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Review

Osteoarthritis Year in Review 2014: genetics and genomics

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SUMMARY

Recent developments in genetics/genomics of osteoarthritis (OA) are discussed to improve our understanding of OA pathophysiology. The discovery of a novel variant near the *NCOA3* (nuclear receptor coactivator 3) gene associated with hip OA and the regulation of *GDF5* gene by four transcription factors via the OA susceptibility locus rs143383 are among important findings in OA genetics. Several microarray-based gene expression studies were published for different tissues of the joint. In OA synovium elevation of collagens and cross-linking enzymes (COL1A1, COL5A1, PLOD2, LOX and TIMP1) responsive to TGF-β was found as well as differential expression pattern between different areas of the osteoarthritic synovial membrane. In OA peripheral blood the role of apoptotic genes was highlighted, while whole genome expression profiling in OA subchondral bone and cartilage revealed common genes in cartilage and bone to be involved in OA development. In epigenetics, several microRNAs (miRNAs) were found to regulate genes' expression in chondrocytes, among which miR-125, miR-127b miR-21, miR-148a and their use as potential drug targets was highlighted. Future studies must focus on the integration of genetics, genomics and epigenetics for the identification of signaling pathways and regulatory networks responsible for OA development.

Introduction

The goal of this review is to present highlights from the published literature related to genetics, functional genomics and epigenetics of human osteoarthritis (OA). A summary of studies published in PUBMED between April 2013 and May 2014, as well as data presented during the 2014 OARSI meeting were selected by the author and are included in the review.

OA is the most common degenerative joint disease and is predicted to be the single greatest cause of disability in the general population by 2030[1]. It has been estimated that 35% of persons suffering from OA are active and therefore its negative impact on work is liable to grow in view of the aging of the population and the longer working lives in developed countries[2]. Despite its high prevalence and substantial public health impact, disease etiology is not fully understood. OA is a multifactorial disease with strong genetic component and heritability estimates ranging from 40% to 65% depending on the joint site[3–5]. The identification of genes associated with OA will help reveal the underlying molecular mechanisms and pathways and may lead to development of OA' gene targeted therapies.

Genetics of OA

Numerous candidate gene association studies aiming to identify disease susceptibility genes have been published in recent years, although few positive results have been firmly replicated across multiple populations. As with other complex diseases, Genome Wide Association Studies (GWAS) have tested the association between thousands of single nucleotide polymorphisms (SNPs) in the whole genome and OA. To date GWAS have identified 15 common variants associated with knee or hip OA in European and Asian populations that have surpassed or reached the genome wide significance level ($P < 5 \times 10^{-8}$)[6,7]. However, the identified individual risk alleles have been found to exert only moderate to small effects to the overall susceptibility to OA development[7]. Among them loci on chromosome 13q34 near the *MCF2L*[8] gene, on chromosome 7q22[9,10], rs143383 polymorphism in *GDF5* gene[11–13], *DVWA*, (HLA) class II/III and *BTNL2* genes[14,15], 9q33 (*ASTN2*), 6q14 (*FILIP1*/*SENP6*), 12p11 (*KLHDC5*/*PTHLH*) and 12q23 (*CHST11*)[16] were strongly associated with hip or knee OA susceptibility. In addition, rs12982744 on 19q13 in *DOT1L* gene was associated with hip OA and cartilage thickness[17,18] and with lower height[19,20]. Growing evidence implicates a functional polymorphism in the *DIO2* gene as an OA risk factor with a current meta-analysis *P* value for the association of this gene with OA of 2.02×10^{-5}[21].

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Recently, a large GWAS meta-analysis from the TREAT-OA consortium consisting of 11,277 cases with radiographic and symptomatic hip OA and 67,473 controls, identified a novel variant rs6094710 at 20q13 near the nuclear receptor coactivator 3 gene (*NCOA3)* associated with hip OA[6]. The SNP is a G/A transition, conferring to A allele carriers about 30% greater risk to develop hip OA and this association reached genome wide significance level with *P* value 7.9×10^{-9} and odds ratio 1.28. Castano-Betancourt *et al.* in a GWAS of 13,013 participants tested for associations between minimal joint space width (mJSW) genetic risk score and mJSW/hip OA. They identified 5 novel loci, there of which, *TGF-a, RUNX-2, FGFR3, FGF3* were significantly associated with cartilage thickness and hip OA with *P* value $<10^{-4}$, suggesting that the identified loci for mJAW may be used to risk-stratify individuals for hip OA[22].

In addition, several meta-analyses of candidate gene association studies have been conducted with positive and negative association for OA susceptibility. In a recent meta-analysis several BMD-identified SNPs were nominally associated with knee OA risk. The strongest signal mapped to 12q3, which contains a gene coding for *SP 7* with odds ratio 1.22 and a *P* value of 9×10^{-4}. Additional loci map to 7p14.1 (*TXNDC3*), 11q13.2 (*LRP5*) and 11p14.1 (*LIN7C*). For all four loci the allele associated with higher BMD was associated with higher odds of OA supporting the hypothesis that BMD may be a risk factor contributing to OA development[23].

An assessment of OA candidate gene approach in a meta-analysis of 9 GWAS in Europeans including 5,636 knee OA patients and 16,972 controls and 4,349 hip OA and 17,836 controls found that SNPs at only two genes, *COL11A1* and *VEGF,* of the 199 analyzed OA candidate genes were associated with hip OA[24]. *COL11A1* showed two independent associations, rs4907986 with odds ratio 1.12, 95 % CI 1.06–1.17 and a *P* value of 1.29×10^{-5} and rs1241164 with OR 0.82, CI 0.74–0.89 and a *P* value of 1.47×10^{-5}, while *VEGF* was associated in a male-specific analysis (rs833058, odds ratio 0.85, CI 0.79–0.91 and a *P* value of 1.35×10^{-5}), pointing to the lack of reproducibility of OA candidate gene studies[24]. No association was found between knee and hip OA and the D13, D14 and D15 repeats of asporin gene (*ASPN*) in Caucasian and Asian populations in a meta-analysis including 4,417 OA patients and 3,403 controls[25] and between *VDR* BsmI, TaqI and ApaI polymorphisms and OA in a meta-analysis including 1,626 knee, hip, hand and lumbar spine OA cases and 2,024 controls[26,27]. Another meta-analysis including 5,409 knee OA patients, 4,355 hip OA patients and 5,362 healthy controls showed there is no direct implication of the *FTO* gene with OA susceptibility and that the effect of the *FTO* variant rs8044769 on OA is solely due to its effect on BMI[28].

