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REVIEW

Landscape of Histone Posttranslational Modifications in Osteoarthritis

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Abstract: Osteoarthritis (OA) is a complex, progressive, and age-associated disease characterized by aberrant epigenetic expression. Epigenetic analysis has helped clarify the role of histone post-translational modifications (PTMs) in OA. PTMs affect histone structure and function and, therefore, regulate the expression of genes implicated in various biological processes. The roles of histone methylation and acetylation in OA progression—including extracellular collagen degradation and matrix destruction—have been thoroughly analyzed. Though several studies have shown that histone PTMs are related to OA, summative investigations in this area are lacking. The present literature review examines the relationships between histone PTMs and OA. It focuses mainly on methylation, acetylation, phosphorylation, lactylation, ubiquitination, and the roles of the histone methyltransferase (HMT)/histone demethylase (HDMT) and histone acetyltransferase (HAT)/histone deacetylase (HDAC) families in OA development. We used epigenetic tools for discovering new OA treatments. This review offers new perspectives for future studies on OA pathogenesis and treatment.

Keywords: osteoarthritis, histone modifications, epigenetic, cartilage, drug targets

Introduction

Osteoarthritis (OA) is an age-associated disease characterized by chronic joint pain resulting from the degradation of articular cartilage, inflammation of the synovial lining, and changes to the subchondral bone.[1] The worldwide incidence of OA in the adult human population is about 303 million. Of these, approximately 96 million are permanently handicapped because of this condition.[2] Thus, OA is the leading global cause of age-related disability. As of 2017, there were about 61.2 million reported cases of OA in China.[3] In end-stage OA, joint replacement is often required, which entails a significant financial burden and an inherent risk of postoperative complications.

Major risk factors for primary OA include advancing age and obesity.[4,5] Recent studies have demonstrated that epigenetic modifications are implicated in OA pathophysiology. The well-structured extracellular matrix (ECM) is the cornerstone of the function of articular cartilage tissue, mainly composed of type II collagen and proteoglycans. The degradation of the cartilage extracellular matrix (ECM) is recognized as a pivotal aspect of OA pathogenesis,[6] ultimately contributes to the progressive deterioration and structural collapse of joints. A substantial body of research underscores the crucial role played by four collagenolytic matrix metalloproteinases (MMPs; specifically, MMP-1, 8, 13, and 14) in mediating the breakdown of type II collagen,[7] while a distinct class of enzymes known as a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) is primarily responsible for degrading aggrecan.[8] Additionally, stromal cells within the synovium and other joint tissues exhibit enhanced production of cytokines and chemokines.[9–11] Notably, OA chondrocytes themselves upregulate the expression of pro-catabolic cytokines, such as IL-8, IL-12, and IL-17, which can act in an autocrine or paracrine fashion to exacerbate cartilage degradation, further perpetuating the pathological cascade of OA.[12]

The results of genome-wide scans and epigenetic studies on joint tissues indicated that the genetic risk polymorphisms associated with OA are mediated through epigenetic mechanisms and their effects on gene expression.[12,13]

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Currently, the emerging epigenetic tools for detecting histone post-translational modifications (PTMs) mainly include the following categories: CUT&Tag, a highly sensitive chromatin analysis technique, combines antibodies with transposases to efficiently capture histone modifications and transcription factor binding sites, making it suitable for small sample applications. High precision mass spectrometry analysis can be employed to identify the types and sites of histone modifications, which is applicable to both quantitative and qualitative research. Antibody array technology, on the other hand, can detect multiple histone modifications using specific antibodies, being suitable for high throughput screening and rapid detection. These tools offer highly sensitive solutions for the detection and functional study of histone modifications, thus propelling the progress in the field of epigenetics. Epigenetic modifications cause reversible and heritable changes in gene function but have no impact on nuclear DNA sequences. The alterations related to epigenetic modifications include DNA methylation, histone modifications, and RNA interference.[14] Core histones are evolutionarily conserved and consist of globular domains and flexible charged N-terminal tails. Various enzymes covalently modify the latter mainly at specific lysine and/or arginine residues.[15] Histone PTMs affect specific amino acid residues by regulating different enzymes such as writers (add), readers (recognize), or erasers (remove). These markers may control gene expression.[16,17] Methylation and acetylation are the most common histone PTMs. The former usually occurs at the lysine (K) residues of histone 3 (H3)[3] (Figure 1). Abnormalities in the post-translational regulation of histones are a hallmark of several diseases, including cardiovascular disease (CVD), Alzheimer's disease and multiple sclerosis (MS). Histone-modifying enzymes are also capable of modifying non-histone proteins. Recent studies (2024) have shown that HDAC3 can drive non-histone deacetylation outside the nucleus. The loss of HDAC3, induced by ECM stiffening, activated Parkin acetylation, thereby stimulating chondrocyte senescence and accelerating the initiation and progression of OA.[18] Recently, several studies have shown that OA development and cartilage degeneration are associated with classic histone modifications. Compared to the synovial fibroblasts of healthy individuals, those of patients with OA present with histone hyperacetylation in their interleukin (IL)-6 promoter regions.[19] Relative to the chondrocytes of normal controls, those of patients with OA display increased histone H3 at lysine 9 (H3K9) and H3K27 methylation in the SRY-Box Transcription

