REVIEW

Epigenetic and microRNA regulation during osteoarthritis development [version 1; referees: 3 approved]

Di Chen[1], Jie Shen[2], Tianqian Hui[1]

[1]Department of Biochemistry, Rush University Medical Center, Chicago, IL, 60612, USA
[2]Department of Orthopedic Surgery, Washington University, St. Louis, MO, 63110, USA

v1 **First published:** 20 Oct 2015, **4**(F1000 Faculty Rev):1092 (doi: 10.12688/f1000research.6548.1)
Latest published: 20 Oct 2015, **4**(F1000 Faculty Rev):1092 (doi: 10.12688/f1000research.6548.1)

Abstract

Osteoarthritis (OA) is a common degenerative joint disease, the pathological mechanism of which is currently unknown. Genetic alteration is one of the key contributing factors for OA pathology. Recent evidence suggests that epigenetic and microRNA regulation of critical genes may contribute to OA development. In this article, we review the epigenetic and microRNA regulations of genes related to OA development. Potential therapeutic strategies may be developed on the basis of novel findings.

This article is included in the F1000 Faculty Reviews channel.

Open Peer Review

Referee Status: ✓ ✓ ✓

	Invited Referees 1	2	3
version 1 published 20 Oct 2015	✓	✓	✓

F1000 Faculty Reviews are commissioned from members of the prestigious F1000 Faculty. In order to make these reviews as comprehensive and accessible as possible, peer review takes place before publication; the referees are listed below, but their reports are not formally published.

1 **Kenneth B. Marcu**, Stony Brook University USA

2 **Alexander Lichtler**, University of Connecticut Health Center USA

3 **Tatsuya Kobayashi**, Massachusetts General Hospital and Harvard Medical School USA

Discuss this article

Comments (0)

Corresponding author: Di Chen (di_chen@rush.edu)

How to cite this article: Chen D, Shen J and Hui T. **Epigenetic and microRNA regulation during osteoarthritis development [version 1; referees: 3 approved]** *F1000Research* 2015, **4**(F1000 Faculty Rev):1092 (doi: 10.12688/f1000research.6548.1)

Grant information: This research was supported by grants from the National Institutes of Health (AR-055915 and AR-054465) and the North American Spine Society to Di Chen.

Competing interests: The authors declare that they have no competing interests.

First published: 20 Oct 2015, **4**(F1000 Faculty Rev):1092 (doi: 10.12688/f1000research.6548.1)

Introduction

Osteoarthritis (OA) is the most common form of arthritis and is the leading cause of impaired mobility in the elderly[1]. It has been projected that more than 67 million people will be affected by OA in the US by 2030, resulting in an extremely high socioeconomic burden[2,3]. In recent years, the surgically induced destabilization of the medial meniscus (DMM) model[4] and genetic mouse models[5–12] have been developed to delineate the potential roles of affected genes in OA pathogenesis. However, a full understanding of the factors affecting the initiation and progression of the disease has not yet been revealed. Thus, there is no clinical diagnosis for early OA and no effective disease-modifying treatment for late-stage OA, except pain-relieving medication and surgical replacement of the damaged joints[13–15]. Compelling evidence has revealed that epigenetic and microRNA (miRNA) alterations occur in OA chondrocytes and in patients with OA, including several well-documented OA-related genes, indicating, to a certain extent, that epigenetic and miRNA regulation contributes to OA pathogenesis[16–18]. In this short review, we will summarize the current understanding of OA, speculate on the potential mechanism(s) of epigenetic and miRNA regulation underlying OA development and progression, and in this context propose potential therapeutic targets for the treatment of OA.

Pathogenesis of osteoarthritis

OA is a degenerative joint disease with major clinical symptoms, including chronic pain, joint instability, stiffness, and radiographic joint space narrowing. During OA progression, articular chondrocytes undergo hypertrophy, leading to extracellular matrix (ECM) degradation and articular cartilage breakdown, followed by vascular invasion, subchondral bone sclerosis, and osteophyte formation eventually developing at the margins of the joint[19–21]. OA is a complex multi-factorial disease, and the effects of aging and obesity, mechanical influences, and environmental and genetic factors have been identified as major factors contributing to the initiation or progression (or both) of OA[22,23]. Because articular cartilage damage is the primary pathologic feature leading to the joint dysfunction, it has received much of the attention in OA studies. Normal articular cartilage emerges during the postnatal stage as a permanent tissue distinct from the growth plate. The articular cartilage tissue lining the surface of all diarthrodial joints is a smooth, hard, white tissue, which cushions and absorbs the shock between joints. Collagens and proteoglycans are the principal ECM molecules of articular cartilage[24–27]. Mutations of ECM-related factors, including, types II, IX and XI collagen, have been reported in human OA patients[28–30]. It has been established that articular chondrocytes are the cells responsible for maintaining joint cartilage homeostasis. Thus, dysregulation of articular chondrocytes is directly connected to the process of cartilage degradation in OA. An understanding of the phenotypic behavior of articular chondrocytes in homeostasis and disease has revealed several key environmental and genetic factors that impact OA development and progression.

Genetic contributions to osteoarthritis

A genetic predisposition to OA has been established for many years through several twin studies, segregation analyses, linkage analyses, and candidate gene association studies[31–33]. Although the genetics of OA are complex, the genetic contribution to OA is highly significant. It has been demonstrated that the heritability of OA may be as high as 40–65%, depending on the joint site and population studied[34]. In the past decade, the potential roles of genes and signaling pathways in OA pathogenesis have been demonstrated by *ex vivo* studies with tissue derived from OA patients and *in vivo* studies with surgically induced OA animal models as well as mouse genetic models. Transforming growth factor-beta (TGF-β), Wnt/β-catenin, Indian Hedgehog (Ihh), Notch, fibroblast growth factor (FGF), and hypoxia-inducible factor (HIF) pathways, by stimulating chondrocytes toward hypertrophy, have demonstrated the critical and unique roles of chondrocytes during OA development and progression in genetic mouse models[5–7,9,10,35]. These recent genetic findings further suggest that Runt-related transcription factor 2 (*Runx2*), *Mmp13*, and *Adamts5* are common target genes involved in the above-mentioned signaling networks, disrupting the anabolic and catabolic balance in chondrocytes and eventually degrading the cartilage matrix by upregulation of matrix metalloproteinase (MMP) and a disintegrin and metalloprotease with thrombospondin motif (ADAMTS) activity, which leads to degradation of type II collagen and aggrecan[8,11,36–38]. Although these studies have been important in determining the genetic components of OA, only a few OA-related genes have been identified by using human genetic and epidemiological approaches. More recent newer technologies, such as genome-wide association studies (GWASs), have been used to analyze large numbers of OA and control populations throughout the world in hopes of uncovering more genes associated with OA. To date, even these larger exploratory human genetic studies have produced very few genes important to the development and pathogenesis of human OA. Whereas some of the genes identified are important structural and ECM-related factors (*Col2a1*, *Col9a1*, and *Col11a1*) as well as critical signaling molecules in the Wnt (*Sfrp3*), bone morphogenetic protein (BMP) (*Gdf5*), and TGF-β (*Smad3*) signaling pathways, most have been previously implicated in OA or articular cartilage and joint maintenance by using mouse models of induced genetic alteration or surgically induced OA[28–30,39–42]. New single-nucleotide polymorphisms were identified in several genes, including GNL3, ASTN2, and CHST11, in recent genome-wide screen studies[43], and these findings need to be further confirmed.