Furthermore, in the period covered in this review, several OA candidate gene association studies have been published. However, only studies with large numbers of participants and/or functional studies will be mentioned. The polymorphism rs11564299 in the N-cadherin (*CDH2*) promoter region was associated with OA risk in 312 OA patients and 259 controls, with odds ratio 1.14, 95% CI 0.49–2.62 and a *P* value of 1.5×10^{-3}, with carriers of the minor allele of rs11564299 displaying increased N-cadherin levels in synovial fluid[29]. In silico analysis showed that the minor allele generated a novel transcription factor binding site and hnRNPK was found to be involved in the regulation of elevated N-cadherin expression in OA patients carrying the minor allele of rs11564299[29]. The functional exon 3 deleted growth hormone receptor gene polymorphism *(d3-GHR)* was associated with symptomatic hip OA independently of age and BMI in a combined analysis consisting of 2,175 female cases and 2,623 controls with pooled odds ratio 1.17, 95% CI 1.04–1.32 and a *P* value of 8×10^{-3}[30]. Vidal-Bralo *et al.* identified a new functional microsatellite in macrophage migration inhibitory factor (*MIF*) gene associated with hip OA in a case-control study including 1,775 knee OA patients, 1,782 hip OA patients and 1,878 controls from three European cohorts with *P* of the Mantel–Haenszel analysis 1.8×10^{-2} in women and 2.9×10^{-2} in men[31]. For all above candidate gene association studies, replication studies in different ethnic populations, as well as functional studies for the identification of the mechanisms that confer increased OA risk are needed.

Until now, all identified OA-associated variants explain only a small fraction of less than 10% of the genetic component. Large-scale studies with whole-genome sequencing focusing on variants with low minor allele frequency (MAF 1–5%) and rare variants (MAF <1%) have already starting to emerge[7]. Complete sequence of large OA cohorts will undoubtedly result in novel DNA-variants contributing to disease susceptibility. A recent GWAS identified through whole-genome sequencing of 2,230 individuals, two genome-wide significant loci, rs4238326(C/T) with odds ratio1.44, 95% CI 1.29–1.60 and a *P* value of 8.6×10^{-11} and rs3204689(C/G) with odds ratio 1.46, CI 1.31–1.63 and a *P* value of 1.1×10^{-11} at 15q22 in the *ALDH1A2* gene and a rare variant at 1p31 with odds ratio 47.7 and a *P* value of 1.53×10^{-9}[32]. The variants within the *ALDH1A2* gene were confirmed in replication sets from the Netherlands and the UK yielding an overall association with odds ratio 1.46 and a *P* value of 1.1×10^{-11}[32]. Allelic imbalance analysis for rs3204689 showed that the transcript with the risk-conferring C allele was expressed at a lower level in cartilage and adipose tissue compared to the non-risk allele, suggesting that *ALDH1A2* mediates the effect of the OA risk variants in the associated locus[32]. It is interesting that carriers of the rare variant at 1p31 belonged to an Icelandic family, in several members of which, the risk allele segregated with hand and generalized OA[32]. An exome-sequencing study conducted in 199 hip OA cases and 1,337 controls and in a group of hip OA and mJSW candidate genes (*ASTN2, DIO2, DOT1L, FGFR3, FILIP1, GLT8D1, GNL3, MCF2L, NCOA3, PIK3R1, PTHLH, RUNX2, SENP6, TGF-*α) identified 761 variants in these genes associated with hip OA and mJSW[33]. The strongest signal for mJSW was a rare variant in the *FGF3* gene with a *P* value of 8.6×10^{-5}, which however was not associated to the GWAS signal identified before by the same group[22]. *FGFR3* has previously been shown to be involved in endochondral bone formation and mutations in *FGFR3* result in achondroplasia[33]. Functional assessment of the identified variant is awaited.

Functional studies in OA loci

So far there are limited functional studies that provide possible mechanisms by which genetic variation at OA susceptibility genes confer increased OA risk. Genetic variation at the type II deiodinase (D2) gene *(DIO2)* has been identified as OA risk factor. Bos *et al.* showed that in OA cartilage, ligaments and subchondral bone there is differential allelic expression of *DIO2* mRNA, with the OA-associated 'C' allele of rs225014 in the *DIO2* gene being more abundant in heterozygous carriers (1.3-fold higher presence) than the wild type allele, suggesting that genetic variation at *DIO2* might confer to OA risk[34]. The same group recently identified a possible molecular mechanism of *DIO2* susceptibility in symptomatic OA[35]. It was shown that OA-related changes in methylation at CpG-2031, upstream of *DIO2,* caused significant upregulation of its expression, with β 4.96 and a *P* value of 1.6×10^{-3}, despite the conventional inverse relation between CpG methylation and gene expression, and this effect appeared to be driven by the *DIO2* rs225014 risk allele, with β 5.58 and a *P* value of 6×10^{-4}[35]. Using an *in vitro* chondrogenesis model with genetically modified hBMSC it was shown that up-regulation of *DIO2* induced *EPAS1* and *RUNX2* mediated up-regulation of cartilage degrading enzymes *(MMP-13* and *ADAMTS5*) and markers of mineralization (*ALPL*)[35]. However, as

no CTCF binding site was identified at rs225014 locus and as the previously assessed allelic imbalance[34] was not demonstrated, it was suggested that SNP rs225014 probably affects three-dimensional chromatin conformations, underlying the relation between the rs225014 tagged allelic imbalance and methylation-dependent up-regulation of *DIO2* among rs225014 risk allele carriers[35]. To conclude on the functional role of SNP rs225014 in *DIO2* gene in OA susceptibility, further studies are awaited. In addition, the recently identified *DOT1L* gene was suggested to play a role in chondrogenic bone development via regulation of Wnt-signaling[17]. The *GDF5* SNP rs143383 is the best-understood OA locus. It has been shown to exert its effect via regulation of transcription of the gene in which the T susceptibility allele leads to lower expression levels[11]. Recently, Sydall *et al.* identified four trans-acting factors Sp1, Sp3, P15, and DEAF-1 that bind differentially to the alleles of rs143383 and which contribute to the differential allelic expression that is mediated by this OA susceptibility locus. Knockdown and over expression of these factors demonstrated that Sp1, Sp3, and DEAF-1 are repressors of *GDF5* expression[36]. The authors proposed a binding model of the four trans-acting factors to rs143383, according to which DEAF-1, Sp1 and Sp3 are forming a repressive complex that forms directly over rs143383 and are differentially modulating the expression of the C and T alleles. P15 may be interacting with this complex and serving as a linker between Sp1 and the general transcription machinery[36]. The identified transcriptional factors could serve as potential therapeutic targets as their depletion might restore *GDF5* expression's levels in patients with the OA susceptibility T allele[36].

