Osteoarthritis (OA) is a common and disabling joint disorder that is mainly characterized by cartilage degeneration and narrow joint spaces. The regulatory functions of non-coding RNAs (long non-coding RNAs, microRNAs [miRNAs], and circular RNAs [circRNAs]) in OA progression have attracted considerable attention, and the function of circular RNAs in the context of OA has been an increasingly popular research topic in the last 6 years. Recent studies have reported that various circRNAs can delay or aggravate diverse aspects of the OA process, including extracellular matrix formation, apoptosis, proliferation, inflammation, and autophagy, via circRNA/miRNA/mRNA pathways. Thus, circRNAs and related pathways are potential therapeutic targets for OA. Our review provides comprehensive information about circRNAs, including their biogenesis, functions, and characteristics, and it reveals their critical roles in the pathogenesis of OA via a large regulatory network of sponges. Considering their regulatory functions and characteristics, we hypothesize that circRNAs not only can be transferred through bodily fluids to serve as diagnostic biomarkers, but they can also be released from mesenchymal stem cell-derived exosomes and delivered to OA chondrocytes acting as therapeutic circRNAs. Further investigations of the in-depth molecular mechanisms of action of circRNAs in OA are expected to provide effective and safe OA treatment strategies.

INTRODUCTION

Osteoarthritis (OA) is a chronic and progressive cartilage degeneration disease with a high morbidity and disability rate and is characterized by cartilage degeneration, osteocyte formation, thickening of subchondral bone, synovial inflammation, meniscal injuries, and ligament deterioration. At present, more than 500 million people worldwide are being affected by OA, and the peak of incidence is around the age of 75 years. Multiple factors leading to OA include aging, sex, obesity, genetics, metabolic environment, and joint alignment; however, the exact molecular mechanisms regulating OA pathogenesis remain elusive, and no effective interventions or therapies, with the exception of surgery, can slow or reverse OA progression. Chondrocytes are the only cell type present in the mature cartilage and undergo pathological changes with considerable involvement of non-coding RNAs when OA occurs. Therefore, the exploration of the pathophysiological and molecular mechanisms regulating chondrocytes in OA is of critical significance.

Non-coding RNAs, including long non-coding RNAs (lncRNAs), microRNAs (miRNAs), and circular RNAs (circRNAs), influence biological processes via the modifications of DNA structure, RNA transcription, and protein translation. As techniques such as RNA sequencing (RNA-seq) and bioinformatics analysis have been advanced, an increasing number of circRNAs have been discovered, and the principles behind their formation and biological functions have been progressively revealed. The functions of circRNAs are coming into focus, and increasing evidence has shown that circRNAs play key regulatory roles in diverse cellular processes, such as cell proliferation, apoptosis, differentiation, and invasion. In addition, several remarkable characteristics of circRNAs, including stability, specificity, conservatism, and universality, have been identified as potential biomarkers for diagnostics and as therapeutic targets in diseases, such as ciRS-7 in Alzheimer’s disease, circ-PRMT5 in breast cancer, hsa_circ_0000658 in osteosarcoma, circRIMS1 in bladder cancer, and circVMA21 in intervertebral disc degeneration.

Since 2015, the number of studies on circRNAs in OA has been increasing, and related publications have predominantly originated from China (Figure 1). Increasing evidence has shown that circRNAs are closely associated with chondrocyte proliferation, apoptosis, inflammation, autophagy, and ECM metabolism in OA and delay or aggravate OA progression. Moreover, the circRNAs/miRNAs/mRNAs axis was pointed out to have a significant role in OA progression, and circRNAs can act as sponges of miRNAs to inhibit the translation of miRNAs, thus participating in the occurrence and development of OA. Therefore, circRNAs with significant regulatory roles may become new biological markers and therapeutic
targets in OA; however, the mechanisms of action of circRNAs in OA pathogenesis need to be examined in detail. The present review provides an overview of biological roles and therapeutic potential of circRNAs in OA, which may contribute to the understanding of the molecular mechanism of OA pathogenesis and provide novel potential targets for OA diagnosis and therapy.

BIODIVERSITY, FUNCTIONS, AND CHARACTERISTICS OF circRNAs

Biogenesis of circRNAs

Precursor mRNAs (pre-mRNAs) undergo spliceosome-mediated splicing to generate linear mRNAs and backsplicing to generate circRNAs with the assistance of RNA polymerase II (RNA Pol II). In this reaction, a downstream 5′ splice site (ss) is bound to an upstream 3′ ss, and the final RNA circle is ligated by a 3′-5′ phosphodiester bond at the junction site. The patterns of overlap between the dominant circular and linear transcripts can be used to classify circRNAs into the following three categories according to shared exons: (1) overlapped, both use the same subset of exons; (2) partially overlapped, some but not all exons are shared; and (3) not overlapped, no exons are shared (Figure 2). Furthermore, circRNAs can be divided into three classes according to the genomic origin of exons and introns: circular intronic RNAs (ciRNAs), exonic circRNAs (ecircRNAs), and exon-intron circRNAs (EIciRNAs) (Figure 3).