Epigenetic alterations in osteoarthritis pathogenesis

In addition to GWAS analyses, growing evidence suggests that the gene expression profile can be largely regulated by epigenetic machinery that modulates local transcriptional activity and mRNA expression in chondrocytes[44]. In normal adult chondrocytes, like other somatic cells, the genomic arrangement and packaging are regulated by genetic and epigenetic mechanisms that provide instruction on how, where, and when genetic information should be used. In mammals, the major epigenetic regulatory mechanisms include DNA methylation and histone modification. miRNAs could be loosely defined as epigenetic factors and play important roles in OA[45].

DNA methylation

DNA methylation is mediated by DNA methyltransferase (DNMT), which transfers the methyl group from the donor, methylated S-adenosyl-methionine (methyl-SAM), to DNA bases, particularly cytosine (CpG island). DNA methylation occurs in both the gene promoter region and gene bodies and regulates gene transcription[46–48]. Recent studies found that DNA methylation is dynamically regulated

through a cyclic enzymatic cascade composed of cytosine methylation by DNMTs and demethylation by ten-eleven translocation methylcytosine-(TET) dioxygenases (TET1, 2, and 3)[49]. In mammals, there are three enzymatically active DNMTs, DNMT1, DNMT3a, and DNMT3b, and one related regulatory protein, DNMT3L[48]. DNMT1 is primarily a "maintenance" methyltransferase that recognizes the hemi-methylated DNA strand and preserves the methylation pattern throughout cell replication and division. The global knockout of the *Dnmt1* gene is embryonically lethal at E10.5 because of a significant loss of global DNA methylation, suggesting that DNA methylation is essential for normal mammalian development[50]. In contrast, two *de novo* DNMTs, 3a and 3b, have tissue-specific expression patterns and create unique methylation signatures. Knockout mice with *Dnmt3b* deletion showed embryonic lethality between E11.5 and E15.5 as well as several skeletal defects, including growth impairment. However, loss of the *Dnmt3b* gene does not affect the entire genome methylation pattern[51].

In recent decades, researchers have studied changes in the DNA methylation status of individual genes during OA development and progression and found that the promoter of *Col10a1* appeared to be hypomethylated during chondrocyte hypertrophy and maturation followed by its upregulation[52]. Similarly, the CpG sites within the promoter area of a number of metalloproteinases, including MMP2, MMP9, MMP13, and ADAMTS4, showed decreased methylation profiles in OA compared to normal cartilage, correlating with elevated gene expression and resulting in ECM degradation[53,54]. Reduced CpG methylation was reported in the *MMP13*, *IL-1β*, and inducible nitric oxide synthase (*iNOS*) promoter in OA tissue which correlates with the increased *MMP13*, *IL-1β*, and *iNOS* expression in OA chondrocytes[55,56]. During the chondrocyte maturation process, changes in DNA methylation patterns were observed in several transcription factors, such as Sox9 and Runx2[57]. Hypomethylation in promoter regions of those genes promoted gene transcription, which further activated downstream signaling molecules, including MMPs, and eventually stimulated chondrocytes toward hypertrophy and terminal maturation. Either hypomethylation or hypermethylation occurred in promoter regions within a subset of OA-specific genes, including ligands (e.g., BMP7 and IL-1β)[58,59], receptors, transcription factors (e.g., Sox9 and Runx2)[57], enzymes (e.g., MMPs and ADAMTS4/5)[53,54], and ECM proteins (e.g., aggrecan, Col2a1, and Col10a1)[52,60].

Recent methylome screening data further confirmed that alterations in DNA methylation occurred in OA chondrocytes and that chondrocyte transcriptomes may be changed in OA patients, indicating that DNMTs influence OA susceptibility and severity by modulating pathways or signals leading to OA[16–18,61,62]. However, which DNMT factor or factors mediate these changes genome-wide remains largely unknown. In one of our ongoing experiments, we have found that DNMT3b, but not DNMT 1 or 3a, was highly expressed in articular chondrocytes, but its expression was significantly decreased in chondrocytes derived from patients with OA or from several OA mouse models, including the aging animal model, meniscal ligamentous injury (MLI) model, and obesity model (Shen *et al.*, unpublished data). Recent reports demonstrated that TET1, 2, and 3 are present in human chondrocytes and that *TET1* expression was significantly reduced by inflammatory factors, such as IL-1β or TNFα[63]. Recent studies have also revealed a significant increase in 5-hydroxymethylcytosine levels in OA chondrocytes because of TET1 downregulation[64,65]. Because DNA methylation is a reversible process, the role of the TET family members in OA development needs further investigation to better understand the regulation of DNA demethylation during OA development and progression.

The regulation of transcription factors on chondrocyte-specific genes through alterations of DNA methylation and histone modification has been reported in recent years. For example, it has been reported that methylation of the -110 bp CpG site in the *Mmp13* promoter strongly correlates with the high *Mmp13* expression in chondrocytes. This CpG site resides within a HIF consensus motif. The methylation of this site will decrease HIF-2α binding to the *Mmp13* promoter[55]. AT-rich interactive domain 5b (Arid5b) is a newly identified transcriptional co-regulator of Sox9. Arid5b recruits Phf2, a histone lysine demethylase, to the promoter region of Sox9 target genes and stimulates H3K9me2 demethylation of these genes. In the promoters of chondrocyte marker genes, H3K9me2 levels are increased in Arid5b knockout chondrocytes[66].

Histone modification

Working closely with DNA methylation, histone modification—including acetylation, phosphorylation, methylation, and ubiquitination—regulates gene expression by controlling the accessibility of the transcriptional machinery[67,68]. Recent studies demonstrated that histone acetylation and deacetylation are involved in OA pathogenesis by affecting chondrocyte anabolic and catabolic processes. Histone acetylation is mediated by histone acetyltransferases (HATs) and is a critical step in loosening the DNA structure, which allows regulatory factors to access the transcriptional machinery and the subsequent initiation of gene expression, whereas deacetylation is considered the termination or repression of gene expression[69]. Histone deacetylation is mediated by histone deacetylases (HDACs), including the classic HDAC and NAD^+-dependent silent information regulator 2 (SIR2) families[70,71]. The use of large-scale analysis (ChIP-seq) of chondrocyte histone acetylation did not find global alterations in OA chondrocytes but did find changes in specific gene loci, encoding MMPs, ECM molecules, and inflammatory factors.

