HISTONE DEACETYLASE INHIBITORS

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Abstract

Histone deacetylase inhibitors (HDAC) are new class of agents which is used as anticancer drugs. A large number of HDAC inhibitors have been purified from natural sources or have been synthesized. It increases the acetylation of lysine residue on histone proteins as well as non-histone proteins by inhibiting the activity of HDAC enzymes. It is used in combination therapy with radiation, cytotoxic agents and different targeted therapeutic agents. Multiple clinical and preclinical studies suggest that HDAC inhibitors have an additive or synergistic role in the target modification of many novel biological therapeutics and chemotherapy in both hematological and solid tumor malignancies. It is promising new targeted anticancer agents which causes cancer call growth arrest, differentiation and or apoptosis both in vitro and in vivo of a broad spectrum of malignant cells. Normal cells are much less sensitive to HDAC inhibitors than are transformed cells. HDAC inhibitors are classified into hydroxamic acid analogs, cyclic peptides, benzamides, and short chain fatty acids. The hydroxamic acid analogs acts as Zn++ chelates and inhibit HDAC activity at nanomolar to micromolar concentrations. Apicidin and depsipeptide are cyclic peptides that inhibit HDAC at nanomolar concentration. Benzamides inhibit HDAC in vitro at micromolar concentrations. Short chain fatty acid has low potency because of their short side chains have limited contact with catalytic pocket of HDAC activity in vitro atmillimolar concentration. Thus specific natural and synthetic HDAC inhibitors are useful tools for dissecting HDACs role in both normal aberrant biological processes.

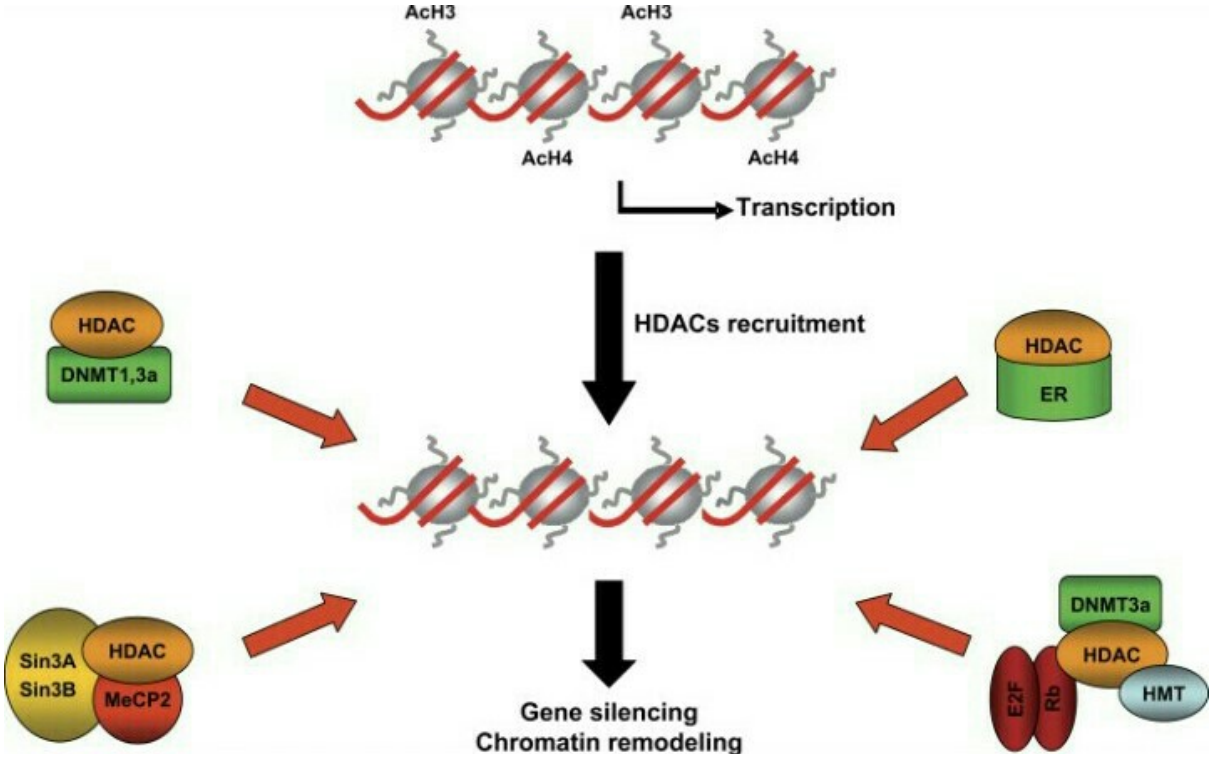
Keywords- Histone deacetylase inhibitors, Anticancer

