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Epigenetics in osteoarthritis: Potential of HDAC inhibitors as therapeutics

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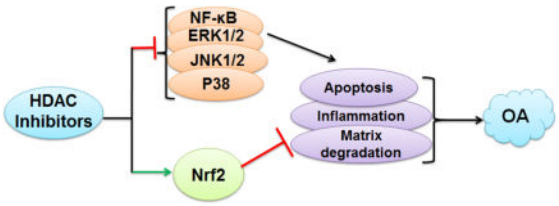
Abstract

Osteoarthritis (OA) is the most common joint disease and the leading cause of chronic disability in middle-aged and older populations worldwide. The development of disease modifying therapy for OA is in its infancy largely because the regulatory mechanisms for the molecular effectors of OA pathogenesis are poorly understood. Recent studies identified epigenetic events as a critical regulator of molecular players involved in the induction and development of OA. Epigenetic mechanisms include DNA methylation, non-coding RNA and histone modifications. The aim of this review is to briefly highlight the recent advances in the epigenetics of cartilage and potential of HDACs (Histone deacetylases) inhibitors in the therapeutic management of OA. We summarize the recent studies utilizing HDAC inhibitors as potential therapeutics for inhibiting disease progression and preventing the cartilage destruction in OA. HDACs control normal cartilage development and homeostasis and understanding the impact of HDACs inhibitors on the disease pathogenesis is of interest because of its importance in affecting overall cartilage health and homeostasis. These findings also shed new light on cartilage disease pathophysiology and provide substantial evidence that HDACs may be potential novel therapeutic targets in OA.

Graphical Abstract



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Keywords

Osteoarthritis; Epigenetics; HDACs; miRNA; lncRNA; DNA methylation

1. Introduction

Osteoarthritis (OA), the most common form of joint disease, is associated with cartilage degradation, disability and poor quality of life and is a leading cause of chronic disability in middle-aged and older populations affecting more than 27 million Americans [1]. Aging is a major risk factor for OA, however other factors such as gender, obesity, joint injury, genetics and mechanical abnormalities have been shown to contribute to the development of OA [2]. There is no single specific cause that has been identified for OA till date, however, there is a growing body of evidence that suggest that OA is a result of the interactions between molecular events and mechanical issues in the affected joint [3]. Although OA is a disease of the whole joint and affect all the joint tissues, cartilage degradation is the main characteristic of OA [4]. The underlying molecular mechanisms of OA pathogenesis involve multiple components and include dysregulation of different layers of regulatory mechanisms.

Altered gene expression of matrix degrading proteases (MMPs), inflammatory mediators and extracellular matrix (ECM) related genes such as collagens and proteoglycans in articular chondrocytes isolated from OA cartilage has been documented [4–8]. However, the underlying regulatory mechanism for the expression of these genes in OA cartilage has not been fully understood. Epigenetics is an important layer of regulation of gene expression and is associated with the pathogenesis of a number of human diseases [9]. Epigenetics is defined as a stable change in gene expression between cell divisions, and sometimes generations, that involves no change in the underlying DNA sequence [10]. The “NIH Roadmap Epigenomics Project” defined epigenetics as heritable changes in gene activity and expression and stable, long-term alterations in the transcriptional potential of a cell that are not necessarily heritable [11]. Here we reviewed the recent findings in this field with an emphasis on the potential of HDACs inhibitors for the management of OA. If we have missed a reference, it is inadvertent and not because the findings are not important.

2. Epigenetic regulation of OA pathogenesis

Although epigenome of each cell is unique but can undergo temporal and spatial changes in response to environmental stimuli such as diet, exercise, smoking and disease status. Aberrant epigenetic modifications due to environmental factors are associated with a number of pathological conditions and include DNA methylation, non-coding RNAs (ncRNAs) expression and histone modifications that regulate the gene expression at transcriptional and/or post-transcriptional levels (Figure 1). Here, we will briefly highlight the first two epigenetic mechanisms namely DNA methylation and ncRNA mediated regulation of gene expression in OA and will focus on HDACs mediated regulation of OA pathogenesis and explore the potential of HDACs inhibitors (HDACi) for the management of OA.

