Title: Osteoarthritis Year in Review 2017: Genetics and Epigenetics

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Summary

Objective: The purpose of this review is to describe highlights from original research publications related to osteoarthritis (OA), epigenetics and genomics with the intention of recognising significant advances.

Design: To identify relevant papers a Pubmed literature search was conducted for articles published between April 2016 and April 2017 using the search terms ‘osteoarthritis’ together with ‘genetics’, ‘genomics’, ‘epigenetics’, ‘microrna’, ‘IncRNA’, ‘DNA methylation’ and ‘histone modification’.

Results: The search term OA generated almost 4000 references. Publications using the combination of descriptors osteoarthritis and genetics provided the most references (82 references). However this was reduced compared to the same period in the previous year; 8.1% to 2.1% (expressed as a percentage of the total publications combining the terms osteoarthritis and genetics). Publications combining the terms osteoarthritis with genomics
(29 references), epigenetics (16 references), IncRNA (11 references; including the identification of novel IncRNAs in OA), DNA methylation (21 references), histone modification (3 references) and microRNA (79 references) were reviewed. Potential OA therapeutics such as histone deacetylase inhibitors have been identified. A number of non-coding RNAs may also provide targets for future treatments.

Conclusion: There continues to be a year on year increase in publications researching microRNAs in OA (expressed as a percentage of the total publications), with a doubling over the last 4 years. An overview on the last year’s progress within the fields of epigenetics and genomics with respect to OA will be given.

**Keywords**

Osteoarthritis, genetics, epigenetics, non-coding RNA

**Introduction**

Epigenetics are a group of genome function mechanisms that do not solely result from the DNA sequence. The term epigenetics encompasses DNA and chromatin modifications and their associated functions as well as non-coding RNAs (ncRNAs). Epigenetic control of gene expression is essential for normal organismal development and cellular function. Abrogation of epigenetic regulation is evident in osteoarthritis (OA). In addition to understanding the pathogenesis of OA through epigenetic research, abnormal epigenetic profiles may act as biomarkers for disease stratification or predictors of disease outcome. Thus epigenetics is a crucial area in the diagnosis, prognosis, and treatment of this disease.

Interestingly not all OA tissues or joints are studied to the same extent, and thus it is difficult to gain a complete, integrated understanding of the epigenetics systems which contribute to OA. Whilst this review summarises the main levels of epigenetic control studied over the last
12 months (between May 2016- May 2017), we also highlight potential additional directions required by the field.

GENETICS

Genetics of Osteoarthritis

OA is known as a complex heterogeneous disease, in which one of the contributing factors to disease progression is a genetic component [1, 2]. Genome-wide association studies (GWAS) has enabled the discovery of novel genetic variants that could be used as prognostic biomarkers for early diagnosis, or establish risk groups prone to the disease development. There have been five articles published employing GWAS for discovery of genetic variants associated with OA this year [3-7]. Most of the variants were found in the non-translated regions within the genes or on the areas remote from the gene, suggesting the regulatory changes in genes involved in OA. Whereas changes within the gene itself point to structural changes of the synthesized proteins related to early OA onset. Styrbardsottir et al. (2017) [5] demonstrated a missense variant of the COMP gene (p.Asp369His) and a frameshift mutation in the CHADL gene (p.Val330Glyfs*106), corresponding to hip replacement surgery on average 13.5 years and 4.9 years earlier in these patients, respectively. Results from these studies have discovered novel gene variants, suggesting additional genes involved in OA progression. Although each has a small effect size, combined with other factors these may contribute to OA.

Endophenotype studies

Sample size is an important factor in GWAS studies, increasing the power and consequently, the number of single nucleotide polymorphisms (SNPs) tested in the experiment [8]. However, it is not the only feature that can be used in order to find more
statistically significant genetic variants in heterogeneous diseases such as OA. Stratification of endophenotypes, in OA particularly can lead to the discovery of novel variants. Recently published articles (Table 1) clearly demonstrate that using intermediate endophenotypes such as site of maximal joint space narrowing (maxJSN), bone remodeling, cartilage thickness and radiographic progression can help to yield more loci than previously reported. Panoutsopoulou et al. (2016) [3] compared variants in hypertrophic with non-hypertrophic OA. The most significant variant was located between STT3B and GADL1 genes (rs6766414), and this association was fully attenuated in non-stratified analyses of all hip OA cases versus population controls.