Introduction

Epigenic modification, mainly DNA methylation and acetylation, are responsible for malignant phenotype. Acetylation and deacetylation of histone play an important role for the regulation of gene expression. Histones are proteins nucleosomes.Histone acetylase andhistone deacetylase regulate cell proliferation, differentiation, and apoptosis in various hematological and solid malignancies and shows the changes in expression pattern of selected genes, whereas deacetylation mediates eukaryotic chromatin condensation and gene expression silencing. [(1)]

Histone deacetylases (HDACs) is an enzyme thatremove acetyl groups from anamino acid on a histone as DNA is wrapped around histones and DNA expression is regulated by acetylation and deacetylation. HDACs protein regulated by cell cycle progression, differentiation and tumorigenesis. Abnormal HDSCs can produce many human diseases like cancer, neurodegenerative disorders, cardiac hypertrophy and pulmonary diseases. [(2)]

Figure 1: Different ways by which HDACs are restricted to gene promises. [3]



The histone deacetylase superfamily showed protein domains. There proteins are of four families (Class I, II a, II b and IV) which is different in structure, enzymatic function, subcellular localization and expression patterns. [4]

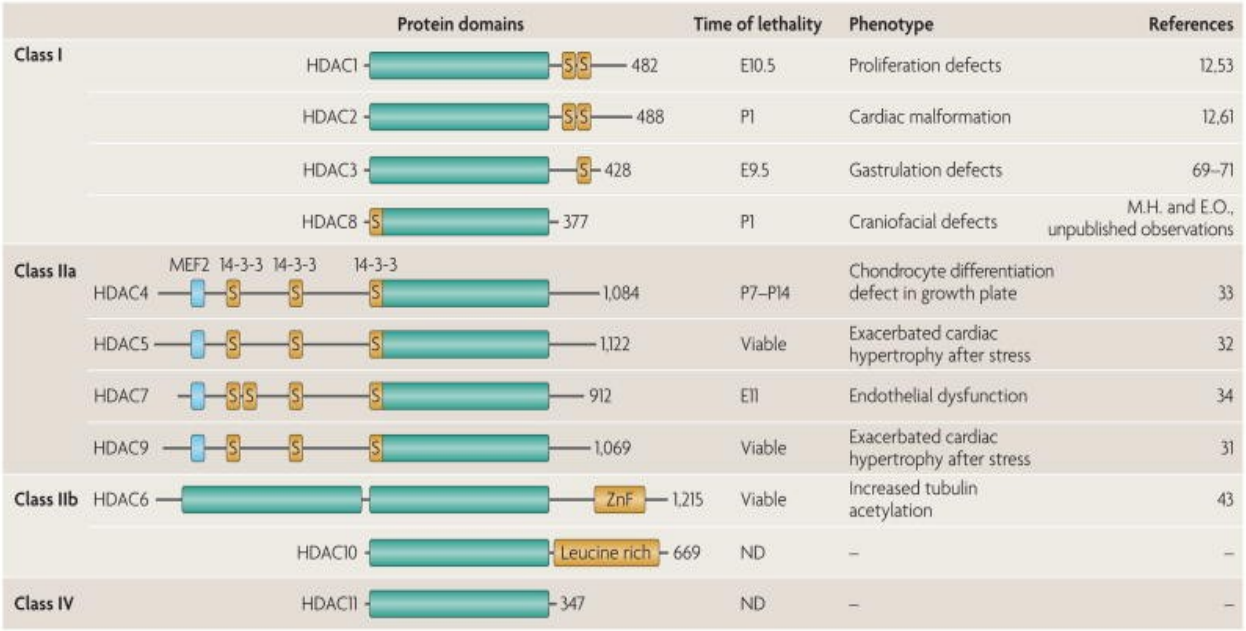
Class I HDACs : The class I HDAC family consist of HDAC 1,2,3 and 8. They possess relatively simple structures consisting of deacetylase domain contain short amino and carboxy terminal extensions [5-7]

