interaction with catalytic site of HDAC through X ray crystallized detection, which blocks substrate approach active zinc ion of enzymes (8). Other HDAC inhibitors bind to HDAC active site powerfully and the effect of inhibit HDAC is stronger. The extensive used compound in clinic is short-chain fatty acid, like butyrate, but the action of these compound present non-specificity, week effect and large toxic and side effect, and it's hard to achieve effective inhibiting concentration *in vivo*. Another short-chain fatty acid drug valproic acid, which was used to treat epilepsy and mental disease in clinic, can inhibit the activity of HDAC at clinical application dose, and inhibit the effect of class I HDAC better than class II HDAC (9). More effective and lower toxic HDAC inhibitor, for example, TSA, SAHA, Depsipeptide and MS-27-275, are in tissue culture and animal experiment of preclinical phase or phase I clinical research.

Clinical experiment of HDAC inhibitors

Many lines of evidence indicate that histone hypo-acetylation induces repression of tumor suppressor gene expression. Small molecular inhibitors of HDAC (HDACI) are highly effective in up-regulating tumor suppressor gene expression, reducing tumor growth and inducing programmed cell death *in vitro* and in cancer patients in phase I and II clinical trials (10). Warrell et al. first used HDAC inhibitor for treatment of acute promyelocytic leukemia patient in 1998 after solo all-trans retinoic acid treatment; then applied sodium phenylbutyrate and ATRA for combined chemotherapy, the dose of ATRA and PB increased to 90 mg/m^2/d and 210 mg/kg/d after three weeks treatment; and leukemia cells percentage of bone marrow reported decreased from 23% to 9% after two weeks; next bone marrow report showed leukemia cells were cleared and reached complete remission

Table 2. Natural and synthetically produced inhibitors of HDAC

Group	Examples
Hydroxamic acid-derived compounds	Trichostatin (TSA) Suberoylanilide hydroxamic acid (SAHA) M-carboxycinnamic acid bis-hydroxamide (CBHA) Azelaic bis-hydroxamic acid (ABHA) NVP-LAQ824 LBH589 Oxamflatin PXD101 Scriptaid Pyroxamide
Cyclic tetrapeptides	Depsipeptide (FK228, FR901228) Apicidine Trapoxin HC-toxin Chlamydocin Depudesin CHAPS
Short-chain fatty acids	Valproic acid (VA) Phenyl butyrate (PB) Phenyl acetate (PA) Sodium butyrate (SB) AN-9 (Pivanex)
Synthetic pyridyl carbamate derivative	MS-275
Synthetic benzamide derivatives	CI-994 (N-acetyldinaline)
Ketones	Trifluoromethyl ketone α-ketomides