Table 1. The use of endophenotypes in OA-related GWAS studies

<table>
<thead>
<tr>
<th>Joint</th>
<th>Endophenotype</th>
<th>Sample size</th>
<th>Population; study</th>
<th>Variants</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip</td>
<td>Radiographic; max JSN, bone remodelling</td>
<td>OA:2118, Cx:6500</td>
<td>European; arcOGEN</td>
<td>LRCH1, STT3B, GADL1, STT3B</td>
<td>Panoutsopoulou et al, 2016 [3]</td>
</tr>
<tr>
<td>Hip</td>
<td>Radiographic; min JSN, cartilage thickness</td>
<td>OA:13,013, Cx:8227</td>
<td>European, US, Asian; Rotterdam Study I Rotterdam Study II TwinsUK, SOF MrOS</td>
<td>TGFA PIK3R1 FGFR3 TREH</td>
<td>Castaño-Betancourt et al., 2016 [4]</td>
</tr>
<tr>
<td>Hip</td>
<td>No</td>
<td>OA:5657, Cx:207,514</td>
<td>Icelandic; novel</td>
<td>COMP CHADL</td>
<td>Styrkarsdottir et al., 2017 [5]</td>
</tr>
<tr>
<td>Knee</td>
<td>Radiographic progression; KL</td>
<td>CHECK:431, meta:1603</td>
<td>European; CHECK, OAI, Spain</td>
<td>mtDNA variants; superhaplogroup JT</td>
<td>Fernandez-Moreno et al., 2016 [6]</td>
</tr>
<tr>
<td>Knee</td>
<td>Radiographic; definite osteophytes, min JSN, TJR</td>
<td>OA:3,898, Cx:3,168</td>
<td>North American; Osteoarthritis Initiative, Johnston County Osteoarthritis</td>
<td>LSP1P3</td>
<td>Yau et al., 2017 [7]</td>
</tr>
</tbody>
</table>
EPIGENETICS

Epigenetics play a key role in the development of OA and explains the relationship between heritable traits, the environment, other factors (particularly ageing in relation to OA, as it is an age-related disease) and OA itself. DNA plasticity is mediated in part by epigenetic changes, and it is proposed that it can be passed to subsequent generations. This was studied in the epidemiological study of the consequences of the Dutch famine which concluded that early-life environmental conditions can cause epigenetic changes in humans that persist throughout life [9]. Thus epigenetics establishes that joint health can be affected by the interplay of our genes and environment in addition to the proposed inherited effects of our ancestors' genes and environment. Epigenetic traits are both highly dynamic, and tissue specific (indeed even down to the level of different areas of the same tissue). Epigenetics enables tight control at the transcriptional level via gene expression (DNA methylation and histone modification; through methylation and acetylation of histones) resulting in changes to chromatin 3D structure, and the translational level (ncRNAs; microRNAs (miRs), long non-coding RNAs (lncs), small nucleolar RNAs (snoRNAs); mRNA editing and mRNA stability) affecting protein expression (reviewed [10]).

DNA Methylation
The methylation of base cytosines (5-methyl cytosine) within CpG containing nucleotides is a stable epigenetic marks that results in gene silencing [11] and is known as DNA methylations. In previous years genome-wide DNA methylation studies have concentrated principally upon cartilage tissue. This is because it is composed of a single cell type; the chondrocyte, making it less problematic to study. Hence genuine alterations in DNA methylation can be assessed as these are not affected by disease-related changes in cell proportions [12]. Table 2 summarises the genome-wide DNA methylation studies published in the last year. OA-related studies prior to this have already been discussed [13]. The methodology of choice published continues to be the Human IlluminaMethylationBead-Chip 450K array. Studies published in the last year are distinct from those previously reported as currently experiments involving other tissues such as subchondral bone [14] and fibroblast-synoviocytes [15] are being undertaken. Additionally a number of studies have investigated OA progression [14, 16]. These investigated different regions within the tibial plateau as indicators of OA development. Methylation changes appeared to occur at a later stage of disease indicating that these are a consequence rather than a cause of OA. Similar to other studies [17] it was found that joint specific methylation patterns are independent of disease, indicating location specific epigenetic marks [15]. However Ai et al. [15] also identified OA or rheumatoid arthritis (RA) specific methylation patterns.

