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Histone Deacetylase Inhibitors As Potential Therapeutic Agents For Various Disorders

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Abstract Epigenetic modification acetylation or deacetylation of histone considered as an important element in various disorders. Histone acetyltransferases (HATs) and histone deacetylases (HDACs) are the enzymes which catalyse the acetylation and deacetylation of histone respectively. It helps in regulating the condensation of chromatin and transcription of genes. Lysine acetylation and deacetylation present on the nucleosomal array of histone is the key factor for gene expression and regulation in a normal working living cell. Modification in histone protein will lead to the development of cancer and can cause various neurodegenerative disorders. To safeguard the cells or histone proteins from these diseases histone deacetylase inhibitors are used. In this review, the main focus is upon the role of histone deacetylases inhibitors in various diseases.

Keywords: Epigenetic; Histone; Acetylation; Deacetylation; Lysine; Histone deacetylases inhibitors

1. INTRODUCTION

Eukaryotic cell nuclei contain a highly alkaline protein known as histone which helps DNA to attain its helical structure. An octad of four core histones forms a fundamental subunit of chromatin termed as the nucleosome (Kornberg, 1999; Ito *et al*. 2000). The nucleosome represents a principle protein-nucleic acid relationship of chromatin, (Kornberg, 1999). Four core histones are H3/H4 tetramer and two H2A/H2B dimers (Ito *et al*. 2000; Strahl, 2000). A chromatin strand consists of 146 base pairs of DNA wrapped around the histone protein give rise to the nucleasomal array (200bp). All these four core histones all contain an N-terminal tail that passes through and around the DNA double

helix. This N-terminal of histones is prior to modification during activation of gene transcription and gene expression. The various modifications that can take place are methylation, phosphorylation, and the acetylation. Among this modification, acetylation is widely occurring and understandable modification of histone proteins. Modifications of histones H3 and H4 are much more extensively characterized than those of H2A and H2B (Wade, 2001). Acetylation mainly takes place on the amino acid Lysine (Lys). Other post-translational modifications of histone include methylation of Lys and arginine, ubiquitination of lysine phosphorylation of serine and ubiquitination of lysine (Zhang, 2001; Jenuwein, 2001). On histone H3 important positions for acetylation are Lys9 and 14 and on histone H4 positions for acetylation are Lys5, 8, 12, 16 (Bjerling *et al*. 2002). Acetylation of histone is affected by two classes of enzymes-histone acetyltransferases (HATs) and histone deacetylases (HDACs). This acetylation and deacetylation determine the gene expression (Ito *et al*. 2000; Wade, 2001; Forsberg, 2001)

2. HISTONE ACETYL TRANSFERASE ACETYLATION

Acetylation by HATs leads to the uncoiling of the nucleosomal array, which is due to the development of negative charge on histone due to modification process destabilization of the inter-nucleosomal interactions and also due to interaction of phosphate backbone of DNA with histone. Hyperacetylation increased the accessibility of chromatin to transcriptional factor (Cress, 2000).

Generally, hyperacetylation leads to increased transcriptional activity of a gene, whereas hypoacetylation cause repression of gene expression (Ito *et al*. 2000; Wade, 2001; Forsberg, 2001). A pattern of post-translational modifications (acetylation) makes a "code" which is recognized and translated by nonhistone proteins and multiprotein complexes. These complexes are important aspects for transcription-activation and transcription-repression. HATs are categorised into two big families GNAT (Gcn5-related N-acetyl Transferase) and the MYST (Moz, Ypf2-Sas3, Sas2, Tip60) group and one small family p300/CBP (CREB Binding proteins) family. Nonhistone protein substrate which is targeted by HATs enzyme is collectively termed as FATs (Factor acetyltransferases) including p53, E2F, and GATA1 9 (GATA-binding factor 1) (Roth *et al*, 2001).