2.1 DNA methylation in OA

DNA methylation is the most widely studied epigenetic control mechanism and involves addition of a methyl group to the 5′ position of cytosine within a CpG dinucleotide to form 5-methylcytosine in presence of DNA methyltransferase (DNMT). Methylation within the gene promoter regions is associated with the suppression of gene expression, whereas methylation within gene bodies correlates with the enhanced gene expression [12, 13]. The pioneer findings of DNA methylation studies in OA lead to the discovery of hypomethylation of catabolic genes and hypermethylation of anabolic genes in chondrocytes [14]. Methylation changes of a few specific sites inside the promoter region or the gene itself can be crucial in determining transcription and expression of a gene in OA.

The candidate gene approach to examine the DNA methylation of matrix degrading proteases such as MMP3, MMP9, MMP13 and ADAMTS4 was the first study to describe the possible impact of DNA methylation in OA [15]. These studies demonstrated the hypomethylation in the promoter regions of selected catabolic genes in OA chondrocytes compared to control chondrocytes and found that this was associated with the increased expression of the gene [15]. The inflammatory cytokine IL-1β, which is recognized as a critical player in OA pathogenesis, is also epigenetically regulated and methylation levels within its proximal promoter region were found to be inversely correlated with gene transcription in OA chondrocytes [16]. Genome-wide DNA methylation studies in OA cartilage using Illumina Human Methylation 450K array allowing the quantitation of nearly 470,000 CpG sites covering all the coding genes identified 550 differentially methylated CpG sites among OA patients, with the RUNX1 (runt-related transcription factor) being most differentially methylated gene [17]. Further investigations are needed to clearly define the impact of methylation in the promoter region of a gene on the disease process in OA.

2.2 Non-coding RNAs in OA

Non-coding RNAs (ncRNA) are functional RNA molecules that regulate gene expression but do not translate into proteins. There are two types of ncRNAs- short ncRNAs which are <30 nucleotides and long ncRNAs (lncRNAs) which are >200 nucleotides in length [18, 19]. Further, short ncRNAs have been classified as mainly of three types- microRNAs (miRNAs), piwi-interacting RNAs (piRNAs) and short interfering RNAs (siRNAs) [20]. These ncRNAs regulate gene expression at transcription, splicing or translation levels. The miRNAs in general modify the protein expression thus acting mainly at the post-transcriptional level by binding to a specific complimentary sequence in the target mRNA and block its translation [21]. Recent advances in the field of ncRNAs have revealed their importance in the pathogenesis of many diseases including OA [22].

2.2.1 miRNAs in OA—miRNAs are small, 20–23 base pair long cytoplasmic RNAs that regulate post-transcriptional gene expression through binding to target mRNAs via complementary base pairing between the miRNA and the “seed sequence” present in the 3′-UTR or the ORF of the target mRNA [23]. The interaction of miRNA with the target mRNA results in the degradation of mRNA leading to translational suppression [21]. The first studied miRNA in osteoarthritis was miR-140, which is specifically expressed in the cartilage and has been shown to play an important role in chondrogenesis [24–28]. The

expression of miR-140 was reduced in human OA cartilage and its deletion lead to an accelerated OA phenotype in mouse [24–26]. Table 1 describes a brief summary and function of miRNAs differentially expressed in OA. Several miRNAs have been shown to affect the OA progression by mitigating the inflammation and influencing the anabolic function in cartilage.

