Histone deacetylases and their inhibitors (HDACis) for bone formation and regeneration A review

〔Review〕

Histone deacetylases and their inhibitors (HDACis) for bone formation and regeneration : A review

Shamima SULTANA[1)], Osamu UEHARA[2)], Koki YOSHIDA[3)], Takashi SAITO[1)], Yoshihiro ABIKO[3)]

1)Division of Clinical Cariology and Endodontology, School of Dentistry, Health Sciences University of Hokkaido
2)Division of Disease Control and Molecular Epidemiology, Department of Oral Growth and Development, School of Dentistry, Health Sciences University of Hokkaido
3)Division of Oral Medicine and Pathology, Department of Human Biology and Pathophysiology, School of Dentistry, Health Sciences University of Hokkaido

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Abstract

The major epigenetic mechanisms affecting gene expression are histone modifications, DNA methylation, and activities of noncoding RNAs. Histone modifications by two distinctive enzymes histone acetyltransferases (HATs) and histone deacetylases (HDACs) display different mechanisms of histone substrate binding and catalysis, and affect gene transcriptions. Recently, HDAC inhibitors (HDACis) that increase acetylation of histones have been clinically applied for certain types of diseases including cancer, epilepsy, bipolar disorder, and blood diseases. Although HDAC is controlled osteogenesis both in vitro and in vivo, no clinical application of HDACi for bone regeneration has been performed. This review introduces how HDACis affect bone regeneration in vitro and in vivo. Certain types of HDACis may be clinically useful for bone regeneration.

Introduction

Epigenetics is defined as heritable changes in gene expression that are not linked to changes in the DNA sequence. Epigenetic events are one of the important mechanisms that regulate the differentiation of different types of cells during both prenatal and postnatal development. The major epigenetic mechanisms that affect gene expression are histone modification, genomic DNA methylation, and activities of noncoding RNAs (Gibney & Nolan, 2010). Histone modifications via two distinctive enzymes histone acetyltransferases (HATs) and histone deacetylases (HDACs) involve different mechanisms of histone substrate binding and catalysis (Buchwald, et al., 2009 ; de Ruijter, et al., 2003). Histone acetylation is generally associated with transcriptional activation, whereas deacetylation of histones represses gene expression. DNA methylation plays an important role via the addition of a methyl group to the 5th carbon of cytosine in the CpG dinucleotide sequence during DNA repair, recombination, and replication (Chin, et al., 2011). A noncoding RNA (ncRNA) is a functional RNA molecule that is transcribed from DNA, but not translated into a protein. The epigenetic related ncRNAs include miRNA, siRNA, piRNA and lncRNA (Peschansky & Wahlestedt, 2014).

A greater understanding of the epigenetic events in bone cells could help improve tissue engineering strategies in the bone and identify novel anabolic targets. Recently, several types of histone deacetylase inhibitors (HDACis) have been used to induce calcification and promote osteogenesis. However, variations in the results of these studies exist, and a consensus on the usefulness of HDACis has not been reached thus far (Haberland, et al., 2009). In this review, we summarized on the effectiveness of several types of HDACis on osteogenesis and discussed the possibility of using them in the clinical setting.

Histone deacetylases (HDACs) and histone deacetylase inhibitors (HDACis)

The acetylation of histone proteins is a balance between the activities of both HATs and HDACs. HDACs with his-

tone acetylation are generally associated with an increase in gene transcription, whereas deacetylation results in decreased gene transcription. Eighteen HDACs have been identified in humans, and are divided into four subclasses based on the homology to the yeast genes as follows : class I (HDAC1, HDAC2, HDAC3, and HDAC8), class IIa (HDAC4, HDAC 5, HDAC7, and HDAC9), class IIb (HDAC6 and HDAC10), class III (sirtuin [SIRT1] to −7), and class IV (HDAC11) (Haberland, et al., 2009). HDACs often induced pathogenic transcriptions ; therefore their inhibition might prove useful for the treatment of various diseases (Chuang, et al., 2009). HDACis have been chemically synthesized and applied for the treatment of psychiatric and neurological diseases (van Bokhoven H., 2011). In addition, several classes of HDACis, including hydroxamic acids, cyclic peptides, butyrates, and benzamides have been discovered (Yoshida, et al., 1990 ; Komatsu, et al., 2001 ; Candido, et al., 1978). The hydroxamates include vorinostat, givinostat, abexinostat, panobinostat, belinostat, and the prototypical HDACi, trichostatin A (TSA). The cyclic peptides include compounds such as depsipeptide and troponin, whereas the benzamides include entinostat (MS−275), and mocetinostat. Some of these HDACis have been approved for use as pharmaceutical drugs (Jones, et al., 2016).