In patients with OA, elevated HDAC7 expression has been reported to contribute to cartilage degradation by inducing *Mmp13* expression in OA cartilage. The inhibition of HDAC7 *in vitro* leads to suppression of inflammatory factor-induced *Mmp13* expression[72]. The expressions of HDAC1 and HDAC2 are upregulated in OA synovial tissue as well, and this may lead to repression of *Col2a1* expression in chondrocytes by interfering with the recruitment of Snail[73,74]. Therefore, HDAC inhibitors have been extensively studied in various OA models. Specific HDAC inhibitors can inhibit cytokine-induced MMP expression in chondrocytes to protect against proteoglycan loss and cartilage degradation[75–77]. HDAC inhibitors can also stimulate the expression of ECM components—such as Col2a1, cartilage oligomeric matrix protein (COMP), and aggrecan—in chondrocytes[74,78]. In the rabbit anterior cruciate ligament transection (ACLT) model, an HDAC inhibitor significantly decelerated injury-induced cartilage erosion, mainly due to reduced expression of MMPs and inflammatory cytokines, indicating that HDAC inhibitors may provide a potential treatment for OA[79].

In the SIR2 family, SIRT1 has been extensively studied. SIRT1 is highly expressed in chondrocytes and its expression was found to be decreased in OA cartilage[80,81]. SIRT1 can promote expression of ECM genes, such as *Col2a1*, *Col9a1*, and *COMP*, possibly through deacetylation of Sox9, while inhibiting *Col10a1* and *Adamts5*[82]. SIRT1 also prevents apoptosis in chondrocytes by enhancing insulin-like growth factor (IGF) signaling to inactivate p53. The reduction of SIRT1 expression leads to an increase in chondrocyte apoptosis in OA cartilage[83]. Interestingly, the function of SIRT1 is closely linked to the inflammatory response and the hypoxic response as well, although SIRT1 has not been approved for use to treat OA. In a variety of tissues, SIRT1 initiates a gene-specific transcriptional repression program to terminate inflammatory response by deacetylating the p65 subunit of nuclear factor-kappa-B (NF-κB) and blocking NF-κB binding to the DNA elements[84,85]. SIRT1 can also directly deacetylate and activate HIF-2α, which is upregulated in OA cartilage, to promote MMP expression and eventually degrade the articular cartilage[86,87].

In addition to histone acetylation, histone H3K4 methylation mediated by histone-lysine N-methyltransferase (HMT) was recently investigated. HMT expression level was found elevated in OA cartilage, which resulted in H3K4 methylation at the iNOS and COX-2 promoter areas and induction of gene expression[88]. Similarly, an age-dependent increase in H3K4me2 occurs in the nuclear factor of activated T cells 1 (*Nfat1*) promoter, which led to suppression of *Nfat1* expression in adult articular chondrocytes and eventually developed OA-like phenotype in mice[89,90]. Increased demethylation mediated by histone demethylase LSD1 was also found in OA chondrocytes. Elevated LSD1 contributed to H3K9 demethylation in the microsomal prostaglandin E synthase 1 (mPGES-1) promoter and induction of gene expression in human OA chondrocyte[91]. Moreover, the architecture of histone acetylation and methylation in local genome can further guide the long-range chromatin interaction to regulate specific gene regulatory DNA elements[92].

MicroRNA regulation

The role of miR-140 in osteoarthritis pathogenesis

miRNAs are endogenous non-coding RNAs and play important roles in negative regulation of RNA stability and protein expression[93,94]. Several miRNAs have been found to be more abundant in articular chondrocytes than in undifferentiated mesenchymal stem cells. The best example of this is miR-140[95]. miR-140 is found in an intron of the *Wwp2* gene coding for WWP2 E3 ubiquitin ligase[96]. Deletion of *miR-140* did not alter the expression level of *Wwp2* in chondrocytes[97]. Analysis of the intronic sequence found two miR-140s: miR-140-5p and miR-140-3p[98]. The expression levels of miR-140-5p and -3p were both significantly reduced in OA chondrocytes[98]. During chondrocyte differentiation, *miR-140* expression increased in parallel with *Sox9* and *Col2a1*. However, in OA tissues, *miR-140* expression is reduced and *Adamts5* expression was upregulated[95]. *In vitro* treatment of chondrocytes with IL-1β suppresses *miR-140* expression[95]. miR-140 is the only miRNA with a cartilage-specific expression pattern[95,99]. *miR-140* deficiency accelerates chondrocyte differentiation into hypertrophic chondrocytes and inhibits differentiation of resting chondrocytes into columnar proliferating chondrocytes[100]. The reduction in *miR-140* expression in OA cartilage may contribute to abnormal gene expression during OA development[95]. For example, miR-140 regulates the expression of histone deacetylase 4 (HDAC4), a co-repressor of *Runx2* and myocyte-specific enhancer factor 2 (*Mef2*)[101]. miR-140 also targets *Cxcl12*[99] and *Smad3*[102], both of which are implicated in chondrocyte differentiation. In *miR-140* null mice, OA-like changes were observed and characterized by proteoglycan loss and fibrillation of articular cartilage, probably due to increased *Adamts5* expression[103]. This increased *Adamts5* expression was reversed by transfection of ds-miR-140 into *miR-140*-deficient chondrocytes[103]. In addition, cartilage-specific *miR-140*-overexpressing transgenic mice had no abnormal skeletal phenotype during embryonic development but did show a protective effect in an antigen-induced arthritis model[103]. However, the upregulation of *Adamts5* and *Hdac4* expression in chondrocytes was not found in the other *miR-140* knockout mouse model generated by Nakamura *et al.*[97]. Instead of upregulation of *Hdac4* expression, miR-140 enhances HDAC4 function in chondrocytes[100]. miR-140 could interact with PTHrP-HDAC4 pathway to control chondrocyte differentiation. *miR-140* deficiency and *PTHrP* or *Hdac4* heterozygosity synergistically impair skeletal growth. Loss of *miR-140* upregulates MEF2C expression. miR-140 negatively regulates p38 mitogen-activated protein kinase (MAPK) signaling, and inhibition of p38 MAPK signaling reduces MEF2C expression[104]. The functional role of miR-140 in cartilage homeostasis is also involved in the regulation of MMP13[105]. MMP13 is a well-known key player in cartilage biology and OA pathology. It has been reported that miR-140 is a negative feedback regulator of MMP13[106]. In addition, transfection with pre-miR-140 significantly decreased IGFBP-5 expression. In contrast, transfection with anti-miR-140 significantly increased IGFBP-5 expression[107].

The role of Runx2 in osteoarthritis development

Significant progress has been made in recent years in OA research, and several OA mouse models, including genetic models and surgically induced OA models, have been developed and reported. One common feature of these animal models is upregulation of Runx2[5,9,36], leading to further increases in genes coding for matrix degradation enzymes, such as *Mmp9*, *Mmp13*, and *Adamts5*, because Runx2 is a key transcription factor regulating the transcription of these genes[108–110]. Key questions are how Runx2 is regulated and whether a therapeutic strategy can be developed by downregulation of Runx2 in OA cartilage.

During skeletal development, Runx2 mRNA expression was detected in skeletal elements as early as E10.5 and E11.5; however, hypertrophic chondrocytes and primary ossification centers do not form until E14.5, although Runx2 is a key transcription factor driving chondrocyte hypertrophy[111]. These findings suggest that Runx2 protein expression is suppressed because of post-transcriptional regulation during early skeletal development since chondrocyte proliferation and expansion are needed at this stage. These findings also suggest that there is an endogenous negative regulatory mechanism for Runx2 protein expression.

