The non-coding RNA interactome in joint health and disease

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Abstract | Non-coding RNAs have distinct regulatory roles in the pathogenesis of joint diseases including osteoarthritis (OA) and rheumatoid arthritis (RA). As the amount of high-throughput profiling studies and mechanistic investigations of microRNAs, long non-coding RNAs and circular RNAs in joint tissues and biofluids has increased, data have emerged that suggest complex interactions among non-coding RNAs that are often overlooked as critical regulators of gene expression. Identifying these non-coding RNAs and their interactions is useful for understanding both joint health and disease. Non-coding RNAs regulate signalling pathways and biological processes that are important for normal joint development but, when dysregulated, can contribute to disease. The specific expression profiles of non-coding RNAs in various disease states support their roles as promising candidate biomarkers, mediators of pathogenic mechanisms and potential therapeutic targets. This Review synthesizes literature published in the past 2 years on the role of non-coding RNAs in OA and RA with a focus on inflammation, cell death, cell proliferation and extracellular matrix dysregulation. Research to date makes it apparent that 'non-coding' does not mean 'non-essential' and that non-coding RNAs are important parts of a complex interactome that underlies OA and RA.

Non-coding RNAs constitute 99% of total cellular RNA content and, alongside DNA methylation and histone modification, represent one of three major epigenetic mechanisms that contribute to health and disease[1]. Although non-coding RNAs are encoded in DNA and transcribed to RNA, they are not translated to protein; however, this does not negate their important role in regulating cellular processes. The precise mechanism of action is dependent on the class of non-coding RNA — short non-coding RNAs (such as microRNAs (miRNAs)), long non-coding RNAs (lncRNAs) or circular RNAs (circRNAs) — although all types ultimately function to regulate the expression of specific gene targets[1]. As such, non-coding RNAs are essential for establishing and maintaining homeostatic balance in biological systems, including regulating the signalling pathways and biological processes that govern joint development[2]. Deregulation of this balance contributes to the pathogenesis of joint diseases such as osteoarthritis (OA) and rheumatoid arthritis (RA)[3,4].

Non-coding RNAs are found in almost all joint tissues and biofluids across different species, demonstrating their biological importance[5]. In joint disease, non-coding RNAs have been explored as potential biomarkers, mediators of pathogenesis and therapeutic targets. Adding to the complexity of these epigenetic regulators, the different classes of non-coding RNAs can provide redundancy by targeting the same genes, work in concert by targeting the same pathways and directly interact to regulate gene expression[6]. Although this putative 'interactome' of non-coding RNAs has yet to be comprehensively explored in joint health and disease, its elucidation is improving with the use of technologies for high-throughput profiling and integrative computational analysis.

To demonstrate that 'non-coding' does not mean 'non-essential', in this Review we discuss literature published in the past 2 years on non-coding RNAs in OA and RA. We first describe the classes of non-coding RNAs and their mechanisms of action, followed by the role of non-coding RNAs in osteogenesis and chondrogenesis, two vital biological processes in joint development. We next review non-coding RNAs in OA and RA joint tissues and biofluids, and their roles in inflammation, cell death, cell proliferation and extracellular matrix (ECM) dysregulation. Finally, we discuss the therapeutic potential of non-coding RNAs in OA and RA and the deep-dive efforts that will be required in the future to unravel the complex interactions among non-coding RNAs.

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Key points

- An increasing body of literature on non-coding RNAs in joint health and disease has revealed important regulatory functions that indicate that 'non-coding' does not equate to 'non-essential'.
- Non-coding RNAs, including microRNAs, long non-coding RNAs and circular RNAs, can directly interact and have co-regulatory functions.
- In osteoarthritis and rheumatoid arthritis, non-coding RNAs are important contributors to pathogenesis and serve as potential biomarkers and therapeutic targets.
- With the emergence of data from high-throughput studies, detailed reporting and accurate annotation of results are required to integrate individual studies and enable interrogation of the non-coding RNA interactome.
- An expanded understanding of the non-coding RNA interactome could reveal essential regulatory mechanisms and novel therapeutic opportunities for osteoarthritis, rheumatoid arthritis and other related joint diseases.

Classes of non-coding RNAs

Non-coding RNAs are classified on the basis of their biogenesis, length and mechanism of action (FIG. 1a). Following transcription, non-coding RNAs are processed to form short, long or circular non-coding RNAs with unique secondary and tertiary structures. The first class are short non-coding RNAs, which are fewer than 200 nucleotides in length. This class includes miRNAs, small nucleolar RNAs (snoRNAs), small nuclear RNAs, Piwi-interacting RNAs (piRNAs), small interfering RNAs (siRNAs), transfer RNAs (tRNAs), tRNA-derived fragments (tRFs) and Y RNA fragments (YRFs)[5]. The most frequently studied of the short non-coding RNAs are miRNAs. miRNA biogenesis begins with a primary miRNA transcript from the intron, exon or intergenic region of the host gene, followed by processing within the nucleus to produce a precursor miRNA. After export to the cytoplasm, the precursor miRNA undergoes cleavage to produce the mature miRNA. Mature miRNAs are single stranded, 18–24 nucleotides in length and function to inhibit target gene expression through mRNA degradation or repression of translation[4] (FIG. 1b).

The second class of non-coding RNAs are lncRNAs, which are greater than 200 nucleotides in length. Similar to short non-coding RNAs, lncRNAs function to modulate mRNA stability and translation in the cytoplasm through multiple mechanisms, including the post-translational modification of target molecules[7] (FIG. 1c). Circular forms of lncRNAs, or circRNAs, comprise 1–5 introns or exons and form a covalently closed loop structure that functions as an miRNA sponge, protein sponge or scaffold for translation[5,6] (FIG. 1d). miRNA sponging depends on the presence of miRNA response elements within lncRNAs and circRNAs that can specifically bind and sequester miRNAs, thereby blocking their activity. This sponging is a type of competing endogenous RNA activity and is a mechanism through which the different classes of non-coding RNAs can directly interact. circRNAs primarily function as competing endogenous RNAs, binding to miRNA response elements and reducing the quantity of miRNAs available to target mRNA, thereby promoting mRNA stability or protein expression[6]. In this Review, we focus on miRNAs, lncRNAs and circRNAs, as these types of non-coding RNA have been explored the most in OA and RA to date[3,8].