The first large scale screening of hundreds of miRNAs in OA cartilage was performed by Iliopoulos et al [29]. The screening of 365 differentially expressed miRNAs in articular cartilage established the cartilage specific profile of miRNA and identified 16 miRNAs (9 upregulated and 7 downregulated) and collaborative metabolic and inflammatory networks in OA pathogenesis [29, 39]. Later, Akhtar N et al were the first to demonstrate that miR-27b was differentially expressed in both normal and OA chondrocytes and involved in the regulation of MMP-13 expression in IL-1β stimulated human OA chondrocytes [38]. In other studies, the closely related miR-27a was also shown to exert anti-inflammatory effects by suppressing MMP13 and IGFBP-5 expression in cultured chondrocytes [34]. Yamasaki K et al (2009) showed that miR-146 is upregulated in IL-1β stimulated OA chondrocytes and regulate the expression of IRAK-1 (IL-1-receptor associated kinase 1) and TRAF-6 (TNF-receptor associated factor 6) by binding to the “seed sequence” present in the 3′-UTR of their mRNAs [40]. Several studies analyzed the miRNAs expression profile in the plasma and synovial fluid of OA patients and the data suggested that monitoring synovial fluid and plasma miRNAs have the potential as diagnostic biomarkers for OA and can be used for the analysis of the disease pathogenesis or outcome [41, 42]. These and other studies highlighted the importance of miRNA networks in the pathogenesis of OA and suggest that detection and targeting of specific miRNAs may be of value in early diagnosis and therapy of OA [31, 33, 35, 43, 44].

2.2.2 lncRNAs in OA—Long noncoding RNA (lncRNA) is defined as a regulatory ncRNA greater than 200 nucleotides in length and lacks an open reading frame of significant length and is not translated into a protein [20, 45]. LncRNAs have widespread biological functions and have been shown to exhibit 5′-cap, 3′-polyA tail and involved in splicing into multi-exons that exhibit transcriptional activity [19, 46]. Recent literature showed that lncRNAs are aberrantly expressed in OA cartilage and thus contributed to the degeneration of chondrocyte extracellular matrix [47, 48]. Table 2 provides a brief summary of differentially expressed lncRNAs in human OA cartilage tissue and potentially playing a role in OA.

Xing D et al (2014) using lncRNA microarray analysis identified several differentially expressed lncRNAs (73 upregulated lncRNAs and 48 downregulated) in OA cartilage compared with normal cartilage [49]. These differentially expressed lncRNAs included the upregulated expression of HOTAIR, growth arrest-specific 5 (GAS5), PMS2L2, RP11-445H22.4, H19 and CTD-2574D22.4 [49]. Additionally, Fu and colleagues have demonstrated that there are 3007 upregulated lncRNAs and 1707 downregulated lncRNAs in OA cartilage when the expression was compared to the lncRNAs expression profile in normal cartilage samples [47]. Altogether, there are a number of differently expressed lncRNAs in human OA cartilage and functional investigation of these lncRNA is required to establish their role in OA pathogenesis.

Some recent studies have identified the role of lncRNAs in the regulation ECM degradation and the inflammatory response. Liu et al. (2014) identified a novel lncRNA termed as cartilage injury-related lncRNA (lncRNA-CIR) which was highly expressed in OA cartilage and OA chondrocytes and its knockdown was shown to inhibit the expression of MMP-13 and ADAMTS-5 and enhanced the expression of anabolic genes COL2A1 and ACAN in OA chondrocytes [48]. Additionally, Pearson et al. identified two novel chondrocyte lincRNAs (CILinc01 and CILinc02) having a role in the regulation of inflammation in OA

2.3 Histone modifications in OA

Histones are alkaline proteins found in the nucleus that envelope the DNA to form the nucleosomes. Histones undergo modifications that altered the chromatin conformation and influenced the binding of transcription factors with the promoter region. There are more than 150 histone modifications reported which have variable effects on gene transcription and such modification includes acetylation, methylation, phosphorylation and ubiquitination of histone residues [55]. A specific combination of histone marks is associated with silenced regions, promoters, enhancers, and transcribed regions of the genome. Acetylation/deacetylation and methylation/demethylation of histones are the primary modifications studied in OA.