Involvement of HDACs in bone development

Bone development is a dynamic and complex process that requires precise control of the transcriptional events in multiple cell types, and is sensitive to changes in HDACs levels (Dudakovic, et al., 2013). HDACs play important roles in maintaining the balance between osteoblastic bone formation and osteoclastic bone resorption, processes that are crucial for bone tissue homeostasis (Destaing, et al., 2005). The crucial roles of several HDACs in both intramembranous and endochondral bone development are shown in Table 1.

a. Class I HDACs (HDAC 1, HDAC 2, HDAC 3, and HDAC8)

The roles of HDACs in bone development have been evaluated mainly by the genetic deletion of each HDAC (Schroeder & Westendorf, 2005). Class I HDACs are essential regulators for both intramembrane and endochondral bone development. Targeted deletion of HDAC1 is lethal resulting in severe proliferation defects and retardation in development (Lagger, et al., 2002 ; Trivedi, et al., 2007). Germline deletion of HDAC2 has partialy embryonic lethality, and causes significant decreases in body size and long bone length as a result of abnormal endochondral ossification (Trivedi, et al., 2007). HDAC1 and HDAC2 inhibit os-

Table 1 : Role of histone deacetylases (HDACs) in bone development

Class	HDACs	Targeted protein	Protein expression	Mode of action	Terminal bone phenotype	References
I	HDAC1	RUNX2	↓	Inhibition of osteoblast differentiation	Severe proliferation defects and retardation in bone development	Lagger, et al., 2002
	HDAC2	RUNX2	↓	Inhibition of osteoblast differentiation	Reduced body size and long bone length	Lee, et al., 2006 Dou, et al., 2016
		FoxO1	↓	Increased osteoclastogenesis		
	HDAC3	RUNX2	↓	Suppression of osteoblast differentiation Decreased matrix mineralization	Embryonic lethal Severe endochondral bone defects Severe craniofacial malformations in skull	Singh, et al., 2013 Schroeder et al., 2004
	HDAC8	Otx2 and Lhx1	↑	Decreased intramembranous ossification	Ossification defects in frontal bone	Haberland, et al., 2009
II	HDAC4	RUNX2	↓	Premature endochondral ossification by repressing transcriptional activity	Skeletal defects and premature skull ossification	Vega, et al., 2004
	HDAC5	RUNX2	↓	Suppression of osteoblast differentiation	Reduced trabecular bone density Juvenile osteoporosis	Obri, et al., 2014 Kang, et al., 2005
	HDAC6	RUNX2	↓	Cytoskeletal changes in osteoclasts and bone resorption	Increased cancellous bone density	Westendorf, et al.., 2002 Zhang, et al., 2008
	HDAC7	RUNX2	↓	Regulation of endochondral ossification by deacetylation− independent manner	Reduced femur lengths, and decreased trabecular bone density	Jensen, et al., 2008 Bradley, et al., 2015
III	Sirt1	NA	NA	Osteoblast differentiation of mesenchymal stem cells	Developmental defects, including shorter stature, craniofacial abnormalities, increased cartilage apoptosis Reduced endochondral ossification	Bradley, et al., 2015 Cheng, et al., 2003 Backesjo, et al., 2006
	Sirt6	NA	NA	Facilitates endochondral ossification by controlling chondrocyte proliferation and differentiation	Bone growth retardation	Mostoslavsky, et al., 2006

HDAC : Histone deacetylase ; RUNX2 : Runt−related transcription factor 2 ; ↑ : Up regulation ; ↓ : Down regulation ; Otx2 : Orthodenticle homeobox 2 ; Lhx1 : LIM homeobox 1 ; Sirt : Sirtuin ; NA : Not applicable.

teoblast differentiation via down−regulation of the Runt−related transcription factor2 (Runx2), a key factor for osteoblast differentiation (Lagger, et al., 2002 ; Lee, et al., 2006). HDAC2 also inhibits Forkhead box protein O1 (FoxO1), a negative regulator of osteoclast differentiation to promote osteoclastogenesis (Dou, et al., 2016). Furthermore, germline deletion of HDAC3 has been shown to cause early embryonic lethality (Montgomery, et al., 2008), whereas, HDAC3 suppression caused severe endochondral bone defects due to decreased amount of cartilage matrix formation, fewer osteoblasts, and poor cortical as well as trabecular bone architecture in animals (Bradley, et al., 2013 ; Razidlo, et al., 2010). HDAC3 is also involved in intramembrane bone development. Loss of HDAC3 in the neural crest cells resulted in severe craniofacial malformations, including microcephaly, cleft palate, impaired bone formation in the skull, and hypoplasia of the teeth (Singh, et al., 2013). Similarly, HDAC3 conditional knockout mice in osterix−expressing progenitor cells resulted decreases in calvarial bone thickness and density (Razidlo, et al., 2010). The global deletion of the HDAC8 gene in mice leads to perinatal lethality due to altered cranial and facial features, and this is phenocopied by the conditional deletion of HDAC8 in cranial neural crest cells (Haberland, et al., 2009). Both, HDAC3 and 8 are transcriptional co−repressors of several transcription factors ; therefore, the suppression of HDAC3 in preosteoblasts reduces matrix mineralization and the expression levels of several genes that target Runx2 (Schroeder et al., 2004). HDAC8 represses the aberrant expression of homeobox transcription factors, specifically, orthodenticle homeobox 2 (Otx2) and LIM homeobox 1(Lhx1), essential for proper head development (Haberland, et al., 2009). Taken together, HDAC1, 2, and 3 play important roles in bone development via Runx2 activation. HDAC8 contributes to normal bone formation via its inhibitory effect on the aberrant expression of homeobox proteins.