3. HISTONE DEACETYLASES

The interaction of histone deacetylases with histone tends to increase electrostatic bond of histones which contains both positively and negatively charged DNA. It leads to more rigid and strong structure of chromatin and

restrains transcription of gene by controlling the penetrability of transcription factors (Polo and Almouzni, 2005) accompanied by removing neutralizing acetyl groups from the histone Lys tail (Timmermann *et al*. 2001). HDACs categorized in two major classes. The human class 1 deacetylases contains enzymes similar to yeast transcriptional regulator such as HDACs 1, 2, 3 and 8 (Joseph *et al*. 2000). They share homology in their catalytic sites (De Ruijter *et al*. 2003). All class 1 enzymes which are present everywhere in human cell lines and tissues have nuclear location. Another one is human class 2 deacetylase; co-enzymes in this category are similar to HDA1P. Another class which is of class 2 is divided in different sub classes such as class 2a (HDAC4, 7, 5 and 9) and class 2b (HDAC6 and 10) (Glass, 2000). These share similarities in two regions, the one is C-terminal catalytic domain and another one is N-terminal regulatory domain (Grozinger *et al*. 2001).

Class 2 enzymes have tissue specific expression and free to move across nucleus and cytoplasm. Class 2 also helps in introduction of acetyl group in non-histone proteins. Some other categories are the sirtuins (SIRTI-7) family and maize HD2 (Grozinger *et al*. 2001; Verdel *et al*. 1999). Proteins in SIRT group are in much resemblance with yeast SIR2 family of proteins (Glass and Rosenfeld, 2000). HDAC11 which is new member of HDAC family was discovered recently (Verdel *et al*. 1999).

HDACs enzymes have important role in regulation of basic process of cell cycle growth and programmed cell death (Robertson *et al*. 2000). HDAC also have important function in cancer growth. It is not only restricted to histone deacetylation (Juan *et al*. 2000). Down regulation of post translational histone modifications leads to failure of gene transcription. A study showed the loss of acetylated Lys16 of H4 is normal even in cancer of human (Fraga *et al*. 2005).

4. HISTONE DEACETYLASE INHIBITORS

The HDAC inhibitors (HDACi) consist of 3 parts: a 'can' part of 'surface recognition domain', which opens gate of active site; a group of zinc binders which chelates zinc ion at the active site and is helpful for catalytic function; and a 'linker' region which bring together the two. The shape of HDAC inhibitors have been refined in various studies of homologue of trichostatin A (TSA) and suberoylanilide hydroxyamic acid (SAHA) (Finnin *et al*. 1999). The crystal shape of hydroxamate complex which is also known as HDAC8 has been mentioned (Somoza JR *et al*. 2004). The studies in various labs explored the 3-d structure of catalytic site in HDACs and have also explained about the mechanism of acetylated lysine substrates deacetylation. There is a proper interaction of inhibitors with the active site of zinc on the

base of catalytic pocket. Various HDAC enzymes have different biological activities and HDAC1 and HDAC2 class plays crucial role in transformation of proliferation of cell leading to obtain selective HDAC inhibitors. Tubacin which is a small molecule is created that mainly stops HDAC6 activity and lead to accumulation of acetylated alpha-tubulin, but it doesn't change and stops cell cycle progression and histones acetylation (Haggarty SJ *et al*. 2003).

HDAC inhibitors discovered till now can be classified into different structural classes which include hyroximates, different cyclic peptides, some of aliphatic acids and also benzamides (Marks PA *et al*. 2004). TSA, the first natural hydroximate product was discovered which inhibit HDACs. SAHA looks alike TSA structurally and is nanomolar antagonist of HDAC class 1 and 2 (Richon VM *et al*. 1996). HDAC class 3 is neither inhibited by TSA or SAHA.

CBHA (Carboxycinnamic-m acid Bis-hydroxamide- HDAC inhibitor) which is also known as M-carboxycinnamic acid bishydroxamide is a potent HDAC inhibitor. It shows the structural basis for different derivatives such as LAQ824 and sulfonamide. PXD-101 also inhibit class 1 and 2 HDACs in very small concentrations. The cyclic peptides are structurally very complex group of HDAC inhibitors. They include the natural product which is depsipeptide also known as FK228, another molecule apicidin and sum molecules of chaps group. They all are active in small concentrations. FK228 is a pro drug of red Fk which is an active agent. Other cyclic tetrapeptides which have trifluoroethyl and pentafluoroethyl ketone and also contains zinc binding functional groups are synthesized and are strong HDAC inhibitors (Jose B *et al*. 2004).

