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Review

Osteoarthritis year in review 2018: genetics and epigenetics

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SUMMARY

Objective: This review was designed to identify highlights of the osteoarthritis (OA) genetics and epigenetics literature published between April 2017 and January 2018.
Design: A Pubmed literature search was conducted using the keywords 'osteoarthritis' and each of the following: 'genomic', 'genetic', 'epigenomic', 'epigenetic', 'histone', 'noncoding RNA', 'miRNA', 'lncRNA', 'DNA methylation', 'DNA hydroxymethylation', 'DNMT', and 'TET'. The dates of publication were restricted to 4/1/2017–1/15/2018. Results were compared to the same search terms limited to 4/1/2016–1/15/2017.
Results: Virtually all search term combinations demonstrated a decrease in papers published this year compared to last, with epigenetic and miRNA/lncRNA research being stable. Despite this, numerous advances were made this year, including the second large genome-wide association study (GWAS) study of hand OA, a new twin study of hip and knee OA concordance, an extensive study of *GDF5* evolution, analyses of the contribution of *Dnmt3a* to OA, a description of DNA methylation in a nonhuman primate model of OA, and an integrated, multi-omics analysis of DNA methylation, mRNA, and protein expression in human OA samples, among others. A variety of micro- and a few circular-RNA studies were also published, highlighting the importance of noncoding RNA in both the pathogenesis and potential treatment of OA.
Conclusion: Although publications have decreased slightly in the last year, genetics and epigenetics continue to be a topic of substantial research in OA, and considerable progress continues to be made in the field.

Introduction

Osteoarthritis (OA) is a heterogeneous chronic disease with multiple genetic and environmental risk factors. Over the past several years, our increasingly sophisticated methodologies of DNA sequencing and the quantification of epigenetic modifications have contributed greatly to our understanding of the pathophysiological mechanisms underlying OA. In this review, we will highlight advances in genetic and epigenetic studies of OA over the past year. We will discuss in detail seven articles that we consider the most important or interesting of the year and offer brief overviews of additional genetic and epigenetic studies published, and finish by highlighting some of the areas of particular importance for the field in the near future. An overview of the publication rates for various OA genetics and epigenetics search terms this year and last are given in Table I.

Genetics

This year, five large genome-wide association study (GWAS) added to our knowledge regarding OA genetic risk. These included one hand OA study[1], one hip OA study[2], and two knee OA studies in Chinese cohorts[3,4]. One additional study examined variation associated with neuropathic pain following total joint replacement[5] (summarized in Table II).

The continued search for hand OA risk alleles

This year saw only the second large genome-wide association study (GWAS) of hand OA[1]. Published by den Hollander and colleagues, it used a semi-quantitative bilateral measure of hand OA (based on the Kellegren and Lawrence score) and included the three Rotterdam Study cohorts (n = 9,743) and replication in the

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Table I
Publication trends in OA genetics and epigenetics research, 2016–2017 vs 2017–2018. Based on Pubmed searches performed 3/28/18

Search Term:	This year (4/1/17–1/15/18)		Last year (4/1/16–1/15/17)		% Change (all results this year vs last year)
Osteoarthritis +:	*All Results*	*Reviews*	*All Results*	*Reviews*	
Genomic	86	10	125	21	−31%
Genetic	130	23	167	42	−22%
Epigenomic	4	0	5	0	−20%
Epigenetic	23	8	25	11	−8%
Histone	14	4	25	7	−44%
Noncoding RNA	46	4	88	16	−48%
miRNA	73	9	78	17	−6%
lncRNA	17	3	15	3	+13%
DNA methylation	16	6	22	6	−27%
DNA hydroxymethylation	0	0	1	0	−100%
DNMT	1	0	0	0	+100%
TET	0	0	0	0	0%