b. Class II HDACs (HDAC4, HDAC5, HDAC6, and HDAC7)

Class II HDACs mainly contribute to endochondral bone development. Unlike the class I HDACs, germline deletion of most class II HDACs does not cause embryonic lethality but results in some level of functional redundancy. HDAC4 deficiency leads to premature endochondral ossification resulting in skeletal defects such as vertebrae body fusion, decrease in the length of the long bone, and premature skull ossification (Vega, et al., 2004). Although HDAC5 knockout mice showed no abnormal structures or growth defects, they presented with reduced trabecular bone density at 2−3 months of age, despite modest increases in the rates of bone formation (Obri, et al., 2014). The genetic deletion of murine HDAC6 modestly increased the density of the cancellous bone (Zhang, et al., 2008 ; Westendorf, et al., 2002). Postnatal deletion of HDAC7 in the same population of chondrocytes led to an expansion of the proliferative zone, narrowing of the hypertrophic zone, reduction in femur lengths, and decrease in trabecular bone density (Bradley, et al., 2015a). Class II HDACs have low intrinsic deacetylase activity and work through functional complexes involving a class I HDAC. All class II HDACs have been shown to deacetylase Runx2 thereby, repressing its transcriptional activity, decreasing osteoblast differentiation, and promoting osteoclastogenesis (Table 1) (Kang, et al., 2005 ; Westendorf, et al., 2002 ; Jensen, et al., 2008).

c. Class III HDACs (Sirt1 and Sirt6)

Class III HDACs, Sirt1 and Sirt6, play important roles in endochondral ossification. The activation of Sirt1 in mesenchymal stem cells promotes osteogenic differentiation, essential for endochondral ossification (Barter, et al., 2012). Germline Sirt1 deficiency increased p53−mediated apoptosis and produced severe developmental defects, including shorter stature, craniofacial abnormalities, increased cartilage apoptosis, and reduced endochondral ossification and cortical thickness in mice (Cheng, et al., 2003). Sirt6 facilitates endochondral ossification by controlling chondrocyte proliferation and differentiation. Sirt6 knock out mice displayed growth retardation shortly after birth, failed to thrive, and died at around 3.5 weeks of age due to genomic instability and degeneration of multiple organs (Mostoslavsky, et al., 2006). Although Sirt1 and Sirt6 have been shown to play important roles in bone development, the involvement of the other types of Sirts remains to be elucidated.

Involvement of histone deacetylase inhibitors (HDACis) in osteogenesis

HDACis affect many cellular properties, such as the cell cycle, Progression proliferation rates, gene expression, differentiation potential, accumulation of reactive oxygen species, and changes in cell death pathways (Khan & La

Thangue, 2012 ; Conte & Altucci, 2012 ; Dawson & Kouzarides, 2012). Attempts to apply HDACis for the regeneration of different tissues, such as cardiac, neural/nervous, dental, liver, and cartilaginous tissues, have been made (Ohtani & Dimmeler, 2011 ; Hsieh, et al., 2004 ; Duncan, 2011, 2012 ; Kurinna, et al., 2011 ; Hong, et al., 2009). Among them, the involvement of HDACis in bone regeneration is well documented (Boer, et al., 2006 ; Cho et al., 2005 ; Huynh et al., 2016, 2017). The osteogenic differentiation of different cell types is accelerated by several types of HDACis including sodium butyrate (NaB), valproic acid (VPA), trichostatin A (TSA), suberoylanilide hydroxamic acid (SAHA), and Benzamide (MS−275) (Fig. 1 ; Table 2). NaB promoted osteoblast bone formation by enhancing the activities of Runx2 and ALP in vitro (Iwami & Moriyama, 1993) ; the effects of NaB on the osteoblastic cell line and periodontal ligament fibroblast were reported for the first time in this study. Similarly, VPA and TSA enhanced osteogenic differentiation with the upregulation of several osteoblast marker genes (Lee, et al., 2006, 2009 ; Cho, et al., 2005 ; Xu, et al., 2009, 2013 ; Jeon, et al., 2006). SAHA, another pan HDACi, promoted mineralization and migration in primary osteoblasts by inducing the expression and activity of metalloproteinase (MMP)−13 (Duncan, et al., 2016). In addition, MS−275 has been found to stimulate bone formation by inducing the transcription of tissue−nonspecific alkaline phosphatase (TNAP) (Kim, et al., 2011). Together, these data indicate that the suppression of HDAC activity with these HDACis sufficiently promote the osteogenic differentiation of several cells via the upregulation of various transcription−related proteins, which may distinct roles during this process.