2.3.1 Histone acetylation in OA—Acetylation of specific lysine residues on the N-terminal tails of histones is mediated through enzymatic activity of histone acetyltransferases (HATs) which oxidize amine to amides and nullifies the positive charge of histones. Thus acetylation decreases the binding ability of histones with DNA, thereby preventing condensation of chromatin and therefore allows the binding of transcription factor leading to initiation of gene expression [56]. On the contrary, deacetylation is carried out by histone deacetylases (HDAC) that provide a positively charged histone tail, encouraging high affinity binding between the DNA backbone and histones, resulting in chromatin condensation, and thus preventing transcription leading to repression of gene expression. The HDAC proteins are classified into two functional groups based on DNA sequence similarity and activities. Classic HDAC proteins (class I, II, and IV) possess a zinc-dependent active site and these families have 11 known members named HDAC 1 to 11. HDAC class III proteins require the NAD^+ cofactor for activity and are known as sirtuins that are further grouped into 7 subtypes named chronologically (SIRT 1 to 7) [57–59]. The balance between HAT and HDAC has a strong impact on the chondrocyte phenotype and was shown to be altered by biological treatments used in arthritis depicting the important role of histone modifications in the disease [60].

Recent studies demonstrated that altered activation of HDACs and their differential expression patterns contribute to the initiation and progression of OA. Expression levels of HDAC1 and HDAC2 were higher in OA chondrocytes and were shown to repress the expression of genes encoding COL2A1, ACAN, COMP, COL11A1 [61–64]. HDAC4 is known to be a major regulator of chondrocyte hypertrophy and abnormal expression of HDAC4 in OA cartilage suggests its involvement in promoting the catabolic activity of chondrocytes associated with OA pathogenesis [65]. Cao et al. further demonstrated that decreased HDAC4 expression in OA chondrocytes corresponds with increased expression of

Runx2 and other MMPs suggesting that HDAC4 has a chondroprotective effect in OA cartilage [66]. Additionally, Higashiyama et al (2010) demonstrated the enhanced expression of HDAC7 in OA cartilage which correlated with the increased production of MMP-13 and ECM degradation [67]. These studies suggest that inhibiting or augmenting the expression of specific HDACs may be useful in the management of OA.

Class III HDAC family (Sirtuins family), which is composed of seven members, seems to play a pivotal role in chromatin regulation in cartilage. It has been shown that chondrocytes isolated from OA patients SIRT1 activity was essential for cartilage-specific expression of extracellular components ACAN and COL2A1 [68]. Other studies showed the *in vivo* relevance of SIRT1 in cartilage biology by demonstrating that the articular cartilage in Sirt1−/− mice had altered chondrocyte phenotype with high levels of MMP13 and increased chondrocyte apoptosis [69, 70]. Furthermore, over-expression of SIRT1 in chondrocytes under stimulation with IL-1β reduced the expression of matrix degrading proteases MMPs 1, 2, 9, 10, 11, 12, and 13 and ADAMTS-5 suggesting a protective role of SIRT1 in cartilage [71]. Recently, a known SIRT1 activator has been shown to inhibit the destruction of cartilage by increasing SIRT1 activity in mouse OA cartilage [72]. Collectively, these studies suggest that SIRT1 activators may be useful in the management of OA. In addition to SIRT1, SIRT6 has also been shown to play a protective role in OA. Wu Y et al (2015) in his recent study demonstrated that SIRT6 protein levels were significantly low in OA chondrocytes compared to normal human chondrocytes and over-expression of SIRT6 in mouse joints protected from cartilage degeneration by reducing the expression of NF-κB-dependent inflammatory genes [73].