Table II
Large OA GWAS studies published in 2017–2018

Joint/endpoint	Sample size (total)	Population	Genes identified/associated	SNP/genomic location	Effect size/beta value	Reference
Hand OA, semiquantitative radiographic measure	12,754	European	*MGP*	rs4764133	beta = 0.83	1
Hip OA, total hip replacement	212,171	European (Icelandic discovery, other cohorts confirmation)	*COMP, CHADL*	c.1141G -> C, rs532464664	OR = 16.7; OR = 7.71	2
Knee OA, unclear if radiographic or clinical endpoint	1,000	Chinese	*EN1*	rs4144782	OR = 1.35	3
Knee OA, radiographic + pain	638	Chinese	*ALDH1A2*	rs4238326	OR = 0.65	4
Knee and Hip OA, post-joint-replacement neuropathic pain on painDETECT questionnaire	1,733	European (English)	*PRKCA*	rs887797	OR = 2.41 for post-TJR pain	5

Leiden Study, Framingham Heart Study, and Twins UK ($n = 4,011$). The discovery set yielded two novel loci, an intergenic region between matrix GLA protein (*MGP*) and the endoplasmic reticulum *ERP27* gene, along with an intronic region in *CCDC91*, a gene involved in trans-Golgi traffic. Both of these loci reached genome-wide significance with $p \leq 5E-8$, and both were located on chromosome 12. One SNP reached statistical significance in the replication cohorts: rs4764133 [C->T] (beta = 0.83, effect allele frequency EAF = 0.39,*p*-value in replication cohort 3.4E-7, *p*-value in meta-analysis $p = 1.8E-15$). This SNP exists in high LD with several others spanning a ~80 kb region. Of note, two variants are located in a region predicted to be an active promoter of the aforementioned *MGP* gene (rs1800801 and rs9668569), and subsequent analysis suggested allele-specific expression in SNP heterozygotes. The authors speculate that disruptions in the expression of *MGP*, an essential inhibitor of cartilage calcification, as a result of this genetic variation may play a role in increasing the risk for hand OA.

Rare genotypes with strong OA associations

Moving now towards rare variants with stronger risk association, this year also saw the publication of a new hip OA GWAS by Styrkarsdottir and colleagues[2]. Whole-genome sequencing of 8,453 individuals with subsequent imputation into 150,656 individuals previously chip-typed and their first-degree and second-degree relatives was performed. Two variants reached genome-wide significance under a multiplicative model: a rare missense (c.1141 G->C) in the cartilage oligomeric matrix protein (*COMP*) gene, with $p = 3.1E-9$, odds ratio (OR) 10.4, and EAF of 0.00033, and a frameshift within the chondroadherin-like (*CHADL*) gene (rs532464664, ins. GGCGCGCG), with $p = 1.5E-7$, OR 1.37, EAF 0.0392. The *COMP* mutation was validated via direct genotyping ($p = 4.0E-12$, OR 16.7, EAF 0.00026). This gene encodes an extracellular matrix component and has been previously associated with cartilage breakdown[6]. Notably, the authors were able to determine that the individuals in their patient population with heterozygosity for c.1141 G->C formed a genealogical cluster arising from a single historical founder. Under a recessive model, the rs532464664 variant exhibited strong association with hip replacement ($p = 4.5E-18$, OR 7.7). The frameshift encoded by this variant results in early termination of the CHADL protein. SNP data from several additional geographic locations identified rs532464664 in a variety of populations, including European, Middle Eastern, and, to a lesser extent, East Asian individuals; they further identified five individuals from the UK who were homozygotes, noting that these individuals demonstrated a trend towards lower age at THR ($p = 0.08$) compared to heterozygotes and controls.

Towards an understanding of the evolutionary history of OA genetic risk

Cappellini and colleagues published a notable article this year which sought to examine the functional relevance and evolutionary advantage conferred by genomic variation within the OA-associated growth differentiation factor 5 (*GDF5*) gene[7]. Several previous studies have suggested links between *GDF5* variants (risk allele = 'A') and knee, hip, and hand OA (ORs in the 1.2 to 1.8 range[8,9]), and has been positively selected for multiple times in human evolution[10–12]. Using a bacterial artificial chromosome (BAC) approach, they identified a 2.54-kb downstream enhancer which drove expression in multiple joints and contained joint-control elements, which they denoted *GROW1*, which they further subdivided into *GROW1A*, conserved evolutionarily through amniotes, and *GROW1B*, conserved through mammals.