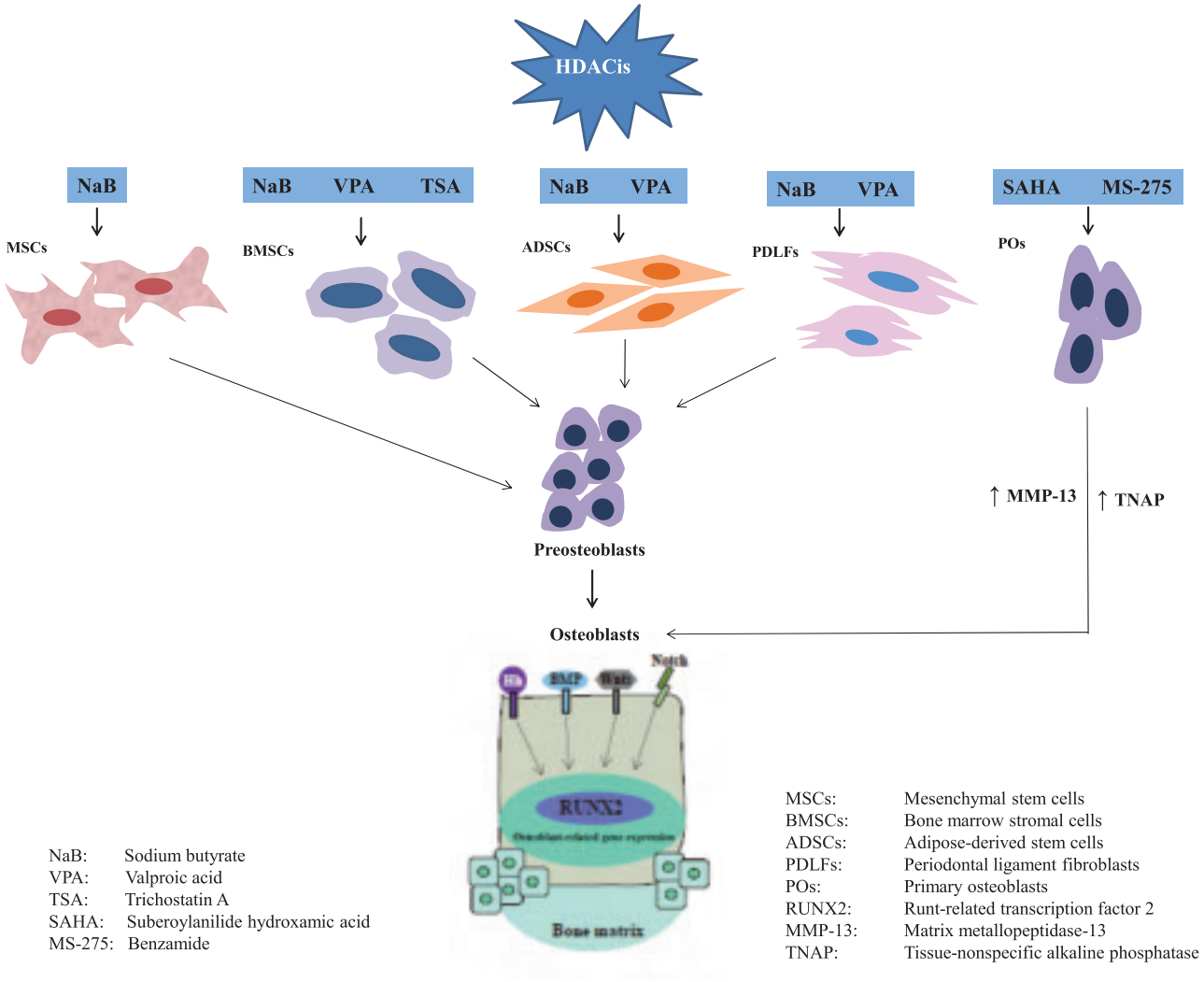

Fig 1 : Schematic representation showing role of HDACis on several cells for osteogenesis

Table 2 : The role of HDAC inhibitors (HDACis) on osteogenesis

Inhibitor	Targeted cell	Mechanism of action	Effect	References
NaB	Cloned osteoblastic cell lines Periodontal ligament fibroblasts	Increased ALP activity	Enhancement of bone formation	Iwami & Moriyama, 1993
	Primary bone marrow cells Rat osteosarcoma cells Calvaria cells	Increased the expression of Runx2, OC and ALP	Osteogenesis	Lee, et al, 2006, 2009
	Adipose-derived stromal cells	Decreased oxygen tension	Osteogenesis	Xu, et al., 2009
VPA	Adipose cells Bone marrow stromal cells	Increased the expression of Runx 2, OSX, OPN, BMP2 and ALP	Osteogenic differentiation	Cho, et al., 2005 Jeon, et al., 2006
	Adipose-derived stromal cells	Decreased oxygen tension	Osteogenesis	Xu, et al., 2009
	Dental pulp stem cells	Increase OC, BSP, OPN	Osteogenesis	Shen, et al., 2002
TSA	Primary bone marrow cells Rat osteosarcoma cells Calvaria cells	Increased the expression of Runx2, OC and ALP	Osteogenesis	Lee, et al, 2006, 2009
	Bone marrow stromal cells	Increased the expression of Runx2 and ALP	Osteogenic differentiation	Cho, et al., 2005
	Human periodontal ligament cells	Increased the expression of Runx2	Osteogenesis and enhanced mineral deposition	Huynh, et al., 2016
SAHA	Primary osteoblasts	Increased MMP-13	Osteogenesis	Duncan, et al., 2016
MS-275	Primary osteoblast precursors	Increased TNAP	Osteoblast bone formation	Kim, et al., 2011