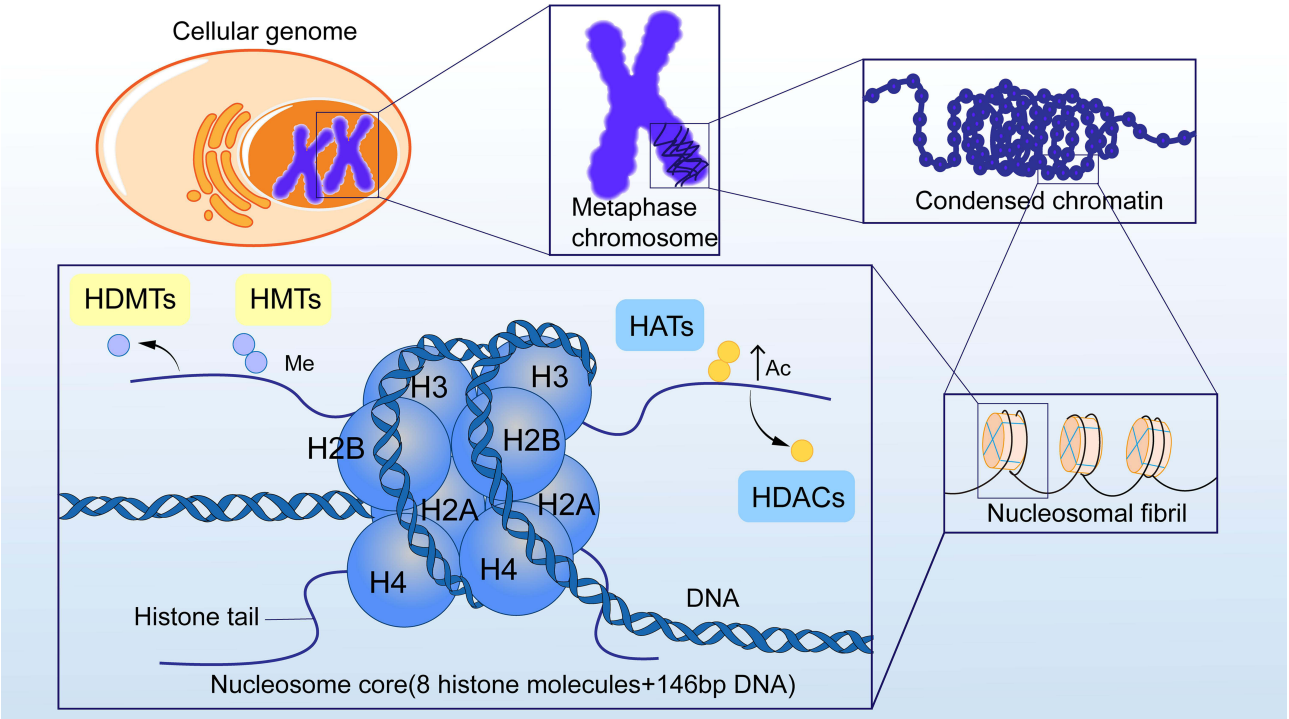

Figure 1 Levels of chromatin organization in eukaryotic cells. Eukaryotic chromatin is organized into multiple levels, with nucleosomes as the basic building blocks. A nucleosome consists of 146 bp of DNA wrapped around a core histone octamer, which includes two copies each of H2A, H2B, H3, and H4. The core histones contain globular domains and flexible N-terminal tails, which are the primary sites for post-translational modifications.

Abbreviations: Bp, Base pair; Ac, Acetylation; HMTs, Histone Methyltransferases; HDMTs, Histone Demethylases; HATs, Histone Acetyltransferases; HDACs, Histone Deacetylases.

Factor 9 (Sox9) promoter region, leading to decreased expression of Sox9.[20] The reduction in Sox9 expression dysregulates chondrocyte metabolism,[3] and alters the cartilage phenotype.

Despite the high incidence of OA, treatment options have not progressed to the same extent as they have for other musculoskeletal and chronic non-communicable diseases.[21] No disease-modifying drugs are currently available for OA treatment. Prescription drugs internationally indicated for OA management merely alleviate pain, and their long-term administration may be associated with side effects and hepatotoxicity.[3] Histone PTMs affect a wide range of gene programs. Histone-targeted treatments have demonstrated potential efficacy against OA as they attenuate some of the molecular and physiological changes characteristic of the disease. The present review shows that certain histone modifications regulate OA and may be implicated in its treatment, and an epigenome-based approach could be an efficacious therapeutic modality for OA.

Histones: Their Structure, Functions, and Post-Translational Modifications

Nucleosome surfaces have abundant modifications.[22] A recent study showed that covalent histone and DNA modifications alter chromatin organization and function.[23] However, the factors affecting nucleosome structure and dynamics, nucleosome-nucleosome interactions, and linker histone-binding and chromatin-binding proteins must be examined to elucidate the functions of chromatin fibers.[24]

The enzymes transducing histone tail modifications target specific amino acid positions. The N-terminal tails of histone and histone H3 are the most commonly modified. Lee et al suggested that histone tails restrict the access of transcription factors (TF) to DNA. This restriction is removed by directing tail dissociation from DNA, changing the DNA configuration on the histone core, and allowing TF binding.[25] Numerous modifications are associated with both active and inactive chromatin regions.

Certain histone amino-terminal modifications synergistically or antagonistically modify the interaction affinities for chromatin-associated proteins, and the latter control the dynamic transitions between transcriptionally active and inactive chromatin states. Methylation, acetylation, and phosphorylation are the most common histone PTMs. Anti-acylated antibodies and ultrasensitive mass spectrometry (MS) have identified and characterized novel histone lysine acylations such as lysine propionylation (Kpr), butyrylation (Kbu), succinylation (Ksucc), crotonylation (Kcr), malonylation (Kma), 2-hydroxyisobutylation (Khib), and lactylation (Kla).[26]

Histone methylation is vital to the formation of active and inactive genomic regions. Whether it activates or silences transcription depends on the types of residues being modified and the number of methyl groups being added.[27] The main classes of HMTs include SET domain lysine methyltransferases, non-SET domain lysine methyltransferases, and arginine methyltransferases.[15] There is no pattern to the genomic distribution of histone residue methylation.[28] H3K4, H3K36, and H3K79 are methylation markers linked to open chromatin and transcriptional activation and occur in all eukaryotes.[29] High degrees of H3K4, H3K79, and H3K36 trimethylation are observed in active gene transcription regions whereas low histone acetylation and high H3K9, H3K27, and H4K20 dimethylation and trimethylation levels are characteristic of the inactive regions.[30]

