Review Article

CMJ

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The Role of Histone Acetylation in Mesenchymal Stem Cell Differentiation

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The mechanism and action concerning epigenetic modifications, especially that of histone modifications, are not fully understood. However, it is clear that histone modifications play an essential role in several biological processes that are involved in cell proliferation and differentiation. In this article, we focused on how histone acetylation may result in differentiation into mesenchymal stem cells as well as histone acetylation function. Moreover, histone acetylation followed by the action of histone deacetylase inhibitors, which can result in the differentiation of stem cells into other types of cells such as adipocytes, chondrocytes, osteocytes, neurons, and other lineages, were also reviewed.

Key Words: *Mesenchymal Stem Cell; Cell Differentiation; Histone Acetylation; Epigenesis, Genetic*

Article History:
Received November 29, 2021
Revised December 27, 2021
Accepted December 29, 2021

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INTRODUCTION

Epigenetic modifications are one of the primary mechanisms causing early programming of cell proliferation, differentiation, death, and disease. Mesenchymal stem cells (MSCs) differentiation through epigenetic manipulation into specialized cells has the potential to advance the field of regenerative medicine through several tissue engineering processes. Several studies support the involvement of epigenetic mechanisms through gene expression control, stem cell self-renewal and lineage fate determination. During differentiation into a particular lineage, the specific genes of this lineage undergo active transcription. Consequently, the genes responsible for self-renewal and pluripotency are repressed. This on-off mechanism is associated with posttranslational modifications, especially histone acetylation/methylation and promoter DNA methylation. These epigenetic modifications are critical for regulating gene expression, and several researchers have shifted their focus to one or the other.

HISTONE MODIFICATION

Chromatin is an instructive DNA scaffold that can regulate several functional features of DNA and plays a vital role in histone modification. Histone modifications exert their function through specific enzymes, and different enzymes modify different sites (based on specificity at the enzyme's active site) or have different functions. For example, Gcn5 and p300-CBP acetylate H3K9/H3K27 sites, Ezh2 methylates H3K27 sites, and Suv39h1 plays a role in H3K9 methylation. The enzyme, DNA methyltransferase (DNMT)-1, is responsible for maintenance of DNA methylation, and DNMT3a/b is responsible for *de novo* DNA methylation.[1,2] However, it remains unclear which specific enzymes are involved in MSC differentiation and how these enzymes interact with one another.

1. Histone acetylation and methylation

Histone acetylation was first reported by Allfrey et al.[3] in 1964, who suggested that histones are post-translationally modified. The acetylation of lysine residues is highly dynamic and regulated by the opposing action of two families of enzymes, i.e., histone acetyltransferases (HATs) and histone deacetylases (HDACs).

There are two general categories of HATs in humans: Type A HATs are nuclear and acetylate nucleosomal histones and other chromatin-associated proteins. Examples of type A HATs are the GCN5-related N-acetyltransferase family, Moz-Ybf2/Sas3-Sas2-Tip60 family, and p300/CREB-

https://doi.org/10.4068/cmj.2022.58.1.6

binding protein (CBP/CREBBP) family.[4] Typically, each of these enzymes modifies multiple sites within the histone N-terminal tails. Type B HATs are located in the cytoplasm and acetylates the newly synthesized histone H4 at K5 and K12, where this pattern of acetylation is important for deposition of the histones. Additionally, type B HATs share sequence homology with scHat1 and have no direct impact on transcription.[5]

HDAC inhibitors are a class of compounds that increase acetylation of lysine residues on histone proteins as well as other, nonhistone, proteins by inhibiting the activity of HDAC enzymes. HDACs contain the presence of cellular and target proteins involved in cancer progression, apoptosis, cell cycle control, angiogenesis, and cell invasion. This is corroborated by HDAC inhibitors that show involvement in the activation of the apoptotic pathway, cell cycle arrest, and apoptotic induction via the extrinsic (death receptor) pathway or the intrinsic (mitochondrial) pathway, both of which lead to caspase activation and cell death induction. HDAC inhibitors can induce cell cycle arrest at G1/S or G2/M transcription, resulting in differentiation and/or apoptosis.