2.3.2 Histone methylation in OA—Histones methylation is an important modification resulting in the formation of active and inactive genomic regions which is associated with both transcriptional activation and silencing [74]. Methylation of lysine or arginine residues on histone tails is catalysed by histone methyl transferases (HMTs) and protein arginine methyltransferases (PRMTs) whereas demethylation of histone is catalyzed by histone demethylases [75]. Histone methylation adds one or more methyl groups to regulate transcription. Depending on the residue involve in the histones methylation, various transcriptional consequences occur such as the addition of three methyl groups to lysine 27 of histone 3 (H3K27) which results in transcriptional repression whereas methylation of lysine 4 in histone 3 (H3K4) leads to transcriptional activation [76]. Few reports are available regarding histone methylation in chondrocytes. A recent study showed that IL-1 induces histone H3K4 di- and trimethylation around the COX2 and iNOS promoters but not that of MMP-13 and histone methyltransferase inhibition prevented the IL-1-induced COX-2 and iNOS expressions in chondrocytes [77]. Only limited number of studies investigated the role of histone methylation in OA and this field lack large studies of genome-wide histone modification patterns in OA, particularly integrated studies of histone methylation and gene expression patterns; this should be a focus of future research efforts.

2.4 Potential of HDAC inhibitors as therapeutics in OA

HDACs including HDAC1, HDAC2 and HDAC7 are upregulated in OA chondrocytes and their inhibition using specific HDAC inhibitor (HDACi) has been shown to confer protection

and prevent the ECM degradation in human OA chondrocytes [14, 65, 78]. Inhibiting HDAC activity offers potential solutions to prevent or reverse the molecular events involved in OA pathogenesis. Although HDACi exerts chondroprotective effect and provide benefits to permanent and adult articular cartilage by decreasing production of catabolic cartilage matrix genes, there are few reports demonstrating that genetic and chemical inhibition of HDAC during development causes multiple skeletal deformities and negatively affects chondrocyte biology. HDACi includes a range of naturally occurring as well as synthetic compounds, which differ in terms of function and HDAC specificity. Pan-HDACi such as Trichostatin A and Vorinostat inhibit the activity of class I and II HDACs (HDAC 1 to 10), whereas others are class/isoform-selective inhibitors such as FK-228 inhibits HDAC 1 and 2.

Recent evidence demonstrates that HDAC inhibitors have chondroprotective effects in OA models. Wang X et al (2009) showed that broad-spectrum HDACi Trichostatin A prevents IL1β-mediated upregulation of MMPs in human OA chondrocyte [79]. Additionally, Culley et al. (2013) found that inhibition of Class I HDACs via two other agents (Valproic acid and MS275) was sufficient to prevent IL1β-induced upregulation of matrix degrading proteases-MMP-1 and MMP-13 in human OA chondrocytes [80]. These authors further demonstrated that systemic administration of Trichostatin A (TSA) prevents cartilage destruction in a model of surgically induced OA [80]. Similarly, other studies also demonstrated the chondroprotective potential of TSA in a rabbit experimental OA model where TSA prevented cartilage degradation and production of matrix degrading MMP1, MMP3, and MMP13; Cathepsins K, B, L, and S; and Cystatin C, as well as IL-1 [81]. Young et al. further demonstrated the chondroprotective effects of HDAC inhibition by demonstrating the TSA and sodium butyrate mediated inhibition of MMPs and ADAMTS5 expression in pro-inflammatory cytokine treated human chondrocytes [82].

Cai et al. using Nrf2−/− mice explored the systemic histone deacetylase inhibition as a novel strategy to prevent OA and identify a role for Nrf2 in preventing the cartilage degeneration in preclinical model of OA [83]. These authors showed that loss of Nrf2 in mice causes severe cartilage damage in OA models and administration of TSA promotes the expression of Nrf2 in wild type mouse joint tissues and reduces cartilage destruction [83]. However, TSA did not offer significant protection from OA in Nrf2−/− mice, suggesting that Nrf2 is required for TSA-dependent protective benefits in OA [83]. Further an earlier study by Nasu et al. demonstrated the efficacy of systemic TSA administration in reducing the expression of various MMPs, as well as measures of cartilage damage in a collagen antibody-injection OA mouse model [84]. Chen et al demonstrated the alleviation of OA by TSA and found that elevated levels of MMPs and IL-1 were significantly reduced by TSA treatment in an experimental model of OA [85]. Further Saito et al (2013) has demonstrated that TSA suppressed the mechanical stress induced expression of RUNX-2 and ADAMTS-5 by inhibiting the activation of MAPK signaling (ERK1/2, p38MAPK, JNK) in human chondrocytes [86].