NaB : sodium butyrate ; VPA : valproic acid ; TSA : Trichostatin A ; SAHA : suberoylanilide hydroxamic acid ; MS-275 : benzamide ; ALP : alkaline phosphatase ; Runx2 : runt-related transcription factor 2 ; OC : osteocalcin ; OSX : osterix ; OPN : osteopontin ; BMP2 : bone morphogenetic protein 2 ; BSP : bone sialoprotein ; MMP-13 : matrix metallopeptidase ; TNAP : tissue-nonspecific alkaline phosphatase.

Possible clinical applications of histone deacetylase inhibitors (HDACis) for bone regeneration

To date, four HDACis have been approved by the United States Food and Drug Administration (US FDA) for the following anti-cancer drugs : Vorinostat, Romidepsin, Belinostat, and Panobinostat. Vorinostat (SAHA ; trade name, Zolinza®) is a linear hydroxamate compound that was approved for the treatment of cutaneous T-cell lymphoma (CTCL) (Mann, et al., 2007). Romidepsin (FK228 or depsipeptide ; trade name, Istodax®) is a cyclicpeptide HDACi that was originally approved for the treatment of CTCL by the US FDA ; subsequently, its use was extended for the treatment of peripheral T-cell lymphoma (PTCL) (Whittaker, et al., 2010). A third FDA approval was given for the HDACi Belinostat (PXD 101 ; trade name, Beleodaq®), which is a hydroxamic acid compound licensed for the treatment of relapsed or refractory PTCL. Like the other two FDA-approved HDACis, Belinostat is in the clinical trial phase for solid tumors (Poole, 2014). Panobinostat (LBH-589 ; trade name, Farydak®) is the most recently approved HDACi (Oki, et al., 2013) and was licensed for the treatment of multiple myeloma. Additionally, more than five HDACis are in phase III clinical trials, including repositioning of already approved HDACis (Jeon, et al., 2006). In addition to cancer treatment, the use of HDACis has been evaluated in various non-cancer diseases including neurodegenerative disease, inflammatory disease, osteoporosis, cardiovascular disease, HIV, and neurological diseases (Choi & Mostoslavsky, 2014 ; Dinarello, et al., 2011 ; Falkenberg & Johnstone, 2014 ; Lakshmaiah, et al., 2014). Some HDACis have been used for the treatment of experimentally-induced osteoporosis and fractures, and have successfully promoted bone regeneration in animal models (Boer et al., 2006 ; McGee-Lawrence & Westendorf, 2011). Thus, they may be applied for bone regeneration as a clinically secure drug.

Conclusion

Recently, it has been demonstrated that HDACis can improve tissue engineering strategies. Bone tissue engineering has found early success in studies combining mesenchymal stem cells (MSCs) with HDACis ; therefore, there is a potential to translate this research into the clinical settings. Presently, researchers aim to combine scaffolds with growth factors, suitable cells, and environmental stimuli to generate functional tissue, such as bone and dentin in hard tissue regeneration region. This review shows that HDACis could be utilized as chemical cues to improve the efficacy of current tissue engineering techniques.

References

Barter MJ, Bui C & Young DA. Epigenetic mechanisms in cartilage and osteoarthritis : DNA methylation, histone modifications and microRNAs. Osteoarthritis Cartilage 20 (5) : 339−349, 2012.

Boer J, Licht R & Bongers M. Inhibition of histone acetylation as a tool in bone tissue engineering. Tissue Eng. 12 : 2927–2937, 2006.

Bradley EW, Carpio LR & Westendorf JJ. Histone deacetylase 3 suppression increases PH domain and leucine−rich repeat phosphatase (Phlpp) 1 expression in chondrocytes to suppress Akt signaling and matrix secretion. J Biol Chem 288 : 9572–9582, 2013.

Bradley EW, Carpio LR, Olson EN & Westendorf JJ. Histone deacetylase 7 (Hdac7) suppresses chondrocyte proliferation and beta−catenin activity during endochondral ossification. J Biol Chem 290 : 118–126, 2015.

Buchwald M, Kramer OH & Heinzel T. HDACi–targets beyond chromatin. Cancer Lett 280(2) : 160−167, 2009.

Candido EP, Reeves R & Davie JR. Sodium butyrate inhibits histone deacetylation in cultured cells. Cell 14(1) : 105−113, 1978.

Cheng HL, Mostoslavsky R, Saito S, Manis JP, Gu Y, Patel P, Bronson R, Appella E, Alt FW &Chua KF. Developmental defects and p53 hyperacetylation in Sir2 homolog (SIRT1)−deficient mice. Proc Natl Acad Sci 100 : 10794–10799, 2003.