Vorinostat is also structurally similar to TSA (Richon *et al*. 1998). The different types of aminosuberoyl hydroxamic acids have been established recently which modify proliferation of cells at low concentrations (Belvedere *et al*. 2007). The first therapeutically FDA approved HDAC inhibitor is vorinostat. Vorinostat is inhibitors of class 1 and class 2 HDAC proteins (Duvic *et al*. 2007). The Novartis discovered product panobinostat is analogue of hydroxamic acid of CBHA (Marks *et al*. 2007). Another HDACi, the IF2357 have a hydroxamic acid moiety attached to benzene ring (Leoni *et al*. 2005). Another series of HDACi at small concentrations are aryloxyalkanoic acids which have been recently developed (Marson *et al*. 2007).

Cyclic peptide is a class of structurally complex group and are HDACi which consist different herbal drugs such as depsipeptide, another name is FK228 and romidepsin, manufactured by Gloucester Pharmaceutical Inc (Jose B *et al*. 2004). Apicidin and other cyclic hydroxamic acid which contains peptide group are all active at low amount. Depsipeptide also known as FK228 is an active agent and also prodrug for red FK. Cyclic peptides containing

aliphatic chain to a hydroxamic acid is new HDACi and are active at very minute concentrations such as millimolar (Liu T *et al*. 2007).

Another class of compounds such as aliphatic acids which contains butyrate, phenylbutyrate and valproic acid, these all are weak antogonist of the HDACs and have action at very low concentrations (Xu W *et al*. 2005). Drugs like valproic acid and phenyl butyrate have recently shown activity as HDACi. Apart from that they are used in market for non-oncological uses. Pivaloyloxymethyl butyrate also known as AN-9 is manufactured by Titan Pharmaceutical, Inc. It is crucial pro drug for butyric acid (Rasheed WK *et al.* 2007).

MS-275 which is manufactured by Syndax Pharmaceutical Inc is derivative of benzamide. Another one is MGCD0103 and is dihydobromide salt of aminophenyl benzamide (Gelmon K *et al.* 2005). M-275 shows more inhibitory action at HDAC1 in comparison to HDAC3 and it have low effect against HDAC6 and very low at HDAC8. Other molecules like SK7041 and SK7068, they only show action against HDAC1 and HDAC2. Another compound name tubacin which is a small molecule, it particularly inhibits the activity of HDAC6 and lead to accumulation of acetylated tubulin. It doesn't stop cell cycle progression (Haggarty SJ *et al*. 2003).

5. MECHANISM OF HISTONE DEACYTYLASE INHIBITORS

HDACi work induce inhibition of cell growth by causing introduction of acetyl group in histones proteins which help in expression of gene, cell growth, cell migration and cell death (Xu *et al*. 2007). They work by inducing apoptosis by energizing both intrinsic pathway and extrinsic pathway. They mediate tumours cell death due to introduction of apoptosis which result in caspase activation and cell death. Extrinsic pathway start with the attachment of the ligand likely to be as Fas ligand, TNF (Tumour necrosis factor) ligand and TNF related apoptosis inducing ligand also known as TRAIL (Tumour necrosis factor-related apoptosis -inducing ligand) on the surface of cell death receptor (DR) (Johnstone *et al*. 2002). Intrinsic pathways works through destruction of membrane of mitochondria of cell by stress like radiation, chemical therapies and withdrawing growth factors. HDACi also works by blocking angiogenesis of tumour by stopping HIF which is known as hypoxia inducible factors. Hypoxia regulates expression of gene in VEGF (Vascular endothelial growth factor) by balancing factors such as HIF 1-apha and VHL (Von hippl Lindau) which is tumour suppressor gene. In conditions like hypoxia TSA work by upregulating VHL and p53 and blocking angiogenesis by downregulating VEGF and HIF 1-alpha (Kim *et al.* 2001). These HDACi shows anti-angiogenic cycle by degrading HSP90 regulating function and exposing of HIF1-alpha

(Qian *et al*. 2006). HDACi also cause destruction of DNA with making changes in chromatin conformation at histone acetylation. Another mechanism is production of ROS which is also known as reactive oxygen species which lead to cell death by damage to DNA. HDACi increases production of ROS by downregulation of thioredoxin (Trx) (Marks *et al*. 2006).