The United States Food and Drug Administration (FDA) approved several broad-acting HDACi for clinical use for various diseases. Vorinostat or SAHA, Zolinza; Romidepsin were approved for cutaneous T cell lymphoma, myeloma, other hematopoietic cancers and solid tumors, whereas Valproic acid, Valproate, Divalproex sodium, Depakote were approved for

epilepsy and bipolar disorder. Other HDACis such as Panobinostat or LBH589; Entinostat or MS-275; Givinostat or ITI2357 are currently under evaluation in various clinical trials for treatments of other cancers and conditions such as inflammation, neurodegeneration, and diabetes [87]. There are 609 HDACi related human clinical trials completed/ongoing (https://clinicaltrials.gov; last accessed July 31, 2017); however, none of them are related to OA. One study has assessed the safety and efficacy of an oral HDACi Givinostat (ITF2357) in systemic-onset juvenile idiopathic arthritis and found significant therapeutic effects with regard to the arthritic component of the disease [88].

Vorinostat has emerged as a promising HDACi which is orally bioavailable and acts as a broad-spectrum inhibitor of class I and II HDACs. Vorinostat, chemically known as Suberoylanilide hydroxamic acid, and clinically as Zolinza, is clinically the most advanced HDACi [89]. Approximately half of all of the reported clinical trials on HDACi are with Vorinostat. Vorinostat was first approved in 2006 by the US Food and Drug Administration for the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma in whom other treatments have failed. Zhong et al in his recent study used Vorinostat, a broad-spectrum HDACi and demonstrate that Vorinostat inhibits IL1β-induced upregulation of various MMPs as well as nitric oxide production in human chondrocytes *in vitro*, selectively acting through p38 and ERK1/2 inhibition [90]. Further Wang et al. demonstrated another indirect mechanism by which Vorinostat prevents cartilage degeneration in OA [91]. The HDACi- Vorinostat and Panobinostat has been shown to elevate miR-46, which is a negative regulator of inflammatory responses, in fibroblast-like synoviocytes from OA joints [91]. A recent report by Makki et al (2016) indicated that Vorinostat is an effective suppressor of IL-6 induced signaling events in OA [92]. This study opens a new avenue in the management of OA by demonstrating the Vorinostat-mediated suppression of MMP-13 through inhibition of IL-6 in human OA chondrocytes suggesting the potential of Vorinostat as a therapeutic agent for the management of OA. The molecular aspect of Vorinostat mediated protective effect demonstrate that it down-regulates iNOS (inducible nitric oxide synthase), and selectively inhibits NF-kB signaling and represses IL-1β induced p38-MAPK and ERK 1/2 activation without affecting JNK activation [90]. These studies indicate that the inhibition of HDACs could have a beneficial effect in the management of osteoarthritic conditions through selective inhibition of known molecular targets of OA (Figure 2).

Interestingly class III HDACs (Sirtuins family) has also been shown to play a pivotal role in chromatin regulation in cartilage. SirT1 has recently been show as essential regulator of chondrocyte survival through activation of insulin-like growth factor signaling and inhibition p53 mediated apoptosis [93]. Additionally, SirT1 also promotes the expression of cartilage matrix gene such as ACAN, COL2A1, COL9A1 and COMP through deacetylation of SOX9 and activation of HIF-2α [68]. The inhibition of SIRT1 by siRNA induces significant downregulation of ACAN and upregulation of COL10A1 and ADAMTS-5 [94]. The inhibition of SirT1 leads to an increase in chondrocyte apoptosis while addition of resveratrol, a sirtuin activator, protects chondrocytes from cell death [95]. Thus, recent evidence suggests that HDACi have the potential to protect articular cartilage from destruction by preventing matrix degradation.