Furthermore, the expression level of the latest identified variant rs6094719 in *NCOA3* gene was found to be significantly lower in OA cartilage compared to preserved cartilage (macroscopically normal but isolated from the same joint) with a P value of 6.4×10^{-3}[6]. The molecular mechanism by which *NCOA3* contributes to OA is not clear. *NCOA3* is involved in the co-activation of different receptors, as steroids, retinoids, thyroid hormone, vitamin D3 and prostanoids, several of which are involved in skeletal metabolism and OA[6]. *NCOA3* knockout mice showed growth retardation and reduced adult body size, while female knockout mice exhibited abnormal development and function of their reproductive system and lower eostrogen levels compared with the wild type, indicating a possible role of *NCOA3* in steroid regulation[37]. Other possible mechanisms by which *NCOA3* might be involved in cartilage homeostasis is through transcriptional regulation in mechanotransduction or through regulation of the target tissue responses to thyroid hormone (T3)[38,39].

Rushton *et al.* in the 2014 OARSI meeting showed reduced expression of *NCOA3* in individuals carrying a copy of the OA associated A-allele in fat pad and synovial membrane from OA patients[40]. Furthermore, *NCOA3* was shown to be up-regulated in hip OA cartilage relative to the control non-OA cartilage OA[40], in contrast to the observed downregulation by Evangelou *et al.*[6]. The discrepancy in *NCOA3* gene expression between the two studies could be attributed to the different source of control cartilage, as Evangelou *et al.* used as control macroscopically normal cartilage from an OA joint (preserved cartilage) and not non-OA hip cartilage. Previous studies have demonstrated that cartilage from macroscopically and histologically intact regions from an OA joint (preserved cartilage) exhibits differential gene (leptin (LEP)) expression levels than normal (non-OA) cartilage[41].

Microarray-based gene expression studies

Several studies have analyzed the expression pattern of different genes, using microarray technology to determine their involvement in OA pathogenesis. Catabolic enzymes such as *ADAMTS5, ADAMTS1* and *MMP1* were found increased in knee OA and decreased in hip OA strengthening the idea that OA is characterized by joint specificity[42]. In addition, osteophytic cartilage showed increased expression of genes involved in terminal chondrocytes differentiation and endochondral ossification such as *BGLAP, BMP8B, COL1A2, SOST, RUNX2*, compared to articular cartilage, which showed increased levels of antagonists and inhibitors of the BMP- and Wnt-signaling pathways *as GREM1, FRZB, WISP3*[43].

Recently, incorporation of microarray-based studies along with network analysis has led to advancement in our understanding of pathways involved in OA pathogenesis. Several microarray-based gene expression-profiling studies have been performed in different tissues of the OA joint. In the period covered in this review, gene expression analysis in two different regions of OA synovial membrane of the same patient, inflamed and normal, revealed differentially expressed genes belonging to pathways related to inflammation, cartilage metabolism, Wnt signaling and angiogenesis[44]. In the inflammatory network, *TREM1* and *S100A9* were strongly up-regulated, *MMP-3* and *-9*, *cathepsin H* and S were up-regulated in the cartilage catabolism pathway, *Wnt-5A* and *LRP5* were up-regulated in the Wnt signaling and *STC1* coding for a protein involved in angiogenesis was the most up-regulated gene in the inflammatory region of the synovial membrane[44]. The alarmin *S100A9* might a be a gene of interest, as it was shown that it stimulates osteophyte formation in experimental OA and predicts osteophyte progression in early OA patients[45], pointing towards the potential use of S100A9 as a biomarker predictive of joint destruction. Another microarray-based gene expression analysis in end-stage OA synovium revealed increased expression of transforming growth factor-beta responsive genes in OA-related fibrosis, such as *COL1A1* (7-fold, $P < 10^{-3}$) and *COL5A1* (4-fold, $P < 3.6 \times 10^{-2}$) and genes encoding for collagen cross-linking enzymes, such as *PLOD2* (25)-fold, $P < 10^{-3}$ and *LOX* (3-fold, $P < 10^{-3}$), speculating that PLOD2 might be an attractive and promising target to interfere in OA-related synovial fibrosis[46].

In the first whole-genome expression profiling study of subchondral bone, Chou *et al.* identified 972 differentially expressed genes in chondrocytes from 20 OA and 5 non-OA knee lateral tibial and medial tibial plateaus (>2-fold, $P < 5 \times 10^{-2}$)[47]. Pathway analysis with the most up-regulated and down-regulated genes identified a novel signaling network in OA characterized by up regulation of bone mineralization or collagen-associated genes, such as *COL3A1, BMP1, BMP7, POSTN, WISP1, HTRA1, SOST, ITGA11*, angiogenesis genes as *ANGPTL1* and by down-regulation of genes associated with cellular metabolism, proliferation or differentiation, such as *NMB, LEP, CHRDL2, GRB14, CIDEC, CIDEA, BTG2, PLAC8, and PRDM16*. A novel finding was the implication of periostin (*POSTN*) and leptin (*LEP*) in bone remodeling by osteoblasts[47].

In addition, gene expression profiling in peripheral blood of non-OA and patients with familial OA revealed 694 unique genes differentially expressed between cases and controls, including 86 genes expressed with at least 1.5-fold difference[48]. *ATF4, GPR18* and *H3F3B* were among the top identified genes with a P value of 4.5×10^{-8}. It is interesting that in OA patients, apoptosis pathway genes were found significantly enriched including *CASP3* and FAS-associated death domain (*FADD*). However, the identified genes need to be validated in a population-based setting before being considered as early OA markers[48].

DNA methylation and OA

DNA methylation is at the moment the most well studied epigenetic mechanism in OA[49]. Methylation profiling of bone has revealed differentially methylated regions between osteoporosis and OA, including regions that were enriched in genes associated

with cell differentiation and skeletal embryogenesis[50]. Moreover, several genes have been reported with altered DNA methylation patters in OA. Reduced methylation of specific CpG sites was associated with increased *MMP-3, 9, 13* and *ADAMTS-4* expression levels in end-stage OA chondrocytes[51–53], while the DNA methylation status of *MMP-13* and *iNOS* was shown to affect their transcriptional regulation in OA through changes of the binding affinity of transcriptional factors[54–56]. In *MMP-13* promoter, the sites at −104 and −110 bp site have been demonstrated as methylation modulated *CREB* and *HIF-2a* binding sites, respectively[54,56]. The methylation of CpG sites at −5853 and −5842 in an enhancer of *iNOS* repressed the binding of p65 subunit of NF-kB, suggesting the epigenetic regulation of *iNOS* in OA[55]. Moreover, hypermethylation of *SOD* and *SOX-9* promoter has been associated with decreased gene expression in OA cartilage in an animal model of OA[57].