Class II a HDACs: HDAC 4,5,7 and 9 belong to class IIa HDAC family. These HDACs have large N-terminal extensionswithconservedbindingsitesforthetranscriptionfactor**.** Theregulatedphosphorylationof class IIa HDACs provides for linking extracellular signals with transcription and has key roles in numerous tissues during development and diseases. [8-10] HDAC 5 and HDAC 9 are highly enriched in muscles, the heart and brain. HDAC 4is highly expressed in the brain and growth of skeleton. HDAC 7 is enriched in endothelial cells and thymocytes. [11,12]

Class II b HDACs: HDAC 6 and HDAC 10 is IIb family. HDAC 6 is the main cytoplasmic deacetylase in mammalian cell where as little is known for HDAC 10. [13]

Class IV HDACs : HDAC 11 is the sole class IV HDAC which is enriched in brain, heart, muscle, and kidney. It contains deacetylase domain that shows homology to class I and class II HDAC domains with small N and C-terminal extensions. [14,15]

Figure 2: The histone deacetylase (HDAC) superfamily.



Histone Deacetylase Inhibitors –

The various novel therapies produce beneficial results in newly diagnosed and replace patients with multiple myeloma (MM). Hence, there is need for new safe and beneficial therapies for continued improvement. HDAC inhibitors have been tried in multiple myeloma various HDAChelped to understand the antimyeloma activity of different HDAC in MM as a single agents or in combinations with conventional novel and immune therapies. Microarray analysis has shown that HDAC induce transcriptional modulations of 7-10 % of the genes by acetylation of histones and nonhistones. (16-18)

HDAC inhibitors are not only used in cancer treatment but also having potential therapeutic effects agent's non-malignant diseases. HDAC inhibitors are useful in treatment of neurodegenerative diseases such as stoke, Huntington's disease, spinal muscular atrophy, Parkinson's disease and Alzheimer's disease. It might be useful to treat osteopousis and fractures HDAC inhibitors may be used to treat diabetes, sickle cell anemia, inflammation and HIV infections. (19-20)

HDAC inhibitors in clinical trials used in monotherapy or combination therapy for solid tumors and hematological malignancies. It is used in combination therapy with radiation, cytotoxic agents and different targeted therapeutic agents. (21)

HDAC inhibitors have been used with demethylation agents to synergistically activate expression of methylated genes. For exa0mple, contentment of AR-negative cell line D0145 with 5-Aza-R TSA is more effective in restoring functional expression of the AR gene and its downstream targets, compared with either agent alone. HDAC inhibitors have also been shown to synergize with gamma radiations to kill tumor cells in vitro; HDAC inhibitors can be divided into hydroxamates, cyclic peptides, aliphatic acids and benzamides. (22)

The mechanisms of HDAC inhibitors induced transformed cell growth arrest and cell death are complex and not completely elucidated. HDAC inhibitors can cause the accumulation of acetylated histones and many non-histone proteins that are involved in regulation of gene expression, cell proliferation, cell migration, and cell death. (23)

Figure3: Selected Histone Deacetylase (HDAC) inhibitors. [24]

Class	HDAC Inhibitor	Target HDAC Class	Clinical Status
hydroxamic acids	Trichostatin A	pan	preclinical
	SAHA	pan	approved for cutaneous T-cell lymphoma
	Belinostat	pan	approved for peripheral T-cell lymphoma
	Panabiostat	pan	approved for multiple myeloma
	Givinostat	pan	phase II clinical trials—relapsed leukemia and multiple myeloma
	Resminostat	pan	phase I and II clinical trials—hepatocellular carcinoma
	Abexinostat	pan	phase II clinical trial—B-cell lymphoma
	Quisinostat	pan	phase I clinical trial—multiple myeloma
	Rocilinostat	II	phase I clinical trial—multiple myeloma
	Practinostat	I, II and IV	phase II clinical trial—prostate cancer
	CHR-3996	I	phase I clinical trial—advanced/metastatic solid tumors refractory to standard therapy
short chain fatty acids	Valproic acid	I, IIa	approved for epilepsia, bipolar disorders and migraine, phase II clinical trials—several studies
	Butyric acid	I, II	phase II clinical trials—several studies
	Phenylbutyric acid	I, II	phase I clinical trials—several studies
benzamides	Entinostat	I	phase II clinical trials—breast cancer, Hodgkin´s lymphoma, non-small cell lung cancer, phase III clinical trial—hormone receptor positive breast cancer
	Tacedinaline	I	phase III clinical trial—non-small cell lung cancer and pancreatic cancer
	4SC202	I	phase I clinical trial—advanced hematological malignancies
	Mocetinostat	I, IV	phase II clinical trials—Hodgkin´s lymphoma
cyclic tetrapeptides	Romidepsin	I	approved for cutaneous T-cell lymphoma
sirtuins inhibitors	Nicotinamide	all class III	phase III clinical trial—laryngeal cancer
	Sirtinol	SIRT 1 and 2	Preclinical
	Cambinol	SIRT 1 and 2	Preclinical
	EX-527	SIRT 1 and 2	cancer preclinical, phase I and II clinical trials—Huntington disease, glaucoma