Within the *GROW1B* region, they found a common variant (MAF>0.05), rs4911178 G->A in high LD with others previously associated with increased OA risk (rs143383, risk allele 'A', $r^2 = 0.92$) and decreased height (several SNPs, $r^2 = 0.64–1.0$). In extant humans, the proportion of derived 'A' alleles and ancestral 'G' alleles in rs4911178 varies geographically by continent of origin, with modern Africans having nearly all ancestral alleles, whereas

some Eurasian and Central/South American clades exhibiting derived alleles. Other extinct hominid species showed similar changes following historical migrations out of Africa. Both Neanderthals and Denisovans were characterized by the derived A allele of *GROW1B*; however, these extinct species did not share the same derived-SNP changes that have been previously linked to OA in other GWAS studies, suggesting that the variant was present in a shared ancestor prior to evolutionary divergence. The authors speculate that the height-reducing properties of these variants may be driving conservation and suggest Allen's rule (cold-adapted animals tend to have shorter limbs to aid in thermoregulation) may have been at play during migrations to colder Northern latitudes.

Twin studies: still more to learn

Moving now away from examinations of specific genomic variations' OA-associated risk and towards a more general view of genetic contribution to hip and knee OA, Magnusson *et al.* published a quite large and well-done OA twin study this year[13] in which they linked the Norwegian Twin Registry and Norwegian Arthroplasty Registry, which allowed them to analyze 18,058 twins in 9,029 twin pairs who underwent knee or hip arthroplasty due to primary OA.

As expected, an increasing percentage of non-index twins required knee or hip replacement with increasing time following the index-twin's joint replacement, and monozygotic twin pairs were more likely to become concordant for joint replacement than dizygotic twins in both knee and hip OA: the lifetime concordance rate in hip replacement was 0.71 in monozygotic (MZ) vs 0.45 in dizygotic (DZ); conversely, MZ knee replacement concordance was 0.45 whereas DZ was 0.23. This suggests a potentially lower genetic contribution to knee replacement due to OA than to hip replacement. Using classical twin models, they estimated that 73% of hip arthroplasty variance could be explained by genetic factors alone, whereas only 45% of knee arthroplasty variance was genetically determined, although these data should be interpreted with caution given the potential confounding of several other unmeasured variables.

Epigenetics: DNA methylation

Over the past several years, there has been substantial interest in epigenetic modifications associated with human OA, evidenced by the publication of multiple genome-wide methylation studies. This slowed a bit over the past year, with four new publications. The first, by Zhao and colleagues, compared OA and RA chondrocytes, and compared each to neck of femur fracture controls, with DNA methylation quantitation by Illumina 450 k array. They identified 45 genes with significant DNA methylation differences, including three genes which were hypomethylated in both OA and RA patients[14]. The second, by Wang and colleagues, was a small study which included five OA, five normal (neck of femur fracture), and five Kashin-Beck disease (KBD), an endemic osteochondropathy associated with accelerated OA in Siberia, Korea, and China[15]. They identified several differentially methylated positions (DMPs) by Illumina 450 k array associated with both KBD and OA, including 367 which overlapped (were associated with both OA and KBD), corresponding to 182 genes, all with matching methylation directions in both OA and KBD (i.e., hypermethylated or hypomethylated in both compared to control).

Although it was not a true genome-wide analysis, Wang and colleagues this year published the first methylation analysis (by MethylTarget, a next-generation-sequencing-based assay, here analyzing 31 target genes) of a small rodent model of OA, the rat knee induced via the Hulth method[16]. Genes were selected by the authors to be “directly or indirectly related to the metabolism of bone or cartilage through a common mechanism.” They identified hypomethylation of C/ebpα-2, Cdk2, Bak1, and Fas in OA cartilage compared to sham-operated cartilage 16 weeks after surgery. Although they did not provide quantitative measures of gene mRNA expression, they did analyze apoptosis through TUNNEL staining and immunohistochemistry of a variety of apoptosis-related kinases and found increases by both measures in the knee OA group. The fourth study was published as part of a larger multi-omics analysis by Steinberg and colleagues[17] and is discussed in detail below.