Chin SP, Dickinson JL & Holloway AF. Epigenetic regulation of prostate cancer. Clin Epigenet 2 (2) : 151−169, 2011.

Cho HH, Park HT, Kim YJ, Bae YC, Suh KT & Jung JS. Induction of osteogenic differentiation of human mesenchymal stem cells by histone deacetylase inhibitors. J Cell Biochem 96(3) : 533–542, 2005.

Choi JE & Mostoslavsky R. Sirtuins, metabolism, and DNA repair. Curr Op in Genet Dev 26C : 24 –32, 2014.

Chuang DM, Leng Y, Marinova Z, Kim HJ & Chiu CT. Multiple roles of HDAC inhibition in neurodegenerative conditions. Trends Neurosci 32(11) : 591−601, 2009.

Conte M & Altucci L. Molecular pathways : the complexity of the epigenome in cancer and recent clinical advances. Clin Cancer Res, 18 : 5526−5534, 2012.

Dawson MA & Kouzarides T. Cancer epigenetics : from mechanism to therapy. Cell 150(1) : 12−27, 2012.

Destaing O, Saltel F, Gilquin B, Chabadel A, Khochbin S, Ory S & Jurdic P. A novel Rho−mDia2−HDAC6 pathway controls podosome patterning through microtubule acetylation in osteoclasts. J Cell Sci 118 (13) : 2901−2911, 2005.

de Ruijter AJ, van Gennip AH, Caron HN, Kemp S & van Kuilenburg AB. Histone deacetylases (HDACs) : characterization of the classical HDAC family. Biochem J 370 : 737−749, 2003.

Dinarello CA, Fossati G & Mascagni P. Histone deacetylase inhibitors for treating a spectrum of diseases not related to cancer. Mol Med 17 : 333–352, 2011.

Dou C, Li N, Ding N, Liu C, Yang X, Kang F, Cao Z, Quan H, Hou T, Xu J & Dong S. HDAC2 regulates FoxO 1 during RANKL－induced osteoclastogenesis. Am J Physiol Cell Physiol 310(10) : C780−7, 2016.

Dudakovic A, Evans JM, Li Y, Middha S, McGee−Lawrence ME, van Wijnen AJ, Westendorf JJ. Histone deacetylase inhibition promotes osteoblast maturation by altering the histone H4 epigenome and reduces Akt phosphorylation. J Biol Chem 288(40) : 28783−91, 2013.

Duncan HF, Smith AJ, Fleming GJ & Cooper PR. HDACi : cellular effects, opportunities for restorative dentistry. J Dent Res 90 : 1377–1388, 2011.

Duncan HF, Smith AJ, Fleming GJP & Cooper PR. Histone deacetylase inhibitors induced differentiation and accelerated mineralization of pulp derived cells. J Endod 38 : 339–345, 2012.

Duncan HF, Smith AJ, Fleming GJ, Partridge NC, Shimizu E, Moran GP, Cooper PR. The histone−deacetylase−inhibitor suberoylanilide hydroxamic acid promotes dental pulp repair mechanisms through modulation of matrix metalloproteinase−13 activity. J Cell Physiol 231 (4), 798 –816, 2016.

Falkenberg KJ & Johnstone RW. Histone deacetylases and their inhibitors in cancer, neurological diseases and immune disorders. Nat Rev Drug Discov13 : 673–691, 2014.

Gibney ER & Nolan CM. Epigenetics and gene expression. Heredity 105 : 4−13, 2010.

Haberland M, Mokalled MH, Montgomery RL & Olson EN. Epigenetic control of skull morphogenesis by histone deacetylase 8. Genes Dev 23 : 1625–1630, 2009.

Hong S, Derfoul A, Pereira−Mouries L & Hall D J. A novel domain in histone deacetylase 1 and 2 mediates repression of cartilage−specific genes in human chondro-

cytes. FASEB J 23, 3539–3552, 2009.

Hsieh J, Nakashima K, Kuwabara T, Mejia E & Gage FH. Histone deacetylase inhibition− mediated neuronal differentiation of multipotent adult neural progenitor cells. Proc Natl Acad Sci 101, 16659–16664, 2004.

Huynh NC, Everts V, Pavasant P & Ampornaramveth RS. Inhibition of histone deacetylases enhances the osteogenic differentiation of human periodontal ligament cells. J Cell Biochem 117(6) : 1384−1395, 2016.

Huynh NC, Everts V, Nifuji A, Pavasant P & Ampornaramveth RS. Histone deacetylase inhibition enhances in −vivo bone regeneration induced by human periodontal ligament cells. Bone 95 : 76−84, 2017.

Iwami K & Moriyama T. Effects of short chain fatty acid, sodium butyrate, on osteoblastic cells and osteoclastic cells. Int J Biochem 25 : 1631–1635, 1993.