MicroRNA regulation of Runx2 expression

In recent studies, we have examined potential miRNAs that may bind the 3′-non-coding region of the Runx2 gene and found that miR-204 and miR-211, two homologous miRNAs, bind Runx2 and regulate Runx2 expression in mesenchymal progenitor cells[112]. To

further investigate the functions of these miRNAs in the regulation of Runx2 protein expression in articular chondrocytes and in cartilage homeostasis, chondrocyte-specific miR-204 and miR-211 transgenic mice and conditional knockout mice need to be generated and tested. In addition to miR-204 and miR-211, several other miRNAs have been reported to regulate Runx2 expression[113]. Their functions in OA development also need further investigation.

The role of miRNA regulation in OA development involves upstream regulation and downstream gene targeting. For example, it has been reported that IL-1β, an inflammatory cytokine, suppresses the expression of miR-140, which in turn causes upregulation of *Adamts5*, a target gene of miR-140, in chondrocytes[95,103], so miR-140 could serve as a mediator during OA development. In addition, it has been reported that TGF-β/Smad3 regulates miR-140 expression in OA chondrocytes[114]. TGF-β signaling is one of the key signaling pathways in OA development and responds to mechanical loading. Monocyte chemoattractant protein-induced protein 1 (MCPIP-1) is a novel post-transcriptional regulator of IL-6 expression and is targeted by miR-9. MCPIP-1 mRNA expression was low, but expression of miR-9 and IL-6 was high, in damaged OA cartilage. MCPIP-1 protein directly binds with IL-6 mRNA, and overexpression of wild-type MCPIP-1 destabilized the IL-6 mRNA. MCPIP-1 expression was altered by overexpression or inhibition of miR-9. These findings implicate miR-9-mediated suppression of MCPIP-1 in the pathogenesis of OA via upregulation of IL-6 expression in IL-1β-stimulated human OA chondrocytes[115]. These studies also suggest that miRNAs may serve as important mediators in OA, although they may not be able to trigger the OA occurrence.

Summary

Although OA is a multi-factorial disease, genetic factors may play a significant role in OA development and progression. Recent evidence suggests that epigenetic and miRNA regulation of genes related to OA development may contribute to OA pathology. To fully understand how mechanical instability and inflammation cause epigenetic and miRNA alteration, further leading to OA development and progression, more in-depth studies need to be conducted. These studies may lead to uncovering novel molecular targets for drug development to prevent and treat OA.

Abbreviations

ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; Arid5b, AT-rich interactive domain 5b; BMP, bone morphogenetic protein; COMP, cartilage oligomeric matrix protein; DNMT, DNA (cytosine-5)-methyltransferase; ECM, extracellular matrix; GWAS, genome-wide association study; HDAC, histone deacetylase; HIF, hypoxia-inducible factor; HMT, histone-lysine N-methyltransferase; IL, interleukin; IGF, insulin-like growth factor; iNOS, inducible nitric oxide synthase; MAPK, mitogen-activated protein kinase; MCPIP-1, monocyte chemoattractant protein-induced protein 1; Mef2, myocyte-specific enhancer factor 2; miRNA, microRNA; MMP, matrix metalloproteinase; Nfat1, nuclear factor of activated T cells 1; NF-κB, nuclear factor-kappa-B; OA, osteoarthritis; Runx2, Runt-related transcription factor 2; SIR2, silent information regulator 2; TET, ten-eleven translocation methylcytosine dioxygenase; TGF-β, transforming growth factor-beta.

Competing interests

The authors declare that they have no competing interests.

Grant information

This research was supported by grants from the National Institutes of Health (AR-055915 and AR-054465) and the North American Spine Society to Di Chen.

References

F F1000 recommended

1. Felson DT: **Clinical practice. Osteoarthritis of the knee.** *N Engl J Med.* 2006; **354**(8): 841–8.
PubMed Abstract | Publisher Full Text

2. Hunter DJ, Schofield D, Callander E: **The individual and socioeconomic impact of osteoarthritis.** *Nat Rev Rheumatol.* 2014; **10**(7): 437–41.
PubMed Abstract | Publisher Full Text

3. Hootman JM, Helmick CG: **Projections of US prevalence of arthritis and associated activity limitations.** *Arthritis Rheum.* 2006; **54**(1): 226–9.
PubMed Abstract | Publisher Full Text

4. Glasson SS, Blanchet TJ, Morris EA: **The surgical destabilization of the medial meniscus (DMM) model of osteoarthritis in the 129/SvEv mouse.** *Osteoarthritis Cartilage.* 2007; **15**(9): 1061–9.
PubMed Abstract | Publisher Full Text

5. F Shen J, Li J, Wang B, *et al.*: **Deletion of the transforming growth factor β receptor type II gene in articular chondrocytes leads to a progressive osteoarthritis-like phenotype in mice.** *Arthritis Rheum.* 2013; **65**(12): 3107–19.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

6. Serra R, Johnson M, Filvaroff EH, *et al.*: **Expression of a truncated, kinase-defective TGF-beta type II receptor in mouse skeletal tissue promotes terminal chondrocyte differentiation and osteoarthritis.** *J Cell Biol.* 1997; **139**(2): 541–52.
PubMed Abstract | Publisher Full Text | Free Full Text

7. F Yang X, Chen L, Xu X, *et al.*: **TGF-beta/Smad3 signals repress chondrocyte hypertrophic differentiation and are required for maintaining articular cartilage.** *J Cell Biol.* 2001; **153**(1): 35–46.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

8. F Little CB, Barai A, Burkhardt D, *et al.*: **Matrix metalloproteinase 13-deficient mice are resistant to osteoarthritic cartilage erosion but not chondrocyte hypertrophy or osteophyte development.** *Arthritis Rheum.* 2009; **60**(12): 3723–33.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

9. F Lin AC, Seeto BL, Bartoszko JM, *et al.*: **Modulating hedgehog signaling can attenuate the severity of osteoarthritis.** *Nat Med.* 2009; **15**(12): 1421–5.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

10. Mirando AJ, Liu Z, Moore T, *et al.*: **RBP-Jκ-dependent Notch signaling is required for murine articular cartilage and joint maintenance.** *Arthritis Rheum.* 2013; **65**(10): 2623–33.
PubMed Abstract | Publisher Full Text | Free Full Text

11. F Glasson SS, Askew R, Sheppard B, *et al.*: **Deletion of active ADAMTS5 prevents cartilage degradation in a murine model of osteoarthritis.** *Nature.* 2005; **434**(7033): 644–8.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

12. F Stanton H, Rogerson FM, East CJ, *et al.*: **ADAMTS5 is the major aggrecanase in mouse cartilage *in vivo* and *in vitro*.** *Nature.* 2005; **434**(7033): 648–52.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

13. Anderson DD, Chubinskaya S, Guilak F, *et al.*: **Post-traumatic osteoarthritis: improved understanding and opportunities for early intervention.** *J Orthop Res.* 2011; **29**(6): 802–9.
PubMed Abstract | Publisher Full Text | Free Full Text