Histone methyltransferase (HMT) are histone-modifying enzymes involved in inhibiting gene expression and heterochromatin formation. Previous studies have reported that HMTs interact with HATs at the H3K9 site and affect histone methylation levels in this region. It has been indicated that histone methylation is a vital part of epigenetic modification interactions. DNA methylation is best known for its role in gene silencing for it can alter gene expression without changing a given gene's base sequence. Among epigenetic mechanisms, post-translational histone modification plays a central role and are brought about by a series of 'writing' and 'erasing' events by histone-modifying enzymes.[2,6,7]

2. Histone modifying enzymes; writers, erasers, and readers

A wide range of post-translational modifications (PTMs) primarily targeting amino acids within the N-terminal tails of histone proteins occurs, including phosphorylation, acetylation, methylation, ubiquitination, SUMOylations, and GlcNAcylation. Governance of chromatin structure through histone PTMs has emerged as an essential driver of transcriptional responses in numerous cells. Like histone writers, erasers, and readers, the protein machinery that adds, removes, or recognizes PTMs has become revolutionary in our understanding of physiological responses.[8] In this review, we summarize how histone acetylation or methylation are regulated by histone acetyltransferases or methyltransferases (writers), deacetylases or demethylases (erasers), and domain-containing proteins (readers), as depicted in Table 1.

1) Writers

Writers are enzymes that add PTMs to histones and are divided into classes based on the specific PTM, HATs, and HMTs. In humans, there are three major families of HATs: the Gcn5-related N-acetyltransferase family (GNAT), the MYST family (MOZ, YbF2, Sas2, TIP60), and the orphan family (DBP/EP300 and nuclear receptors), whose structure and mechanism of action are elaborated by Marmorstein and Zhou[9] in a paper published in 2014. In general, HATs function as components within a diverse set of multiprotein complexes that target promoters and enhancers in order to regulate specific transcriptional responses.

In 1999, Allis's group first reported a link between histone methylation and DNA transcription,[10] and discovered and identified specific HMTs the following year.[11] There are several families of HMTs, such as the SET family, which has a SET domain or non-SET domain-containing methyltransferases, and SUV39, which was the first protein identified in the SET family. Modifications associated with active transcription include di- or tri-methylation of H3K4 (H3K4me2, H3K4me3) and mono-methylation of H3K9 (H3K9me1). However, di- and tri-methylation of H3K9 (H3K9me2, H3K9me3), as well as H3K27 (H3K27me2, H3K27me3), are repressive markers. Unlike histone acetylation, histone methylation can be linked to either transcriptional repression or activation depending on the context and extent of methylation.[8,12]

2) Erasers

Similar to writers, erasers are enzymes that remove specific PTMs from histone substrates. Erasers are classified on HDACs and histone demethylases. Currently, 18 mammalian HDACs have been identified and categorized into four major classes: Class I: HDACs 1, 2, 3, and 8; class IIa: HDACs 4, 5, 7, and 9; and class IIb: HDACs 6 and 10. The sirtuins comprise class III, and HDAC 11 comprising the sole HDAC in class IV. Identify the HDAC component molecules as well as understanding their activity is essential in for their emergence as a potential therapeutic strategy for treatment of disease, including cancer, immune disorders, and heart disease.[8,13,14]

Histone demethylases play regulatory roles in transcription for demethylation of histones, including the Jumonji C family, JHMD1, JMJD3, and JMJD2D. Similar to HDACs, small molecular inhibitors of demethylase activity are being developed for use as potential therapeutics to modulate DNA transcription in disease.[8,15,16]

3) Readers

Readers are dedicated protein factors that recognize either specific post-translational marks on histones or a combination of marks and histone variants to direct a particular transcriptional outcome. Just as the function of histone PTM is carried out by writers and erasers, their actions that govern DNA transcription are mediated by readers. They have domains, which have a high affinity for sites of histone methylation, chromo, Tudor, MBT, or acetylation Bromo. These domains are located within the chromatin modifying proteins and respond to histone PTMs. In addition, both the chromatin remodeler complex switching defective/sucrose non-fermenting (SWI/SNF) and the bromodomain and extra-terminal domain (BET) families are examples of readers.[17,18]

TABLE 1. Summary of principal writer, eraser, and reader protein for histone acetylation and methylation in mesenchymal stem cells