Histone acetyltransferases (HATs) mediate histone acetylation, are localized to specific lysine residues on the N-terminal tail of histone, and are associated mainly with transcriptional activity. Active regions exhibit high histone acetylation levels, especially near the promoter and transcription start sites.[30] Humans have 18 Zn- or NAD (+)-dependent histone deacetylases (HDACs) that act on acetyl lysine substrates.[31] The 18 known HDACs in the human genome are categorized into Classes I–IV depending on their structure, function, localization, and expression patterns. Class I includes HDACs1–3 and 8; Class II includes HDACs4–7 and 9–10; Class III HDACs are also known as sirtuins (Sirt1–7); and Class IV consists of HDAC11 alone.[32] Class I HDACs are essential for cell survival and their global deletion is lethal at the embryo stage.[32,33] HDACs result in low acetylation levels and heterochromatin and gene silencing. Histone H3 is hyperacetylated in heavily transcribed genome regions but hypoacetylated in silent regions such as telomeres.[23]

Zhang et al reported the discovery of histone marker lysine lactylation (Kla). Like histone acetylation, histone lactylation facilitates gene transcription under the described conditions.[34]

Though numerous histone modifications have been detected, the mechanisms regulating epigenetics remain to be elucidated.

Histone Post-Translational Modifications in OA

Histone Methylation in OA

Methylation was one of the first histone PTMs to be discovered. It was reported by Allfrey et al in 1964.[35] Histone methylation is often associated with gene expression. Genetic changes and HMT dysregulation are closely related to the deterioration of articular cartilage. Methylation commonly occurs at the lysine residues of histone 3. In mice, post-traumatic OA induction resulted in the rapid decay of H3K79 methylation in articular cartilage. The maintenance of H3K79 methylation is vital to the preservation of joint health and the prevention of OA onset and progression. A recent study (2023) reported a KDM2/7 subfamily inhibitor enhanced H3K79me and exerted protective effects in cartilage in vivo, thereby mitigating cartilage damage and osteophyte and hypertrophic chondrocyte formation in articular cartilage.[36] Taken together, the foregoing findings indicate that maintaining H3K79me is essential for preserving joint health and preventing the onset and progression of OA. DOT1L (Disruptor of Telomeric Silencing 1-Like), the gene encoding the H3K79 histone methyltransferase, plays a protective role in OA pathogenesis, as DOT1L-deficient mice exhibit heightened susceptibility to both posttraumatic and spontaneous OA compared to normal controls.[1] The loss of DOT1L activity disrupts chondrocyte homeostasis, primarily through its suppression of the Wnt/β-catenin signaling pathway. This pathway, which is highly conserved, includes downstream effectors such as MMP-3 and MMP-13, both of which are known to drive OA progression, highlighting the pathway's critical involvement in OA development.[37] Furthermore, hypoxia induces DOT1L activation in articular cartilage, enhancing its role in maintaining cartilage homeostasis.[38] DOT1L also attenuates Wnt signaling by inhibiting sirtuin-1 (SIRT1), thereby slowing OA progression.[39] This mechanism is evidence that interactions occur between histone modifications.

Lawson et al reported that conditional ESET histone methyltransferase knockdown results in ectopic articular chondrocyte hypertrophy, articular cartilage degeneration, and other overt signs of terminal differentiation.[40] The histone methyltransferase Enhancer of Zeste 2 Polycomb Repressive Complex 2 Subunit (EZH2) regulates the metabolic activity of chondrocytes in OA. Inactivating EZH2 induces micro-RNA (miR)-128a transcription which, in turn, promotes the loss of autophagy-related (Atg)12, represses chondrocyte autophagy, and accelerates OA progression.[41] EZH2 is upregulated in OA cartilage and mediates silencing of the Wnt inhibitor secreted frizzled-related protein (SFRP)-1 in OA chondrocytes. Intra-articular injection of the EZH2 inhibitor EPZ005687 impeded OA progression in mice.[42] However, a recent study demonstrated that EZH2 ameliorates OA by activating tumor necrosis factor ligand superfamily member (TNFSF)13B.[43] This discrepancy may be attributed to the fact that in the first study, EZH2 was inhibited in the cartilage alone through genetic loss whereas in the second study it was inhibited in the entire joint by intra-articular EPZ005687 injection.[1]

In 2022, our team discovered that PRMT5 (Protein Arginine Methyltransferase 5), an HMT (Histone Methyltransferase), is specifically upregulated in the cartilage of OA (osteoarthritis) patients. Inhibition of PRMT5 suppresses the expression of cartilage matrix-degrading enzymes by reducing the activation of the MAPK (Mitogen-Activated Protein Kinase) and NF-κB (Nuclear Factor kappa B) signaling pathways, thereby slowing OA progression. Additionally, PRMT5 inhibition delays articular cartilage degeneration in the destabilization of the medial meniscus (DMM) mouse model.[44]

Chondrocytes express the five demethylases LSD1/KDM1, JMJD1A/JHDM2A/KDM3A, KIAA1718/JHDM1D/KDM7A, PHF8/JHDM1F/KDM7B and PHF2/JHDM1E/KDM7C, which are responsible for the demethylation of specific substrates.[27] JMJD3 is also called Kdm6b and its protein expression levels and anabolic markers were significantly lower in human OA than in healthy normal cartilages.[45] Kdm6b promotes chondrocyte proliferation and hypertrophy during endochondral bone formation.[46–49] LSD1 more strongly immunostains in OA than in healthy cartilage. It downregulates the α1 chain of COLIX[50] by interacting with the TF SOX9. In human OA chondrocytes, Sox9 suppression is a key target for OA progression.[20] Sox9 inactivation is associated with abnormal cartilage differentiation and the obstruction of cartilage and bone formation in OA. Kim et al observed a significant increase in

the trimethylation of H3K9 and H3K27 at the SOX9 promoter in OA chondrocytes, as well as a decrease in the acetylation of H3K9, H3K15, H3K18, H3K23, and H3K27, which led to a reduction in the expression of SOX9 and exacerbated the development of OA. Since the synergistic effects of histone modifications at different sites may not clearly determine which modification is responsible for the decrease in SOX9 expression, further research is still needed.[51] Recently, a study has pointed out that the overexpression of H3K27 demethylase UTX in mice will lead to the enrichment of H3K27me3 at the SOX9 promoter, thus exacerbating the symptoms of OA. This indicates that controlling H3K27me3 may be a new strategy in the development of OA.[52] The post-translational modifications of histones at the H3K4 site are also involved in the occurrence and development of OA. The methyltransferase Set7/9 promotes the expression of COL2A1 by enhancing the level of H3K4me3.[53–55]