Non-coding RNAs in joint development

Healthy joint development is dependent on precise regulation of the signalling pathways that govern osteogenesis and chondrogenesis, among other processes, and if these become dysregulated, joint pathologies can result. miRNAs, lncRNAs, circRNAs and even piRNAs are differentially expressed during the early stages of osteogenic and chondrogenic differentiation in human bone marrow-derived mesenchymal stromal cells and/or bone marrow-derived mesenchymal stem cells (BMSCs), suggesting that non-coding RNAs might affect these processes[9,10]. Non-coding RNAs can also regulate important signalling pathways, including the Wnt–β-catenin and Hedgehog signalling pathways, which are essential for tissue induction, patterning, growth and morphogenesis[11]. For example, overexpression of miR-378 in transgenic mice results in abnormal bone formation and quality, as well as compromised osteogenic differentiation in both mouse and human BMSCs[12]. Interestingly, miR-378 targets two Wnt family members, Wnt6 and Wnt10a, thereby attenuating Wnt–β-catenin signalling[12]. These results suggest that miRNAs might be upstream regulators of certain developmental signalling pathways, which has implications for bone health.

Chondrogenesis is essential for endochondral and intramembranous ossification and for tissue homeostasis, and is also subject to regulation by non-coding RNAs. The Indian Hedgehog signalling pathway is well known to regulate chondrogenesis during normal development[13]. The gene encoding Indian Hedgehog contains two putative sites at which miR-1 can bind and inhibit its activity, resulting in increased expression of type II collagen and aggrecan and decreased expression of type X collagen and matrix metalloproteinase 13 in mouse thorax chondrocytes[14]. These results suggest that miR-1 induces an anabolic effect in chondrocytes through inhibition of the Indian Hedgehog pathway, which is consistent with previous findings that aberrant activation of the Indian Hedgehog pathway can have catabolic effects on cartilage[15]. Furthermore, the transcription factor SOX9, which is critical for mesenchymal condensation prior to chondrogenesis, is targeted by miR-30a to inhibit chondrogenic differentiation in human BMSCs[16], again demonstrating a direct

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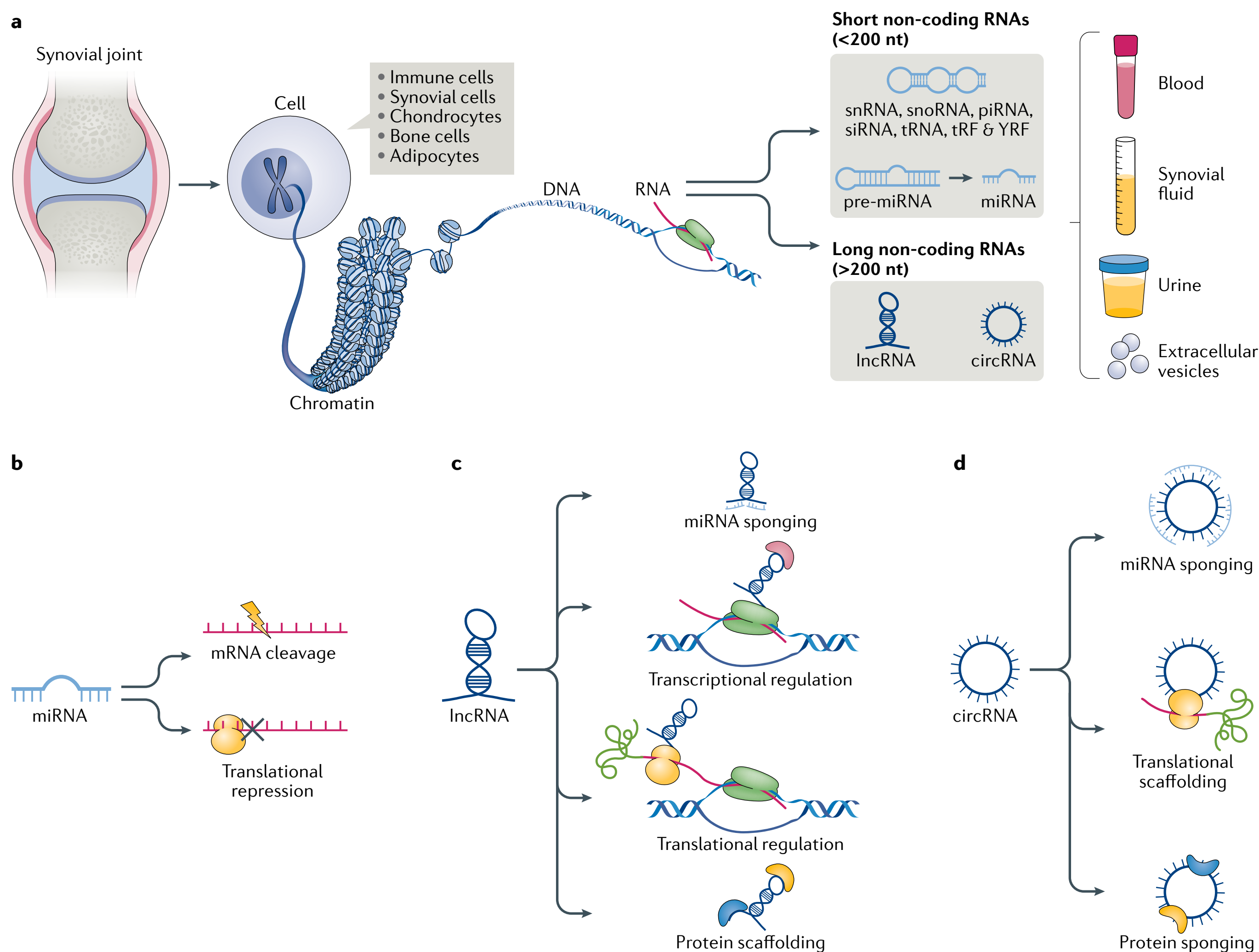

Fig. 1 | **Biogenesis and function of microRNAs, long non-coding RNAs and circular RNAs.** Within the synovial joint, several cell types can be a source of non-coding RNAs that are transcribed from DNA (part **a**). Non-coding RNAs can function within the producing cell or in a target cell, and are secreted into biofluids as free molecules or within extracellular vesicles. Potential functions for microRNAs (miRNAs) include mRNA cleavage and translational repression (part **b**); for long non-coding RNAs (lncRNAs) include transcriptional regulation, translational regulation, protein scaffolding and miRNA sponging (part **c**); and for circular RNAs (circRNAs) include miRNA sponging, protein sponging and translational scaffolding (part **d**). nt, nucleotides; piRNA, Piwi-interacting RNA; siRNA, small interfering RNA; snRNA, small nuclear RNA; snoRNA, small nucleolar RNA; tRF, tRNA-derived fragment; tRNA, transfer RNA; YRF, Y RNA fragment.

regulatory role for miRNAs in established mechanisms that govern chondrogenesis.