A non-human primate model of OA epigenetic changes

Much has been published over the past decade regarding epigenetic changes in human tissues associated with both knee and hip OA, but there has been relatively little published in animal models of OA. One of the biggest hurdles has been that most human epigenetics work in OA has been performed using Illumina's human DNA methylation arrays, which provide a cost-effective solution which is not available in non-human formats. A paper published this year by Housman and colleagues was the first to demonstrate the use of Illumina's human epigenetics arrays on a non-human primate model of OA[18].

Although not particularly popular in the literature, the baboon model of OA is quite a good one, as *Papio* species develop knee OA spontaneously and at rates similar to humans. For this study, the authors analyzed post-mortem cartilage and subchondral bone samples from knee specimens collected from five age-matched female baboons with knee OA, and five without knee OA. Following DNA extraction, they then queried DNA methylation levels using the Illumina HumanMethylation 450 k assay. Given that this assay was designed with the human genome in mind, Housman and colleagues first had to evaluate which of the roughly 450,000 CpG sites on the array had analogues in the baboon genome. They used two approaches to do this, both computational in nature. The first was based on sequence similarity, described as an ‘alignment filter’, which required that probes must have 0 mismatches within the 5 base pairs upstream and downstream of a target CpG site, with only 0 to 2 mismatches in the 45bp surrounding the CpG site. This criterion yielded 133,264 putatively measurable probes. The second filter relied on identifying the baboon gene most proximate to the probe alignment site and analyzed the gene name similarity with the corresponding human gene; only those probes with partial or complete gene name matches were retained. This filter was designated a ‘gene symbol filter’ and passed 130,307 compatible probe locations. The group also removed cross-reactive probes, probes containing SNPs, etc., yielding a final set of 120,305 probes from the alignment filter, and 112,760 probes from the gene symbol filter.

They identified several DMPs comparing OA cartilage, but not in subchondral bone. When using the alignment filter criteria, six significant differentially methylated positions (DMPs) were identified, one of which has been previously reported in multiple studies as hypomethylated in human cartilage, the runt-related transcription factor 1 (*RUNX1*)[19,20]. A single locus, *RFXAP*, was found using both filtering methods, although its potential pathophysiological mechanism in OA remains elusive. Despite the correlation of babboon OA-associated differential methylation, we nonetheless see a very low number of overlapping results with human OA studies. There are several potential explanations for this; perhaps the most likely is the low power of this study to detect DMPs. The authors went on to describe that the hybridization efficiency of CpG probes was highly correlated with the *in silico* alignment quality of each probe to the baboon genome, and that the majority of filtered probes using both methods passed the internal Illumina quality controls.

A curious role for DNMT3b in OA

Although much has been published over the past several years regarding specific epigenetic changes (i.e., differential DNA methylation or histone post-translational modification) associated with OA, less attention has been paid to alterations in the cellular machinery responsible for writing the epigenetic code in the first place. In a paper published in JCI insight this year, Shen and colleagues set about to investigate the role of the *de novo* DNA methyltransferases in the development of murine OA[21]. First, they found by immunohistochemistry that Dnmt3a was undetectable within articular and growth plate cartilage, whereas Dnmt3b was found in articular chondrocytes but absent in growth plate cells. The authors then went on to show that Dnmt3b protein expression is substantially decreased in murine cartilage with aging, by induction of post-traumatic OA by meniscal ligament injury (MLI, 4 weeks post-surgery), and by high fat diet. The authors confirmed a reduction in DNMT3b expression, both protein and mRNA in human OA sections, and showed that this decrease in expression could be recreated by exposing primary human articular chondrocytes to inflammatory challenge with IL-1β.