Imbalances between proinflammatory and anti-inflammatory factor expression levels also contribute to extracellular collagen degradation and matrix destruction. Fahmi et al showed that the histone lysine methyltransferase SET-1A was upregulated in OA cartilage compared to normal cartilage,[56] and H3K4 dimethylation and trimethylation at the inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX)-2 promoters contribute to IL-1β-induced iNOS and COX-2 expression.

The results of the preceding studies indicate that clarifying the roles of HMT/HDMT in OA may facilitate the development and application of efficacious histone-targeted therapy. Table 1 summarizes the representative histone modifications enzymes involved in osteoarthritis.

Table 1 Representative Histone Modifications Enzymes Involved in Osteoarthritis

Enzyme Type	Enzymes	Biological Function of Key Enzymes	Refs
Histone methyltransferases (HMTs)	*SET domain lysine methyltransferases* (*EZH2, SET1*, etc)	ESET, a histone methyltransferase with a SET domain. ESET can inhibit the terminal differentiation of articular chondrocytes, playing a crucial role in maintaining the health of articular cartilage.	ESET, Lawson et al, 2013[40]
	Non-SET domain lysine methyltransferases (*DOT1L, METTL10*, etc)	DOT1L, whose activity helps maintain the homeostasis of the cartilage microenvironment.	DOT1L, Grandi et al, 2020[1]
	Arginine methyltransferases (PRMT1–9)	The expression of PRMT5 is significantly elevated in the cartilage tissue of OA patients, where it promotes OA progression by upregulating the expression of cartilage matrix-degrading enzymes.	PRMT5, Dong Y et al, 2020[44]
Histone demethylases (HDMs)	Lysine-specific demethylase family (LSD1, LSD2, etc)	LSD1 can downregulate COL9A1, a critical component of the extracellular matrix, thereby exacerbating OA.	LSD1, Durand et al, 2020[50]
	JmjC domain-containing family (JHDM1A, JMJD3, etc)	JMJD3 can cause aberrant force-induced osteoarthritis through controlling the demethylation of H3K27me3 in the promoter region of NR4A1.	JMJD3, Zhou, T et al, 2022[47]
	PAD4/PADI4, JMJD6		
Histone acetyltransferases (HATs)	Gcn5-related N-acetyltransferases (HAT1, GCN5, etc)	The expression of HAT1 is significantly reduced in postmenopausal OA patients, suggesting that dysregulation of HAT1 may exacerbate OA.	HAT 1, Zupan et al, 2018[57]
	MYST-family (*MORF, HBO1*, etc)		
	CBP / p300		
Histone deacetylase (HDACs)	Class I (HDAC1, 2, 3, and 8)	HDAC1, HDAC2, and HDAC3 are considered to the suppression of aggrecan and COL2A1 production, contributing to the progression of OA.	HDAC1, HDAC2, HDAC3, Hong, S et al, 2009[58]

(*Continued*)

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Table 1 (Continued).

Enzyme Type	Enzymes	Biological Function of Key Enzymes	Refs
	Class II (HDAC4, 5, 6, 7, 9, and 10)	HDAC4 expression is markedly increased in OA cartilage tissue, potentially participating in the disease process through enhancing chondrocyte catabolic activity and inducing chondrocyte hypertrophy.	HDAC4, Martin, L et al, 2023[59]
	ClassIII (SIRT1-7)	SIRT1 is essential for ensuring the expression of aggrecan within the chondrocyte extracellular matrix.	SIRT1, Fujita, N et al, 2011[60]
	ClassIV (HDAC11)		

Abbreviations: Refs, References; EZH2, Enhancer of Zeste Homolog 2; SET1, SET Domain Containing 1; ESET, ERG-associated protein with SET domain; DOT1L, Disruptor of telomeric silencing 1-like; METTL10, Methyltransferase-like 10; PRMT, protein arginine methyltransferase; LSD, Lysine-Specific Demethylase; COL9A1, Collagen Type IX Alpha 1 Chain; JHDM1A, Jumonji C Domain-Containing Histone Demethylase 1A; JMJD3, Jumonji Domain-Containing Protein D3; NR4A1, Nuclear Receptor Subfamily 4 Group A Member 1; PAD, Peptidyl Arginine Deiminase; MYST, MYST is an acronym for a family of histone acetyltransferases (HATs); MORF, Methyltransferase-Interacting Open Reading Frame; HBO1, Histone Acetyltransferase Binding to ORC1; CBP, CREB-Binding Protein; p300, E1A Binding Protein p300; COL2A1, Collagen Type II Alpha 1 Chain; RUNX2, Runt-Related Transcription Factor 2; SIRT, Sirtuin.

Histone Acetylation in OA

Hyperacetylation usually marks transcriptionally active genes.[61] Lysine acetylation neutralizes the charges on histone tails, weakens their binding to DNA, and relaxes nucleosomal DNA.[62] The role of histone lysine acetylation/deacetylation in the progression of OA has been thoroughly studied, aberrant HAT/HDAT-mediated acetylation/deacetylation modifies gene expression in both OA and normal chondrocytes.