Looking at interactions between classes of non-coding RNAs in osteogenesis and chondrogenesis, evidence exists of competing endogenous RNA activity. The lncRNA LINC00707 sponges miR-145 in human BMSCs and increases the expression of lipoprotein receptor-related protein 5, a co-receptor for Wnt proteins, thereby promoting osteogenic differentiation[17]. Similarly, the lncRNA ADAMTS9-AS2 sponges miR-942-5p in human BMSCs and increases expression of the transcription factor SCRG1, thereby promoting chondrogenic differentiation[18]. circRNAs have also emerged as novel orchestrators of signalling pathways that govern osteogenesis[19]. Relevant to development, an axis has been identified whereby circRNA_0079201 sponges miR-140-3p in human chondrocytes and increases expression of the transcription factor SMAD2, thereby suppressing cell proliferation, hypertrophy and endochondral ossification[20]. Taken together, these examples illustrate an important role for non-coding RNAs in governing signalling pathways and biological processes in joint development that have implications for joint health and disease.

Non-coding RNAs in OA and RA

Expression in joint tissues

Strong evidence exists to support cell-specific and tissue-specific expression patterns of non-coding RNAs in OA and RA[21,22]. Two studies used microarrays to compare cartilage from patients with OA and healthy individuals and identified 58 and 70 differentially expressed miRNAs, respectively[23,24]. Beyond miRNAs, a diverse range of non-coding RNAs have been identified

in primary human OA chondrocytes and cartilage, including lncRNA MFI2-AS1, lncRNA LOXL1-AS1, tRF-3003a and U3 snoRNA[25–28]. In primary human synoviocytes and synovial tissue in OA and RA, reports have focused on lncRNAs such as MALAT1, NEAT1 and PVT1 (REFS[29–31]). MALAT1 expression crosses tissue types, being increased in both the synovium[29] and subchondral bone[32] of patients with OA compared with healthy individuals. Similarly, NEAT1 expression crosses both tissue types and diseases, being increased in OA cartilage[30] and in RA synovium[33]. These examples demonstrate a non-coding RNA expression pattern that is not only tissue specific, but potentially also disease specific, and support the need for further studies focused on profiling non-coding RNAs in other tissues and cells implicated in OA and RA, including bone[34,35], adipose tissue[36], meniscus[37] and macrophages[38,39]. Furthermore, this profiling should take into account unique patient endotypes[40,41] and apply appropriate inclusion and exclusion criteria during the selection of participants to facilitate the interpretation of findings and integration with other studies.

Sequencing is the gold standard approach for identifying tissue-specific non-coding RNAs, their targets and their interactions. In a 2019 study that compared lesioned with preserved cartilage from patients with knee or hip OA, RNA sequencing was used to identify 142 miRNAs and 2,387 mRNAs that were prioritized into a regulatory network comprising 62 miRNAs that targeted 238 mRNAs[42], which showed joint-specific expression patterns. Similarly, 1,068 mRNAs, 21 miRNAs and 395 miRNA–mRNA pairs were identified in synovial tissue from patients with knee OA using RNA sequencing[43]. Given the large number of candidate non-coding RNAs identified through sequencing, a deeper dive into the biological relevance of prioritized candidates is required through validation studies. In synovium, canonical correlation analysis of RNA sequencing and small RNA sequencing data has been used to identify miRNA–mRNA co-expression patterns[44]. Specifically, five miRNAs and four genes were predicted to be associated with pain in knee OA, suggesting their potential utility as biomarkers.

Although obtaining tissue samples by biopsy might be considered too invasive for use in biomarker detection, evidence from RA suggests that the amount of non-coding RNAs in the circulation might differ from that found in tissues. For example, the amount of miR-22 is increased in plasma from patients with RA compared with that from healthy individuals and is associated with disease activity in RA[45,46], but is decreased in synovial tissue from patients with RA compared with synovium from healthy individuals[47]. It is unclear whether this tissue-specific difference in miR-22 expression is due to sponging (as is the case for miR-145-5p, which is sponged by the lncRNA PVT1 in RA synovium to produce lower concentrations in the synovium than in the serum[31]) or other mechanisms of non-coding RNA regulation. Nevertheless, these data suggest that, in addition to tissue-specific expression patterns, biofluid-specific patterns of non-coding RNA expression must also be considered.

Expression in biofluids

Non-coding RNAs can be secreted by cells either as free RNA molecules or encapsulated into extracellular vesicles such as exosomes and can be identified in biofluids including blood, urine and synovial fluid[36,48,49] (FIG. 1). Given their association with disease activity, non-coding RNAs are thought to represent excellent candidate biomarkers[50]. Non-coding RNA classes are broadly altered in plasma from patients with RA, in which sets of miRNAs and tRFs are enriched and sets of YRFs are depleted compared with healthy individuals[46]. Such non-coding RNA class shifts might be caused by broad changes in RNA processing mechanisms, such as the upregulation of Dicer and Drosha in RA peripheral blood mononuclear cells (PBMCs)[51], which are a major source of non-coding RNAs in plasma. Surprisingly, non-coding RNAs of microbial origin have also been detected in human plasma; the abundance of microbial small RNAs and specific microbial tRFs were inversely associated with disease activity in two separate cohorts of patients with RA and also predicted response to therapy, suggesting that they might be useful as biomarkers[52].

Non-coding RNA profiling in OA biofluids has focused on miRNAs in the circulation because samples are accessible by minimally invasive blood draw (TABLE 1). Approaches used include real-time PCR[53,54], real-time PCR miRNA arrays[55], miRNA microarrays[35,38] and, most recently, miRNA sequencing of serum[56], plasma[57] and plasma-isolated extracellular vesicles[58]. miRNA sequencing is of particular interest as it enables the discovery of novel miRNAs that are potentially unique to a disease stage or phenotype[57,59]. Fewer reports have described miRNA profiles in urine or synovial fluid than in blood[60,61]. Real-time PCR miRNA arrays were used to interrogate synovial fluid samples taken before and 6 months after high tibial osteotomy in six patients with knee OA at Kellgren–Lawrence grade II or III[60]. Three miRNAs were identified as being differentially expressed at the two time points and, following validation by real-time PCR in 22 additional patients, increased miR-30c-5p was found to correlate with reduced postoperative pain[60]. Looking beyond miRNAs, lncRNAs and circRNAs are also dysregulated in OA biofluids[62]. For example, the expression of lncRNAs CAIF, LUADT1 and SNHG9 are decreased in OA synovial fluid[63–65], whereas CTBP1-AS2, MCM3AP-AS1 and CASC2 are increased[66–68], although the utility of these lncRNAs as biomarkers requires further research.