Recently, a genome-wide DNA methylation analysis of articular chondrocytes in 25 OA patients and 20 healthy controls showed different methylation status between patients and controls[58]. Genome-wide expression analysis in the same cohort, revealed the existence of a tight cluster of OA patients with differential gene expression characterized with increased inflammatory response. The most consistent genes were validated in an independent OA cohort, identifying thus novel genes as potential OA markers[58]. Taylor *et al.* identified a new epigenetic mark, 5 hydroxymethylcytosine (5 hmC) globally increased in knee OA chondrocytes compared to normal. 5 hmC is an intermediate in DNA demethylation generated from the conversion of 5 mC to 5 hmC through TET1,2,3 enzymes[59,60]. The increase in 5 hmC (5–6-fold) was concomitant with loss of TET1 in OA chondrocytes. In addition, the enrichment of 5 hmC at specific CpG sites in the *MMP-1* and *MMP-3* promoters correlated with increased *MMPs* expression in OA chondrocytes. This site was proximal to the CpG site undergoing significant DNA demethylation in OA chondrocytes (−635 bp) suggesting a role of 5 hmC in active DNA demethylation[60]. It is important, however, to analyze other CpG sites in MMP genes, especially in exons, to clarify the role of 5 hmC in regulating MMPs gene expression in OA. In a genome wide DNA methylation profiling of knee and hip osteoarthritic and preserved (macroscopically normal cartilage from OA joint) articular cartilage den Hollander *et al.* showed that methylation of CpG dinucleotides differs substantially between hips and knees[61]. Also, the identified methylation changes at a multitude of CpG dinucleotides were associated with gene expression in articular cartilage of novel genes, such as *IGFBP7*, *LOXL3*, *MALL*, *BFSP1* and *SLC7A5,* as well as OA associated genes, such as *CRLF1*, *COL6A3*, *CD44*, *CILP* and *TGFBI*[61]. In another genome-wide methylation study in knee and hip OA cartilage, Rushton *et al.* found differential methylation profile between OA and non-OA cartilage and also between hip and knee OA[62]. In addition, two groups of expression patterns were identified in knee OA cartilage and these two groups were also present in hip OA cartilage, confirming the differences in methylation profile between knee and hip OA[62]. Differences in whole genome methylation profiling between knee and hip OA cartilage were a common finding in both of the above-mentioned genome-wide methylation profiling studies, pointing to the contrasting nature of OA progression between the two joints.

MicroRNAs and OA

To date, almost all studies into the role of non-coding RNAs (ncRNAs) in cartilage biology and OA have concentrated on microRNAs (miRNAs). MicroRNAs are small, 18–24 nucleotides in length, single-stranded noncoding RNA molecules, that negatively regulate the expression of target genes in a post-transcriptional manner by binding to specific sequences within target messenger RNAs (mRNAs)[63].

Previous large-scale microarray miRNA analysis identified nine up regulated microRNAs, miR-16, miR-22, miR-23b, miR-30b, miR-103, miR-223, miR-377, miR-483 and miR-509 and seven down-regulated microRNAs, miR-25, miR-26a, miR-29a, miR-140, miR-210, miR-337 and miR-373 in OA compared to normal cartilage[64]. Functional experiments identified miR-22 to be implicated in obesity and inflammation[64], miR-9 in MMP-13 regulation and miR-9, miR-98 and miR-146 in the control of tumor necrosis factor (TNF) expression, suggesting that these miRNAs may have a protective role in OA[64,65]. Another microarray based microRNA study revealed that miR-483-5p was upregulated in OA chondrocytes, while miR-149, miR-582-3p, miR-1227, miR-634, miR-576-5p, and miR-641 were up-regulated in normal chondrocytes. These miRNAs were predicted to function in articular cartilage via the TGF, Wnt, and Erb signaling[66]. MicroRNA-140, is a critical miRNA in OA as it is specifically expressed by chondrocytes and plays important role in chondrogenesis and cartilage development[67,68]. Knockout or overexpression of miR-140 *in vivo* was shown to have profound effects on the development of OA and it was shown to directly mediate *MMP-13* expression in *vitro*[69,70]. Other studies identified miR-27a and 27b to regulate the expression levels of *MMP-13* in OA chondrocytes, in an indirect or direct manner, respectively[71,72], whereas miR-146a has also been suggested to function as a negative feedback regulator of *MMP-13*. miR-146a is strongly expressed in cartilage with mild OA but its expression gradually decreases with advancement of disease and is inversely correlated with the expression of *MMP-13* in OA cartilage[73,74]. Recently, Wang *et al.* showed that HDAC inhibitors increase miR-146a expression and enhance negative regulation of interleukin-1b signaling in OA fibroblast-like synoviocytes[75]. However, due to toxicity and off-target side effects of HDAC inhibitors, their use in OA may be problematic.

Recent studies in knee OA cartilage and healthy articular cartilage showed that miR-125b is down regulated in OA cartilage and that it directly regulates ADAMTS-4 through IL-1β activation[76]. In addition, Park *et al.* showed that miR-558 is down regulated in OA chondrocytes and that it directly targets COX-2 and regulates IL-1b stimulated catabolic effects in chondrocytes[77]. Another microRNA, miR-127-5p was also down regulated in knee OA cartilage compared to normal and the IL-1β-induced up regulation of *MMP-13* expression was correlated with miR-127-5p down regulation in chondrocytes. MicroRNA-127-5p suppressed IL-1β-induced *MMP-13* production, while anti-miR-127-5p significantly increased *MMP-13* production, suggesting that miR-127-5p may be an important regulator of *MMP-13* expression in human chondrocytes[78]. In addition, miR-148a was found down-regulated in knee OA chondrocytes compared to normal[79]. Its overexpression decreased *COL10A1, MMP-13* and *ADAMTS5* and increased *COL2A1* expression. The matrix deposited by miR-148a overexpressing chondrocytes contained more proteoglycans and collagen, in particular collagen type II, pointing to its role as a potential disease-modifying compound in OA[79]. Furthermore, endogenous miR-21 was found up-regulated in knee OA cartilage compared to control and overexpression/inhibition experiments showed that miR-21 suppresses the maturation of CH8 cells and chondrogenesis process[80]. In addition miR-21 overexpression resulted in significant increase in *MMP1, MMP2, MMP3, MMP9* expression, while miR-21 inhibition decreased their expression. Bioinformatic analysis predicted miR-21 to be a target of GDF-5 and a luciferase activity assay showed that *GDF-5* is directly targeted by miR-21, which induces *GDF-5* mRNA decay, suggesting that it might be a potential therapeutic target[80]. Swingler *et al.* using chocndrocytes from an animal model of OA as