In some contexts, HDACs are more sensitive to environmental or developmental cues than the HATs and can provide a regulatory role in transcription.[63] Few studies have explored the functions of histone acetyltransferases (HATs) in OA. Only Zupan et al reported that the upregulation of HAT1 is associated with the formation of high-quality bone tissue and a tightly structured trabecular network. They also found that the expression of HAT1 is significantly reduced in postmenopausal osteoarthritis patients, suggesting that dysregulation of HAT1 may exacerbate OA.[57] Differential HDAC expression modes are associated with the maintenance of cartilage homeostasis and the initiation and progression of OA. Whereas the upregulation of certain HDACs disrupts chondrocyte homeostasis and accelerates OA progression, the overexpression of other deacetylases is chondroprotective.[32] HDAC1,3 and Sirt1,2,3,6,7 are the principal histone deacetylases in normal chondrocytes whereas HDAC1,2,4,7 are highly expressed in OA cartilage (Figure 2).

Class I HDACs have been widely studied and include HDAC1, HDAC2, HDAC3, and HDAC8. Genetic deletion of Class I HDACs devastates endochondral bone formation.[64] In human chondrocytes, HDAC1, HDAC2, and HDAC3 repress aggrecan and Col2a1,[58] and induce IL-1β-induced MMPs expression and catabolic activity.[65,66] HDAC2/8 upregulation is observed in patients with OA, prevents chondrogenic differentiation, and inhibits cartilage matrix synthesis.[67] You et al suggest that HDAC4 and HDAC8 could drive cartilage degeneration by activating the MAPK signaling pathway. The MAPK (mitogen-activated protein kinase) pathway plays a pivotal role in OA progression, as its overexpression can stimulate the activation of multiple inflammatory factors, leading to the degradation of chondrocytes and the ECM. Consequently, activation of the MAPK pathway hastens the onset and progression of OA.[68]

The Class IIa HDACs include HDAC4, HDAC5, HDAC7, and HDAC9 (HDAC7b) while the Class IIb HDACs include HDAC6 and HDAC10:[69] Class IIa, which has a large C-terminus, and class IIb, which has two deacetylase domains.[70]

Class II HDACs play a role in maintaining the properties and maturation of chondrocytes. HDAC4 is highly expressed in OA cartilage, suggesting its involvement in promoting the catabolic activity of chondrocytes associated with OA pathogenesis. The expression level of HDAC4 is significantly elevated in OA cartilage tissue, and it may contribute to the pathogenesis of OA by upregulating the catabolic activity of chondrocytes. Additionally, during endochondral ossification, HDAC4 plays a critical regulatory role in the occurrence of chondrocyte hypertrophy, which is one of the typical pathological features of OA cartilage.[59,63] HDAC4 is also an upstream mediator of MAPK and promotes ADAMTS4, ADAMTS5, and COX2 expression in rat articular chondrocytes and stimulates IL-1β.[68,71] Study shows that MiRNA-222 is minimally expressed in OA cartilage and downregulates MMP-13 by targeting HDAC4

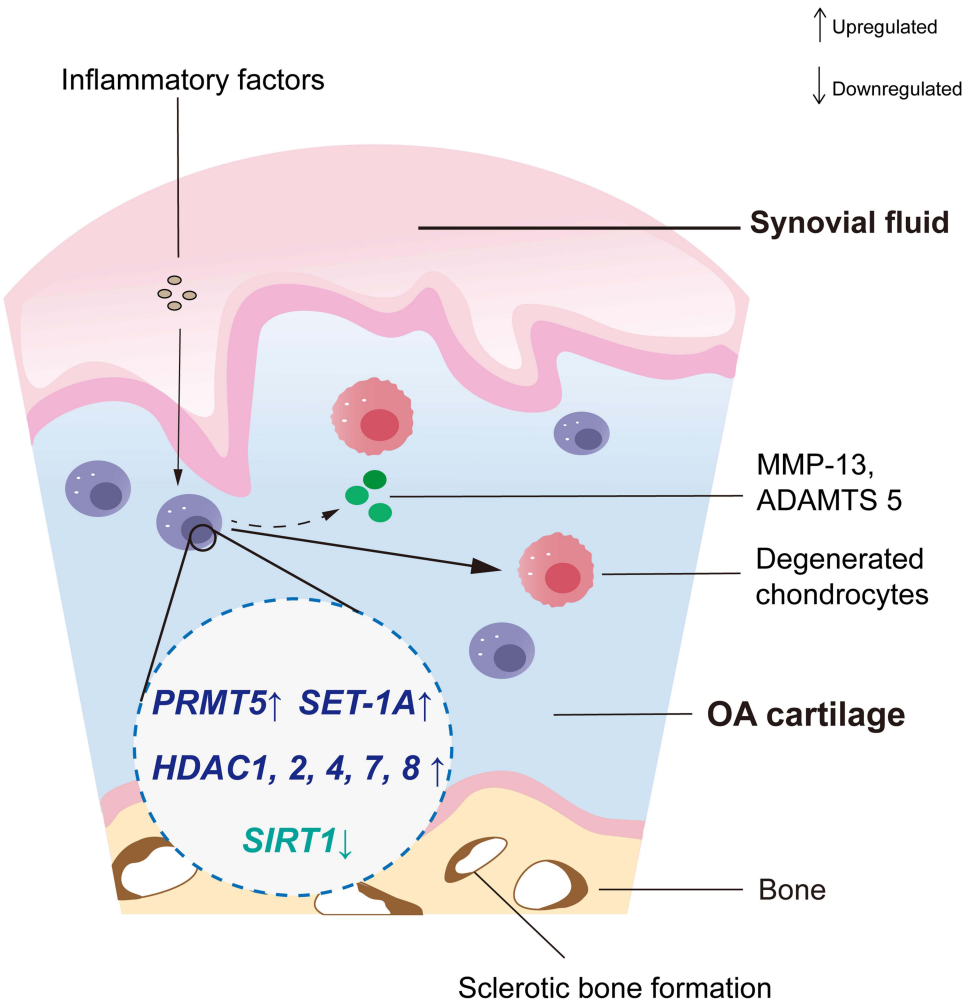

Figure 2 Alterations of histone-modifying enzymes in OA cartilage. In OA cartilage tissue, the expression levels of HDAC1, 2, 4, 7, 8, PRMT5, and SET-1A were found to be upregulated. This upregulation promotes the increased expression of IL-1β-induced MMPs, which exacerbates cartilage degradation in OA. Meanwhile, SIRT1 expression is decreased in OA cartilage, and the inhibition of its activity also upregulates the expression of cartilage-degrading enzymes MMP-13 and ADAMTS5, thereby promoting the progression of OA.