Jensen ED, Schroeder TM, Bailey J, Gopalakrishnan R & Westendorf JJ. Histone deacetylase 7 associates with Runx2 and represses its activity during osteoblast maturation in a deacetylation−independent manner. Journal of Bone and Mineral Research 23(3) : 361−372, 2008.

Jeon EJ, Lee KY, Choi NS, Lee MH, Kim HN, Jin YH, Ryoo HM, Choi JY, Yoshida M, Nishino N, Oh BC, Lee KS, Lee YH, Bae SC. Bone morphogenetic protein−2 stimulates Runx2 acetylation. J Biol Chem 281 : 16502−16511, 2006.

Jones PA, Issa JP & Baylin S. Targeting the cancer epigenome for therapy. Nat Rev Genet 17(10) : 630−641, 2016.

Kang JS, Alliston T, Delston R, Derynck R. Repression of Runx2 function by TGF−beta through recruitment of class II histone deacetylases by Smad3. Embo J 24 : 2543−2555, 2005.

Khan O & La Thangue NB. HDAC inhibitors in cancer biology : emerging mechanisms and clinical applications. Immunol Cell Biol 90(1) : 85−94, 2012.

Kim HN, Lee JH, Bae SC, Ryoo HM, Kim HH, Ha H & Lee ZH. Histone deacetylase inhibitor MS−275 stimulates bone formation in part by enhancing Dhx36−mediated TNAP transcription. J bone Miner Res 26 : 2161−2173, 2011.

Komatsu Y, Tomizaki KY, Tsukamoto M, Kato T, Nishino N, Sato S, Yamori T, Tsuruo T, Furumai R, Yoshida M, Horinouchi S & Hayashi H. Cyclic hydroxamic−acid−containing peptide 31, a potent synthetic histone deacetylase inhibitor with antitumor activity. Cancer Res 61(11) : 4459−4466, 2011.

Kurinna S & Barton MC. Cascades of transcription regulation during liver regeneration. Int J Biochem. Cell Biol 43 : 189–197, 2011.

Lagger G, O'Carroll D, Rembold M, Khier H, Tischler J, WeitzerG, Schuettengruber B, Hauser C, Brunmeir R & Jenuwein T. Essential function of histone deacetylase 1 in proliferation control and cdk inhibitor repression. EMBO J 21 : 2672–2681, 2002.

Lakshmaiah KC, Jacob LA, Aparna S, Lokanatha D & Saldanha SC. Epigenetic therapy of cancer with histone deacetylase inhibitors. J Cancer Res Ther 10 : 469 – 478, 2014.

Lee HW, Suh JH, Kim AY, Lee YS, Park SY & Kim JB. Histone deacetylase 1−mediated histone modification regulates osteoblast differentiation. Mol Endocrinol 20 : 2432–2443, 2006.

Lee S., Park J.R., Seo M.S., Roh K.H., Park S.B., Hwang J.W., Sun B., Seo K., Lee Y.S., Kang S.K., Jung J.W., Kang K.S. Histone deacetylase inhibitors decrease proliferation potential and multilineage differentiation capability of human mesenchymal stem cells. Cell Prolif 42(6) : 711–720, 2009.

Mann BS, Johnson JR, Cohen MH, Justice R &Pazdur R. FDA approvalsummary : vorinostat for treatment of advanced primarycutaneous T−cell lymphoma. Oncologist 12 : 1247−1252, 2007.

McGee−Lawrence ME & Westendorf JJ. Histone deacetylases in skeletal development and bone mass maintenance. Gene 474 : 1–11, 2011.

Montgomery RL, Potthoff MJ, Haberland M, Qi X, Matsuzaki S, Humphries KM, Richardson JA, Bassel−Duby R & Olson EN. Maintenance of cardiac energy metabolism by histone deacetylase 3 in mice. J Clin Invest 118 : 3588–3597, 2008.

Mostoslavsky R, Chua KF, Lombard DB, Pang WW, Fischer MR, Gellon L, Liu P, Mostoslavsky G, Franco S, Murphy MM, Mills KD, Patel P, Hsu JT, Hong AL, Ford E, Cheng HL, Kennedy C, Nunez N, Bronson R, Frendewey D, Auerbach W, Valenzuela D, Karow M, Hottiger MO, Hursting S, Barrett JC, Guarente L, Mulligan R, Demple B, Yancopoulos GD & Alt FW. Genomic instability and aging−like phenotype in the absence of mammalian SIRT6. Cell 124 : 315–329, 2006.

Obri A, Makinistoglu MP, Zhang H & Karsenty G. HDAC 4 integrates PTH and sympathetic signaling in osteoblasts. J Cell Biol 205 : 771–780, 2014.

Ohtani K & Dimmeler S. Epigenetic regulation of cardiovascular differentiation. Cardiovasc Res 90 : 404－412, 2011.

Oki Y, Buglio D, Fanale M, Fayad L, Copeland A, Romaguera J, Kwak LW, Pro B, de Castro Faria S, Neelapu S, Fowler N, Hagemeister F, Zhang J, Zhou S, Feng L, Younes A. Phase I study of panobinostat plus everolimus in patients with relapsed or refractory lymphoma. Clin Cancer Res 19(24) : 6882−90, 2013.