Three studies undertook RNA sequencing in parallel with DNA methylation analysis [15, 18, 19]. This is becoming an increasingly used methodology enabling methylation variation, and the functional consequences at the transcriptional level to be assessed together. Each of these studies found different correlations between the DNA methylated genes within contrasts and level of gene expression, both identified and their direction. It appears that in these studies most CpG sites with variable methylation are unconnected to gene expression variation. The
properties of these associations seem complex, with the location of CpG probes with respect
to the corresponding gene offering little information with regards to the type of correlation.
All studies in Table 2 contain limited sample sizes which reduces the ability to detect weak
associations that may be pertinent to our understanding of this epigenetic mark in OA.

The role of the epigenetic clock was investigated in OA for the first time (including work by
Jefferies et al [20]). DNA methylation age-measures (DmAM), which combine methylation
levels at CpG sites that experience methylation changes with ageing are potential biomarkers
of epigenetic ageing [21]. The potential role of DNA methylation in cartilage ageing in OA
was investigated. Studying methylation changes at both the local and systemic level Vidal-
Bralo et al. identified premature epigenetic ageing due to DNA methylation changes specific
to OA cartilage [22]. Interestingly similar findings were not extended to blood cells and bone.
Other joint tissues and larger sample sizes are required for clarification of these interesting
findings.

Table 2. Genome-wide methylation studies in OA

<table>
<thead>
<tr>
<th>Study; joint and disease</th>
<th>Number of donors</th>
<th>Tissue/cell type</th>
<th>Contrasts</th>
<th>Technique</th>
<th>Results (DE DMS)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee; OA progression</td>
<td>12 donors; early, inter, late OA from each</td>
<td>Subchondral bone</td>
<td>Early vs inter, Early vs severe, inter vs severe</td>
<td>450K array</td>
<td>72, 397, 257</td>
<td>Zhang et al., 2016 [14]</td>
</tr>
<tr>
<td>Knee; OA progression</td>
<td>12 donors; early, inter, late OA from each</td>
<td>Chondrocytes</td>
<td>Early vs inter, Early vs severe</td>
<td>450K array</td>
<td>0, 519</td>
<td>Zhang et al., 2016 [16]</td>
</tr>
<tr>
<td>Hip; fracture and OA</td>
<td>22 fracture, 18 OA</td>
<td>MSCs</td>
<td>Fracture vs OA</td>
<td>450K array* parallel RNASeq</td>
<td>9038</td>
<td>Del Real et al., 2017 [19]</td>
</tr>
<tr>
<td>Hip and knee; RA, OA</td>
<td>30 RA; 12 knee, 10 hip, 16 OA; 10 knee, 5 hip</td>
<td>Fibroblast-like synoviocytes</td>
<td>RA vs OA, RA hip vs RA knee, RA vs OA</td>
<td>450K array* parallel RNASeq</td>
<td>1714, 3739, 9589, 2172</td>
<td>Ai et al., 2016 [15]</td>
</tr>
<tr>
<td>Study Description</td>
<td>Genotype</td>
<td>Sample Details</td>
<td>Array Details</td>
<td>Fold Change</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------------------------------</td>
<td>------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>---------------</td>
<td>-------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee; normal and OA</td>
<td>11 normal, 12 OA</td>
<td>Cartilage Normal vs OA</td>
<td>450K array*</td>
<td>929</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alvarez et al., 2016 [18]</td>
<td></td>
<td></td>
<td>parallel RNASEq</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee and hip; cartilage neocartilage derived from knee chondrocytes or hip MSCs</td>
<td>6 knee, 6 hip cartilage; 4 neocartilage from MSCs, 4 neocartilage from chondrocytes</td>
<td>Chondrocytes and MSCs Neocartilage MSC vs chondrocytes</td>
<td>450K array</td>
<td>5884</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bomer et al., 2016 [23]</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

OA; osteoarthritis, RA; rheumatoid arthritis, MSC; mesenchymal stem cells, DE DMS; differentially expressed DNA methylation sites.