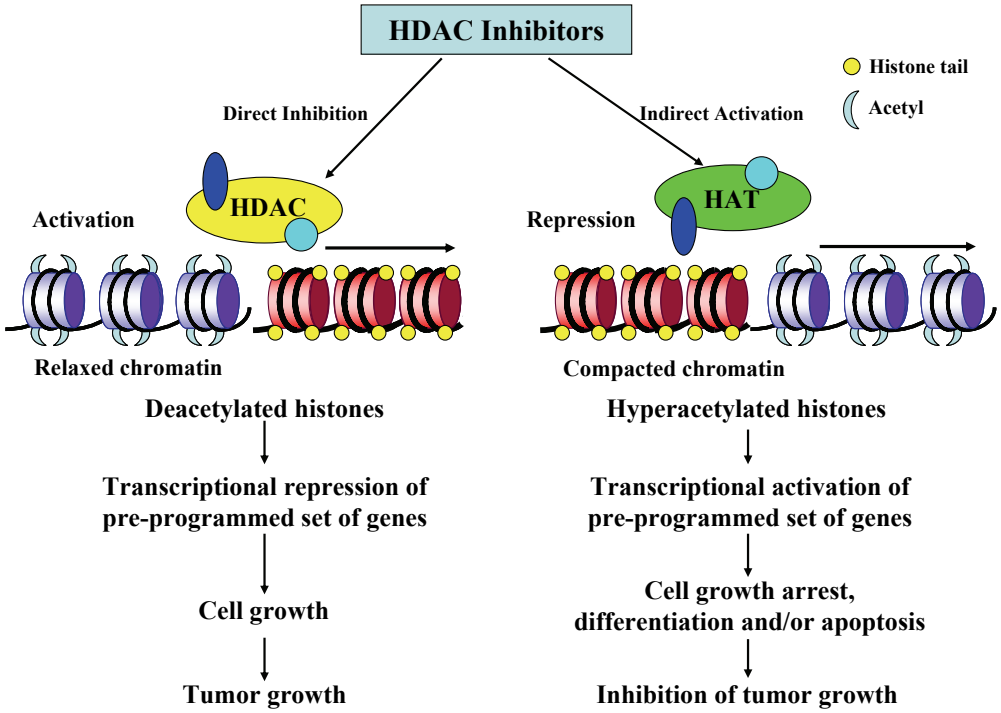

Figure 1. Molecular mechanism of HDAC inhibitors in anticancer effects. Transcriptional repression in chromatin with HDAC can lead to cell growth and tumor growth; transcriptional activation in chromatin with HAT can lead to cell growth arrest, differentiation and/or apoptosis and inhibition of tumor growth. HDAC inhibitor can directly inhibit HDAC and indirectly activate HAT.

ten days later. This patient procured remission at molecular level (PML-RARα negative) in the second course of treatment, and maintained complete remission condition more than seven months (11). Recently, some phase I and phase II clinical trial of HADC inhibitor were undertaking. FK228 (12) and SAHA (13) were the hots spot of them. Phase I clinical test of FK228 in National Cancer Institute of American showed that three cases of T cell lymphoma patients involved skin obtained partial remission and one case of peripheral T cell lymphoma patient gained complete remission (14). In hematologic malignancies, such as diffuse large B-cell lymphoma, the HDAC inhibitor (HDACI), suberoylanilide hydroxamic acid (SAHA), was recently allowed for phase II and III clinical trials (15). Many of the HDAC inhibitors demonstrated pharmacological activity against different tumor cell lines *in vitro*. However, despite such positive preclinical results, some compounds had limited clinical applicability. TSA, for example, showed excessive cardiotoxicity and is unstable under *in vivo* conditions (16). These findings have led to the search for agents with proven preclinical and clinical efficacy.

Molecular mechanism of HDAC inhibitors in anticancer effects

There are several enzymes, including acetylases and deacetylases, that can regulate transcription by modifying the acetylation state of histones or other promoter-bound transcription factors. These enzymes reveal their involvement in cell-cycle regulation and differentiation. Furthermore, accumulating evidence suggests that deregulation of acetylase and deacetylase activity plays a causative role in the generation of cancer (17). Restraining HDAC activity and preventing the deacetylation of histone may induce hyperacetylation of histone, then unfolding ordered chromosome and promote transcription factors combined with DNA, so genes which are inhibited can express and exert the effect of cure tumor (18) (Figure 1). HDAC enzymes remove the acetyl group from the histone (hypoacetylation), thereby decrease the space between the nucleosome and the DNA wrapped around it, diminishing transcription factor access and leading to transcriptional repression (19). The catalytic domain of the HDAC is formed by a stretch of 390 amino acids containing a set of conserved residues. The active site of the enzyme consists of a curved tubular pocket with a wider bottom. Removal of an acetyl group occurs *via* a charge-relay system, an important component of which is the zinc-binding site at the bottom of the pocket. The presence of a zinc ion at this site is an important factor in the mechanism of action of HDAC inhibitors.

Effects of HDAC inhibitors on solid tumor cells

In HT-29 cells, sodium butyrate-mediated growth inhibition is associated with a marked decrease in cyclin B1 mRNA levels. The decrease in cyclin B1 occurred in a delayed