In chondrocyte-specific *Dnmt3b* loss-of-function mice, spontaneous OA changes were noted at 5 months of age, including loss of proteoglycan staining and cartilage tears, as well as an increase in apoptotic cells, accompanied by increases in reactive oxygen species. Osteophyte formation followed at 8 months of age, as did decreases in cartilage area and increases in subchondral bone thickness, all consistent with a primary-OA phenotype. The authors examined genome-wide epigenomic and transcriptomic patterns in articular chondrocytes from these mice at 2 months of age and found widespread changes in both DNA methylation and gene expression. Notably, they did not find an expected loss of DNA methylation globally, probably reflecting the low metabolic rate of already-terminally-differentiated chondrocytes. They also demonstrated increased mitochondrial metabolism in Dnmt3b loss-of-function chondrocytes, although the mechanism underlying this is unclear. It should be noted here that mitochondrial genes are not generally thought to be epigenetically controlled, especially from a DNA methylation perspective, as cytosine methylation is quite rare in mitochondrial DNA[22].

Finally, they then evaluated the effects *in vivo* of Dnmt3b gain of function (overexpression) by generating a chondrocyte-specific *Dntm3b* gain of function mouse. They then induced post-traumatic OA, again using MLI surgery (in somewhat young 10-week-old male mice) wherein the mice were fully protected from the deleterious effects of MLI. As expected, the mitochondrial changes previously identified as characteristic of *Dnmt3b* loss of function were abrogated in *Dnmt3b* gain of function chondrocytes, including reductions in both basal and maximal respiration rates. Unfortunately, we are not given comparisons of genome-wide DNA methylation or transcriptomic patterns between *Dnmt3b* gain of function chondrocytes post-OA-induction and controls; presumably, this would have identified an epigenetic pattern more closely resembling non-OA cartilage. The authors point out that Dnmt3b-mediated mechanisms may be important in maintaining post-natal cartilage homeostasis and, particularly, may be important in preventing catabolic gene expression.

Integration of multi-omics domains: the next frontier in OA big data research

Although we have seen substantial work over the past several years investigating the role of multiple epigenetic modifications in OA, our understanding of the functional consequences of these epigenetic aberrations is still lacking. One way to address this, and to give us a deeper understanding of which epigenetic and transcriptomic changes are relevant in the disease process, is to perform multi-omics investigations on a single sample set. One good example was published by Steinberg and colleagues this year[17]. In this article, the authors sought to perform an analysis of epigenetic (DNA methylation by Illumina 450 k array), transcriptomic (via RNA-Seq), and proteomic (by LC-MS) changes associated with the development of knee and hip OA in human patients using eroded and intact tissues from patients at the time of joint replacement. They analyzed 12 paired (eroded and intact) knees from OA patients in their discovery cohort and included 17 paired knee and 9 paired hip specimens in confirmation cohorts. They identified 9,896 DMPs in their epigenetic analysis, these corresponded to 271 differentially methylated regions (DMRs) overlapping with 296 genes. They also identified 349 differentially expressed genes in RNA-Seq analysis (most overexpressed in eroded sections), and 209 proteins of differential abundance (most with reduced abundance in eroded sections).

Further, they identified 49 genes which exhibited differential regulation in at least two of the -omics domains, and three which were present in all three analyses (aquaporin, *AQP1*, collagen *COL1A1*, and c-lectin *CLEC3B*). Reassuringly, all three of these genes behaved in the "expected" way; that is, decreased methylation in epigenetic analysis, associated with increased expression in both RNA-seq and proteomics analysis, and gene expression differences were replicated for all three in an independent cohort. The majority of genes with both differential protein and mRNA expression had concordant directions of change, as did genes which were both differentially methylated and expressed at an mRNA level. Among the 49 genes which were differentially regulated in at least two domains, the direction of change was concordant in 36 in the knee replication cohort (73%) and 26 in the hip replication cohort (53%). The lower confirmation rate in hips is not all that surprising, since previous reports have demonstrated that differences exist in multiple -omics domains between knee and hip OA cartilage.