Table I
MicroRNAs in OA

miRNA	Tissue	Regulation in OA	Biological function/pathways involved	Target genes	Reference
mir-16, mir-23b, mir-30b, mir-103, mir-223, mir-377, mir-483, mir-509	Cartilage	Up-regulated			64
miR-25, miR-26a, miR-29a, miR-210, miR-337, miR-373	Cartilage	Down-regulated			64
miR-22	Cartilage	Up-regulated	Inflammatory response, aging	PPARa, BMP7	64
miR-140	Cartilage	Down-regulated	Cartilage homeostasis	ADAMST5, Aggrecan, MMP-13, IGFBP5	64,72,73
miR-149	Chondrocytes	Down-regulated	TGF-β, Wnt, Erb and mTOR signaling		66
mir-27a	Chondrocytes	Down-regulated	Cartilage homeostasis	MMP-13	72
mir-27b	Chondrocytes	Down-regulated	Cartilage homeostasis	MMP-13	71
mir-146a	Cartilage/Synoviocytes	Up-regulated	Chondrocyte apoptosis	VEGF, SMAD4	73–75
miR-146	Cartilage	Down-regulated	Inflammatory response (NF-κB pathway)	TRAF6, IRAK1	65
miR-9	Cartilage/Bone	Up-regulated	Inflammatory process	MMP-13	65
miR-98	Cartilage/Bone	Up-regulated	Inflammatory process	TNF-a	65
miR-483-5p	Cartilage	Up-regulated	TGF-β, Wnt, Erb and mTOR signaling		66
miR-576-5p, mir-634, mir-641, mir-1227	Cartilage	Down-regulated	TGF-β, Wnt, Erb and mTOR signaling		66
miR-125b	Cartilage	Down-regulated	Cartilage homeostasis	ADAMTS-4	76
miR-127-5p	Cartilage	Down-regulated	Cartilage homeostasis	MMP-13	78
miR-558	Cartilage	Down-regulated	Cartilage homeostasis	COX-2	77
miR-21	Chondrocytes	Up-regulated	Inhibition of chondrocyte proliferation	GDF-5	80
let-7e	Serum	Down-regulated			82
miR-148a	Cartilage	Down-regulated	Cartilage homeostasis	COL10A1, MMP-13, ADAMTS5	79

well as primary human chondrocytes identified the microRNA-29 family as microRNAs which act early in OA development, are regulated by important factors in OA, as TGF-β, SOX-9 and have functional impact on relevant pathways, as NF-kB, canonical Wnt, Smad[81]. In addition, novel genes, as *ADAMTS5, ADAMTS6, ADAMTS14, ADAMTS17, ADAMTS19, FZD3, DVL3, FRAT2, CK2A2* were validated as direct targets of microRNA 29 family. Identification of pathways through which miR-29 family regulates development and OA progression is awaited[81]. In a recent study, Beyer *et al.* identified in a population-based cohort including 816 Caucasians with OA necessitating arthroplasty, differentially expressed circulating microRNAs[82]. Among the identified microRNAs, three microRNAs, let-7e, miR-454 and miR-885-5p were identified as predictors for severe knee or hip OA. After the application of very stringent criteria for arthroplasty and statistical analysis, let-7e emerged as a potential predictor for severe knee or hip OA arthroplasty, as its association to OA was independent of age, sex and BMI with 95% CI 0.61–0.97 and a *P* value of 2.8×10^{-2}[82]. To assess let-7e value, its validation in different cohorts and different applications is awaited. Table I shows the microRNAs that have been identified to have a role in OA, the biological processes they are involved and their targets.

As more and more microRNAs are revealed to play roles during chondrogenesis, cartilage ho-meostasis and OA pathogenesis, the identification of microRNAs key targets that functionally impact OA pathogenesis and disease progression and the mechanisms of microRNAs regulation are necessary.

Summary

Only a few loci have been associated with OA at genome-wide significance levels despite extensive efforts and even these signals have a small effect size. As a proportion of the genetic susceptibility to OA is due to low frequency and rare variants, next-generation sequencing in large populations is expected to lead to the detection of rare variant associations with OA risk. To obtain a better understanding of OA, integration of functional genomics, microarray-based gene expression studies and network-based analysis, along with epigenetics is essential for the identification of signaling pathways regulated during disease development.

Author contribution

Aspasia Tsezou searched the literature, summarized the results and wrote the manuscript.

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References

1. Thomas E, Peat G, Croft P. Defining and mapping the person with osteoarthritis for population studies and public health. Rheumatology (Oxford) 2014;53:338–45.
2. Taieb C, Bruel P, Auges M. Knee arthritis: a confirmed burden. Osteoarthritis and Cartilage 2014;22:S224–5.
3. Jordan JM, Kraus VB, Hochberg MC. Genetics of osteoarthritis. Curr Rheumatol Rep 2004;6:7–13.
4. Kraus VB, Jordan JM, Doherty M, Wilson AG, Moskowitz R, Hochberg M, *et al.* The genetics of generalized osteoarthritis (GOGO) study: study design and evaluation of osteoarthritis phenotypes. Osteoarthritis Cartilage 2007;15:120–7.
5. Spector TD, Cicuttini F, Baker J, Loughlin J, Hart D. Genetic influences on osteoarthritis in women: a twin study. BMJ 1996;312:940–3.
6. Evangelou E, Kerkhof HJ, Styrkarsdottir U, Ntzani EE, Bos SD, Esko T, *et al.* A meta-analysis of genome-wide association studies identifies novel variants associated with osteoarthritis of the hip. Ann Rheum Dis 2013, http://dx.doi.org/10.1136/annrheumdis-2012-203114.
7. Panoutsopoulou K, Zeggini E. Advances in osteoarthritis genetics. J Med Genet 2013;50:715–24.