To date, no consistent profile of non-coding RNAs has been identified and validated in biofluids across OA or RA studies. Among the challenges faced by researchers are differences across studies in the joints characterized, the profiling platforms used, the biofluids profiled and how the patient groups are defined, all of which make it difficult to directly compare findings (TABLE 1). Going forward, panels of non-coding RNAs (potentially from multiple classes) could prove to be more reliable as biomarkers than an individual entity or class owing to the variable expression and interactions of individual non-coding RNAs. In addition to their roles as biomarkers, non-coding RNAs in biofluids might also function as systemic regulators of disease in

Table 1 | **Circulating microRNAs with potential for use as biomarkers in OA and RA**

Disease	Platform	Biofluid	Number of patients	Number of controls (type)	Differentially expressed miRNAs	Ref.
Knee OA	Real-time PCR	Plasma	150	150 (healthy individuals, traumatic amputation or meniscus injury)	Reduced in OA: miR-200c-3p, miR-100-5p and miR-1826	53
Knee OA	Real-time PCR	Serum	10	10 (trauma)	Reduced in OA: let-7e	54
Hip OA	Real-time PCR	Serum	28	2 (femoral neck fracture)	Increased in OA: miR-146a-5p	169
RA	Real-time PCR	Plasma	125	30 (healthy individuals)	Reduced in RA: miR-155	170
RA	Real-time PCR	Serum	20	20 (healthy individuals)	Increased in RA: miR-138	171
RA	Real-time PCR	Blood	90	30 (healthy individuals)	Increased in RA: miR-155, miR-150, miR-146a, miR-146b, miR-125a-5p and miR-223	172
RA	Real-time PCR	Serum	18	76 (SLE, SSc or MCTD)	Increased in RA: miR-145 and miR-181a	173
Knee OA	Real-time PCR array	Serum	114 (high pain relief 1 year post-TKR)	22 (low pain relief 1 year post TKR)	Increased in low pain relief group: miR-146a-5p, miR-145-5p and miR-130b-3p	55
Knee OA	Microarray	Blood	5	5 (healthy individuals)	Decreased in OA: miR-582-5p and miR-424-5p	35
RA	Microarray	Blood	5 (early RA)	5 (healthy individuals), 5 (CPP$^+$ healthy individuals)	Increased in RA: miR-361-5p	174
RA	Microarray	Serum	9 (divided into 3 pools)	15 (healthy individuals; divided into 5 pools)	Increased in RA: miR-187-5p, miR-4532 and miR-4516; decreased in RA: miR-125a-3p, miR-575, miR-191-3p, miR-6865-3p, miR-197-3p, miR-6886-3p, miR-1237-3p and miR-4436b-5p	175
RA	Microarray	Serum exosomes	22 (in clinical remission)	20 (not in clinical remission)	Increased in clinical remission group: miR-1915-3p and miR-6511-5p	176
Knee OA	Next-generation sequencing	Serum	10	10 (healthy individuals)	Increased in OA: miR-146a-5p and miR-186-5p	56
Knee OA	Next-generation sequencing	Plasma	41 (early-stage OA)	50 (late-stage OA)	Increased in early-stage OA: miR-335-3p, miR-199a-5p, miR-671-3p, miR-1260b, miR-191-3p, miR-335-5p and miR-543	57
Knee, hip or hand OA	Next-generation sequencing	Plasma extracellular vesicles	23	23 (healthy individuals)	None	58
RA	Next-generation sequencing	Plasma	167	91 (healthy individuals)	Increased in RA: miR-22-3p, miR-24-3p, miR-96-5p, miR-134-5p, miR-140-3p and miR-627-5p	45

Includes articles published between 2019 and 2021. CPP, cyclic citrullinated peptide antibody; MCTD, mixed connective tissue disease; miRNA, microRNA; OA, osteoarthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; TKR, total knee replacement.

distal joints. Two studies from 2020 found alterations in the concentrations of circulating miRNAs that directly target single-nucleotide polymorphisms in *CXCR4* and *ADAMTS5* loci[69,70], both of which are related to OA risk. These results point to non-coding RNAs as circulating epigenetic factors that regulate risk loci in arthritis as an exciting new avenue for future research.

Role in pathogenesis

As important regulators of gene expression, non-coding RNAs can be expected to have pleiotropic effects in polygenic diseases such as OA and RA. Data suggest that non-coding RNAs can have both beneficial (such as maintaining tissue homeostasis) and detrimental (such as inducing tissue destruction) effects on the joints[4,22]. In fact, miRNAs regulate a diverse range of cellular processes (including inflammation[71–74], apoptosis[75–78], ECM dysregulation[79,80], chondrocyte differentiation[81], oxidative stress[82] and autophagy[83–85]), signalling pathways (including transforming growth factor-β[86,87], fibroblast growth factor (FGF)[88], Wnt–β-catenin[89–91] and Hedgehog[92]) and mediators (including the transcription factors FOXM1, SOX5, SOX6 and SOX9, and oestrogen receptor-α[93–98]) that are relevant for OA and RA. Similarly, lncRNAs (TABLE 2) and circRNAs (TABLE 3) can have multi-target regulatory effects on cell phenotype and tissue homeostasis and have the potential to mediate pathogenic mechanisms in OA and RA[6,62,99].

Table 2 | **Long non-coding RNAs of mechanistic importance in OA and RA**

lncRNA	Change in expression	Mechanism	Effects	Ref.
CTBP1-AS2	Increased in OA synovial fluid	Increased methylation of *miR-130a*	Promotes proliferation in OA chondrocytes	66
XIST	Increased in OA cartilage	Binds *TIMP3* promoter and accelerates methylation	Increases collagen degradation in OA chondrocytes	106
LINC01534	Increased in OA cartilage	Sponges miR-140-5p	Promotes ECM degradation (decreases aggrecan, type II collagen and increases MMP3, MMP9 and MMP13) and increases pro-inflammatory mediators (NO, PGE_2, IL-6, IL-8 and TNF) in IL-1β-treated chondrocytes	138
H19	Increased in OA cartilage	Sponges miR-140-5p	Increases apoptosis, reduces cell proliferation, increases ECM degradation (increases MMP1 and MMP13 and decreases type II collagen) and increases ECM calcification in chondrocytes	137
	Increased in RA FLSs and synovium	Sponges miR-103a, which negatively regulates *IL15* and *DKK1*	Increases inflammation and joint destruction in mice with CAIA	177
NEAT1	Increased in OA cartilage	Sponges miR-377-3p, which negatively regulates *ITGA6*	Reduces cell proliferation and increases apoptosis, ECM degradation and inflammation in IL-1β-treated chondrocytes	30
	Increased in RA FLSs and synovium	Sponges miR-410-3p, which negatively regulates *YY1*	Increases cell proliferation and TNF and MMP9 expression and decreases apoptosis in RA FLSs	33
	Increased in RA PBMC exosomes	Sponges miR-23a, which negatively regulates the MDM2–SIRT6 axis	Increases FLS proliferation and inflammation	135
	Increased in RA PBMCs and T_H17 cells	Reduces ubiquitylation of STAT3	Increases T_H17 cell differentiation and disease severity in mice with CIA	114
PINT	Decreased in RA FLSs and synovium	Sponges miR-155-5p, which negatively regulates *SOCS1*	Increases cell proliferation, invasion and pro-inflammatory cytokine production in RA FLSs	178
PVT1	Increased in RA synovium	Sponges miR-145-5p	Increases cell proliferation and pro-inflammatory cytokine production and decreases apoptosis in RA FLSs	31
	Increased in RA synovium	Sponges miR-543, which negatively regulates *SCUBE2*	Increases cell proliferation and IL-1β expression and decreases apoptosis in RA FLSs	179

Includes articles published between 2019 and 2021. CAIA, collagen antibody-induced arthritis; CIA, collagen-induced arthritis; ECM, extracellular matrix; FLS, fibroblast-like synoviocyte; lncRNA, long non-coding RNA; MDM2, E3 ubiquitin-protein ligase MDM2; MMP, matrix metalloproteinase; NO, nitric oxide; OA, osteoarthritis; PBMC, peripheral blood mononuclear cell; PGE_2, prostaglandin E_2; RA, rheumatoid arthritis; SIRT6, sirtuin 6; STAT3, signal transducer and activator of transcription 3; T_H17 cell, T helper 17 cell.