The investigators then applied the 49 genes differentially regulated among at least two -omics domains to Drugbank, a comprehensive online database with biochemical and pharmacological information about drugs, mechanisms, and targets[23]. This yielded ten compounds which interact with this gene list. A few were expected, like NSAID inhibition of *PTGIS* (prostacyclin synthase), but several were novel and deserve further follow-up; for instance, the carbonic anhydrase inhibitor Acetazolamide, which inhibits *AQP1*, and Palifermin, the recombinant human keratinocyte growth factor presently being used to treat mucositis in oncology patients undergoing chemotherapy, which also inhibits *FGFR2*.

Epigenetics: histone post-translational modifications

Relatively few articles were published this past year describing post-translational histone modifications in OA. Among them, an article by Monteagudo and colleagues[24] examined the role of the histone methylase *DOT1L*, which directs inhibition of the Wnt signaling pathway by inhibiting sirtiun-1 (SIRT1). In their article, they demonstrated the OA patient eroded cartilage was characterized by loss of methylated histone 3 lysine 79 (H3K79), a process mediated by *DOT1L*, although they did not see direct changes in *DOT1L* gene expression by mRNA analysis. Intraarticular injection of a DOT1L inhibitor in adult mice both inhibited H3K79 methylation and caused a spontaneous cartilage damage phenotype, accompanied by increased Wnt gene signaling. This spontaneous cartilage damage phenotype was abrogated by the addition of either a Wnt pathway antagonist (XAV-939) or SIRT1 inhibition (EX527). A second study published by Aury-Landas and colleagues evaluated the effects of 3-Deazaneplanocin A (DZNep), an inhibitor of the histone

methylase EZH2, which is upregulated in OA[25]. They demonstrated that DZNep reduces nitric oxide and prostaglandin E2 production in cultured human articular chondrocytes and reduced the production of matrix metalloproteinases following IL1β treatment; however, there were no direct analyses of histone modification changes following treatment with DZNep.

Epigenetics: noncoding RNAs

This year saw a flurry of activity in OA noncoding RNA research (Table III), which we will briefly highlight. Kung *et al.* performed a miRNA screen in B6 mice one and 6 weeks post-DMM surgery but did not find significant changes in either miRNA or mRNA expression between DMM and sham mice at either time point[26]. In the rat anterior cruciate ligament - medial meniscus resection model (ACLT+MMx), Si and colleagues demonstrated that a single intra-articular injection of an miRNA-140 agomir 1 week after surgery substantially reduced both the presence of pathological OA lesions and reduced OA-related behavioral changes[27].

In human studies, Wu and colleagues examined the miRNA expression profiles of cartilage samples from OA, RA, and Kashin-Beck disease[28]. They found 18 differentially expressed miRNAs which were shared between KBD and OA vs RA patients, including several with previous links to OA. In a curious interaction between two distinct epigenetic mechanisms, Mao and colleagues found that miR-92a-3p expression was reduced in cartilage from OA patients[29]. Overexpression of miR-92a-3p in human mesenchymal stem cells *in vitro* substantially reduced expression of the histone deacetylase HDAC2 and expression of a variety of OA-associated transcripts, including Col10a1, MMP13, ADAMTS4, and ADAMTS5, and increased expression of aggrecan and Col2a1, among others. Wu and colleagues also explored the effects of miR-200b-3p, which targets the *de novo* DNA methyltransferase DNMT3a, on proliferation and apoptosis of primary chondrocytes from OA patients[30]. Decreases in miR-200b-3p were found in OA tissues concomitant with overexpression of *DNMT3A*. Transfection with miR-200b-3p mimics greatly decreased the expression of various matrix metalloproteinases including MMP-1, -3, -9, and -13, and increased expression of collagen type II, and enhanced chondrocyte viability by suppressing cell apoptosis.