Although, many of HDACi are synthetic compounds but some HDACi are derived naturally from microbial metabolites (eg, TSA, isolated from *Streptomyces hygroscopicus*). The first molecule identified to affect histone acetylation status was allyl derivative isolated from garlic extract. Other prominent plant-based HDACi includes Sulforaphane (found in cruciferous vegetables) and Quercetin (found in a variety of fruits and beverage) [57]. Because HDACi seems to possess therapeutic potential against a variety of diseases, there is increasing interest in the potential of dietary compounds that possess HDAC inhibitory activities. However, some of the natural agents appear to have dual effects on HDACs. For example, Resveratrol is a reported activator of class III HDAC SIRT1 but also has been shown to inhibit the other 3 class of HDACs (class I, II, and IV) [96]. Other examples are of Curcumin and Genistein, which exhibit both HDAC inhibitory and histone acetylation activator activities [57]. It appears that further research is required to determine whether the naturally occurring HDAC modulators may be useful in the management of OA.

2.5 Conclusions

There is an increasing interest in exploiting the therapeutic use of epigenetics and HDACi in the treatment of a variety of disorders linked to HDAC dysfunction. HDACs post-translationally alter the histone and non-histone proteins, which affect the final gene expression outcome. Expression of certain HDACs has been shown to be deregulated in OA. In recent years, the roles of HDACs in cartilage development and homeostasis, as well as in the advancement of OA pathogenesis, have become better clarified; however, this area of research is still in its infancy and detailed investigations are needed to understand the functional and therapeutic significance of specific HDACs inhibition in OA. There is still much to be discovered about their mechanisms of action. Most studies investigating the roles of HDACs in cartilage have studied in the context of chondrocytes from young animals, but there are limited mechanistic studies in articular cartilage of adults or aged animals. Determining which HDAC is to be targeted and whether a selective HDACi or a pan-HDACi would be useful in the therapeutic management of OA is an important area of future research. A recent report from our lab is an important effort in this direction that provides substantial evidence for the potential use of HDACi-Vorinostat in the management of OA. Although use of HDACi as a therapeutic intervention in OA is promising, use of newer generations of HDACi is expected to be useful for the selective and effective inhibition of molecular events involved in OA pathogenesis.

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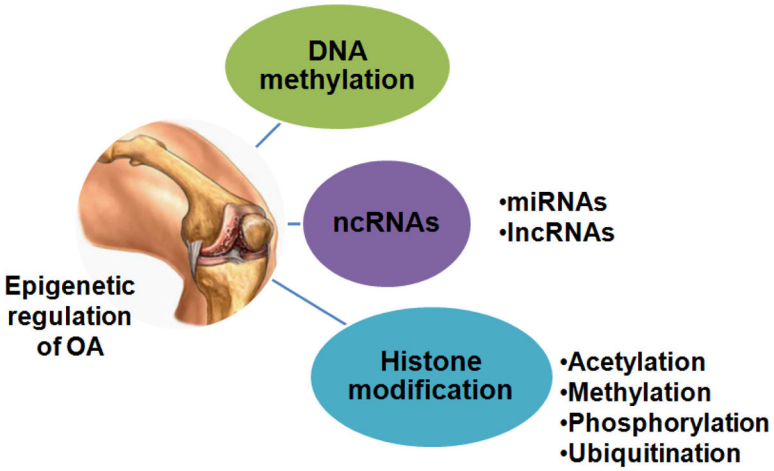

Figure 1. Epigenetic regulation of osteoarthritis

Three different epigenetic regulation of molecular pathogenesis of OA. DNA methylation, non-coding RNAs (ncRNAs: miRNAs and lncRNAs) expression and histone modifications regulate the gene expression involved in the etiology of OA at transcription and/or post-transcription levels. Histone acetylation, histone methylation, phosphorylation and ubiquitination are major histone modifications involved in OA.