Control over gene expression is primarily kept by HATs and HDAC. The stability between the HATS AND HDACs activity is necessary for normal cellular function. Deregulation as over expression and hypo expression of HDACs/HATs is found to be causative and progressive agents in various cancers and neurodegenerative diseases.

6. ROLE OF HISTONE DEACETYLASE IN CANCER

Histone acetylation and deregulation of methylation of DNA are considered as the feature for the development of cancer and further causing deregulation of gene transcriptional factors. Acetylation of Lys16 (K16-H4) and Lys20 (K20-H4) residues are responsible for the relaxed state of chromatin plus the activation of the transcription of genes and has been correlated with genomic functions (Polo, 2005; Vidanes *et al*. 2005). Deacetylation of the Lys 16, 20 causes are responsible interactions between the histones (negatively charged) and DNA (positively charged) will out turn the compressed structure of chromatin and silence the genes (Johnstone, 2002; Iizuka, 2003). In tumours of GIT, it has been achieved that decrease in acetylation occurs in tumour development as well as in aggregation of tumour and metastasis (Yasui *et al*. 2003).

There are many ways for HDACs to regulate the expression of genes. In the absence of ligand they form corepressor complexes like N-CoR, SMRT, and mSin3 (Glass and Rosenfeld, 2000) and mark particular genomic sites by binding to the transcriptional factors, receptors of a nucleus and some specific genes like MBDs (methyl -CpG-binding domain), DNMTs (DNA methyl Transferase), and HMTs (histone methyl Transferase). Binding of these factors will cause the suppression of genes (Jones *et al*. 1998; Nan *et al*. 1998).

Translocation of the chromosome is a genetic feature of hematological malignancies as it yields the fusion proteins (RAR-PML, RAR-PLZF) which interacts with the RARE's and initiate the HDAC repressor complex to repress the gene expression by inhibiting the retinoic acid so as to improve the normal functioning of myeloid cells (Lin *et al*. 2001).

In humans there are different types of HDACs which are responsible for tumourigenesis. Elevation of HDAC1 expression is found in GIT (Choi *et al*. 2001), colon (Wilson *et al*. 2006), prostate (Halkidou *et al*. 2004), colorectal (Zhu *et al*. 2004) and breast cancer breast (Zhang *et al*. 2005). The HDAC3 level

is also elevated in colon cancer (Zhang *et al*. 2004) and HDAC6 levels are also elevated in the breast (Wilson *et al*. 2006). The SIRT1 plays a crucial role in cancer as its level is seen to be either increasing or decreasing in cancerous cells. As in lung cancer, prostate cancer and in leukemia the level of SIRT1 is tend to be increasing, whereas in colon cancer there is an attenuation in the level of SIRT1 (Yeung *et al*. 2004; Kuzmichev *et al*. 2005; Bradbury *et al*. 2005; Ozdag *et al*. 2006). HDAC inhibitors promote p21 expression; p21 regulates p53 which is a tumour suppressor. They also inhibit the proliferation of the cell.

Following are some novel inhibitors which can be used in various kind of cancer:

6.1 1, 3, 4-oxadiazolealanine.

Pidugu *et al* prepared the compound (R)-2-Amino-N-((5-phenyl-1, 3, 4-oxadiazol-2-yl) methyl) propanamide (10b) (Pidugu *et al*. 2016) and considered as a potent HDAC8 inhibitor for the treatment of cancer (Gryder *et al*. 2012). Bax, Bcl2, cytochrome c, and PARP are the apoptotic proteins. The Bcl2 and Bax proteins generates the apoptosis, the levels of Bcl2 tends to decrease in cancerous cells leading to the formation of homodimers of Bax generating apoptosis in cancerous cells. The HDAC8 inhibitor dose-dependently promotes the expression of p21 in cancer cells which further inhibits the CDK1 expression. The compound also contributes to the increase in the level of cytochrome c and breakage of PARP which further inhibits the CDK1 expression by increasing the expression of p21 in cancer cells. The compound also activates the caspase 3 and 9 in cancerous cells (Pidugu *et al*. 2017).