For example, lncRNAs can function through regulation of histone methylation[100], targeting single-nucleotide polymorphisms[101] and miRNA sponging[30,102] to regulate cellular processes as diverse as apoptosis[103,104], cell proliferation[103] and ECM degradation[102,105,106]. In the following sections, we curate literature published in the past 2 years on non-coding RNAs in inflammation, cell death, cell proliferation and ECM dysregulation in OA and RA. Overall, although further research is required to elucidate the interrelated effects of non-coding RNAs on the pathogenesis of OA and RA, existing evidence suggests that there could be merit to therapeutically targeting non-coding RNAs in these diseases.

Inflammation. A variety of signalling molecules, including non-coding RNAs, can induce and regulate joint inflammation. Cytokines such as IL-1β, TNF and IL-6 are often used as markers to gauge inflammatory responses in chondrocytes and fibroblast-like synoviocytes (FLSs). Amounts of these three cytokines were reduced in mouse primary chondrocytes by an increase in miR-410-3p[107], and in supernatant from lipopolysaccharide-treated human chondrocytes by a decrease in miR-20a[108]; both outcomes were mediated by nuclear factor-κB (NF-κB) signalling. NF-κB can regulate the expression of miRNAs, but miRNAs can also regulate the expression of NF-κB; for example, an increase in miR-382-3p leads to a decrease in phosphorylated NF-κB in IL-1β-stimulated human OA chondrocytes[109]. Furthermore, miR-140-5p can reduce human chondrocyte senescence[110] and can work synergistically with miR-146a to reduce NF-κB phosphorylation and the production of pro-inflammatory cytokines in OA chondrocytes[111]. These studies suggest that miRNAs regulate inflammatory responses through mechanisms that include canonical signalling pathways (such as NF-κB) and cytokines (such as IL-1β, IL-6 and TNF) in OA, and similar results have been reported in RA[47]. lncRNAs are also important mediators of inflammation in human OA chondrocytes. The lncRNAs PACER, CILinc01 and CILinc02 all show rapid and transient induction in response to IL-1β and other pro-inflammatory stimuli, indicating important regulatory roles[112].

In RA, non-coding RNAs in circulating immune cells, synovial immune cells and FLSs contribute to excess inflammation. T helper 17 (T_H17) cells that produce cytokines such as IL-17 and IL-22 stimulate inflammatory responses from FLSs and macrophages in RA to further promote synovial inflammation[113]. In RA PBMCs, the lncRNA NEAT1 (which is present in increased amounts compared with healthy individuals)

targets signal transducer and activator of transcription 3, causing decreased ubiquitylation-mediated degradation and leading to an increase in T_H17 cell differentiation[114]. Similarly, a lack of the miRNA let-7g-5p in patients with RA promotes the differentiation of naive $CD4^+$ T cells into T_H17 cells, whereas the treatment of mice with collagen-induced arthritis (CIA) with let-7g-5p mimics decreases the number of T_H17 cells in the blood and spleen, leading to reduced synovial hyperplasia, pannus formation and cartilage destruction[115]. Macrophages with a pro-inflammatory phenotype (M1-like) are also enriched in active RA synovium[116]. An increase in miR-155 in monocytes from patients with RA impairs monocyte differentiation into an inflammation-resolving phenotype (M2-like)[117] and, in RA synovial tissue and fluid, an increase in miR-221-3p leads to decreased IL-10 production (via direct targeting of Janus kinase 3) in M2-like macrophages and acts synergistically with miR-155-5p to increase the production of IL-12 (which is specific to M1-like macrophages)[118]. Given the role of inflammation in OA and RA, understanding the contribution of non-coding RNAs to its underlying mechanisms could provide new insights.

Cell death and cell proliferation. Abnormal cell death and cell proliferation in joint tissues create hallmark features of OA (such as cartilage degeneration) and RA (such as synovial hyperplasia). Studies have reported the effects of a variety of miRNAs on chondrocyte apoptosis. For example, increased expression of miR-33b-3p, miR-9-5p or miR-27a decreased chondrocyte apoptosis[119–121], whereas increased expression of miR-486-5p, miR-363-3p or miR-455-3p increased chondrocyte apoptosis[75,122,123]. The mechanisms through which unique miRNAs affect cell death and cell proliferation can often converge onto a single pathway, such as the phosphoinositide 3-kinase (PI3K)–AKT signalling pathway[124–131]. Beneficial effects produced by miRNAs through regulation of the PI3K–AKT pathway include a reduction in apoptosis and cartilage degeneration caused by an increase in miR-455-3p[124], the promotion of chondrocyte proliferation and reduced apoptosis caused by a decrease in miR-34a[125] and a reduction in chondrocyte apoptosis and inflammation caused by an increase in miR-128-3p[126]. Conversely, increased amounts of miR-155, miR-1236 or miR-103 all promote chondrocyte apoptosis by targeting PI3K[127–129].