14. van den Berg WB: **Osteoarthritis year 2010 in review: pathomechanisms.** *Osteoarthritis Cartilage.* 2011; **19**(4): 338–41.
PubMed Abstract | Publisher Full Text

15. Bijlsma JW, Berenbaum F, Lafeber FP: **Osteoarthritis: an update with relevance for clinical practice.** *Lancet.* 2011; **377**(9783): 2115–26.
PubMed Abstract | Publisher Full Text

16. F Fernández-Tajes J, Soto-Hermida A, Vázquez-Mosquera ME, *et al.*: **Genome-wide DNA methylation analysis of articular chondrocytes reveals a cluster of osteoarthritic patients.** *Ann Rheum Dis.* 2014; **73**(4): 668–77.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

17. F Rushton MD, Reynard LN, Barter MJ, *et al.*: **Characterization of the cartilage DNA methylome in knee and hip osteoarthritis.** *Arthritis Rheumatol.* 2014; **66**(9): 2450–60.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

18. F Delgado-Calle J, Fernández AF, Sainz J, *et al.*: **Genome-wide profiling of bone reveals differentially methylated regions in osteoporosis and osteoarthritis.** *Arthritis Rheum.* 2013; **65**(1): 197–205.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

19. Sandell LJ: **Etiology of osteoarthritis: genetics and synovial joint development.** *Nat Rev Rheumatol.* 2012; **8**(2): 77–89.
PubMed Abstract | Publisher Full Text

20. Bos SD, Slagboom PE, Meulenbelt I: **New insights into osteoarthritis: early developmental features of an ageing-related disease.** *Curr Opin Rheumatol.* 2008; **20**(5): 553–9.
PubMed Abstract | Publisher Full Text

21. F Goldring MB, Goldring SR: **Osteoarthritis.** *J Cell Physiol.* 2007; **213**(3): 626–34.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

22. Krasnokutsky S, Samuels J, Abramson SB: **Osteoarthritis in 2007.** *Bull NYU Hosp Jt Dis.* 2007; **65**(3): 222–8.
PubMed Abstract

23. Wang M, Shen J, Jin H, *et al.*: **Recent progress in understanding molecular mechanisms of cartilage degeneration during osteoarthritis.** *Ann N Y Acad Sci.* 2011; **1240**: 61–9.
PubMed Abstract | Publisher Full Text | Free Full Text

24. Eyre DR, Wu JJ, Fernandes RJ, *et al.*: **Recent developments in cartilage research: matrix biology of the collagen II/IX/XI heterofibril network.** *Biochem Soc Trans.* 2002; **30**(Pt 6): 893–9.
PubMed Abstract | Publisher Full Text

25. Knudson CB, Knudson W: **Cartilage proteoglycans.** *Semin Cell Dev Biol.* 2001; **12**(2): 69–78.
PubMed Abstract | Publisher Full Text

26. F Verzijl N, DeGroot J, Thorpe SR, *et al.*: **Effect of collagen turnover on the accumulation of advanced glycation end products.** *J Biol Chem.* 2000; **275**(50): 39027–31.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

27. Kannu P, Bateman JF, Belluoccio D, *et al.*: **Employing molecular genetics of chondrodysplasias to inform the study of osteoarthritis.** *Arthritis Rheum.* 2009; **60**(2): 325–34.
PubMed Abstract | Publisher Full Text

28. F Rodriguez RR, Seegmiller RE, Stark MR, *et al.*: **A type XI collagen mutation leads to increased degradation of type II collagen in articular cartilage.** *Osteoarthritis Cartilage.* 2004; **12**(4): 314–20.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

29. F Jeong C, Lee JY, Kim J, *et al.*: **Novel *COL9A3* mutation in a family diagnosed with multiple epiphyseal dysplasia: a case report.** *BMC Musculoskelet Disord.* 2014; **15**: 371.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

30. F Carlson KM, Yamaga KM, Reinker KA, *et al.*: **Precocious osteoarthritis in a family with recurrent COL2A1 mutation.** *J Rheumatol.* 2006; **33**(6): 1133–6.
PubMed Abstract | F1000 Recommendation

31. Spector TD, Cicuttini F, Baker J, *et al.*: **Genetic influences on osteoarthritis in women: a twin study.** *BMJ.* 1996; **312**(7036): 940–3.
PubMed Abstract | Publisher Full Text | Free Full Text

32. Felson DT, Couropmitree NN, Chaisson CE, *et al.*: **Evidence for a Mendelian gene in a segregation analysis of generalized radiographic osteoarthritis: the Framingham Study.** *Arthritis Rheum.* 1998; **41**(6): 1064–71.
PubMed Abstract | Publisher Full Text

33. Loughlin J, Mustafa Z, Smith A, *et al.*: **Linkage analysis of chromosome 2q in osteoarthritis.** *Rheumatology (Oxford).* 2000; **39**(4): 377–81.
PubMed Abstract | Publisher Full Text

34. F Zhang Y, Jordan JM: **Epidemiology of osteoarthritis.** *Clin Geriatr Med.* 2010; **26**(3): 355–69.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

35. Wang M, Tang D, Shu B, *et al.*: **Conditional activation of β-catenin signaling in mice leads to severe defects in intervertebral disc tissue.** *Arthritis Rheum.* 2012; **64**(8): 2611–23.
PubMed Abstract | Publisher Full Text | Free Full Text

36. F Hirata M, Kugimiya F, Fukai A, *et al.*: **C/EBPβ and RUNX2 cooperate to degrade cartilage with MMP-13 as the target and HIF-2α as the inducer in chondrocytes.** *Hum Mol Genet.* 2012; **21**(5): 1111–23.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

37. Barnholtz-Sloan JS, Severson RK, Stanton B, *et al.*: **Pediatric brain tumors in non-Hispanics, Hispanics, African Americans and Asians: differences in survival after diagnosis.** *Cancer Causes Control.* 2005; **16**(5): 587–92.
PubMed Abstract | Publisher Full Text

38. F Kim JH, Jeon J, Shin M, *et al.*: **Regulation of the catabolic cascade in osteoarthritis by the zinc-ZIP8-MTF1 axis.** *Cell.* 2014; **156**(4): 730–43.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

39. Loughlin J, Dowling B, Chapman K, *et al.*: **Functional variants within the secreted frizzled-related protein 3 gene are associated with hip osteoarthritis in females.** *Proc Natl Acad Sci U S A.* 2004; **101**(26): 9757–62.
PubMed Abstract | Publisher Full Text | Free Full Text

40. Bijsterbosch J, Kloppenburg M, Reijnierse M, *et al.*: **Association study of candidate genes for the progression of hand osteoarthritis.** *Osteoarthritis Cartilage.* 2013; **21**(4): 565–9.
PubMed Abstract | Publisher Full Text

41. Valdes AM, Spector TD, Tamm A, *et al.*: **Genetic variation in the *SMAD3* gene is associated with hip and knee osteoarthritis.** *Arthritis Rheum.* 2010; **62**(8): 2347–52.
PubMed Abstract | Publisher Full Text