Abbreviations: HDAC, Histone deacetylase; PRMT5, Protein arginine methyltransferase 5; SET-1A, SET Domain Containing 1A; SIRT1, Sirtuin 1; MMP-13, Matrix metalloproteinase-13; ADAMTS5, A disintegrin and metalloproteinase with thrombospondin motifs 5.

during OA progression.[71] HDAC4 and HDAC5 also inhibit Runx2 by transforming growth factor (TGF)-b.[72] In human OA, HDAC7 upregulation may contribute to cartilage degradation by elevating MMP-13 expression.[48,73] HDAC7 has been demonstrated to induce cartilage damage and ECM degradation through the overexpression of MMP-3 and MMP-13 which is consistent with the HDAC7 knockdown in vitro leading to suppression of inflammatory induced MMP13 gene expression.[1,73] Little is known about the functions of HDAC9.

Shen et al reported that HDAC6 was upregulated in the cartilage of a mouse OA model. They also stated that HDAC6 inhibition with tubastatin A (TSA) mitigated oxidative stress in chondrocytes, downregulated apoptotic proteins, increased chondrocyte survival, and suppressed ECM degradation.[74]

Shinomura et al identified the enhancer elements E1 and E2 in the gene encoding type II collagen and Ea and Eb in the gene encoding aggrecan. They also demonstrated that distinct epigenetic modifications by HDAC10 and SIRT6 control E1 and E2 enhancer activity and thus regulate the expression of type II collagen and aggrecan.[75]

Class III HDACs include sirtuins (SIRT)1–7. Of these, SIRT1 is the most extensively studied. Research has demonstrated that SIRT1 protects chondrocytes. It is downregulated in human OA cartilage and its inhibition decreases aggrecan expression in both normal and OA human chondrocytes.[60] SIRT1 represses IL-1β- and TNF-α-induced cartilage-degrading enzyme expression by modulating the NF-κB pathway achieve a protective effect on cartilage.[76,77]

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OA severity increases with decreasing SIRT1 expression (n = 38).[78] Matsushita et al surgically induced OA in SIRT1-CKO mice. Two weeks after the operation, chondrocyte SIRT1 loss accelerated OA development.[79] Upregulated type X collagen, MMP-13, ADAMTS5, and apoptotic markers, and acetylated NF-κB p65 in Sirt1-CKO mice compared with the control mice. Another study showed interactions between histone methylation and acetylation. The histone methyltransferase Set7/9 inhibits the histone deacetylase activity of SIRT1 and causes morphology-dependent Col2a1 transactivation.[54] Hence, SIRT1 protects human cartilage by inducing the genes encoding cartilage extracellular matrix (ECM).[63] A study revealed that SIRT2 inhibited oxidative stress and the inflammatory response in diabetic OA.[80] Griffin et al showed that Sirt3 deletion impaired chondrogenesis in murine bone marrow stem cells whereas Sirt3 expression promoted OA in high-fat-diet-induced mature chondrocytes.[81] A study conducted by Wang et al revealed that the SIRT3 level is decreased in mouse OA cartilage and that SIRT3 knockdown induces mitochondrial dysfunction in chondrocytes.[82–84] Wu et al overexpressed SIRT3 with lentivirus and plasmids and discovered that it ameliorated OA by regulating chondrocyte autophagy and apoptosis via the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) signaling pathway.[85] Dai et al revealed that SIRT4 silencing maintained chondrocyte health, downregulated aggrecan, Col2a1, and antioxidant enzymes, and inhibited the inflammatory response.[86] There are comparatively few studies on the association between SIRT5 and OA. Only Zhu et al observed that SIRT5-/- mice presented signs of cartilage degeneration and calcification as early as age 40 weeks.[87] SIRT6 deficiency exacerbates chondrocyte senescence and accelerates OA progression[88] and it also attenuates synovial inflammation by inhibiting proinflammatory cytokine secretion from macrophages in the synovial membrane. In this manner, it mitigates OA severity.[89] Ji et al found that intra-articular adenovirus-SIRT6 injection attenuated the surgical destabilization of medial meniscus-induced OA.[88] The foregoing findings indicate that SIRT6 may play various roles in OA development.[90] SIRT7 regulates cartilage homeostasis and OA development. Yoshizawa et al found that in ATDC5 mice, SIRT7 attenuation increased glycosaminoglycan-rich ECM deposition and the mRNA expression levels of Col2a1 and aggrecan by suppressing SOX9 transcription.[91]

Class IV histone deacetylases (HDACs): Only one study has demonstrated that HDAC11 is unable to suppress Runx2-induced gene transcription.[92] Its precise function remains unclear.

Other Novel Histone Modifications in OA

Previous studies have primarily focused on histone PTMs such as acetylation and methylation. In contrast, few studies have explored or reported on other histone modifications, such as ubiquitination and SUMOylation, in the context of OA.