Also published this year were two analyses of miRNAs in OA from an easily-accessible biofluid: peripheral blood. The first, by Soyocak and colleagues, examined the expression of miR-146a, miR-155, and JNK in peripheral blood mononuclear cells from 100 knee OA patients and found that miR-155 was increased (1.75-fold) in OA patients' PBMCs with a trend towards increasing miR-155 with increasing K/L (radiographic) grade of OA. This study confirms a previous report of increased miR-155 in OA PBMCs[31]. Ntoumou and colleagues performed a large microarray analysis of OA patient serum[32]. They found a number of miRNAs differentially expressed, including seven which were further validated as biomarkers (using qPCR analysis), each manifesting a receiver operator characteristic area under the curve (ROC-AUC)>0.8. Kong and colleagues obtained serum from 100 knee OA patients (diagnosed according to the American Rheumatism Association 1986 criteria) and 100 age- and gender-matched healthy controls[33]. They evaluated miRNA expression by Affymetrix GeneChip array and identified 70 differentially expressed miRNAs. Logistic regression models were then calculated to test the diagnostic ability of miR-19b, miR-122, and miR-486, alone and in combination; the most accurate model had an ROC-AUC of 0.926.

To close this noncoding RNA section, there were a few examples of a relatively new type of ncRNA, circular RNA, found associated with OA. Circular RNAs are covalently closed continuous loops of RNA resistant to exonuclease-mediated degradation (therefore, more stable than their linear counterparts) of various sizes that have been proposed to work as microRNA "sponges" by presenting multiple binding sites for various miRNAs. Previous studies have implicated circular RNAs as sponges for miR-136 in association with OA[34], and have found substantial elevations of circRNAs in the synovial fluid of OA patients[35]. This year, we have two papers by Zhou and colleagues further elucidating the role of circRNAs in OA; the first demonstrating increases in the expression of a variety of circRNAs following IL1β treatment of mouse articular chondrocytes[36], the other being a specific study of circRNA_Atp9b, which functions as a sponge for miR-138-5p, also implicated in the osteoarthritic response of mouse chondrocytes to IL1β treatment[37].

Emerging areas of study

In the genetics field, further collaboration and integration of already-published data sets will likely give us more insight into the genetic risk associated with various endophenotypes (i.e., pain progressors). From an epigenetics standpoint, further technology development has now made multi-omics investigations more feasible; future studies should focus on performing simultaneous mRNA, protein, and epigenetic (be they DNA methylation, histone post-translational modification, and/or noncoding RNA) analyses. We anxiously await the results of epigenetic studies in commonly-used models of OA where the epigenetic contributions of individual risk factors (i.e., obesity, trauma, aging) can be studied individually; the question here is whether enough tissue can be harvested for effective analysis. Epigenetic analyses in OA animal models also have the potential to elucidate longitudinal epigenetic changes that

Table III
Advances in noncoding RNA research in OA published in 2017–2018

Joint	Population/tissue	miRNA identified	Results	Reference
Knee OA	OA vs RA vs KBD			28
Rat knee OA	Rats by surgical induction	miR-140	miR-140 agomir reduces OA	26
Hip OA	OA patient cartilage vs #NOF control	miR-92a-3p	reduced in OA, linked with increased HDAC2	29
Knee OA	OA patient primary chondrocytes vs normal control	miR-200b-3p	reduced in OA, linked with increased DNMT3a	30
Knee OA	OA patient peripheral blood mononuclear cells vs healthy control	miR-155	increased in OA PBMCs, trend towards association with radiographic grade	39
Knee OA	OA patient serum vs healthy control serum	Multiple, including miR-140-3p, miR-33b-3p, miR-671-3p	regression models show 7 with biomarker capability, with ROC-AUC >0.8 for OA diagnosis	32
Knee OA	OA patient serum vs healthy control serum	miR-19b, miR-122, miR-486	regression model including all 3 with ROC-AUC = 0.93 for OA diagnosis	33
Mouse knee	Mouse articular chondrocytes following IL1 treatment	circRNA_Atp9b	functions as a sponge for miR-138-5p	37

occur as OA develops, no doubt offering important mechanistic (and, potentially, therapeutic) insights. Finally, given the recent advancements in genetic and epigenetic editing that have been published over the past few years (rev[38].), we are hopeful that future studies will finally be able to definitely demonstrate the effects of specific genetic changes and/or particular epigenetic modifications in the development of OA.

Conflict of interest

Dr. Jeffries has no conflicts of interest.

CRediT authorship contribution statement

M.A. Jeffries: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Software, Supervision, Visualization, Writing - original draft, Writing - review & editing.

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