fashion (at 24 h), is completely blocked by concomitant treatment with protein synthesis inhibitors, and appears to be dependent on changes in transcription. Cyclin B1 repression is linked to the differentiation process in colon cancer cells, not merely with growth arrest. The mechanism of cyclin B1 repression by butyrate requires prolonged histone hyperacetylation and is at least partly dependent on p21 expression. In fact, p21/WAF-1 appears to directly repress a minimal cyclin B1 promoter (-90 bp), a process that can be mediated by the amino-terminal portion of the p21 protein (20). TSA or NaBu blocked two colon cancer cell lines (SW1116 and Colo-320) mainly in the G1 phase. In these two human colon cancer cell lines, HDAC inhibitors increased the p21 (WAF1) gene expression by selectively increasing the degree of acetylation of the gene-associated histones, and induced a G1 cell cycle arrest (21). The histone deacetylase inhibitor-induced apoptosis for three pancreatic adenocarcinoma cell lines (IMIM-PC-1, IMIM-PC-2 and RWP-1) due to a serine protease-dependent and caspase-independent mechanism. Initially, histone deacetylase inhibitors increase Bax protein levels without affecting Bcl-2 levels. Consequently, the apoptosis-inducing factor (AIF) and Omi/HtrA2 are released from the mitochondria, with the subsequent induction of the apoptotic program. These phenomena require AIF relocalization into the nuclei to induce DNA fragmentation and a serine protease activity of Omi/HtrA2 (22). Apoptosis of a human lung carcinoma cell line (A549) by TSA was associated with a down-regulation of anti-apoptotic Bcl-2 protein and an up-regulation of pro-apoptotic Bax protein. TSA treatment induced the proteolytic activation of caspase-3 and caspase-9, and a concomitant degradation of poly (ADP-ribose)-polymerase protein. Furthermore, TSA decreased the levels of COX-2 mRNA and protein expression without significant changes at the level of COX-1, which was correlated with an inhibition in prostaglandin E2 synthesis (23). Melanoma cells often retain wild-type p53 tumor suppressor protein and express it at high levels, the p53 mediated apoptosis pathway is suppressed. TSA can stabilized wild-type p53, but p53 protein accumulation was overridden by simultaneous down-regulation of p53 mRNA leading to a decrease in p53 protein. Growth arrest was induced in all cell lines studied and apoptosis in most (6/7), these cellular effects were independent of the p53 status of the cells. Inhibiting p53 function by a dominant negative p53 (175His) confirmed that the HDAC inhibitor induced apoptosis was independent of wild-type p53, even though TSA slightly activated p53 in a reporter assay. The results indicate that while the action of TSA is independent of p53, the activation of the apoptosis pathway by the HDAC inhibitors may provide therapeutic approaches for melanoma treatment (24). Breast cancer cell-conditioned medium enhanced phosphorylation of activator transcription factor-2 (ATF-2) which was the main modulatory subtype in CREB/ATF-2 family. The effect of sodium butyrate on aromatase expression in breast tumor fibroblasts was mediated by inhibition of phosphorylation of ATF-2, and hence, the inhibition of binding of a transcriptional complex containing phosphorylated ATF-2, C/EBP β and CREB binding protein (CBP) to promoter II and I.3 regulatory region. Sodium butyrate reduces the level of aromatase mRNA arising from cancer-induced promoter region. The aberrant activation of promoter II and I.3 in HAF is dependent on the phosphorylation of ATF-2 (25). Exposing A2780 ovarian cancer cells to the histone deacetylase inhibitor TSA produced a marked change in cellular morphology, proliferation, and differentiation. Within 24 h of TSA treatment, there was a morphological transformation of the cells, with increased cytoplasm, a more epithelial-like columnar appearance, and the emergence of distinct cellular boundaries. Commensurate with the morphological transformation, TSA also inhibited cell proliferation. TSA can induce epithelial-like differentiation with increased cytokeratin expression and the reappearance of intercellular plasma membrane junctions and primitive microvillus. In conclusion, the observed TSA-induced changes in p21, Rb, and Id1 are consistent with cell cycle senescence and differentiation of A2780 ovarian cancer cells (26).

Effects of HDAC inhibitors on leukemia cells

Extensive research of the effect *in vitro* of many HDAC inhibitor for different tumor cell lines showed that HDAC inhibitor can lead many leukemia cell lines to different extent of differentiation, apoptosis and block cell circle at G0~G1 period or G2~M period. The effect depends on the type of cell lines, different drugs and action time. Activated fusion proteins such as PML-RARα have been shown to inhibit cellular differentiation by recruitment of nuclear corepressor complexes, which maintain local HDAC in a variety of hematologic lineage-specific gene promoters. This HDAC-dependent transcriptional repression appears as a common pathway in the development of leukemia and could constitute an important target for new therapeutic agents (27). Phenylbutyric acid can induce the differentiation and apoptosis of cell lines U937, HL-60, ML-1, K562, NB4, Kasumi-1, et al. Butyric acid and TSA can induce NB4 cell line differentiation and apoptosis, and obtain same results of acute premyelocytic leukemia patient's primary cell (28, 29). In chronic myelocytic leukemia (CML) the activity of the Bcr-Abl tyrosine kinase is known to activate a number of molecular mechanisms, which inhibit apoptosis. SAHA-induced apoptosis in BV-173 cells, which involves decreased protein expression levels of Bcr-Abl, c-Myc and HDAC3 (30). Depsipeptide can up-regulate IL-3 gene expression of AML1/ETO positive leukemia cell, and IL-3 is essential signal transduction regulating gene for normal haematopoiesis (31). Apicidin might induce apoptosis of HL-60 cell through selective induction of Fas/Fas ligand, resulting in the release of cytochrome c from the mitochondria to the cytosol and subsequent activation of caspase-9 and caspase-3 (32). Low dose of sodium butyrate and Trichostatin can induce K562 cell line differentiation. They can block K562 cell cycle in different stage, but the differentiation both through inducing P21 and cyclin D3 expresses (33). HDAC inhibitors enhance the apoptosis-inducing potential of TRAIL in