8. Day-Williams AG, Southam L, Panoutsopoulou K, Rayner NW, Esko T, Estrada K, *et al.* A variant in MCF2L is associated with osteoarthritis. Am J Hum Genet 2011;89:446–50.
9. Evangelou E, Valdes AM, Kerkhof HJ, Styrkarsdottir U, Zhu Y, Meulenbelt I, *et al.* Meta-analysis of genome-wide association studies confirms a susceptibility locus for knee osteoarthritis on chromosome 7q22. Ann Rheum Dis 2011;70:349–55.
10. Kerkhof HJ, Lories RJ, Meulenbelt I, Jonsdottir I, Valdes AM, Arp P, *et al.* A genome-wide association study identifies an osteoarthritis susceptibility locus on chromosome 7q22. Arthritis Rheum 2010;62:499–510.
11. Miyamoto Y, Mabuchi A, Shi D, Kubo T, Takatori Y, Saito S, *et al.* A functional polymorphism in the 5' UTR of GDF5 is associated with susceptibility to osteoarthritis. Nat Genet 2007;39:529–33.
12. Valdes AM, Evangelou E, Kerkhof HJ, Tamm A, Doherty SA, Kisand K, *et al.* The GDF5 rs143383 polymorphism is associated with osteoarthritis of the knee with genome-wide statistical significance. Ann Rheum Dis 2011;70:873–5.
13. Sanna S, Jackson AU, Nagaraja R, Willer CJ, Chen WM, Bonnycastle LL, *et al.* Common variants in the GDF5-UQCC region are associated with variation in human height. Nat Genet 2008;40:198–203.
14. Miyamoto Y, Shi D, Nakajima M, Ozaki K, Sudo A, Kotani A, *et al.* Common variants in DVWA on chromosome 3p24.3 are associated with susceptibility to knee osteoarthritis. Nat Genet 2008;40:994–8.
15. Nakajima M, Takahashi A, Kou I, Rodriguez-Fontenla C, Gomez-Reino JJ, Furuichi T, *et al.* New sequence variants in HLA class II/III region associated with susceptibility to knee osteoarthritis identified by genome-wide association study. PLoS One 2010;5:e9723.
16. arcOGEN Consortium, arcOGEN Collaborators, Zeggini E, Panoutsopoulou K, Southam L, Rayner NW, Day-Williams AG, Lopes MC, *et al.* Identification of new susceptibility loci for osteoarthritis (arcOGEN): a genome-wide association study. Lancet 2012;380:815–23.
17. Castaño Betancourt MC, Cailotto F, Kerkhof HJ, Cornelis FM, Doherty SA, Hart DJ, *et al.* Genome-wide association and functional studies identify the DOT1L gene to be involved in cartilage thickness and hip osteoarthritis. Proc Natl Acad Sci USA 2012;109:8218–23.
18. Evangelou E, Valdes AM, Castano-Betancourt MC, Doherty M, Doherty S, Esko T, *et al.* The DOT1L rs12982744 polymorphism is associated with osteoarthritis of the hip with genome-wide statistical significance in males. Ann Rheum Dis 2013;72:1264–5.
19. Lango Allen H, Estrada K, Lettre G, Berndt SI, Weedon MN, Rivadeneira F, *et al.* Hundreds of variants clustered in genomic loci and biological pathways affect human height. Nature 2010;467:832–8.
20. Sovio U, Bennett AJ, Millwood IY, Molitor J, O'Reilly PF, Timpson NJ, *et al.* Genetic determinants of height growth assessed longitudinally from infancy to adulthood in the northern Finland birth cohort 1966. PLoS Genet 2009;5:e1000409.
21. Meulenbelt I, Min JL, Bos S, Riyazi N, Houwing-Duistermaat JJ, van der Wijk HJ, *et al.* Identification of DIO2 as a new susceptibility locus for symptomatic osteoarthritis. Hum Mol Genet 2008;17:1867–75.
22. Castano Betancourt M, Evans D, Liu Y, Yau M, Uitterlinden A, Evangelou V, *et al.* Novel variants for cartilage thickness and hip osteoarthritis: revealing genes implicated in cartilage and bone development. Osteoarthritis and Cartilage 2014;22:S41.
23. Yerges-Armstrong LM, Yau MS, Liu Y, Krishnan S, Renner JB, Eaton CB, *et al.* Association analysis of BMD-associated SNPs with knee osteoarthritis. J Bone Min Res 2014;29:1373–9.
24. Rodriguez-Fontenla C, Calaza M, Evangelou E, Valdes AM, Arden N, Blanco FJ, *et al.* Assessment of osteoarthritis candidate genes in a meta-analysis of nine genome-wide association studies. Arthritis Rheumatol 2014;66:940–9.
25. Song GG, Kim JH, Lee YH. A meta-analysis of the relationship between aspartic acid (D)-repeat polymorphisms in asporin and osteoarthritis susceptibility. Rheumatol Int 2014;34:785–92.
26. Liu H, He H, Li S, Yang L, Wang P, Liu C, *et al.* Vitamin D receptor gene polymorphisms and risk of osteoarthritis: a meta-analysis. Exp Biol Med (Maywood) 2014;239:559–67.
27. Zhu ZH, Jin XZ, Zhang W, Chen M, Ye DQ, Zhai Y, *et al.* Associations between vitamin D receptor gene polymorphisms and osteoarthritis: an updated meta-analysis. Rheumatology (Oxford) 2014;53:998–1008.
28. Panoutsopoulou K, Metrustry S, Doherty SA, Laslett LL, Maciewicz RA, Hart DJ, *et al.* The effect of FTO variation on increased osteoarthritis risk is mediated through body mass index: a mendelian randomisation study. Ann Rheum Dis 2013; Feb 4, http://dx.doi.org/10.1136/annrheumdis-2013-203772. [Epub ahead of print].
29. Ruedel A, Stark K, Kaufmann S, Bauer R, Reinders J, Rovensky J, *et al.* N-cadherin promoter polymorphisms and risk of osteoarthritis. FASEB J 2014;28:683–91.
30. Claessen KM, Kloppenburg M, Kroon HM, Bijsterbosch J, Pereira AM, Romijn JA, *et al.* Relationship between the functional exon 3 deleted growth hormone receptor polymorphism and symptomatic osteoarthritis in women. Ann Rheum Dis 2014;73:433–6.
31. Vidal-Bralo L, Rodriguez-Fontela C, Calaza M, Oreiro N, Blanco FJ, Carr A, *et al.* New functional microsatellite associated with osteoarthritis susceptibility. Osteoarthritis and Cartilage 2014;22:S232–3.
32. Styrkarsdottir U, Thorleifsson G, Helgadottir HT, Bomer N, Metrustry S, Bierma-Zeinstra S, *et al.* Severe osteoarthritis of the hand associates with common variants within the ALDH1A2 gene and with rare variants at 1p31. Nat Genet 2014;46:498–502.
33. Boer CG, Jv Rooij, Peters M, Kraaij R, Jhamai M, Arp P, *et al.* Discovery and analysis of rare coding variants for hipOA by exome-sequencing. Osteoarthritis and Cartilage 2014;22:S226–7.
34. Bos SD, Bovee JV, Duijnisveld BJ, Raine EV, van Dalen WJ, Ramos YF, *et al.* Increased type II deiodinase protein in OA-affected cartilage and allelic imbalance of OA risk polymorphism rs225014 at DIO2 in human OA joint tissues. Ann Rheum Dis 2012;71:1254–8.
35. Bomer N, den Hollander W, Ramos YF, Bos SD, van der Breggen R, Lakenberg N, *et al.* Underlying molecular mechanisms of DIO2 susceptibility in symptomatic osteoarthritis. Ann Rheum Dis 2014; Apr 2, http://dx.doi.org/10.1136/annrheumdis-2013-204739. [Epub ahead of print].
36. Syddall CM, Reynard LN, Young DA, Loughlin J. The identification of trans-acting factors that regulate the expression of GDF5 via the osteoarthritis susceptibility SNP rs143383. PLoS Genet 2013;9:e1003557.
37. Xu J, Liao L, Ning G, Yoshida-Komiya H, Deng C, O'Malley BW. The steroid receptor coactivator SRC-3 (p/CIP/RAC3/AIB1/ACTR/TRAM-1) is required for normal growth, puberty, female reproductive function, and mammary gland development. Proc Natl Acad Sci USA 2000;97:6379–84.