Histone phosphorylation mediates transcriptional regulation, DNA damage repair, and chromosome condensation during cell division.[93] H2A phosphorylation is implicated in mitotic chromatin condensation and transcriptional activation during the G1/S transition.[94] Huang et al demonstrated that Wnt10A induces apoptosis in senescent synovial resident stem cells via Wnt/calcium pathway-mediated HDAC5 phosphorylation in the joints of patients with OA.[95] A recent study (2025) has revealed the critical role of GRK5-mediated HDAC6 phosphorylation in OA. The study found that G protein-coupled receptor kinase 5 (GRK5), as a HDAC kinase, promotes the phosphorylation of HDAC6, thereby enhancing its deacetylation activity. The phosphorylation of HDAC6 exacerbates mitochondrial dysfunction and ECM in chondrocytes, further promoting the progression of OA.[96]

Zhao Yingming et al discovered that lactylation is a post-translational histone modification and identified 28 lactylation sites on the core histones in human and mouse cells.[34,97] Ouyang et al found that lactate-induced acidification inhibited both chondrocyte proliferation and ECM expression.[98] However, the mechanism by which neutral lactate regulates cartilage metabolism remains unclear. Wu et al performed joint CUT&Tag and RNA sequencing analyses and revealed that H3K18la lactylation stimulated the transcription of COL1A2, cartilage oligomeric matrix protein (COMP), ectonucleotide pyrophosphatase/phosphodiesterase (ENPP)1, and transcription factor 7 like 2 (TCF7L2) and may, therefore, protect and repair the ECM in articular cartilage.[99,100] Recently, Professor Yu's team discovered that exogenous lactate-mediated elevation of H4K12la promotes the transcription of PD-1 in microglia, thereby enhancing repair after spinal cord injury.[101] Overall, histone lactylation may be part and parcel of the mechanism underlying OA onset and progression.

More comprehensive studies are needed to clarify and understand the precise functions of histone modifications in OA.

Possible Histone Targeted Therapies for Osteoarthritis

Despite the high global incidence of OA, there are few FDA-approved therapies for it, and no currently available drugs prevent or impede the onset of OA.[1] Therefore, therapeutic modalities must be able to target a wide range of deregulated gene programs in the entire joint. Histone modifications impact a wide array of gene programs, facilitating the simultaneous regulation of multiple genes linked to OA, such as ECM-degrading enzymes and inflammatory factors, thereby enabling a more comprehensive intervention in OA progression. The interplay between histone modifications can be cooperative or antagonistic, and by targeting multiple modifications, therapeutic efficacy can be enhanced, overcoming the limitations of single-target approaches. In summary, histone-targeted therapy provides an innovative strategy for OA treatment with broad potential for clinical application (Figure 3).

DOT1L is the principal H3K79 methyltransferase and it protects against OA by suppressing Wnt signaling. Cartilage-specific Dot1l-knockout (Dot1lCART-KO) mice spontaneously developed severe OA.[39] Thus, modulating DOT1L function may be feasible as a therapeutic approach against OA. However, no currently available pharmacological agents induce or activate DOT1L.[1] DOT1L is ubiquitously expressed across diverse cell types. Achieving its cell type specific targeting within chondrocytes represents a challenge.[102] The lack of specificity may lead to side effects on non-target tissues, which limits its application in the treatment of OA. Recently, Cherifi et al demonstrated that daminozide, an inhibitor of KDM2/7 histone demethylases, counteracts H3K79me deficiency in cartilage and protects against OA.[36]

Trichostatin A (TSA) exhibits a time- and dose-dependent hyperacetylation effect on histone H4 in chondrocytes. In vitro experiments have confirmed that it can effectively inhibit the upregulation of MMPs induced by IL-1β in human chondrocytes. Additionally, in an experiment where rats received bilateral knee joint injections of TSA (50 μL each time, with an interval of 4 weeks, for a total of 2 times), it was found that compared with the OA group (induced by monoiodoacetate), the cartilage integrity of the rats in the TSA treatment group was significantly improved.[103,104] Nasu