Table 3 | **Circular RNAs of mechanistic importance in OA and RA**

circRNA	Change in expression	Mechanism	Effects	Ref.
circ_0136474	Increased in OA cartilage	Sponges miR-127-5p, which negatively regulates *MMP13*	Suppresses cell proliferation and increases apoptosis in OA chondrocytes	180
circ_0009119	Decreased in OA cartilage	Sponges miR-26a, which negatively regulates *PTEN*	Protects OA chondrocytes from IL-1β-induced apoptosis	181
circ_0001722 (circCDK14)	Decreased in OA cartilage	Sponges miR-125a-5p, which negatively regulates *SMAD2*	Regulates ECM metabolism (decreases MMP3 and MMP13; increases SOX9 and type II collagen), inhibits apoptosis and promotes cell proliferation in chondrocytes	182
circ_0023404 (circRNF121)	Increased in OA cartilage	LEF1 increases circRNF121 expression, which sponges miR-665, which negatively regulates *MYD88*	Regulates degradation of ECM (increases MMP13 and ADAMTS5; decreases type II collagen and aggrecan), apoptosis and cell proliferation in chondrocytes	163
circ_0000284 (circHIPK3)	Increased in OA cartilage	Sponges miR-124, which negatively regulates *SOX8*	Inhibits apoptosis in chondrocytes	183
circVCAN	Increased in OA cartilage	Inhibits activation of NF-κB signalling pathway	Increases cell proliferation and decreases apoptosis in OA chondrocytes	184
circ_0008956 (circUBE2G1)	Increased in OA cartilage	Sponges miR-373, which negatively regulates *HIF1A*	circUBE2G1 inhibition reduces the effects of LPS in OA chondrocyte viability and apoptosis	185
circPSM3	Increased in OA cartilage	Sponges miRNA-296-5p	Inhibits cell proliferation and differentiation in OA chondrocytes	186
circCDR1as	Increased in OA cartilage	Sponges miR-641, which negatively regulates *FGF2*	Regulates ECM metabolism (increases MMP13 and IL-6; decreases type II collagen)	187
circTMBIM6	Increased in OA cartilage	Sponges miR-27a, which negatively regulates *MMP13*	Regulates ECM degradation (increases MMP13)	188
circ_0000448 (circGCN1L1)	Increased in OA TMJ synovium	Sponges miR-330-3p, which negatively regulates *TNF*	Increases chondrocyte apoptosis and ECM metabolism (increases MMP3, MMP13 and ADAMTS4; decreases type II collagen), and increases synoviocyte hyperplasia and inflammation	189
circ_0088036	Increased in RA FLSs	Sponges miR-140-3p, which negatively regulates *SIRT1*	Increases FLS proliferation and migration	190
circ_09505	Increased in RA PBMCs	Sponges miR-6089, which negatively regulates *AKT1*	Increases macrophage proliferation and cell-cycle progression	191

Includes articles published between 2019 and 2021. ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; circRNA, circular RNA; ECM, extracellular matrix; FLS, fibroblast-like synoviocyte; LEF1, lymphoid enhancer-binding factor 1; LPS, lipopolysaccharide; MMP, matrix metalloproteinase; NF-κB, nuclear factor-κB; OA, osteoarthritis; PBMC, peripheral blood mononuclear cell; RA, rheumatoid arthritis; SOX9, transcription factor SOX9; TMJ, temporomandibular joint.

Other pathways, such as NF-κB[132], can also mediate the effect of non-coding RNAs on chondrocyte apoptosis. In addition, lncRNAs and circRNAs can interact with miRNAs to regulate cell death and cell proliferation. For example, lncRNA CTBP1-AS2 is upregulated in OA synovial fluid and regulates the expression of miR-130a through methylation in OA chondrocytes, but not in healthy chondrocytes, to promote cell proliferation[66]. New evidence to support the importance of non-coding RNAs in regulating cell death and proliferation is also continuing to emerge[133] (TABLE 3).

In RA, expression of miR-483-3p, which is thought to be oncogenic in several human cancers, is increased; in FLSs, this miRNA directly targets *IGF1* mRNA (which encodes insulin-like growth factor 1; IGF1) to impair apoptosis and induce tumour-like proliferation[134]. Expression of the lncRNA NEAT1 is also increased in human RA synovial tissue[33] and PBMCs[114]. Delivery of NEAT1 to RA FLSs via plasma exosomes isolated from humans and mice caused sponging of miR-23a and miR-410-3p and thereby increased the expression of their targets (including E3 ubiquitin-protein ligase MDM2 and transcriptional repressor protein YY1), leading to a decrease in apoptosis and an increase in FLS proliferation and inflammation[33,135]. Furthermore, the reduction of NEAT1 via siRNA can reduce the severity of CIA in mice[114]. These results illustrate the possibility of targeting non-coding RNAs to modulate cell death and cell proliferation.

Extracellular matrix dysregulation. miRNAs, lncRNAs, circRNAs and even snoRNAs have been implicated in ECM dysregulation in joint tissues such as cartilage, synovium and bone. IL-1β is widely used to induce cellular responses that mimic pathological conditions including inflammation[109], apoptosis[127] and cartilage degradation[97]. Researchers often use IL-1β to stimulate a response in chondrocytes in vitro that is subsequently rescued or exacerbated by manipulating a non-coding RNA. In cultured human chondrocytes, increased miR-377-3p expression reversed IL-1β-induced upregulation of inflammatory markers, cartilage degradation markers and chondrocyte apoptosis[30]. In a different experimental model, human chondrocytes transfected with an miR-613 agonist for 48 hours prior to administration of IL-1β had reduced markers of inflammation, apoptosis and cartilage degradation compared with IL-1β-treated cells[136]. A tentative role for the NEAT1–miR-377-3p–*ITGA6* axis has been described in IL-1β-treated chondrocytes, in which NEAT1 might function as an miR-377-3p sponge, thereby upregulating *ITGA6* expression to affect inflammatory responses, apoptosis and ECM degradation[30]. Among other notable lncRNAs, XIST increases collagen degradation in OA chondrocytes via increasing *TIMP3* promoter methylation through the recruitment of a DNA methyltransferase[106]. Furthermore, in OA cartilage, expression of the lncRNAs H19 and LINC01534 is increased and ECM degradation is promoted through their individual binding to miR-140-5p[137,138], an miRNA that is well characterized in OA for its cartilage matrix remodelling effects[139]. Roles for circRNAs (TABLE 3) and snoRNAs[28,140,141] have also been described in ECM metabolism. For example, impaired expression of U3 snoRNA, SNORD26 or SNORD96A alters the protein translation capacity of chondrocytes, chondrocyte differentiation, pro-inflammatory pathways and the expression of markers of OA[28,141].

Notably, ECM dysregulation can actually facilitate intercellular communication by making otherwise dense cartilage and bone matrices more permeable to extracellular vesicles that carry non-coding RNAs. Evidence from RA suggests that both chondrocytes and osteoblasts can respond to miRNAs carried by FLS-derived exosomes. In one study, exosomes from FLSs carrying miR-106b induced chondrocyte apoptosis and reduced proliferation by directly targeting *PDK4* mRNA[142]. In another study, exosomes from FLSs carrying miR-486-5p were phagocytosed by osteoblasts and promoted their differentiation and the expression of ECM markers such as type I collagen[143]. Given that inflamed and hyperplastic synovium is a common feature of RA, exosomes secreted by FLSs could serve as messengers to induce damage in surrounding joint tissues.

Therapeutic potential

Non-coding RNAs represent promising therapeutic targets in OA and RA because their activity can be modulated via small molecules and biological delivery systems (such as exosomes[144–146]) to reduce features of disease, and even pain, in experimental models of arthritis[147,148]. The cargo of these delivery systems can include non-coding RNA mimics (known as agomirs), non-coding RNA inhibitors (known as antagomirs) and other molecules, such as transcription factors. For example, in mouse cells in vitro, the lncRNA MM2P promotes macrophage polarization towards an M2-like phenotype and stimulates the release of exosomes containing SOX9 mRNA and protein from these cells, which can induce the production of ECM components in cultured chondrocytes[149]. As these exosomes contain a functional transcription factor (SOX9) that is known to promote chondrocyte anabolism, they represent a potential therapeutic strategy to restore cartilage homeostasis.