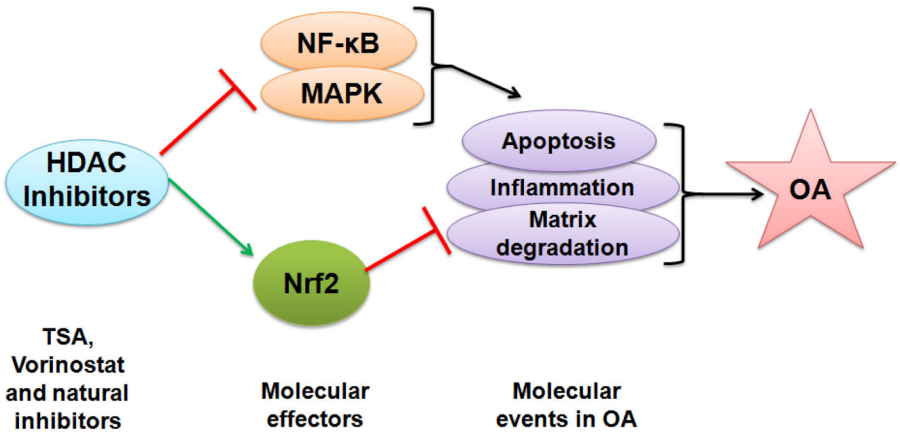

Figure 2. Molecular effectors of HDAC inhibitors in osteoarthritis

HDAC inhibitors (TSA, Vorinostat) inhibits the activation of NF-κB and MAPK (ERK1/2, JNK, p38MAPK) which are major players of OA pathogenesis known to be involved in the matrix degradation, apoptosis and inflammatory response in OA. HDAC inhibitor also activates transcription factor Nrf2 which is known to inhibit the molecular events of inflammation and matrix degradation in OA.

Table 1

Differentially expressed miRNAs and their molecular target(s) in OA

miRNA	Differential expression in OA	Target gene(s)	Biological effects	References
miR-22	Upregulated	PPARα, BMP7, ACAN	Lipid metabolism	[29]
miR-9	Upregulated	MMP-13, MCPIP1	Matrix degradation	[30] [31]
miR-25	Upregulated	COX-2	Inflammation	[30] [32]
miR-602	Upregulated	SHH	Chondrocytes homeostasis	[33]
miR-608	Upregulated	SHH	Chondrocytes homeostasis	[33]
miR-139	Upregulated	MCPIP1	Inflammation	[31]
miR-27a	Downregulated	MMP-13, IGFBP5	Matrix degradation	[34]
miR-27b	Downregulated	MMP-13	Matrix degradation	[35]
miR-140	Downregulated	ADAMTS-5, MMP-13	Matrix degradation	[36]
miR199a	Downregulated	COX-2	Inflammation	[35]
miR-138	Downregulated	Sp1, HIF2α	Chondrocytes differentiation	[37] [38]

Table 2

Differentially expressed lncRNAs and their role in OA pathogenesis

Target lncRNA	Expression in OA	Molecular effects in OA	References
HOTAIR	Upregulation	ECM degradation, Apoptosis,	[49] [50]
GAS5	Upregulation	ECM degradation, Apoptosis	[49]
PCGEM1	Upregulation	Apoptosis	[51]
HOTTIP	Upregulation	ECM degradation	[52]
LncRNA-CIR	Upregulation	ECM degradation	[48]
H19	Downregulation	ECM degradation	[49]
MEG3	Downregulation	Angiogenesis	[53]
CILinc01	Downregulation	Inflammation	[54]
CILinc02	Downregulation	Inflammation	[54]