leukemia cells (HL60, Jurkat, K562, and U937) through multiple mechanisms, which can up-regulate DR4, DR5, Bak, Bax, Bim, Noxa and PUMA, down-regulate IAPs, Mcl-1, Bcl-2, Bcl-XL and cFLIP, release mitochondrial proteins (cytochrome c, Smac/DIABLO and Omi/Htr2) to the cytosol, induct p21WAF1/CIP1 and p27KIP1, activate caspase-3 and cleave poly (ADP-ribose) polymerase (PARP). The up-regulation of death receptors and inhibition of cFLIP by HDAC inhibitors will increase the ability of TRAIL to induce apoptosis, due to enhance activation of caspase-8, cleavage of Bid, release of mitochondrial proteins to the cytosol, and subsequent activation of caspase-9 and caspase-3 (34). The link between altered HDAC activity and tumorigenesis is probably best demonstrated in acute promyelocytic leukemia (APL). The retinoic acid receptor (RAR) transcription factors RARa and its heterodimerization partner RXR bind to retinoic acid response elements (RAREs) and, in the absence of retinoids, repress transcription through a complex involving SIN3/HDAC, NCOR and SMRT. Addition of retinoic acid enables HATs (such as TIF2 and CBP) to replace the HDACs, thereby activating transcription (35, 36). HDAC inhibitor can induce many lymphocytic leukemia differentiation and apoptosis. Depsipeptide induce bd-6 positive Raji cell and lymphocytic leukemia cell cycle blockage and apoptosis, chronic lymphocytic leukemia cell and myeloma cell are sensitive to HDAC inhibitor either (37). SAHA can induce diffuse large cell lymphoma and Hodgkin disease cell lines apoptosis. HDAC inhibitors are very sensitive to IL-2 dependent cell lines, there are extensive acetylation in these cells, but target genes (like myc) of IL-2 pathway were inhibited indicating $CD25^+$（IL-2R）tumor can be treated by HDAC inhibitors (38). As been noted above, the anticancer mechanism of HDAC inhibitor is dependent on the regulation of gene express, large experiments *in vivo* and *in vitro* have confirmed that there are three kinds of anticancer mechanisms: 1) block cell cycle and promote cell differentiation, 2) induce cell apoptosis, 3) inhibit angiogenesis.

Perspective

Anticancer actions of HDAC inhibitors due to inhibit deacetylation of histone mainly thus relieve transcription inhibition of some genes. More genes whose transcription activation is related with histone acetylation should be detected following deep research of cell proliferation, differentiation and apoptosis, and translation to corresponding protein produce further effect. But histone acetylation/deacetylation as a spot of complex gene express regulating net in eukaryotes, is influenced necessarily by other biomolecules. HDAC inhibitor has other drug action target except histone: HDAC can induce some hertones as transcription factor P53, GATA21, NF2YA deacetylation and regulating activity of binding to DNA (39). Therefore HDAC inhibitor may selective induce some gene expression related with tumor cell differentiation and apoptosis through regulating acetylation level of these transcription factors. Careful trial design is important in order to fully exploit agents such as the HDAC inhibitors. The use of surrogate markers of activity will be important, as a detailed appreciation of their mechanism of action to ensure the optimal clinical application of these agents. The fact that several HDAC inhibitors are in early stage clinical trials means we can expect to see an increasing number of published reports on their efficacy and potential clinical application. In a word, only understanding common, concrete, key and special molecular mechanism of certain kind of tumor invasion, can we choose HDAC inhibitor for therapy specially. In this way, HDAC inhibitor may become another successful inducing differentiation agent for some kinds of tumor after all-trans retinoid acid treat acute premyelocytic leukemia.

Acknowledgements

This work was supported by a key project of Shandong Natural Sciences Foundation and a project of international cooperation from Ministry of Science and Technology of the People's Republic of China.