Family	Activity	Major catalytic site	Major classes	Representative member	Classic inhibitors
Writers					
Histone acetyltransferase	Catalyze histone acetylation	H3K9/K14/K56, H4K5/K8/K16, H3AK5	(1) Gcn5/PCAF (2) MYST (3) p300/CBP (4) Rtt109	P300/CBP, Tip60, Gcn5, ELP3, HAT1, MYST	Acetyl-CoA derivatives, anacardic acid, curcumin
Histone methyltransferase	Catalyze histone methylation	H3K4/K9/K27/K 35/K79. H4K20, H3R8	(1) SUV39 (2) SET1 (3) SET2 (4) RIZ (5) PRMTs	DOT1L, EZH2, SUV39H1, SUV4-20, SMYD	EPZ00477, GSK343, UNC1999
Erasers					
Histone deacetylases	Catalyze histone deacetylation	H3K9/K14, H4K5/K12/K8	(1) HDACI (2) HDACII (3) HDACIII (4) HDACIV	HDAC1,2,3,8 HDAC5,6,7,9 SIRT1-6 HDAC11	TCA, vorinostat, romidepsin
Histone demethylase	Catalyze histone demethylation	H3K4/K9/K27/ K36/K79, H4K20	(1) Lysine-specific demethylases (2) Jumonji domain-containing demethylase	JMJD2A, KDM5B, KDM2A	Tranylcypromine, GSJ-J1, 8-hydroxyquinolines
Readers					
Bromodomain-containing proteins	Binding the acetylated lysine residue	H3K14, H4K5/K8/K16	Bromodomains	GCN5, Brdt, Rsc4	JQ1, GSJ2801
PHD-containing proteins	Binding the methylated lysine residue, or the acetylated lysine residue	H3K4/K9/K14	PHD domains	RAG2, BHC80, TAF3, Tandem-PHD	
Methyl-lysine-and/ or methyl-arginine-binding domain-containing proteins	Binding the methylated lysine residue, or the methylated arginine residue	H3J4/K9/K23/K2 7/K36/K79, H4K20, H1K26, H3R17, H4R3	(1) Tudor domains (2) MBT domains (3) Chromodomains (4) PWWP domains	53BP1/Crb2, HP1, PHF20L1, TTD, ZF-CW, MBT, DCD	UNC669, UNC1215

HISTONE ACETYLATION IN MESENCHYMAL STEM CELL DIFFERENTIATION

MSCs are emerging as extremely promising therapeutic agents for tissue regeneration and disease, in part because of their multipotent properties and capacity for self-renewal. Several studies have successfully induced MSC differentiation into specialized cells through different methods. However, the molecular mechanism of differentiation remains unclear, which results in low induction efficiency and limits the clinical application of MSCs. Stem cell self-renewal and differentiation require selective action or silencing of specific transcriptional programs in response to environmental cues. This crosstalk between transcriptional factors and epigenetic modulators regulating the chromatin conformation affects stem cell differentiation following specific gene promoters. The epigenetic mechanisms governing MSC identity and fate determination are not well understood and remain an active area of investigation. Furthermore, the enhancement of stem cell differentiation ability is a challenge for type specialization, and it is possible to increase its ability of stem cells through histone modification in basic research and clinical treatment.

Differentiation requires orchestration of numerous parallel cellular responses and altered physiological states associated with the novel cell fate. These changes are induced by environmental cues, such as soluble factors or cell-to-cell connection, that is expected to transduce and translate gene expression.[19,20] Cell differentiation following histone modification requires the coordination of transcriptomic reprogramming and nucleosome remodeling. We summarize how histone regulator act to differentiate into other cell lineages in mesenchymal stem cells (Fig. 1).

1. Cardiomyogenic differentiation

There are several studies regarding cardiomyogenic differentiation of MSCs. In 2009, Feng et al.[21] reported that histone acetylation, not DNA methylation, might be one of the mechanisms of cardiac differentiation of rat MSCs.

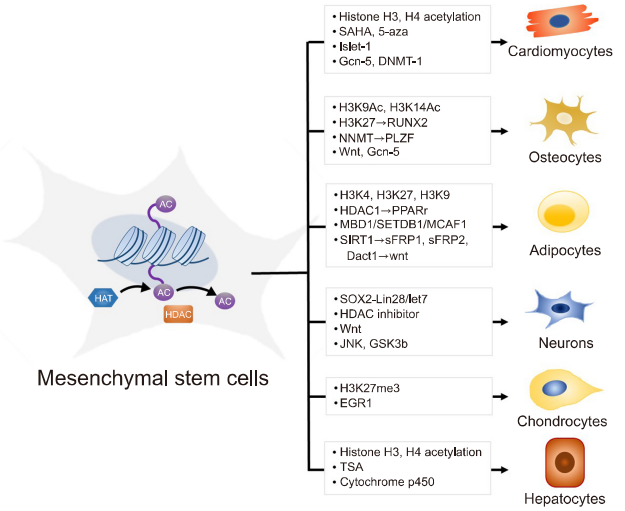

FIG. 1. Role of histone acetylation in MSC differentiation. Histone acetylation is regulated by the histone acetyltransferase (HAT) and histone deacetylase (HDAC) which converts chromatin structures. A variety of histone modifying enzymes is involved in the MSC fate determination with acetylation and methylation of specific catalytic sites through their representative members.