38. Arimura A, vn Peer M, Schröder AJ, Rothman PB. The transcriptional co-activator p/CIP (NCoA-3) is up-regulated by STAT6 and serves as a positive regulator of transcriptional activation by STAT6. J Biol Chem 2004;279:31105–12.
39. Nicholls JJ, Brassill MJ, Williams GR, Bassett JH. The skeletal consequences of thyrotoxicosis. J Endocrinol 2012;213:209–21.
40. Rushton MD, Gee FH, Reynard LN, Loughlin J. The osteoarthritis association marked by SNP rs6094710 mediates its effects by reducing the expression of NCOA3 in joint tissues. Osteoarthritis and Cartilage 2014;22:S237.
41. Simopoulou T, Malizos KN, Iliopoulos D, Stefanou N, Papatheodorou L, Ioannou M, *et al*. Differential expression of leptin and leptin's receptor isoform (Ob-Rb) mRNA between advanced and minimally affected osteoarthritic cartilage; effect on cartilage metabolism. Osteoarthritis and Cartilage 2007;15:872–83.
42. Xu Y, Barter MJ, Swan DC, Rankin KS, Rowan AD, Santibanez-Koref M, *et al*. Identification of the pathogenic pathways in osteoarthritic hip cartilage: commonality and discord between hip and knee OA. Osteoarthritis and Cartilage 2012;20:1029–38.
43. Gelse K, Ekici AB, Cipa F, Swoboda B, Carl HD, Olk A, *et al*. Molecular differentiation between osteophytic and articular cartilage–clues for a transient and permanent chondrocyte phenotype. Osteoarthritis and Cartilage 2012;20:162–71.
44. Lambert C, Dubuc JE, Montell E, Vergés J, Munaut C, Noël A, *et al*. Gene expression pattern of synovial cells from inflammatory and normal areas of osteoarthritis synovial membrane. Arthritis Rheum 2013;66:960–8.
45. Schelbergen RF, de Munter W, van den Bosch MH, Lafeber FP, Vogl T, Roth J, *et al*. Alarmins S100A8/S100A9 stimulate osteophyte formation in experimental osteoarthritis and predict osteophyte progression in the check cohort of early human osteoarthritis patients. Osteoarthritis and Cartilage 2014;22:S303.
46. Remst DF, Blom AB, Vitters EL, Bank RA, van den Berg WB, Blaney Davidson EN, *et al*. Gene expression analysis of murine and human osteoarthritis synovium reveals elevation of transforming growth factor beta-responsive genes in osteoarthritis-related fibrosis. Arthritis Rheumatol 2014;66:647–56.
47. Chou CH, Wu CC, Song IW, Chuang HP, Lu LS, Chang JH, *et al*. Genome-wide expression profiles of subchondral bone in osteoarthritis. Arthritis Res Ther 2013;15:R190.
48. Ramos YF, Bos SD, Lakenberg N, Böhringer S, den Hollander WJ, Kloppenburg M, *et al*. Genes expressed in blood link osteoarthritis with apoptotic pathways. Ann Rheum Dis 2013; Jul 17, http://dx.doi.org/10.1136/annrheumdis-2013-203405. [Epub ahead of print].
49. Oppermann U. Why is epigenetics important in understanding the pathogenesis of inflammatory musculoskeletal diseases? Arthritis Res Ther 2013;15:209.
50. Delgado-Calle J, Fernandez AF, Sainz J, Zarrabeitia MT, Sañudo C, García-Renedo R, *et al*. Genome-wide profiling of bone reveals differentially methylated regions in osteoporosis and osteoarthritis. Arthritis Rheum 2013;65:197–205.
51. Cheung KS, Hashimoto K, Yamada N, Roach HI. Expression of ADAMTS-4 by chondrocytes in the surface zone of human osteoarthritic cartilage is regulated by epigenetic DNA demethylation. Rheumatol Int 2009;29:525–34.
52. da Silva MA, Yamada N, Clarke NM, Roach HI. Cellular and epigenetic features of a young healthy and a young osteoarthritic cartilage compared with aged control and OA cartilage. J Orthop Res 2009;27:593–601.
53. Roach HI, Yamada N, Cheung KS, Tilley S, Clarke NM, Oreffo RO, *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;52:3110–24.
54. Bui C, Barter MJ, Scott JL, Xu Y, Galler M, Reynard LN, *et al*. cAMP response element-binding (CREB) recruitment following a specific CpG demethylation leads to the elevated expression of the matrix metalloproteinase 13 in human articular chondrocytes and osteoarthritis. FASEB J 2012;26:3000–11.
55. de Andres MC, Imagawa K, Hashimoto K, Gonzalez A, Roach HI, Goldring MB, *et al*. Loss of methylation in CpG sites in the NF-kappaB enhancer elements of inducible nitric oxide synthase is responsible for gene induction in human articular chondrocytes. Arthritis Rheum 2013;65:732–42.
56. Hashimoto K, Otero M, Imagawa K, de Andres MC, Coico JM, Roach HI, *et al*. Regulated transcription of human matrix metalloproteinase 13 (MMP13) and interleukin-1beta (IL1B) genes in chondrocytes depends on methylation of specific proximal promoter CpG sites. J Biol Chem 2013;288:10061–72.
57. Scott JL, Gabrielides C, Davidson RK, Swingler TE, Clark IM, Wallis GA, *et al*. Superoxide dismutase downregulation in osteoarthritis progression and end-stage disease. Ann Rheum Dis 2010;69:1502–10.
58. Fernández-Tajes J, Soto-Hermida A, Vázquez-Mosquera ME, Cortés-Pereira E, Mosquera A, Fernández-Moreno M, *et al*. Genome-wide DNA methylation analysis of articular chondrocytes reveals a cluster of osteoarthritic patients. Ann Rheum Dis 2014;73:668–77.
59. Ito S, Shen L, Dai Q, Wu SC, Collins LB, Swenberg JA, *et al*. Tet proteins can convert 5-methylcytosine to 5-formylcytosine and 5-carboxylcytosine. Science 2011;333:1300–3.
60. Taylor SE, Smeriglio P, Dhulipala L, Rath M, Bhutani N. A global increase in 5-hydroxymethylcytosine levels marks osteoarthritic chondrocytes. Arthritis Rheum 2014;66:90–100.
61. den Hollander W, Ramos YF, Bos SD, Bomer N, van der Breggen R, Lakenberg N, *et al*. Genome wide DNA methylation profiling of osteoarthritic articular cartilage. Osteoarthritis and Cartilage 2014;22:S40–1.
62. Rushton MD, Reynard LN, Barter MJ, Rankin KS, Young DA, Loughlin J. Characterisation of the cartilage DNA methylome in knee and hip osteoarthritis using high-density genome-wide analysis. Osteoarthritis and Cartilage 2014;22:S233.
63. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell 2004;116:281–97.
64. Iliopoulos D, Malizos KN, Oikonomou P, Tsezou A. Integrative microRNA and proteomic approaches identify novel osteoarthritis genes and their collaborative metabolic and inflammatory networks. PLoS One 2008;3:e3740.
65. Jones SW, Watkins G, Le Good N, Roberts S, Murphy CL, Brockbank SM, *et al*. The identification of differentially expressed microRNA in osteoarthritic tissue that modulate the production of TNF-alpha and MMP13. Osteoarthritis and Cartilage 2009;17:464–72.
66. Díaz-Prado S, Cicione C, Muiños-López E, Hermida-Gómez T, Oreiro N, Fernández-López C, *et al*. Characterization of microRNA expression profiles in normal and osteoarthritic human chondrocytes. BMC Musculoskelet Disord 2012;13:144.
67. Miyaki S, Nakasa T, Otsuki S, Grogan SP, Higashiyama R, Inoue A, *et al*. MicroRNA-140 is expressed in differentiated human articular chondrocytes and modulates interleukin-1 responses. Arthritis Rheum 2009;60:2723–30.
68. Tuddenham L, Wheeler G, Ntounia-Fousara S, Waters J, Hajihosseini MK, Clark I, *et al*. The cartilage specific microRNA-140 targets histone deacetylase 4 in mouse cells. FEBS Lett 2006;580:4214–7.

