Genes & Diseases (2015) 2, 69–75

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REVIEW ARTICLE

# Epigenetic regulation of gene expression in osteoarthritis

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Received 24 December 2014; accepted 30 December 2014
Available online 9 January 2015

**KEYWORDS**
Epigenetics;
Osteoarthritis;
Transcription factor;
Cytokine;
Matrix proteinase

**Abstract** Osteoarthritis (OA) is the most common form of joint disease and the leading cause of chronic disability in middle-aged and older populations. The development of disease-modifying therapy for OA currently faces major obstacles largely because the regulatory mechanisms for the function of joint tissue cells remain unclear. Previous studies have found that the alterations in gene expression of specific transcription factors (TFs), pro- or anti-inflammatory cytokines, matrix proteinases and extracellular matrix (ECM) proteins in articular cartilage may be involved in the development of OA. However, the regulatory mechanisms for the expression of those genes in OA chondrocytes are largely unknown. The recent advances in epigenetic studies have shed light on the importance of epigenetic regulation of gene expression in the development of OA. In this review, we summarize and discuss the recent studies on the regulatory roles of various epigenetic mechanisms in the expression of genes for specific TFs, cytokines, ECM proteins and matrix proteinases, as well the significance of these epigenetic mechanisms in the pathogenesis of OA.


## Introduction

Osteoarthritis (OA) is the most common form of arthritis in the U.S. and affects approximately 27 million Americans.[1] As OA mainly occurs in weight-bearing joints, such as the knee and hip, OA has long been thought of as a mechanical issue.[2] However, there is a growing body of evidence supporting the notion that OA is a result of the interaction between mechanical and molecular events in the affected joint.[3] There is no single specific cause that has been

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Peer review under responsibility of Chongqing Medical University.

http://dx.doi.org/10.1016/j.gendis.2014.12.005

identified for OA to date. Some risk factors, including age, gender, obesity, joint injury, genetic and mechanical abnormalities, have been shown to be associated with the development of OA.[4] However, how these risk factors trigger the onset of OA still need to be elucidated. While OA is a disease of the whole joint and may affect all of the joint tissues, articular cartilage degradation is a major hallmark of OA.[5] Aberrant gene expression of specific transcription factors (TFs), cytokines, matrix proteinases and extracellular matrix (ECM) structural proteins (e.g., collagens and proteoglycans) in articular chondrocytes (ACs) of human OA and animal models of OA samples has been documented. Nevertheless, the underlying regulatory mechanism for the expression of those genes in OA cartilage is not fully understood.

"Epigenetics" is referred to as changes in gene expression caused by mechanisms other than changes in the underlying DNA sequences. DNA methylation and histone modification are the two best-studied classic epigenetic regulatory mechanisms, which regulate the transcriptional activity of a cell in the nucleus. DNA methylation is a biochemical process where a methyl group is added to the cytosine or adenine, mainly at the C5 position of CpG dinucleotides, by DNA methyltransferase (DNMT). DNA hypermethylation suppresses gene transcription, while DNA hypomethylation enhances gene transcription. Histone modifications are enzymatic post-translational modifications which include methylation, acetylation, phosphorylation, sumoylation and ubiquitination.[6,7] These modifications primarily occur within the amino-terminal tails of histone proteins that regulate gene expression by changing the chromatin structure.[8]

A broader definition of "epigenetics" has been proposed by Egger et al as heritable changes in gene expression that are not coded in the DNA sequences.[9] In this regard, non-coding RNAs (ncRNAs) which possess epigenetic-like properties have also been taken into account as one of the epigenetic mechanisms.[10,11] ncRNAs are functional RNA molecules that regulate gene expression but do not translate into proteins. ncRNAs can be mainly divided into short ncRNAs (<30 nucleotides) and long ncRNAs (lncRNAs, >200 nucleotides). Short ncRNAs include microRNAs (miRNAs), short interfering RNAs (siRNAs) and piwi-interacting RNAs (piRNAs).[12] In general, miRNAs function to modify the protein expression mainly at the post-transcriptional level in cytoplasm by binding to a specific target messenger RNA (mRNA) with a complimentary sequence to induce cleavage, degradation or block translation.[13] Recent progress in the study of ncRNAs has revealed the importance of ncRNAs in development and diseases.[14,15]

Given the importance of epigenetics in normal development as well as cancer and age-related diseases,[11] recent studies on epigenetics in OA have provided new insights into the pathogenesis of OA and new targets to develop potential therapeutic strategies for OA. In this review, we will focus on the epigenetic mechanisms for the expression of TFs, cytokines, matrix proteinases and ECM proteins in ACs, as well as their significance in the pathogenesis of OA (Table 1).

## TFs

TFs are the proteins that bind to specific DNA sequences and control the transcriptional rate of the target genes from genomic DNA to mRNA, which then translate into protein in the cytoplasm. Therefore, abnormal expression of TFs has been found to be involved in the development of many diseases, including OA.

Nfat1 (NFAT1/NFATc2) is a member of the Nuclear Factor of Activated T-cells (NFAT) transcription factor family originally identified as a regulator of the expression of cytokine genes during the immune response.[34,35] NFAT1 has recently been shown to play an important role in maintaining the permanent cartilage phenotype in adult mice. *Nfat1* knockout (*Nfat1*$^{-/-}$) mice exhibit normal skeletal development, but display over-expression of numerous matrix-degrading proteinases and proinflammatory cytokines and loss of collagen-2 and aggrecan during the initiation stage of OA. These initial changes are followed by articular chondrocyte clustering, formation of chondro-osteophytes, progressive articular surface destruction, formation of subchondral bone cysts, and exposure of thickened subchondral bone.[16]

Our recent studies have demonstrated that NFAT1 regulates the chondrocyte function through its age-dependent

**Table 1** Gene expression changes mediated by epigenetic mechanisms in osteoarthritic chondrocytes.

| Category | Gene | Expression[a] | Epigenetic regulation[b] | | | References |
|---|---|---|---|---|---|---|
| | | | DNA methylation | Histone modification | microRNA | |
| TFs | *Nfat1* | ↓ (m) | ↔ | ✓ | ↔ | 16,17 |
| | *SOX9* | ↓ (h) | ✓ | ✓ | ✓ | 18–20 |
| Cytokines | *IL-1B* | ↑ (h) | ✓ | ↔ | ✓ | 21–23 |
| | *TNF-alpha* | ↑ (h) | ↔ | ↔ | ✓ | 23 |
| Proteinases | *ADAMTS4* | ↑ (h) | ✓ | ✓ | ✓ | 24–27 |
| | *ADAMTS5* | ↑ (h) | ✓ | ✓ | ✓ | 20,26,27 |
| | *MMP-13* | ↑ (h) | ✓ | ✓ | ✓ | 24,27,28 |
| ECM proteins | *COL2A1* | ↓ (h) | ↔ | ✓ | ✓ | 20,29–31 |
| | *COL9A1* | ↓ (h) | ✓ | ↔ | ↔ | 32 |
| | *ACAN* | ↓ (h) | ✗ | ✓ | ✓ | 20,33 |

[a] Gene expression information is cited from the references of this manuscript. ↓: decrease; ↑: increase; m: mouse; h: human.
[b] Gene expression changes are associated with specific epigenetic alterations (✓), or not (✗), or unknown (↔).