Functions of circRNAs

The biological functions of circRNAs have been studied in a minor fraction of the molecules and have been described in detail; however, most circRNAs have been proposed to act as miRNA sponges. Intron circRNAs contribute to RNA-mediated inheritance and epigenetics in the cytoplasm, whereas ecircRNAs act as miRNA sponges to regulate miRNAs in the cytoplasm. Moreover, circRNAs can interact with proteins, including those acting as RNA-binding protein (RBP)-related protein sponges/decoys, enhancing particular protein functions by forming RNA-protein complexes. Acting as scaffolds for specific enzymes and substrates, and recruiting proteins to specific locations or subcellular compartments. Another intriguing function involves cap-independent translation of circRNA-encoded peptides; however, most circRNAs are universally acknowledged to be non-coding (Figure 4).

Figure 1. Status of circRNA research in OA

(A) The annual number of publications related to circRNA research in OA in the past 6 years. (B) The sum of publications related to circRNA research in OA from the top six countries.

Regulatory characteristics of circRNAs

circRNAs are involved in the intracellular RNA regulatory network and are closely related to the occurrence and development of diseases, including OA. The information on the circRNA/miRNA/mRNA pathways in diseases has been recently expanded, with these pathways providing novel directions for the pathogenesis, diagnosis, and therapy of the diseases. The competitive endogenous RNA (ceRNA) network has revealed new mechanisms by which RNAs regulate each other at the posttranscriptional level. Various ceRNA molecules, including mRNA, lncRNA, circRNA, and pseudogene species, regulate the expression levels of target genes via miRNA response elements (MREs). It has been reported that circRNAs contain a large number of miRNA binding sites and can function as miRNA sponges or ceRNAs that competitively inhibit the activity of miRNAs via MREs and silence genes by binding to mRNA. However, the mechanisms involved in the pathological process in OA are poorly understood.

BIOLOGICAL ROLES OF circRNAs IN CHONDROCYTES IN OA

The development of OA involves numerous types of cells, including chondrocytes, osteoblasts, osteoclasts, and synoviocytes. Chondrocytes play the main role in OA pathogenesis and have gained the most attention. Thus far, the studies on the role of circRNAs in OA mainly focused on chondrocytes, and the main investigated features include the degradation of extracellular matrix (ECM), apoptosis of chondrocytes, production of inflammatory cytokines, and reductions in proliferation and autophagy. Corresponding interventions to influence these pathological processes can delay the progression of OA. Detailed investigations into the biogenesis, biological functions, and characteristics of circRNAs have demonstrated that circRNAs are involved in numerous aging-related diseases, including cancer, cardiovascular diseases, and neurodegenerative disorders. In this study, we classify OA-related circRNAs based on their involvement in ECM formation (Figure 5), apoptosis (Figure 6), proliferation, inflammation, and autophagy (Figure 7) of chondrocytes and focus on the regulatory functions of circRNAs to demonstrate that certain circRNAs or related pathways can be used as diagnostic and prognostic biomarkers for OA treatment (Table S1).

ROLES OF circRNAs IN ECM FORMATION

The ECM is mainly composed of glycosaminoglycan (GAG), aggrecan, and collagen, and the balance of catabolic and anabolic processes in the ECM is important for ECM homeostasis. ECM degradation is one of the central and most critical features of OA pathogenesis and is...
mainly due to the upregulation of matrix-degrading enzymes, including those in the matrix metalloproteinase (MMP) family and ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) family. Current studies on the roles of circRNAs in the ECM mainly focus on the promotion or inhibition of ECM formation. Next, we discuss two opposite effects of circRNAs on ECM formation.

**circRNAs that promote ECM formation**

circPDE4D derived from the phosphodiesterase 4D (PDE4D) gene was significantly downregulated in OA cartilage. Knocking down circPDE4D downregulated GAG and aggrecan, whereas the matrix catabolic enzymes MMP3, MMP13, ADAMTS4, and ADAMTS5 were significantly upregulated, leading to ECM degradation. circRNAs are known to act as miRNA sponges to eliminate miRNA functions. circPDE4D acts as a sponge to abrogate the function of miR-103a-3p via direct binding, and silencing miR-103a-3p reversed circPDE4D-short hairpin RNA (shRNA)-induced ECM degradation. The targets of circPDE4D and miR-103a-3p include FGF18, a member of the fibroblast growth factor (FGF) family, which is the only gene with cartilage regeneration properties that simultaneously enhances anabolism and suppresses catabolism in healthy controls (HCs). FGF18 was identified as a direct target of miR-103a-3p and was able to reverse an increase in the expression of MMP3, MMP13, ADAMTS4, and ADAMTS5 in circPDE4D-deficient HCs. Thus, the circPDE4D/miR-103a-3p/FGF18 axis was shown to be a potential and critical target for the prevention of ECM degradation in OA.