**Histone modifications**

DNA is wrapped around an octamer of histone proteins forming the complex structure of chromatin. Posttranscriptional modifications of the histone tails can alter the accessibility of chromatin, and change gene transcription by allowing promoter site transcription factor binding and initiating transcription [24]. These modifications are dynamic meaning that these changes can be altered in response to stimuli. Posttranslational modifications occur through sets of enzymes such as histone deacetylases (HDACs). Two studies in the last year have investigated the effects of pharmacological intervention points through targeting these enzymes in order to provide insights into the role of epigenetics in OA and identify exploitable targets for treatments. In one study Vorinostat, a HDACI and II inhibitor was demonstrated as a suppressor of catabolic marker expression in OA through inhibition of IL-6 signaling [25]. Further work by the group showed that it functioned through increased recruitment of CEBPalpha to the MCPIP1 promoter, relieving the miR-9-mediated inhibition of MCPIP1 expression in OA chondrocytes [26]. A further study found that H3K27me3 demethylases regulated *in vitro* chondrocyte activity in OA through the inhibition of TGFβ.
induced gene expression. Targeting the inhibition of H3K27me3 demethylases could provide potential OA therapeutics [27].

NON-CODING RNAs

MicroRNAs

MiRs are small (19-25 nucleotides (nt)) ncRNAs that function at the post-transcriptional level by binding and suppressing the expression of specific mRNA targets [28]. MiRs are involved in different cellular pathways, highlighting the role of these molecules in maintaining tissue homeostasis as well as being implicated in disease [29]. Over the last few years the roles of miRs in OA has been reviewed extensively with studies identifying numerous miR candidates involved in cartilage homeostasis and/or OA pathogenesis [30-34]. Most of the studies published during the last year focused on miRs which have been previously reported to play a role in chondrocyte function and OA, such as miR-140 [35] miR-29 [32], miR-34a [34, 36], miR-9 [37, 38] and miR-98 [33, 39]. Identification of miR-181a-5p and miR-4454 as mediators of facet cartilage degeneration was presented at OARSI 2017 [40]. However, some studies reported for the first time the implication of specific miRs in OA, such as miR-15-5p [41] and miR-410 [42]. The methodologies remain similar, with human primary OA chondrocytes treated with miR mimics and/or inhibitors and qRT-PCR being commonly utilized in order to measure the expression of both specific miRs and cartilage-associated genes (Table 3, a full summary table of MiR studies reviewed is in Supplementary File 1). Additionally many of these studies identified and validated using luciferase reporter assays putative target genes of the miRs in question, and these findings were usually integrated into, or associated with important signalling pathways, such as the NF-kB and AP1 (c-fos/c-jun) [43, 44].
Regarding genome-wide approaches undertaken in the last year, four studies used microarray analysis to test for differentially expressed (DE) miRs in OA chondrocytes treated with various stimulating factors or whole mouse joints from a destabilization of the medial meniscus (DMM) model. Each study identified several DE miRs [31, 32, 45, 46]. One study undertook a next generation sequencing approach using human cartilage from different OA stages [47]. Finally, Kung et al. (2017) measured DE circulating miRs in the serum of DMM mice with the results suggesting that two miRs, miR-3102-5p and miR-3081-5p, demonstrated higher expression in late stage OA compared to controls, although findings were not validated [48]. A role of circulating miRs in OA was presented by Rousseau et al at OARSI 2017 [49].

Although the number of research publications and miRs involved in OA pathogenesis is rising constantly, no miR biomarkers have been validated that could be utilised in early diagnosis of the disease. This is due partially to the fact that OA is a multifactorial heterogeneous disease. As a result, the miR signature responds differently to the type of stimuli involved in OA initiation and progression. Similarly, therapeutic options based on miRs are also hindered by the heterogeneity of the disease, the need for targeted delivery approaches and the lack of evidence on the molecular and cellular processes that orchestrate OA. This clearly highlights the importance of an in-depth understanding of the signalling pathways behind OA but at the same time steps should be taken to integrate the multiple miR findings into the clinical setting, especially for some of the well-studied miRs which provide promising therapeutic targets.