42. Zhang R, Yao J, Xu P, *et al.*: **A comprehensive meta-analysis of association between genetic variants of *GDF5* and osteoarthritis of the knee, hip and hand.** *Inflamm Res.* 2015; **64**(6): 405–14.
PubMed Abstract | Publisher Full Text

43. F arcOGEN Consortium, arcOGEN Collaborators, Zeggini E, *et al.*: **Identification of new susceptibility loci for osteoarthritis (arcOGEN): a genome-wide association study.** *Lancet.* 2012; **380**(9844): 815–23.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

44. Goldring MB, Marcu KB: **Epigenomic and microRNA-mediated regulation in cartilage development, homeostasis, and osteoarthritis.** *Trends Mol Med.* 2012; **18**(2): 109–18.
PubMed Abstract | Publisher Full Text | Free Full Text

45. F Trzeciak T, Czarny-Ratajczak M: **MicroRNAs: Important Epigenetic Regulators in Osteoarthritis.** *Curr Genomics.* 2014; **15**(6): 481–4.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

46. Jones PA: **Functions of DNA methylation: islands, start sites, gene bodies and beyond.** *Nat Rev Genet.* 2012; **13**(7): 484–92.
PubMed Abstract | Publisher Full Text

47. Robertson KD: **DNA methylation and human disease.** *Nat Rev Genet.* 2005; **6**(8): 597–610.
PubMed Abstract | Publisher Full Text

48. Smith ZD, Meissner A: **DNA methylation: roles in mammalian development.** *Nat Rev Genet.* 2013; **14**(3): 204–20.
PubMed Abstract | Publisher Full Text

49. Kohli RM, Zhang Y: **TET enzymes, TDG and the dynamics of DNA demethylation.** *Nature.* 2013; **502**(472): 472–9.
PubMed Abstract | Publisher Full Text | Free Full Text

50. Li E, Bestor TH, Jaenisch R: **Targeted mutation of the DNA methyltransferase gene results in embryonic lethality.** *Cell.* 1992; **69**(6): 915–26.
PubMed Abstract | Publisher Full Text

51. Okano M, Bell DW, Haber DA, *et al.*: **DNA methyltransferases Dnmt3a and Dnmt3b are essential for *de novo* methylation and mammalian development.** *Cell.* 1999; **99**(3): 247–57.
PubMed Abstract | Publisher Full Text

52. Zimmermann P, Boeuf S, Dickhut A, *et al.*: **Correlation of COL10A1 induction during chondrogenesis of mesenchymal stem cells with demethylation of two CpG sites in the COL10A1 promoter.** *Arthritis Rheum.* 2008; **58**(9): 2743–53.
PubMed Abstract | Publisher Full Text

53. F Roach HI, Yamada N, Cheung KS, *et al.*: **Association between the abnormal expression of matrix-degrading enzymes by human osteoarthritic chondrocytes and demethylation of specific CpG sites in the promoter regions.** *Arthritis Rheum.* 2005; **52**(10): 3110–24.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

54. F Cheung KS, Hashimoto K, Yamada N, *et al.*: **Expression of ADAMTS-4 by chondrocytes in the surface zone of human osteoarthritic cartilage is regulated by epigenetic DNA de-methylation.** *Rheumatol Int.* 2009; **29**(5): 525–34.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

55. F Hashimoto K, Otero M, Imagawa K, *et al.*: **Regulated transcription of human matrix metalloproteinase 13 (*MMP13*) and interleukin-1β (*IL1B*) genes in chondrocytes depends on methylation of specific proximal promoter CpG sites.** *J Biol Chem.* 2013; **288**(14): 10061–72.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

56. de Andrés MC, Imagawa K, Hashimoto K, *et al.*: **Loss of methylation in CpG sites in the NF-κB enhancer elements of inducible nitric oxide synthase is responsible for gene induction in human articular chondrocytes.** *Arthritis Rheum.* 2013; **65**(3): 732–42.
PubMed Abstract | Publisher Full Text | Free Full Text

57. Ezura Y, Sekiya I, Koga H, *et al.*: **Methylation status of CpG islands in the promoter regions of signature genes during chondrogenesis of human synovium-derived mesenchymal stem cells.** *Arthritis Rheum.* 2009; **60**(5): 1416–26.
PubMed Abstract | Publisher Full Text

58. Loeser RF, Im H, Richardson B, *et al.*: **Methylation of the OP-1 promoter: potential role in the age-related decline in OP-1 expression in cartilage.** *Osteoarthritis Cartilage.* 2009; **17**(4): 513–7.
PubMed Abstract | Publisher Full Text | Free Full Text

59. F Hashimoto K, Oreffo ROC, Gibson MB, *et al.*: **DNA demethylation at specific CpG sites in the *IL1B* promoter in response to inflammatory cytokines in human articular chondrocytes.** *Arthritis Rheum.* 2009; **60**(11): 3303–13.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

60. Fernández MP, Young MF, Sobel ME: **Methylation of type II and type I collagen genes in differentiated and dedifferentiated chondrocytes.** *J Biol Chem.* 1985; **260**(4): 2374–8.
PubMed Abstract

61. F Jeffries MA, Donica M, Baker LW, *et al.*: **Genome-wide DNA methylation study identifies significant epigenomic changes in osteoarthritic cartilage.** *Arthritis Rheumatol.* 2014; **66**(10): 2804–15.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

62. F den Hollander W, Ramos YFM, Bos SD, *et al.*: **Knee and hip articular cartilage have distinct epigenomic landscapes: implications for future cartilage regeneration approaches.** *Ann Rheum Dis.* 2014; **73**(12): 2208–12.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

63. Haseeb A, Makki MS, Haqqi TM: **Modulation of ten-eleven translocation 1 (TET1), Isocitrate Dehydrogenase (IDH) expression, α-Ketoglutarate (α-KG), and DNA hydroxymethylation levels by interleukin-1β in primary human chondrocytes.** *J Biol Chem.* 2014; **289**(10): 6877–85.
PubMed Abstract | Publisher Full Text | Free Full Text

64. Taylor SEB, Smeriglio P, Dhulipala L, *et al.*: **A global increase in 5-hydroxymethylcytosine levels marks osteoarthritic chondrocytes.** *Arthritis Rheumatol.* 2014; **66**(1): 90–100.
PubMed Abstract | Publisher Full Text

65. Taylor SEB, Li YH, Wong WH, *et al.*: **Genome-Wide Mapping of DNA Hydroxymethylation in Osteoarthritic Chondrocytes.** *Arthritis Rheumatol.* 2015; **67**(8): 2129–40.
PubMed Abstract | Publisher Full Text | Free Full Text

66. Hata K, Takashima R, Amano K, *et al.*: **Arid5b facilitates chondrogenesis by recruiting the histone demethylase Phf2 to Sox9-regulated genes.** *Nat Commun.* 2013; **4**: 2850.
PubMed Abstract | Publisher Full Text

67. F Jenuwein T, Allis CD: **Translating the histone code.** *Science.* 2001; **293**(5532): 1074–80.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

68. Kouzarides T: **Chromatin modifications and their function.** *Cell.* 2007; **128**(4): 693–705.
PubMed Abstract | Publisher Full Text