In cancer cells, p53 is a protein which suppresses the tumour and induces apoptosis in cancer cells (Chen *et al*. 2016). Protein p53 also promotes the expression of p21 which inhibits CDK1/CDK complex and promotes apoptosis (Zhang *et al*. 2009). There are two apoptotic pathways: extrinsic pathway and intrinsic pathway. The extrinsic pathway is disputed due to the over expression of the Bcl2 proteins and the intrinsic pathway conclusion is the damage to the mitochondrial membrane which leads to the discharge of cytochrome c and activation of caspase-3 due to breakage of PARP and fragments of DNA (Naseri *et al*. 2015).

6.2 BEBT-908

The PTEN (tumour suppressor) levels are controlled by PI3K-Akt pathway by altering its transcriptional activity. Akt pathway activates the NF-□B transcriptional factor which regulates PPARβ/δ agonist and TNα which in turn repress PTEN (Georgescu, 2010).The compound BEBT-908 suppressed

p-AKT interpretation and considered as a potent PI3K and HDAC inhibitor. BEBT-908 activates mitochondrial-mediated pathways by persuading apoptosis in the cells (Li *et al*. 2017). BEBT-908 also activates G1 phase in cell cycle captured in the cells. HDAC inhibitors typically induce G1 cell cycle arrest through the upregulation of the cyclin-dependent kinase inhibitor p21 (Yazbeck *et al*. 2015). HDAC inhibitors can also activate the mitochondria-mediated apoptotic pathway and regulate the equilibrium between pro- and anti-apoptotic proteins (Rikiishi, 2011; Zhao *et al*. 2005).

6.3 Diallyl Trisulfides

DATS is HDAC inhibitor which alters the HIF-1α (Hypoxia-inducible factor 1) interpretation in tumour cells. HIF-1α manages homeostasis via stimulation of the transcriptional factors (Mahon *et al*. 2001) of the targeted genes such as ANGPTL4, LOXL4, and LOX under hypoxic conditions (Wei *et al*. 2017). Development of tumour cells initiates the demand of oxygen in the cells and points to angiogenesis (Mazure *et al*. 2006). Excessive expression of HIF-1α leads to inflammation and diminish the capability of cells to migrate (Solinas *et al*. 2009).

The stimulation of the HIF-1α protein is reduced by DATS by controlling the levels of Trx-1 in the cancer cells. In the case of breast cancers, the levels of the Trx1 protein are very high. DATS adequately inhibited HIF-1α to abolish development of breast cancer (Wei *et al*. 2017). The Trx1 system is highly expressed in breast cancers (Lincoln *et al*. 2003; Cha *et al*. 2009) and Trx1 is considered as the marker for breast cancer (Park *et al*. 2014).

7. ROLE OF HISTONE DEACETYLASE INHIBITORS IN NEURODEGENERATIVE DISORDERS.

7.1 Parkinson's disease

In PD brain, dieldrin and paraquat are the neurotoxins which cause acetylation of histone proteins. Not all but H2AK5, H3K9 and H4K5 are implicated in the histone acetulation (Song *et al*. 2010; Song *et al*. 2011). P25/Cdk5 caused neuronal death by inhibiting and deregulation of HDAC1. In an in vivo model for ischemia protection HDAC1 act as potentially protective against DNA damage and cultured neuron's neurotoxicity (Kim *et al*. 2008). Neurotoxicity caused by transcriptional genes (BDNF, GDNE, HSP70, and TH+-IR), α-synuclein and MPP+ is inhibited by using HDAC inhibitors (Harrison and Dexter, 2013). A study of DAT promoter in the cultured rat N27 cell shows a significant role of valproate in regulating DAT expression via elevating the histone acetylation and proves to be neuroprotective (Green *et al*. 2017).