They induced differentiation into cardiomyocyte with suberoylanilide hydroxamic acid (SAHA, a HDAC inhibitor) or 5-azacytidine (5-aza, a DNA methylation inhibitor) and demonstrated that SAHA effectively promoted cardiomyocyte differentiation *in vitro*.[21] In addition, they focused on Gcn, which linked a known transcriptional coactivator with catalytic histone acetyltransferase activity, and determined its importance in differentiating into cardiomyocytes caused by modification of histone H3.[22] Inhibition of HDAC1 or HDAC2 by siRNA targeting increased cardiac-specific gene expression and local enrichment of the level of histone acetylation of H3 and H4 in MSCs, further verifying that HDAC1 and HDAC2 are involved in cardiac differentiation.[23,24]

Recently, several studies reported that Islet-1 induced cardiac differentiation in MSCs. Islet-1 is located in the second heart field and various types of congenital heart disease can be cause by Islet-1 insufficiency.[25,26] Zhu's group investigated that Islet-1 is a main factor in acetylation during heart development and the cardiomyocyte-like differentiation. In addition, Islet-1 upregulated the expression of Gcn5 and enhanced the binding of Gcn5 and promoters; consequently, downregulating DNMT-1 expression.[25-28] In other words, Islet-1 may influence histone acetylation and DNA methylation via Gcn5 and DNMT-1 during differentiation into cardiomyocyte-like cells.

2. Osteogenic differentiation

For long-term cultivation, MSCs in early and late passage were examined for different gene expression; the osteogenic genes increased, while the stemness genes, such as Oct4 and Sox2, declined markedly. Several studies have reported that histone acetylation levels, specially histone H3 acetylation in K9 and K14 and gene promoter DNA methylation, are essential to regulate osteogenic differentiation.[29-31] In addition, valproic acid (VPA), a HDAC inhibitors, promoted the level of histone H3 lysine 9 acetylation (H3K9Ac) and the expression of osteogenesis-related genes, including Runx2, Osterix, osteocalcin, osteopontin, and likalinephosphate, and induced the regulation of Runx2 activity.[32,33] Following the study by Fani et al.,[34] chromatin immunoprecipitation results showed significant changes in the H3K9Ac on regulatory regions of stemness (Nanog, Sox2, Rex1), osteogenic (Runx2, OC, Sp7), and adipogenic (PPARγ, Lpl, adiponection) marker genes between undifferentiated and differentiated cells. In addition, adrenaline inhibited osteogenic differentiation by reducing miRNA-21 expression and enhancing RUNX2, OSX, OCN, and OPN expression in hMSCs.[35] Recently, Fu et al.[36] reported that c-Jun signaling could help facilitate acetylation of H3K27, which has acetyltransferase p300 to RUNX2 promoter, during osteogenic differentiation.

Zhou's group reported that the histone H3K9 acetyltransferase, PCAF has an essential role in osteogenic differentiation of MSCs and controlled BMP signaling both *in vitro* and *in vivo*, especially aged mice.[37] In addition, the activity between histone acetylation and Wnt genes, especially, Wnt1, Wnt6, Wnt10a, and Wnt10b, increased Gcn5 and promoted osteogenic differentiation.[38] These results might represent a therapeutic target for stem cell-based regenerative medicine and the treatment of disease.

Last year, Hansen's group revealed that the activation of the PLZF transcription factors encoded by ZBTB16 plays a role in osteogenic differentiation at the pre-osteoblast stage and is influences H3K27 acetylation and osteogenic gene expression. Furthermore, the nicotinamide N-methyltransferase (NNMT) gene is a promoter of PLZF and requires osteogenic differentiation.[39]

3. Adipogenic differentiation

Adipogenesis is a complex physiological process with gene expression by various adipogenic factors, including, Pref-1, C/EBPβ, C/EBPα, PPARγ2, and aP2.[40,41] In undifferentiated stem cells, inactive lineage-specific promoters are in an enriched combination of trimethylated H3K4m3 and H3K27m3 in the absence of H3K9m3, a heterochromatin mark. Following differentiation, adipogenic and myogenic promoters are enriched in trimethylated H3K4, K27, and K9, which is associated to the potential of activation.[40,42] The balance between osteogenesis and adipogenesis of bone marrow-derived MSCs is known to induce stem cell differentiation and is a promising therapeutic approach in disease.[43] Several studies have suggested that DNA methylation and histone acetylation have been linked by PPARγ in regulating MSC differentiation, which allows for the accumulation of HDAC1 to downregulate the acetylation status. Therefore, the status of DNA methylation and histone acetylation might be regarded as an adipogenic potential.[43-45]