69. Nakamura Y, Inloes JB, Katagiri T, Kobayashi T. Chondrocyte-specific microRNA-140 regulates endochondral bone development and targets Dnpep to modulate bone morphogenetic protein signaling. Mol Cell Biol 2011;31:3019–28.
70. Liang ZJ, Zhuang H, Wang GX, Li Z, Zhang HT, Yu TQ, *et al*. MiRNA-140 is a negative feedback regulator of MMP-13 in IL-1beta-stimulated human articular chondrocyte C28/I2 cells. Inflamm Res 2012;61:503–9.
71. Akhtar N, Rasheed Z, Ramamurthy S, Anbazhagan AN, Voss FR, Haqqi TM. MicroRNA-27b regulates the expression of matrix metalloproteinase 13 in human osteoarthritis chondrocytes. Arthritis Rheum 2010;62:1361–71.
72. Tardif G, Hum D, Pelletier JP, Duval N, Martel-Pelletier J. 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.
73. Li J, Huang J, Dai L, Yu D, Chen Q, Zhang X, *et al*. miR-146a, an IL-1beta responsive miRNA, induces vascular endothelial growth factor and chondrocyte apoptosis by targeting Smad4. Arthritis Res Ther 2012;14:R75.
74. Yamasaki K, Nakasa T, Miyaki S, Ishikawa M, Deie M, Adachi N, *et al*. Expression of MicroRNA-146a in osteoarthritis cartilage. Arthritis Rheum 2009;60:1035–41.
75. Wang JH, Shih KS, Wu YW, Wang AW, Yang CR. Histone deacetylase inhibitors increase microRNA-146a expression and enhance negative regulation of interleukin-1beta signaling in osteoarthritis fibroblast-like synoviocytes. Osteoarthritis and Cartilage 2013;21:1987–96.
76. Matsukawa T, Sakai T, Yonezawa T, Hiraiwa H, Hamada T, Nakashima M, *et al*. MicroRNA-125b regulates the expression of aggrecanase-1 (ADAMTS-4) in human osteoarthritic chondrocytes. Arthritis Res Ther 2013;15:R28.
77. Park SJ, Cheon EJ, Kim HA. MicroRNA-558 regulates the expression of cyclooxygenase-2 and IL-1β-induced catabolic effects in human articular chondrocytes. Osteoarthritis and Cartilage 2013;21:981–9.
78. Park SJ, Cheon EJ, Lee MH, Kim HA. MicroRNA-127-5p regulates matrix metalloproteinase 13 expression and interleukin-1beta-induced catabolic effects in human chondrocytes. Arthritis Rheum 2013;65:3141–52.
79. Vonk LA, Kragten AH, Dhert WJ, Saris DB, Creemers LB. Overexpression of hsa-miR-148a promotes cartilage production and inhibits cartilage degradation by osteoarthritic chondrocytes. Osteoarthritis and Cartilage 2014;22:145–53.
80. Zhang Y, Jia J, Yang S, Liu X, Ye S, Tian H. MicroRNA-21 controls the development of osteoarthritis by targeting GDF-5 in chondrocytes. Exp Mol Med 2014;46:e79.
81. Le L, Swingler TE, Crowe N, Driscoll C, Vincent TL, Barter MJ, *et al*. The microRNA-29 family in osteoarthritis. Osteoarthritis and Cartilage 2014;22:S41–2.
82. Beyer C, Zampetaki A, Lin NY, Kleyer A, Perricone C, Iagnocco A, *et al*. Signature of circulating microRNAs in osteoarthritis. Ann Rheum Dis 2014; Feb 27, http://dx.doi.org/10.1136/annrheumdis-2013-204698. [Epub ahead of print].