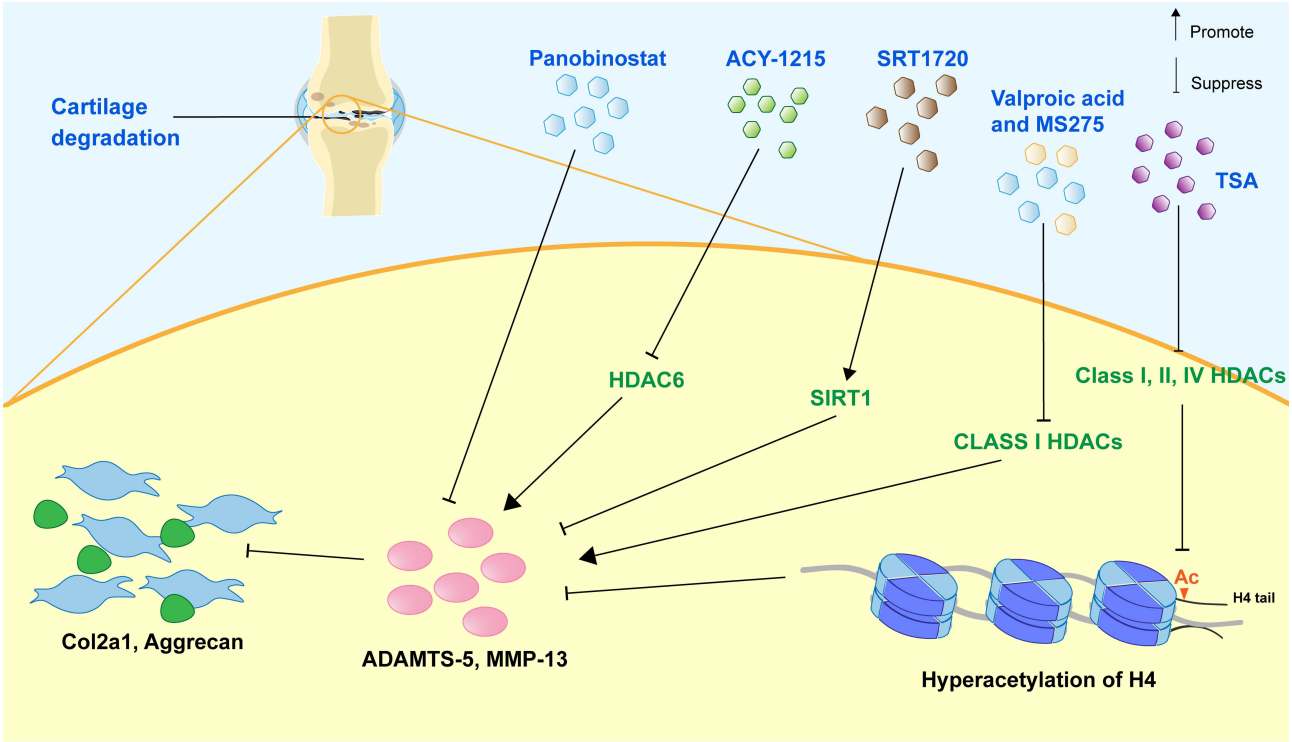

Figure 3 Drugs downregulating MMP-13 and ADAMTS-5 by targeting various HDACs. Trichostatin A (TSA) induced histone H4 hyperacetylation and prevented IL-1β-induced MMP upregulation in human chondrocyte cultures. Valproic acid and MS-275 inhibited Class I HDACs and prevented IL-1β-induced MMP-13 upregulation. SRT1720 upregulated Sirt1, thereby downregulating MMP-13 and ADAMTS-5. The HDAC6 inhibitor ACY-1215 protected human OA chondrocytes and repressed MMPs. The HDAC inhibitor panobinostat inhibited the IL-1β-induced expression of proinflammatory mediators and ECM-degrading enzymes.

Abbreviations: HDACs, histone deacetylase; Col2a1, collagen α1(II); SIRT1, Sirtuin 1; MMP-13, Matrix metalloproteinase-13; ADAMTS5, A disintegrin and metalloproteinase with thrombospondin motifs 5.

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et al also demonstrated the efficacy of systemic TSA in downregulating various MMPs.[53,105] Systemic TSA delivery for more than eight weeks inhibited OA in a mouse DMM model presumably by repressing MMPs. To date, TSA is the only HDACI that has been tested on animal OA models.[59]

Lotz et al reported that the promising HDAC inhibitor panobinostat upregulated autophagy genes and proteoglycan (PRG)4 and inhibited the IL-1β-induced expression of inflammatory mediators, MMP-3, and MMP-13 by upregulating Forkhead Box Protein (Fox)O1.[59] Culley et al found that inhibiting Class I HDACs with valproic acid and entinostat (MS-275) prevented IL-1β-induced MMP-13 upregulation. The selective HDAC3 inhibitor RGFP966 attenuated inflammation in a rat OA model by impeding the nuclear translocation of NF-κB.[106] HDAC4 and HDAC8 may promote IL-1β-induced catabolic cartilage degradation via the MAPK signaling pathways. Thus, inhibiting HDAC4, HDAC8, or both is a promising OA prevention and treatment strategy.[68] Yin et al reported that the HDAC6 inhibitor ACY-1215 protects human OA chondrocytes and suppresses inflammation in them by inhibiting the signal transducer and activator of transcription (STAT)3 and NF-κB signaling pathways.[107] SIRT1 inhibition increases apoptosis in chondrocytes whereas the sirtuin activator resveratrol protects them against it.[1] Though there is preliminary evidence that HDAC6 inhibitors and SIRT activators promote bone formation and/or prevent bone loss, further research is required to confirm these findings.[32] Research has demonstrated that SIRT1 protects chondrocytes. Feige et al developed SRT1720 which increases SIRT1 activity 8.7-fold,[108] and observed that SRT1720 treatment delayed OA progression and downregulated both MMP-13 and ADAMTS-5.[109] Recent evidence suggests that HDAC inhibitors could effectively protect articular cartilage against destruction by preventing ECM degradation.

As certain broad-spectrum HDAC inhibitors are toxic, they are unsuitable for the treatment of chronic non-life threatening conditions.[110] It is challenging to determine in vivo HDAC inhibitor specificity in drug research. HDAC inhibitors are promising as treatments for cancer, inflammation, and neurological diseases, and could prove effective as OA therapy. Several laboratories are developing new HDAC inhibitors that are highly efficacious while triggering few side effects.[31]

Concluding Remarks

The present review focused on the role of several common histone PTMs and enzymes in OA onset and progression. Prior research has indicated that histone PTMs are ubiquitous in the initiation and development of OA. They regulate the chromatin state, gene expression, and other biological processes. Unlike direct DNA sequence mutations, changes in histone PTMs are usually reversible. Future studies on the mechanism by which histone modifications influence OA could help improve the prevention and treatment of this disease.

Despite certain progress in the research of histone PTMs in OA, numerous challenges still persist. Firstly, there is a wide variety of histone modifications, including methylation, acetylation, phosphorylation, lactylation, etc. Additionally, there may be synergistic or antagonistic interactions among different modifications (such as the interaction between acetylation and methylation). This complexity makes it extremely difficult for researchers to comprehensively analyze the specific mechanisms of each modification in OA. Secondly, the roles of histone - modifying enzymes (such as HDACs, HATs, etc) in OA have been extensively studied. However, these enzymes often function in multiple tissues and cell types, and targeted therapies may cause systemic side effects. Finally, one of the goals of histone PTMs research is to develop targeted therapeutic strategies. Currently, there are no FDA approved histone PTMs targeted drugs for the treatment of OA. Some HDAC inhibitors (such as TSA) have shown potential in animal models, but their toxicity and specificity issues limit their clinical application. A deeper understanding of the role of histone modifications in OA can provide a theoretical basis for the development of precise treatment strategies.

With the rapid development of high-throughput omics technologies, novel histone modifications (such as succinylation, etc) have been continuously discovered. However, the specific functions of these modifications in OA have not been fully clarified. In the future, by combining mass spectrometry technology, integrated proteomics, and bioinformatics analysis, we will conduct an in-depth investigation into the mechanisms of action of these modifications in OA. Additionally, the research focus can be placed on developing more specific modifiers enzyme inhibitors or activators, so as to reduce systemic side effects and enhance the precision and effectiveness of treatment.

This article reviews the role of histone PTMs in OA and its potential therapeutic strategies. Future research needs to combine multi-omics technologies and single-cell analysis to deeply analyze the dynamic changes of histone modifications and their specific mechanisms in OA, providing a theoretical basis for the development of precise therapeutic strategies.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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