Table 3. Selected miRs studies focusing on cartilage associated genes

<table>
<thead>
<tr>
<th>MicroRNA</th>
<th>Target genes</th>
<th>Cellular/Biological process</th>
<th>Tissue</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>mir-9</td>
<td>SIRT1</td>
<td>Oxidative stress-induced chondrocyte death</td>
<td>Cartilage</td>
<td>D'Adamo et al. (2017) [37]</td>
</tr>
</tbody>
</table>
### Other non-coding RNAs

The relevance of ncRNAs to OA has mainly focussed on the widespread disruption of miR expression. However we are beginning to understand and study the nature and involvement of other ncRNAs in OA such as piwi-interacting RNAs (piRNAs), snoRNAs and large-intergenic non-coding RNAs (lincRNAs). In the last year an insight into their potential roles in OA has emerged for the first time.

SnoRNAs mediate enzymatic modifications of other RNA species, such as ribosomal RNAs, by forming ribonucleoprotein complexes with enzymes [52]. These modifications include ribose methylation and pseudouridylation. Little data exists on the role of these RNA species in OA. A pubmed search gave only one result regarding the implication of snoRNAs in OA during last year; Steinbusch *et al.* (2017) undertook snoRNAseq analysis in OA joints and serum from DMM mice [53]. Several DE snoRNAs, such as SNORA64, SNORD46 and SNORD116, were identified and validated and the authors concluded that snoRNAs could be used as potential biomarkers for joint degeneration.

PiRNAs (24-32 nt) form RNA-protein complexes with piwi proteins and are linked to both epigenetic and post-transcriptional gene silencing of genetic elements, thus protecting cells from invasive transposable elements in the germline [54]. For the first time piRNAs and their
binding partners were identified in OA and RA synovial fibroblasts and synovial fluid. The study concluded that PIWI/piRNA pathways are involved in innate immunity and may have a role in the pathogenesis of RA [55].

Long non-coding RNAs

There has been an increase in studies published on lncRNAs in OA (up from four in 2015-2016 to 11 in the same period 2016-2017). LncRNAs are an RNA molecule greater than 200 nt. Dysregulated expression of lncRNAs performs a significant role in inflammation-related diseases, and has been demonstrated as being associated with OA progression and cartilage degradation (reviewed [56]). Two discovery studies were undertaken (Table 4). In one study a role in mediating inflammation driven cartilage degeneration for the novel lncRNAs CILinc01 and CILinc02 was identified [57]. Additionally a number of targeted lncRNA studies on both novel [36, 58] and previously studied lncRNAs [59, 60] were undertaken (Figure 1).

Table 4. Long non-coding RNA discovery studies in OA

<table>
<thead>
<tr>
<th>Study</th>
<th>Species</th>
<th>Technology</th>
<th>Method and N</th>
<th>Findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-traumatic OA</td>
<td>Mouse</td>
<td>RNA sequencing</td>
<td>Joints; 1 day (n=5), 1(n=5), 6 (n=3), 12 (n=3) week post injury</td>
<td>18 DE lncRNAs (at least one time point)</td>
<td>Chang et al., 2016 [61]</td>
</tr>
<tr>
<td>Normal versus OA cartilage</td>
<td>Human</td>
<td>RNA sequencing</td>
<td>Chondrocytes; hip OA±IL-1β (n=3 each)</td>
<td>983 lncRNAs identified, 125 DE</td>
<td>Pearson et al., 2016 [57]</td>
</tr>
</tbody>
</table>

N; number donors, OA; osteoarthritis, IL-1β; interleukin 1β, DE; differentially expressed

Emerging areas for future study

Understanding the biology of RNA modifications represents one of the next potential frontiers in arthritis research. [62]. We realise that the control of the transcriptome is pertinent to the diverse aspects of gene regulation, cellular functionality and development,
and that alterations can result in disease. There is an emerging field of research termed ‘epitranscriptomics’; the identification and characterisation of changes in biochemical RNA modifications that do not comprise alterations to the RNA sequence. Epitranscriptomic analysis was the Nature method of the year 2016 [63]. Epitranscriptomics includes modifications to rRNA, tRNA and mRNA. However the role and function of snoRNAs, IncRNAs, anti-sense, and small RNAs derived from tRNAs remains largely unrealized.