69. Clayton AL, Hazzalin CA, Mahadevan LC: **Enhanced histone acetylation and transcription: a dynamic perspective.** *Mol Cell.* 2006; **23**(3): 289–96.
PubMed Abstract | Publisher Full Text

70. Gregoretti IV, Lee YM, Goodson HV: **Molecular evolution of the histone deacetylase family: functional implications of phylogenetic analysis.** *J Mol Biol.* 2004; **338**(1): 17–31.
PubMed Abstract | Publisher Full Text

71. Inoue T, Hiratsuka M, Osaki M, *et al.*: **The molecular biology of mammalian SIRT proteins: SIRT2 in cell cycle regulation.** *Cell Cycle.* 2007; **6**(9): 1011–8.
PubMed Abstract | Publisher Full Text

72. F Higashiyama R, Miyaki S, Yamashita S, *et al.*: **Correlation between MMP-13 and HDAC7 expression in human knee osteoarthritis.** *Mod Rheumatol.* 2010; **20**(1): 11–7.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

73. F Huber LC, Brock M, Hemmatazad H, *et al.*: **Histone deacetylase/acetylase activity in total synovial tissue derived from rheumatoid arthritis and osteoarthritis patients.** *Arthritis Rheum.* 2007; **56**(4): 1087–93.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

74. F Hong S, Derfoul A, Pereira-Mouries L, *et al.*: **A novel domain in histone deacetylase 1 and 2 mediates repression of cartilage-specific genes in human chondrocytes.** *FASEB J.* 2009; **23**(10): 3539–52.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

75. Chabane N, Zayed N, Afif H, *et al.*: **Histone deacetylase inhibitors suppress interleukin-1beta-induced nitric oxide and prostaglandin E_2 production in human chondrocytes.** *Osteoarthritis Cartilage.* 2008; **16**(10): 1267–74.
PubMed Abstract | Publisher Full Text

76. Young DA, Lakey RL, Pennington CJ, *et al.*: **Histone deacetylase inhibitors modulate metalloproteinase gene expression in chondrocytes and block cartilage resorption.** *Arthritis Res Ther.* 2005; **7**(3): R503–12.
PubMed Abstract | Publisher Full Text | Free Full Text

77. Wang X, Song Y, Jacobi JL, *et al.*: **Inhibition of histone deacetylases antagonized FGF2 and IL-1beta effects on MMP expression in human articular chondrocytes.** *Growth Factors.* 2009; **27**(1): 40–9.
PubMed Abstract | Publisher Full Text | Free Full Text

78. Furumatsu T, Tsuda M, Yoshida K, *et al.*: **Sox9 and p300 cooperatively regulate chromatin-mediated transcription.** *J Biol Chem.* 2005; **280**(42): 35203–8.
PubMed Abstract | Publisher Full Text

79. F Chen WP, Bao JP, Hu PF, *et al.*: **Alleviation of osteoarthritis by Trichostatin A, a histone deacetylase inhibitor, in experimental osteoarthritis.** *Mol Biol Rep.* 2010; **37**(8): 3967–72.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

80. Dvir-Ginzberg M, Gagarina V, Lee EJ, *et al.*: **Regulation of cartilage-specific gene expression in human chondrocytes by SirT1 and nicotinamide phosphoribosyltransferase.** *J Biol Chem.* 2008; **283**(52): 36300–10.
PubMed Abstract | Publisher Full Text | Free Full Text

81. Fujita N, Matsushita T, Ishida K, *et al.*: **Potential involvement of SIRT1 in the pathogenesis of osteoarthritis through the modulation of chondrocyte gene expressions.** *J Orthop Res.* 2011; **29**(4): 511–5.
PubMed Abstract | Publisher Full Text

82. F Gagarina V, Gabay O, Dvir-Ginzberg M, *et al.*: **SirT1 enhances survival of human osteoarthritic chondrocytes by repressing protein tyrosine phosphatase 1B and activating the insulin-like growth factor receptor pathway.** *Arthritis Rheum.* 2010; **62**(5): 1383–92.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

83. Takayama K, Ishida K, Matsushita T, *et al.*: **SIRT1 regulation of apoptosis of human chondrocytes.** *Arthritis Rheum.* 2009; **60**(9): 2731–40.
PubMed Abstract | Publisher Full Text

84. Yeung F, Hoberg JE, Ramsey CS, *et al.*: **Modulation of NF-kappaB-dependent transcription and cell survival by the SIRT1 deacetylase.** *EMBO J.* 2004; **23**(12): 2369–80.
PubMed Abstract | Publisher Full Text | Free Full Text

85. Liu TF, Yoza BK, El Gazzar M, *et al.*: **NAD^+-dependent SIRT1 deacetylase participates in epigenetic reprogramming during endotoxin tolerance.** *J Biol Chem.* 2011; **286**(11): 9856–64.
PubMed Abstract | Publisher Full Text | Free Full Text

86. Dioum EM, Chen R, Alexander MS, *et al.*: **Regulation of hypoxia-inducible factor 2alpha signaling by the stress-responsive deacetylase sirtuin 1.** *Science.* 2009; **324**(5932): 1289–93.
PubMed Abstract | Publisher Full Text

87. F Yang S, Kim J, Ryu JH, *et al.*: **Hypoxia-inducible factor-2alpha is a catabolic regulator of osteoarthritic cartilage destruction.** *Nat Med.* 2010; **16**(6): 687–93.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

88. F El Mansouri FE, Chabane N, Zayed N, *et al.*: **Contribution of H3K4 methylation by SET-1A to interleukin-1-induced cyclooxygenase 2 and inducible nitric oxide synthase expression in human osteoarthritis chondrocytes.** *Arthritis Rheum.* 2011; **63**(1): 168–79.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

89. Rodova M, Lu Q, Li Y, *et al.*: ***Nfat1* regulates adult articular chondrocyte function through its age-dependent expression mediated by epigenetic histone methylation.** *J Bone Miner Res.* 2011; **26**(8): 1974–86.
PubMed Abstract | Publisher Full Text | Free Full Text

90. F Wang J, Gardner BM, Lu Q, *et al.*: **Transcription factor Nfat1 deficiency causes osteoarthritis through dysfunction of adult articular chondrocytes.** *J Pathol.* 2009; **219**(2): 163–72.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

91. El Mansouri FE, Nebbaki SS, Kapoor M, *et al.*: **Lysine-specific demethylase 1-mediated demethylation of histone H3 lysine 9 contributes to interleukin 1β-induced microsomal prostaglandin E synthase 1 expression in human osteoarthritic chondrocytes.** *Arthritis Res Ther.* 2014; **16**(3): R113.
PubMed Abstract | Publisher Full Text | Free Full Text

92. Bartkuhn M, Renkawitz R: **Long range chromatin interactions involved in gene regulation.** *Biochim Biophys Acta.* 2008; **1783**(11): 2161–6.
PubMed Abstract | Publisher Full Text

93. Sato F, Tsuchiya S, Meltzer SJ, *et al.*: **MicroRNAs and epigenetics.** *FEBS J.* 2011; **278**(10): 1598–609.
PubMed Abstract | Publisher Full Text