7.2 Alzheimer's Disease

In AD brain, memory destruction, emotional defects and loss of neuron is caused due to the enhanced level of Aβ proteins which further activates the GSK-3β. GSK-3β stimulation leads to phosphorylation of tau proteins (Mucke *et al*. 2012). The HDAC proteins are also indulged in the progression of the AD by conducting the histone acetylation which alters the gene expression and alleviates the emotional balance and destruction of memory (Stridh, 2010). Inhibitors of HDAC inhibit the hyperphosphorylation of tau achieved by Aβ protein activation. HDAC inhibitors also allocate the gene expression via activation of proteins like GluR1 (glutamate receptor 1), PSD95 (postsynaptic density protein 95), MAP2 (microtubule-associated tubule 2), etc. (Xu *et al*. 2011). Various pan-HDAC inhibitors interact with the HDAC proteins that include class I, II and IV (Green *et al*. 2008).

EVP-0334 enhances both short and long-term memories in mice. Histone deacetylase enzyme unwinds the DNA for effective gene expression. EVP-0334 as histone deacetylase inhibitor, prevents the removal of the acetyl group and maintains the structure of DNA but it loses the compact structure of chromatin which is more open to gene expression (Leventhal *et al*. 2008). HDACi has both neuroprotective and neurodegenerative properties (Graff *et al*. 2013). Neuroprotection can be achieved by two ways: activation of transcriptional genes and the other works by maintaining the protein homeostasis comprising various pathways to be involved in controlling protein synthesis to achieve stability and functional properties of the proteasome (Hahnen *et al*. 2008).

7.3 Ischemic stroke

Stroke is caused due to various mechanisms such as excitotoxicity, inflammation, ionic imbalance and oxidative/nitrosative stress (Lo *et al*. 2003). Activation of microglia and infiltered leukocytes consisting of macrophages cause inflammation in the ischemic brain and leads to degeneration of neurons. Microglia on activation releases the proinflammatory mediators which further cause obstruction to brain and excitotoxicity (Gregersen *et al*. 2000). HDAC inhibitors such as valproic acid, sodium butyrate, and hydroxamine acid trichostatin decrease the growth of the cell and contribute to the differentiation of the cells. Sodium butyrate and trichostatin exhibits neuroprotective effects (Kim *et al*. 2007). HDAC inhibitors cause the hyperacetylation of the proteins and change the gene expression. Valproic acid suppresses the inflammation caused by microglia and LPS by suppression of the excretion of TNF-α and preparation of NO. HDAC inhibitors also decrease the p53 levels and levels of proapoptotic proteins (Kim *et al*., 2007; Chen *et al*. 2007).

7.4 Huntington's disease

Huntington disease is a dynamic illness of the brain which causes loss of control in movement, emotional problems, and loss of cognition (Shen *et al*. 2008). In HD brain the histone enzymes alters the frame of chromatin and regulate the expression of the genes. Enzyme H2A is responsible for the acetylation, whereas the H2B is responsible for the methylation, the H3 is responsible for the phosphorylation and the H4 is responsible for the ubiquitination, and sumoylation of the histone that affects the stability of chromosome, mitosis, and transcription 46 (Tanny *et al*. 2007). Acetylation and methylation of the lysine 9 and 14 on H3 lead to transcription and silencing of genes respectively (Nakayama *et al*. 2001). Phosphorylation is also correlated with the gene transcription 46 (Nowak and Corces *et al*. 2004).

The networking between HAT and HDAC regulates the acetylation and deacetylation of histone 47. HAT increases the transcription of genes and the HDAC withdraws the acetyl group causing the genes to repress (Marks, 2010). Polyglutamine proteins accumulation in the nucleus will have abnormal interactions with nuclear proteins altering the transcription of genes (Li, 2004). The mutated htt connects the transcriptional factors like CBP, TBP, p53, and sp1 to destroy the functional activity of mitochondria by attenuating the expression of PGC-1 alpha which controls the biogenesis of mitochondria. HDAC inhibitors like SAHA and sodium butyrate increases the acetylation of histone proteins and slowed the evolution of degeneration of neurons. Mutant Htt decreases the levels of transcriptional factors as well as the level of acetylation by segregating the co-activators like CBP and making their aggregates (Sadri-Vakili *et al*. 2006).

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