References

1. Wang ZY, Chen Z. Differentiation and apoptosis induction therapy in acute promyelocytic leukemia. Lancet Oncol. 2000;1: 101-106.
2. Garcia-Manero G, Issa JP. Histone deacetylase inhibitors: a review of their clinical status as antineoplastic agents. Cancer Invest. 2005;23:635-642.
3. Marks PA, Dokmanovic M. Histone deacetylase inhibitors: discovery and development as anticancer agents. Expert Opin Investig Drugs. 2005;14:1497-1511.
4. Kouraklis G, Theocharis S. Histone deacetylase inhibitors: a novel target of anticancer therapy. Oncol Rep. 2006;15:489-494.
5. Chen WK, Chen Y, Gu JX, et al. Effect of trichostatin A on histone acetylation level and apoptosis in HL-60 cells. Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2004;12:324-328.
6. Myzak MC, Dashwood RH. Histone deacetylases as targets for dietary cancer preventive agents: lessons learned with butyrate, diallyl disulfide, and sulforaphane. Curr Drug Targets. 2006;7: 443-452.
7. Hess-Stumpp H. Histone deacetylase inhibitors and cancer: from cell biology to the clinic. Euro J Cell Bio. 2005;84:109-121.
8. Finnin MS, Donigian JR, Cohen A, et al. Structures of a histone deacstylase homologue bounc to TSA and SAHA. Nature. 1999; 401:188-193.
9. Phiel CJ, Zhang F, Huang EY, Guenther MG, Lazar MA, Klein PS. Histone deacetylase is a direct target of valproic acid, a potent anticonvulsant, mood stabilizer, and teratogen. J Biol Chem. 2001;276:36734-36741.
10. Liu T, Kuljaca S, Tee A, Marshall GM. Histone deacetylase inhibitors: multifunctional anticancer agents. Cancer Treat Rev. 2006;32:157-165.
11. He LZ, Tolentino T, Grayson P, et al. Histone deacatylase inhibitors induce remission in teansgenic models of therapy-resistant acute promyelocytic leukemia. J Clin Invest. 2001;108: 1321-1330.