An important consideration in harnessing the potential of non-coding RNAs as possible therapeutics is the route of administration, whether systemic or intra-articular, so that the therapy can reach the intended target tissues. Systemic administration of non-coding RNAs can be achieved by intravenous injection. Using this method, an miR-365 agomir decreased disease severity in mice with CIA, potentially through downregulation of IGF1 (REF.[78]). Similarly, following intravenous injection, the concentration of an miR-26a mimic was increased in articular cartilage and could reduce disease severity in rats with CIA through the downregulation of connective tissue growth factor (CTGF)[150]. Intravenous injection of exosomes has also been explored. BMSC-derived exosomes enriched with miR-320a, which directly downregulates C-X-C chemokine ligand 9, could decrease disease severity in mice with CIA following intravenous injection[151]. Furthermore, BMSC-secreted exosomes enriched with miR-192-5p could be found in the synovial tissue of rats with CIA after intravenous injection, and could decrease disease

severity, potentially through downregulation of the signalling molecule RAC2 (REF.[152]). These data suggest that non-coding RNAs were able to traffic to the joints in rats and mice with CIA, where they reduced synovial inflammation, cartilage damage and bone erosion. However, because a single non-coding RNA can have multiple gene targets, local modulation (such as direct injection of miRNA agomirs and antagomirs into the joint) is also being explored to avoid unwanted systemic effects. In mice with CIA, intra-articular delivery of miR-146a-5p agomir decreased disease activity, synovial hyperplasia, the invasiveness of the pannus and cartilage erosion, potentially through downregulation of CTGF[153]. Similarly in rats with CIA, intra-articular delivery of miR-141-3p agomir improved disease outcomes via direct binding of the transcription factor FOXC1, which functions as an oncogene to promote tumour and RA FLS proliferation[154]. Intra-articular delivery of exosomes is also possible, and exosomes can even be engineered to target cells of interest. For example, the fusion of chondrocyte-affinity peptide to lysosome-associated membrane glycoprotein 2b molecules on the surface of exosomes promoted the trafficking and fusion of the exosomes to chondrocytes, the efficient delivery of miR-140 and the mitigation of disease progression in a rat surgical model of OA[155].

Alternative strategies for non-coding RNA modulation continue to emerge. For example, transplantation of cartilage pellets derived from human BMSCs that overexpress beneficial miRNAs (such as miR-27b) inhibited hypertrophic chondrocyte differentiation during cartilage defect repair[156]. Similarly, intra-articular injection of human umbilical cord-derived mesenchymal stem cells transfected to overexpress miR-140 had protective effects in a rat model of OA[157]. A biodegradable delivery system for an miR-365 antagomir based on non-pathogenic yeast cell wall particles has been developed that could resist degradation in the gastrointestinal system following oral administration, and which reduced features of disease in a mouse surgical model of OA[102]. Furthermore, cationic liposomes (lipoplexes) have been used for the intra-articular administration of miR-17-5p to reduce synovial immune cell infiltration, inflammation and bone erosion in mice with CIA[72]. As an alternative means of suppressing miRNA function, tough decoy RNAs have been developed, wherein vectors expressing miRNA target sites bind and reduce specific miRNA activity in cells; a tough decoy for miR-195-5p reduced its activity and the occurrence of hypertrophy in cultured chondrocytes[158]. Moreover, miRNA agomirs and antagomirs can be directly modified to improve their therapeutic properties. To improve specific binding, locking the conformation of antagomirs (known as locked nucleic acids) is effective, and intra-articular delivery of locked nucleic acid antagomirs for miR-181a-5p and miR-34a-5p could reduce disease severity in experimental models of OA[159,160]. To improve stability and delivery, non-coding RNAs can be conjugated to other molecules such as atelocollagen; intra-articular administration of an miR-9a-5p agomir–atelocollagen complex could effectively reduce disease severity in rats with CIA[161]. Additional delivery mechanisms and considerations for achieving clinical translation of antisense oligonucleotide-based therapies for OA have been reviewed in detail elsewhere[104,162].

Studying the interactions among non-coding RNAs, including regulators and effectors of circRNA–miRNA–mRNA axes, could also reveal new avenues for targeted treatment. One molecular mechanism proposed as a prospective therapeutic target for OA is the circRNF121–miR-665–*MYD88* axis, which is regulated by the transcription factor LEF1 (REF.[163]). In human chondrocytes, LEF1 increases the expression of circRNF121, which functions as a sponge for miR-665, thereby indirectly targeting *MYD88*. As such, modulation of miR-665 and circRNF121 could alter *MYD88* expression to promote chondrocyte apoptosis, proliferation and ECM degradation, both in vitro in human chondrocytes and in vivo in a rat model of OA. Furthermore, this axis was shown to activate the NF-κB signalling pathway[163]. Although the data suggest that miR-665 could be targeted to mitigate the detrimental effects of circRNF121, it is evident that the upstream regulator (LEF1), circRNA (circRNF121), miRNA (miR-665), gene target (*MYD88*) and downstream pathway (NF-κB) could all be potential targets. These data illustrate the importance of considering the non-coding RNA interactome for therapeutic targeting, as one or more of these factors might need to be modulated to improve disease outcomes (BOX 1).

On the basis of the current literature, outstanding questions remain to be answered before targeting of non-coding RNAs can be translated into a therapeutic strategy to improve patient care. First, the appropriate target must be identified, whether it is the non-coding RNA, its upstream regulator or the downstream mediator. Second, the appropriate tissue or tissues must be identified for targeting, as non-coding RNAs are known to have tissue-specific effects. Third, the appropriate

Box 1 | **The non-coding RNA interactome in gene expression regulation**

The regulation of gene expression is tightly controlled. Non-coding RNAs have important roles in this process, operating through direct mechanisms (such as degradation of gene transcripts) and indirect mechanisms (such as inhibition of other non-coding RNAs). Together, these mechanisms comprise the non-coding RNA interactome, which can be thought of as the complete set of the molecular interactions of non-coding RNAs. Emerging literature suggests that interactions among non-coding RNA entities and classes are common and have considerable implications for joint diseases. High-throughput profiling is a useful approach for beginning to unravel the non-coding RNA interactome. For example, researchers have used three publicly available microarray datasets for synovium from patients with rheumatoid arthritis (RA) to demonstrate potential direct regulation of interconnected gene targets by specific long non-coding RNAs (lncRNAs), wherein the lncRNAs NEAT1 and FAM30A were predicted to interact with major RA hub genes[192]. To explore interactions across non-coding RNA classes, circular RNA (circRNA)–microRNA (miRNA) networks have been constructed for synovium[193], cartilage[194] and chondrocytes[133,195] from patients with osteoarthritis (OA). For example, researchers have used RNA sequencing to identify OA-related circRNAs in cartilage, followed by bioinformatics analyses to discover 166,394 circRNA–miRNA–mRNA axes[194]. LncRNA–miRNA networks have also been explored in OA. In human knee cartilage, publicly available RNA sequencing data have been mined to identify differentially expressed lncRNAs and mRNAs that contribute to an integrated network of competing endogenous RNAs, including 10 lncRNAs, 69 miRNAs and 72 mRNAs[196]. These individual profiling studies are an important first step towards understanding the non-coding RNA interactome, but need to be followed by efforts to integrate findings across studies so that candidates for further validation and potential therapeutic targeting can be prioritized.