A further layer of gene expression control is through alterations in genetic information by RNA editing (epitranscriptomics) or via the establishment of RNA covalent modifications. Interestingly disease-related exome sequencing has contributed to the pivotal attributions of mutations in RNA modifying enzymes to many human diseases [64]. In OA the risk gene fat mass and obesity associated protein (FTO) is an m^6^A mRNA eraser [65]. Improved technologies (reviewed [66]) will enable RNA modifications signatures and dynamics to be discovered.

Within the context of this emerging discipline (as an additional molecular level on control in physiology and disease), and with expanding omics technological advances the discipline of ‘systems biology’ is becoming increasingly influential in our understanding of OA [67] (Figure 2). Its aim is to systematically and comprehensively obtain quality data from all biological hierarchies’ whilst assimilating the data to develop predictive models of the system.

Some of the challenges of systems biology in OA research include that not all tissues are evenly represented in systems studies, not all levels are explored systematically (for instance there are limited studies on histone modifications) and there is difficulty in integrating and correlating the different levels of the system. These challenges thus represent further opportunities to address.

**Author Contributions**
Mandy Peffers, Panagiotis Balaskas and Aibek Smagul searched the literature, summarised results and wrote the manuscript.

Conflict of interest

We have no conflicts of interest.

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References


26. Makki MS, Haqqi TM. Histone deacetylase inhibitor vorinostat (SAHA, MK0683) perturb miR-9-MCPIP1 axis to block IL-1beta-induced IL-6 expression in human OA chondrocytes. Connect Tissue Res 2017; 58: 64-75.


Figure Legend

Figure 1. LncRNA studies in OA targeting different mechanisms of action of IncRNAs.

Three functions of IncRNAs have been investigated; through acting as sponges for miRs, transcriptional activation and repression and the regulation of the chromatin state (miR; microRNA, TMSB4; thymosin-β4, SMSCs; synovium-derived mesenchymal stem cells, IL-1β; interleukin 1β, MMP; metalloproteinase). References: 1. Zhang et al., 2016 [36], 2. Liu et al., 2016 [58], 3. Zhang et al., 2017 [60], 4. Zhang et al., 2016 [59].

Figure 2. Schematic diagram of a systems orientated approach to develop novel diagnostic and treatment solutions to OA. Omics studies enable pictures of the biological hierarchy. Red boxes highlight the areas covered in this review [67].

Supplementary Files

Supplementary File 1 Summary table of miR studies reviewed.
Figure Legend

Figure 1. LncRNA studies in OA targeting different mechanisms of action of lncRNAs. Three functions of lncRNAs have been investigated; through acting as sponges for miRs, transcriptional activation and repression and the regulation of the chromatin state (miR; microRNA, TMSB4; thymosin-β4, SMSCs; synovium-derived mesenchymal stem cells, IL-1β; interleukin 1β, MMP; metalloproteinase). References; 1. Zhang et al., 2016 [34], 2. Liu et al., 2016 [53], 3. Zhang et al., 2017 [55], 4. Zhang et al., 2016 [54].

Figure 2. Schematic diagram of a systems orientated approach to develop novel diagnostic and treatment solutions to OA. Omics studies enable pictures of the biological hierarchy. Red boxes highlight the areas covered in this review [62].
**UFC**
OA chondrocytes; 
↑proliferation, 
↓apoptosis, 
=regulates OA survival through association with miR-34A (1)

**IncRNA function**
↑increase 
↓decrease 
* novel Incs to OA

**MSR**
↑in damaged cartilage, 
Activated mechanical stress, 
=regulates TMSB4 through miRNA-152 (2)

**Transcriptional activation and repression**

**‘Sponge’ for ‘miR’**

**Regulation of chromatin state**

**DANCR**
↑proliferation and 
↑chondrogenesis of SMSCs via expression and stability of Smad3 and STAT3 (3)

**HOTAIR**
↑contributes to IL-1β-induced MMP overexpression and apoptosis in chondrocytes (4)

1. Zhang et al., 2016
2. Liu et al., 2016
3. Zhang et al., 2017
4. Zhang et al., 2016