Sakai's group recently reported that H3K4/H3K9me3

bivalent domain is important in both MSCs and embryonic stem cells. They mentioned that H3K4/H3K9me3 was expressed and inhibited the action of MBD1/SETDB1/MCAF1 complex. However, once H3K4/H3K9me3 was blocked, the cells differentiated into adipocytes and the signals were activated.[46] In addition, SIRT1 (a class III HDAC) overexpression inhibited adipogenic differentiation in MSCs by deacetylation of the histone promoters sFRP1, sFRP2, and Dact1 and activation of the Wnt signaling pathway.[47]

4. Neurogenic differentiation

In mammals, adult neurogenesis is necessary to regenerate neurons and existing neural circuitry for cognitive functions. Terskikh's group reported that SOX2-Lin28/let7 complex play an essential role in neuronal stem cell differentiation and proliferation of neural precursor cells.[48] Several studies reported that histone acetylation has a potential effect of neurogenesis in neurodegenerative diseases and CNS injures.[49,50] Currently, scientist have revealed that microtubules undergo a dynamic process of assembly and disassembly to control cell shape remodeling, cell motility, tubulin stability, and terminal branching in neurons.[51-53] In addition, histone acetylation, which induces HDAC inhibitors, leads to neurogenesis and inhibits inflammation in a rat neonatal hypoxia-ischemia model.[54] Jang et al.[55-57] reported that HDAC inhibitor-mediated histone acetylation enhanced directed neurogenic differentiation in MSCs via upregulation of non-canonical Wnt signaling and activation of JNK and GSK-3β protein levels. These results demonstrated that transcriptional control in chromatic remodeling and epigenetic modifications is a vital factor in neurogenic differentiation in hMSCs.

5. Others

Voncken's group reported that polycomb associated H3K27me3 blocked chromatin access of EGR1 in early chondrogenic epigenetic programming by early gene-environment interactions in chondrogenesis of MSCs. These results suggested that epigenomic remodeling is important in chondrogenesis and depends on the early or late stage during differentiation.[19]

Rogiers's group reported that hepatogenic factors combining TSA could show hepatic differentiation of hMSCs following TSA-induced histone acetylation and inducible cytochrome P450-dependent activity.[58] TSA is known as one of the HDAC class I, II, IV, and has the potential for long-term cultivation and successful transdifferentiation of hMSCs. Other groups examined that VPA (HDAC class I and II) improved histone H3 and H4 acetylation and differentiated hepatocytes in hMSCs.[59] A few years ago, Raut and Khanna[60] studied the role of microRNAs in the control of cell fate determination during hepatic trans-differentiation in hMSCs. During hepatic differentiation, VPA improved hepatic trans-differentiation by enhancing the expression of hepatocyte-specific miRNAs and activation of histone H3 and H4.

There still remains a limitation in the understanding of hair follicle formation and hair genesis in the clinical field. Recently, Guo et al.[61] studied how hair follicles rely on dermis MSCs or are regenerated from skin-derived precursors using spheroid. They found TSA-mediated histone H3 acetylation in K9 and K14 modulated a wide variety of cellular activities and markedly alleviated culture expansion and restored the hair inductive capacity.

CONCLUSION

Recent advances in the field of regenerative medicine, Biochemistry, and Molecular Biology have demonstrated that histone modifications in mesenchymal stem cells play crucial roles in determining stem cell fate, including proliferation and differentiation. In this review, we described that histone acetylation followed by HDAC inhibitors or HATs are involved in MSCs differentiation into specialized cell types. This suggests how epigenetic modifications are a promising technique for stem cell therapy and regenerative medicine. Future investigations are needed to identify the link between histone acetylation and stem cell engineering.

ACKNOWLEDGEMENTS

This study was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2020R1F1A1076616, 2020R1I1A3070388, 2021R1I1A306043511), the Chonnam National University Hospital Biomedical Research Institute [BCRI21039], and a grant from the Jeollanam-do Science and Technology R&D Project (Development of stem cell-derived new drug) funded by the Jeollanam-do, Korea.

CONFLICT OF INTEREST STATEMENT

None declared.

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