Table 4 | **Use of bioinformatics and computational biology tools in non-coding RNA research**

Challenge	Approach	Resources
Analysing high-throughput profiling data for non-coding RNAs in both health and disease contexts	A search tool can be used to discover novel non-coding RNA sequences in deep sequencing data	miRDeep2
Ensuring proper and consistent naming of all non-coding RNA entities so that data can be accurately integrated across studies	Several databases are helpful to ensure the correct use of primary names and identifiers	miRbase for microRNAs; DIANA-lncBase for long non-coding RNAs; circBase and circAtlas for circular RNAs; and Hugo Gene Nomenclature for gene names
Elucidating the potential functions of non-coding RNAs	Multiple tools can be used for target gene prediction, including for novel microRNA sequences	TargetScan; mirDIP; miRDB; and miRanda
Interpreting predicted target genes	Pathway prediction tools can be used to create functional groups with biological relevance (such as signalling cascades)	The Gene Ontology Resource for gene enrichment analysis; pathDIP for integrated pathway enrichment analysis; and integrated web portals, such as Enrichr, for access to diverse types of computational annotation and overrepresentation analysis
Combining non-coding RNA datasets to promote integrative computational analyses	Public repositories can be used to access and deposit high-throughput data	The NCBI Gene Expression Omnibus repository; the NCBI Sequence Read Archive; the NCBI Database of Genotypes and Phenotypes; and the EMBL-EBI European Nucleotide Archive

EMBL-EBI, European Molecular Biology Laboratory European Bioinformatics Institute; NCBI, National Center for Biotechnology Information.

delivery mechanism must be identified, including the vehicle (such as exosomes) and route of administration. For example, intra-articular delivery might offer benefits over systemic administration by providing local modulation and thereby reducing unwanted off-target effects. The answers to these questions and others (such as the best dosage to use) might be patient-specific, and tailored RNA-based therapeutics might need to be administered in a phenotype-dependent manner to achieve precision medicine in OA and RA. The utility of RNA-based therapeutics has now achieved global recognition through RNA vaccines, which were first described over two decades ago[164], and it is therefore reasonable to expect bolstered research efforts into RNA-based therapeutics, which should include non-coding RNAs.

Future directions

Unravelling the complex interactions among non-coding RNAs is becoming an important goal; however, the comprehensive high-throughput profiling of joint tissues and biofluids that will be necessary to achieve this aim comes with its own set of challenges (TABLE 4). Although microarrays are useful for profiling a pre-selected subset of known candidate RNAs, this technique is limited by factors such as the appropriate selection of an endogenous reference, which can vary by tissue type[165]. Increasingly, next-generation sequencing technologies are being used to achieve unbiased and quantitative measures of all varieties of non-coding RNAs. For example, next-generation sequencing can be used to identify the direct binding of miRNAs to target genes through RNA-immunoprecipitation and high-throughput sequencing (RIP sequencing), as has been described in human articular chondrocytes[166]. This approach enables the validation of predicted gene targets that are commonly obtained using prediction tools (TABLE 4). Furthermore, applying sequencing technology to fundamental processes in model systems has the potential to uncover important mechanisms that underlie disease. For example, combinations of RNA sequencing and small non-coding RNA sequencing have been applied to explore chondrogenesis and metabolism in human BMSCs[167], inflammatory cytokine responses in mouse induced pluripotent stem cells[168] and cartilage ageing in horse chondrocytes[140].

Among the limitations of unbiased discovery of non-coding RNAs is that researchers often focus on just one or two molecules for further investigation. How and why these molecules are chosen can be unclear, as other non-coding RNA entities that could have promising roles in joint pathobiology are often not investigated further. Notably, very few non-coding RNA studies in OA and RA include comparisons with other studies or meta-analyses with other available non-coding RNA datasets in order to validate, expand and build a comprehensive interactome of these important epigenetic regulators. However, efforts are ongoing around the world to curate comprehensive databases of published evidence to help researchers to investigate the complex interactions between non-coding RNAs, genes and proteins (TABLE 4). To this end, it is critical that nomenclature and annotations for the non-coding RNAs identified in studies are systematically reported. For example, investigators are encouraged to report the strands of miRNAs (3p or 5p) to ensure accurate integration of their data with other datasets and analyses. Furthermore, reporting of the clinical annotation of samples involved in non-coding RNA studies is required to enable correlation with molecular and clinical phenotypes. Finally, to improve the quality of basic and translational research by applying integrative analytical and machine learning techniques, well-annotated high-throughput data must be made available in the correct format (for example, the raw sequencing datasets) in online repositories.

Conclusions

A substantial surge has occurred in the number of published articles related to non-coding RNAs in OA and RA in the past few years, mostly for miRNAs, lncRNAs and circRNAs, and to a lesser degree for snoRNAs,

tRFs and other non-coding RNAs. This increased research output has been possible because of advances in next-generation sequencing technology and the availability of computational and analytical tools for data mining. Some of the non-coding RNAs that have been identified using these methods, as well as their regulatory interactome, could have crucial roles in joint health and disease, affecting biological processes and functioning as biomarkers, mediators of pathogenesis and potential therapeutic targets. Although these discoveries are promising, a concerted effort is required to validate, integrate and translate findings from current studies to harness the full potential of non-coding RNAs in OA and RA.

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Author contributions
The authors contributed equally to all aspects of the article.

Competing interests
S.A.A. and M.K. declare that they have filed a US Provisional Patent Application no. 63/033,463 titled “Circulating MicroRNAs in Knee Osteoarthritis and Uses Thereof”. The other authors declare no competing interests.

Disclaimer
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Review criteria
A literature search was performed in PubMed for articles published in the past 2 years using combinations of the following key words: “osteoarthritis”, “rheumatoid arthritis”, “microRNA”, “long non-coding RNA”, “circular RNA”, “small nucleolar RNAs” and “transfer RNAs”. Some highly relevant papers outside the search criteria were also included.

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