Hydoxamicacids-In this class includes trichostatin A which is the first HDAC inhibitors, used for the of treatment replaced and refractory cutaneous T-cell lymphoma. It represents the largest class of HDAC inhibitions. Hydroxamic acid- based compounds protect neurons through metal chelation independent of their HDAC inhibitors properties. Novel hydroxamate derivatives produces HDAC enzyme inhibitory activity. This compounds exhibited tumor growth inhibition. [25,26,27]

ShortChainFattyacids – In this class known for the weak inhibitors of HDAC Class I and Class IIa and I and II, respectively. Colorectal cancer is the most common cancer in the western world. Butyrate and short chain fatty acids plays a major role as chemo preventive products of microbial fermentation in colon. Butyrate is a short chain fatty acid that acts as a HDAC inhibitor and it act as anti-neoplastic because of its ability to impose cell cycle arrest differentiation and /or apoptosis in many tumor cell types. [28,29]

Benzamides–Benzamide derivatives showed histone deacetylase inhibiting activity.Chidamide is a new histone deacetylase inhibitor of this class which is under clinical development in cancer indications. Selectivity and potency of Chidamide in inhibition of HDAC isotypes were analyzed by using a panel of human recombinant HDAC proteins. This study aimed to test the effect of Chidamide on proliferation an apoptosis in pancreatic tumor cell line.It is the first oral subtype selective histone deacetylase inhibitors approved in China. It is the first class HDAC of the benzamide class approved for the treatment of replaced and refractory peripheral-cell lymphoma. Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematopoietic stem cell disorders which are characterized by ineffective hematopoiesis, peripheral blood cytopenias and high risk of transformation to acute myeloid leukemia. Chidamide possesses potent inhibitory effect against HDACs and induces inhibition of

growth, cell cycle arrest and apoptosis in MDS and AML cell lines.[30,31,32,33]

CyclicPeptide – Cyclic tetrapeptides containing trifluoromethyl and pentafluoroethylketone as zinc binding functional group is a potent HDAC inhibitors. Depsipeptide is also in clinical trials as monotherapy and in combination therapy with various anticancer agents in patients with hematologic and solid malignancies. [34,35]

AliphaticAcid – Aliphatic acid such as valproic acid are weaker HDAC inhibitors than hydroxaqmic acid or cyclic peptide based agents. Valproic acid is effective as monotherapy in myelodysplastic syndromes. Clinical trials with phenyl acetate have generally shown little anticancer activity. [36]

Mechanism of Action: -

The mechanism of HDAC inhibitors induced transformed cell growth arrest and cell death are complex. It can cause acetylation of histone and non-histone proteins which produces regulation of gene expression, cell proliferation, cell migration and cell death. Normal cells are relatively resistant to HDAC inhibitors induced cell death. [18]

Conclusion

This review has highlighted some of HDAC inhibitors. The development of HDAC I has provided the impetus to develop more potent HDAC inhibitors and to targets others epigenetic enzymes for oncology. The multiple protein targets of HDACs and therefore of HDAC inhibitor with many other anticancer agents may be most promising HDAC inhibitors have therapeutic application in non-malignant diseases i.e anti-inflammatory and specific immune modulator activity. It is beneficial in neurodegenerative diseases such as stoke, Parkinson's disease and Alzheimer's diseases. Thus expansion of their therapeutic application beyond the treatment of cancers has encouraged further development of HDAC inhibitors with defined targets, improved therapeutic effects and minimal adverse effect will be antiapated.

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