Peschansky VJ & Wahlestedt C. Non−coding RNAs as direct and indirect modulators of epigenetic regulation. Epigenetics 9(1), 3−12, 2014.

Poole RM. Belinostat : first global approval. Drugs 74 : 1543−1554, 2014.

Razidlo DF, Whitney TJ, Casper ME, McGee－Lawrence ME, Stensgard BA, Li X, Secreto FJ, Knutson SK, Hiebert SW &Westendorf JJ. Histone deacetylase 3 depletion in osteo/chondroprogenitor cells decreases bone density and increases marrow fat. PloS One 5 : e11492, 2010.

Schroeder TM & Westendorf JJ. Histone deacetylase inhibitors promote osteoblast maturation. J Bone Miner Res 20(12) : 2254–2263, 2005.

Schroeder TM, Kahler RA, Li X & Westendorf JJ. Histone deacetylase 3 interacts with runx2 to repress the osteocalcin promoter and regulate osteoblast differentiation. J Biol Chem 279(40) : 41998−42007, 2004.

Shen J, Montecino M, Lian JB, Stein GS, Van Wijnen AJ, Stein JL. Histone acetylation in vivo at the osteocalcin locus is functionally linked to vitamin D－dependent, bone tissue－specific transcription. J Biol Chem 277 (23) : 20284–20292, 2002.

Singh N, Gupta M, Trivedi CM, Singh MK, Li L & Epstein JA. Murine craniofacial development requires Hdac3 −mediated repression of Msx gene expression. Dev Biol 377 : 333–344, 2013.

Trivedi CM, Luo Y, Yin Z, Zhang M, Zhu W, Wang T, Floss T, Goettlicher M, Noppinger PR, Wurst W, Ferrari VA, Abrams CS, Gruber PJ & Epstein JA. Hdac2 regulates the cardiac hypertrophic response by modulating Gsk 3 beta activity. Nat Med 13 : 324–331, 2007.

van Bokhoven H. Genetic and Epigenetic Networks in Intellectual Disabilities. Annu. Rev. Genet. 45 : 81－104, 2011.

Vega RB, Matsuda K, Oh J, Barbosa AC, Yang X, Meadows E, McAnally J, Pomajzl C, Shelton JM, Richardson JA, Karsenty G & Olson EN. Histone deacelytase 4 controls chondrocyte hypertrophy during skeletogenesis. Cell 119 : 555−566, 2004.

Westendorf JJ, Zaidi SK, Cascino JE, Kahler R, van Wijnen AJ, Lian JB, Yoshida M, Stein GS, Li X. Runx2 (Cbfa1, AML−3) interacts with histone deacetylase 6 and represses the p21(CIP1/WAF1) promoter. Mol Cell Biol 22 : 7982–7992, 2002.

Whittaker SJ, Demierre MF, Kim EJ, Rook AH, Lerner A, Duvic M, Scarisbrick J, Reddy S, Robak T, Becker JC, Samtsov A, McColloch W, Kim YH. Final results from a multicenter, international, pivotalstudy of romidepsin in refractory cutaneous T−cell l ymphoma. J Clin Oncol 28 : 4485−4491, 2010.

Xu Y, Hammerick KE, James AW, Carre AL, Leucht P, Giaccia AJ & Longaker MT. Inhibition of histone deacetylase activity in reduced oxygen environmentenhances the osteogenesis of mouse adipose−derived stromal cells. Tissue Eng A(12) : 3697–3707, 2009.

Xu S, De Veirman K, Evans H, Santini GC, Vande Broek I, Leleu X, De Becker A, Van Camp B, Croucher P, Vanderkerken K & Van Riet. Effect of the HDAC inhibitor vorinostat on the osteogenic differentiation of mesenchymal stem cells in vitro and bone formation in vivo. Acta Pharmacol Sin 34(5) : 699−709, 2013.

Yoshida M, Kijima M, Akita M & Beppu T. Potent and specific inhibition of mammalian histone deacetylase both in vivo and in vitro by trichostatin A. J Biol Chem. 5 ; 265(28) : 17174−17179, 1990.

Zhang Y, Kwon S, Yamaguchi T, Cubizolles F, Rousseaux S, Kneissel M, Cao C, Li N, Cheng HL, Chua K, Lombard D, Mizeracki A, Matthias G, Alt FW, Khochbin S & Matthias P. Mice lacking histone deacetylase 6 have hyperacetylated tubulin but are viable and develop normally. Mol Cell Biol 28 : 1688–1701, 2008.

Shamima SULTANA

2010 : Bachelor of Dental Surgery (BDS), Pioneer Dental College & Hospital, Bangladesh

2011 : Visiting Researcher, Division of Clinical Cariology and Endodontology, School of Dentistry, Health Sciences University of Hokkaido, Japan.

2013 : Ph.D Fellow, Division of Clinical Cariology and Endodontology, School of Dentistry, Health Sciences University of Hokkaido, Japan.