94. Chuang JC, Jones PA: **Epigenetics and microRNAs.** *Pediatr Res.* 2007; **61**(5 Pt 2): 24R–29R.
PubMed Abstract | Publisher Full Text

95. F Miyaki S, Nakasa T, Otsuki S, *et al.*: **MicroRNA-140 is expressed in differentiated human articular chondrocytes and modulates interleukin-1 responses.** *Arthritis Rheum.* 2009; **60**(9): 2723–30.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

96. Yang J, Qin S, Yi C, *et al.*: **MiR-140 is co-expressed with *Wwp2-C* transcript and activated by Sox9 to target *Sp1* in maintaining the chondrocyte proliferation.** *FEBS Lett.* 2011; **585**(19): 2992–7.
PubMed Abstract | Publisher Full Text

97. Nakamura Y, Inloes JB, Katagiri T, *et al.*: **Chondrocyte-specific microRNA-140 regulates endochondral bone development and targets *Dnpep* to modulate bone morphogenetic protein signaling.** *Mol Cell Biol.* 2011; **31**(14): 3019–28.
PubMed Abstract | Publisher Full Text | Free Full Text

98. F Swingler TE, Wheeler G, Carmont V, *et al.*: **The expression and function of microRNAs in chondrogenesis and osteoarthritis.** *Arthritis Rheum.* 2012; **64**(6): 1909–19.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

99. Nicolas FE, Pais H, Schwach F, *et al.*: **Experimental identification of microRNA-140 targets by silencing and overexpressing miR-140.** *RNA.* 2008; **14**(12): 2513–20.
PubMed Abstract | Publisher Full Text | Free Full Text

100. Papaioannou G, Inloes JB, Nakamura Y, *et al.*: **let-7 and miR-140 microRNAs coordinately regulate skeletal development.** *Proc Natl Acad Sci U S A.* 2013; **110**(35): E3291–300.
PubMed Abstract | Publisher Full Text | Free Full Text

101. Tuddenham L, Wheeler G, Ntounia-Fousara S, *et al.*: **The cartilage specific microRNA-140 targets histone deacetylase 4 in mouse cells.** *FEBS Lett.* 2006; **580**(17): 4214–7.
PubMed Abstract | Publisher Full Text

102. Pais H, Nicolas FE, Soond SM, *et al.*: **Analyzing mRNA expression identifies Smad3 as a microRNA-140 target regulated only at protein level.** *RNA.* 2010; **16**(3): 489–94.
PubMed Abstract | Publisher Full Text | Free Full Text

103. F Miyaki S, Sato T, Inoue A, *et al.*: **MicroRNA-140 plays dual roles in both cartilage development and homeostasis.** *Genes Dev.* 2010; **24**(11): 1173–85.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

104. Papaioannou G, Mirzamohammadi F, Lisse TS, *et al.*: **MicroRNA-140 Provides Robustness to the Regulation of Hypertrophic Chondrocyte Differentiation by the PTHrP-HDAC4 Pathway.** *J Bone Miner Res.* 2015; **30**(6): 1044–52.
PubMed Abstract | Publisher Full Text

105. Zhang R, Ma J, Yao J: **Molecular mechanisms of the cartilage-specific microRNA-140 in osteoarthritis.** *Inflamm Res.* 2013; **62**(10): 871–7.
PubMed Abstract | Publisher Full Text

106. Liang ZJ, Zhuang H, Wang GX, *et al.*: **MiRNA-140 is a negative feedback regulator of MMP-13 in IL-1β-stimulated human articular chondrocyte C28/I2 cells.** *Inflamm Res.* 2012; **61**(5): 503–9.
PubMed Abstract | Publisher Full Text

107. Tardif G, Hum D, Pelletier JP, *et al.*: **Regulation of the IGFBP-5 and MMP-13 genes by the microRNAs miR-140 and miR-27a in human osteoarthritic chondrocytes.** *BMC Musculoskelet Disord.* 2009; **10**: 148.
PubMed Abstract | Publisher Full Text | Free Full Text

108. F Pei Y, Harvey A, Yu XP, *et al.*: **Differential regulation of cytokine-induced MMP-1 and MMP-13 expression by p38 kinase inhibitors in human chondrosarcoma cells: potential role of Runx2 in mediating p38 effects.** *Osteoarthritis Cartilage.* 2006; **14**(8): 749–58.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

109. F Thirunavukkarasu K, Pei Y, Wei T: **Characterization of the human ADAMTS-5 (aggrecanase-2) gene promoter.** *Mol Biol Rep.* 2007; **34**(4): 225–31.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

110. F Tetsunaga T, Nishida K, Furumatsu T, *et al.*: **Regulation of mechanical stress-induced MMP-13 and ADAMTS-5 expression by RUNX-2 transcriptional factor in SW1353 chondrocyte-like cells.** *Osteoarthritis Cartilage.* 2011; **19**(2): 222–32.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

111. Ducy P, Zhang R, Geoffroy V, *et al.*: **Osf2/Cbfa1: a transcriptional activator of osteoblast differentiation.** *Cell.* 1997; **89**(5): 747–54.
PubMed Abstract | Publisher Full Text

112. Huang J, Zhao L, Xing L, *et al.*: **MicroRNA-204 regulates Runx2 protein expression and mesenchymal progenitor cell differentiation.** *Stem Cells.* 2010; **28**(2): 357–64.
PubMed Abstract | Publisher Full Text | Free Full Text

113. F Deng Y, Wu S, Zhou H, *et al.*: **Effects of a miR-31, *Runx2*, and *Satb2* regulatory loop on the osteogenic differentiation of bone mesenchymal stem cells.** *Stem Cells Dev.* 2013; **22**(16): 2278–86.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

114. F Tardif G, Pelletier JP, Fahmi H, *et al.*: **NFAT3 and TGF-β/SMAD3 regulate the expression of miR-140 in osteoarthritis.** *Arthritis Res Ther.* 2013; **15**(6): R197.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

115. F Makki MS, Haseeb A, Haqqi TM: **MicroRNA-9 promotion of interleukin-6 expression by inhibiting monocyte chemoattractant protein-induced protein 1 expression in interleukin-1β-stimulated human chondrocytes.** *Arthritis Rheumatol.* 2015; **67**(8): 2117–28.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

Open Peer Review

Current Referee Status: ✓ ✓ ✓

Editorial Note on the Review Process

F1000 Faculty Reviews are commissioned from members of the prestigious F1000 Faculty and are edited as a service to readers. In order to make these reviews as comprehensive and accessible as possible, the referees provide input before publication and only the final, revised version is published. The referees who approved the final version are listed with their names and affiliations but without their reports on earlier versions (any comments will already have been addressed in the published version).

The referees who approved this article are:

Version 1

1 **Tatsuya Kobayashi**, Endocrine Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA
Competing Interests: No competing interests were disclosed.

2 **Alexander Lichtler**, University of Connecticut Health Center, Farmington, CT, USA
Competing Interests: No competing interests were disclosed.

3 **Kenneth B. Marcu**, Department of Biochemistry and Cell Biology, Stony Brook University, Stony Brook, NY, USA
Competing Interests: No competing interests were disclosed.