12. Kwon HJ, Kim MS, Kim MJ, Nakajima H, Kim KW. Histone deacetylase inhibitor FK228 inhibits tumor angiogenesis. Int J Cancer. 2002; 97:290-296.
13. Butler LM, Zhou X, Xu WS, et al. The histone deacetylase inhibitor SAHA arrests cancer cell growth, up-regulates thioredox-in-binding protein-2, and down-regulates thioredoxin. Proc Natl Acad Sci U S A. 2002;99:11700-11705.
14. Piekarz RL, Robey R, Sandor V, et al. Inhibitor of histone deacetylation, depsipeptide (FR901228), in the treatment of peripheral and cutaneous T-cell lymphoma: a case report. Blood. 2001;98:2865-2868.
15. Imre G, Gekeler V, Leja A, Beckers T, Boehm M. Histone deacetylase inhibitors suppress the inducibility of nuclear factor-κB by tumor necrosis factor-α receptor-1 down-regulation. Cancer Res. 2006;66:5409- 5418.
16. Camphausen K, Burgan W, Cerra M, et al. Enhanced radiation-induced cell killing and prolongation of gH2AX foci expression by the histone deacetylase inhibitor MS-275. Cancer Res. 2004; 64:316-321.
17. Kouzarides T. Histone acetylases and deacetylases in cell proliferation. Curr Opin Genet Dev. 1999;9:40-48.
18. Brown R, Strathdee G. Epigenomics and epigenetic therapy of cancer. Trends Mol Med. 2002;8:43-48
19. De Ruijter AJ, van Gennip AH, Caron HN, Kemp S, van Kuilenburg AB. Histone deacetylases (HDACs): characterization of the classical HDAC family. Biochem J. 2003;370:737-749.
20. Archer SY, Johnson J, Kim HJ, et al. The histone deacetylase inhibitor butyrate downregulates cyclin B1 gene expression *via* a p21/WAF-1-dependent mechanism in human colon cancer cells. Am J Physiol Gastrointest Liver Physiol. 2005;289:696-703.
21. Chen YX, Fang JY, Lu J, et al. Regulation of histone acetylation on the expression of cell cycle-associated genes in human colon cancer cell lines. Zhonghua Yi Xue Za Zhi. 2004;84:312-317.
22. Garcia-Morales P, Gomez-Martinez A, Carrato A, et al. Histone deacetylase inhibitors induced caspase-independent apoptosis in human pancreatic adenocarcinoma cell lines. Mol Cancer Ther. 2005;4:1222-1230.
23. Choi YH. Induction of apoptosis by trichostatin A, a histone deacetylase inhibitor, is associated with inhibition of cyclooxygenase-2 activity in human non-small cell lung cancer cells. Int J Oncol. 2005;27:473-479.
24. Peltonen K, Kiviharju TM, Jarvinen PM, Ra R, Laiho M. Melanoma cell lines are susceptible to histone deacetylase inhibitor TSA provoked cell cycle arrest and apoptosis. Pigment Cell Res. 2005;18:196-202.
25. Ma D, Zhou JF. Molecular mechanism of inhibition of sodium butyrate on activation of tumor associated aromatase promoters. Ai Zheng. 2003;22:915.
26. Strait KA, Dabbas B, Hammond EH, Warnick CT, Iistrup SJ, Ford CD. Cell cycle blockade and differentiation of ovarian cancer cells by the histone deacetylase inhibitor trichostatin A are associated with changes in P21, Rb, and Id proteins. Mol Cancer Ther. 2002;1:1181-1190.
27. Martinez-Mancilla M, Zafra-de la Rosa G, Reynoso-Gomez E, et al. Molecular hemato-oncology and new specific treatment strategies for leukemia. Gac Med Mex. 2006;142:145-150.
28. Melnick A, licht JD. Histone deacetylases as therapeutic targets in hematologic malignancies. Curr Opin Hemat. 2002;9:322- 332.
29. Rahmani M, Yu C, Reese E, et al. Inhibition of PI-3 kinase sensitizes human leukemic cells to histone deacetylase inhibitor-mediated apoptosis through p44/42 MAP kinase inactivation and abrogation of p21 (CIP1/WAF1) induction rather than AKT inhibition. Oncogene. 2003;22:6231-6242.
30. Xu Y, Voelter-Mahlknecht S, Mahlknecht U. The histone deacetylase inhibitor suberoylanilide hydroxamic acid down-regulates expression levels of Bcr-abl, c-Myc and HDAC3 in chronic myeloid leukemia cell lines. Int J Mol Med. 2005;15: 169-172.
31. Klisovic MI, Maghraby EA, Parthun MR, et al. Depsipeptide (FR901228) promotes histone acetylation, gene transcription, apoptosis and its activity is enhanced by DNA methyltransferase inhibitors in AML-ETO-positive leukemic cells. Leukemia. 2003;17:350-358.
32. Kwon SH, Ahn Sh, Kim YK, et al. Apicidin, a histone deacetylase inhibitor, induces apoptosis and Fas/Fas ligand expression in human acute promyelocytic leukemia cells. J Biol Chem. 2002;277:2073-2080.
33. Li CR, Liu WL, Zhou JF, et al. The reseach and contrast of the mechanism which sodium butyrate and trichostatin promote K562 cell differentiation. Zhongguo Yao Li Xue Tong Bao. 2004;20:41-45.
34. Shankar S, Singh TR, Fandy TE, Luetrakul T, Ross DD, Srivastava RK. Interactive effects of histone deacetylase inhibitors and TRAIL on apoptosis in human leukemia cells: involvement of both death receptor and mitochondrial pathways. Int J Mol Med. 2005;16:1125-1138.
35. Altucci L, Gronemeyer H. The promise of retinoids to fight against cancer. Nat Rev Cancer. 2001;1:181-193.
36. Johnstone RW. Histone-deacetylase inhibitors: novel drugs for the treatment of cancer. Nat Rev Drug Discov. 2002;1:287-299.
37. Rosato RR, Almenara JA, Cartee L, Betts V, Chellappan SP, Grant S. The cydin-dependent kinase inhibitor flavopiridol cisrupts sodium butyrate-induced p21WAF1/CIP1 expression and maturation while reciprocally potentiating apoptosis in human leukemia cells. Mol Cancer Ther. 2002;1:252-266.
38. Aron JL, Parthun MR, Marcucci G, et al. Depsipeptide (FR901228) induces histone acetylation and inhibition of histone deacetylase in chronic lymphocytic leukemia cells concurrent with activation of caspase-8-mediated apoptosis and down regulation of c-FLIP protein. Blood. 2003;102:652-658.
39. Richon VM, O'Brien JP. Histone deacetylase inhibitors: A new class of potential therapeutic agents for cancer treatment. Clin Cancer Res. 2002;8:662-664.