In addition, circCDK14 (hsa_circ_0001722), which is derived from exons 3 and 4 of the CDK14 gene, was identified as a key factor protecting ECM formation during OA. The overexpression of circCDK14 increased the levels of SRY-related high mobility group-box 9 (SOX9) and collagen II, downregulated MMP3 and MMP13, and inhibited the interleukin (IL)-1β-induced inflammatory response. Similar to other circRNAs, circCDK14 acts as a miRNA sponge. Zhao and colleagues confirmed that miR-125a-5p binds to circCDK14 and is an important downstream target that counteracts the effects of circCDK14 in OA chondrocytes. Furthermore, Smad2 is an important signal transduction protein of the transforming growth factor β (TGF-β) signaling pathway; the 3′ UTR of Smad2 mRNA contains sequences complementary to miR-125a-5p and is thus thought to be downstream of circCDK14/miR-125a-5p. Smad2 overexpression counteracted the effects of circCDK14 knockdown and the miR-125a-5p mimic on SOX9 and collagen II to protect OA chondrocytes. Notably, the circCDK14/miR-125a-5p/Smad2 axis was able to maintain the ECM of chondrocytes but did not downregulate MMP3 or MMP13. Thus, the circCDK14/miR-125a-5p/Smad2 axis provides a potential molecular therapeutic target for OA treatment.

Additionally, circRNA serpin family E member 2 (circSERPINE2, hsa_circ_0008365) plays a role in the modification of ECM homeostasis and has been systematically identified as a protective circRNA in OA. Knocking down circSERPINE2 expression promoted the expression of MMP3, MMP13, and ADAMTS4 and decreased the levels of...
SOX9, collagen type II alpha 1 (COL2A1), and aggrecan, clearly indicating the anticatabolic effects of circSERPINE2 in HCs. Furthermore, circSERPINE2 was able to bind to miR-1271, and E26 transformation-specific (ETS)-related gene (ERG) is a putative target of miR-1271. The effects of miR-1271 on chondrogenic phenotypes were mediated by ERG. Therefore, the circSERPINE2/miR-1271/ERG axis is a novel target for the promotion of ECM formation.

circRNAs that inhibit ECM formation
circRNF121 (hsa_circ_0023404) was increased in chondrocytes induced by IL-1β in vitro and is produced by backsplicing exon 2 and exon 3 regions of RNF121 pre-mRNA. The overexpression of circRNF121 increased the levels of MMP13 and ADAMTS5 and decreased the levels of aggregan and collagen II, indicating that circRNF121 overexpression induces ECM degradation. Thus, the aberrant expression of circRNF121 can mediate OA progression by promoting ECM degradation. It has been reported that circRNA-CDR1as (cerebellar degeneration-related protein 1 antisense transcript) was upregulated in OA chondrocytes, and silencing of circRNA-CDR1as increased collagen II and decreased MMP13, effects that were reversed by the overexpression of circRNA-CDR1as. circRNA-CDR1as contains the binding sites for other miRNAs and functions as a sponge in various diseases. Yu and colleagues investigated whether circRNA-CDR1as functions as a sponge of a certain miRNA to regulate OA. The results showed that circRNA-CDR1as directly targeted miR-641 as a sponge and modulated its downstream functions similar to other circRNAs. In addition, FGF-2 expression was upregulated in OA chondrocytes. Silencing FGF-2 downregulated MMP13, IL-6, and RUNX2 and upregulated collagen II, and knocking down circRNA-CDR1as or miR-641 mimics decreased the levels of FGF-2, phosphorylated (p-)MEK, and p-ERK. Therefore, the circRNA-CDR1as/miR-641/FGF-2 axis may be a potential target for the prevention of the degradation of ECM in the cartilage in OA.
circRNA_Atp9b (circ_15898) is derived from the chr18:80734143−80934058 region of the Atp9b gene and was significantly upregulated in IL-1β-induced mouse chondrocytes, suggesting that circRNA_Atp9b may play a key role in IL-1β-induced chondrocytes. Knocking down circRNA_Atp9b dramatically increased the level of collagen II and decreased the levels of MMP13, IL-6, and COX-2. These data indicate that knocking down circRNA_Atp9b protects against IL-1β-induced ECM degradation and the production of inflammatory factors. In addition, circRNA_Atp9b directly targets miR-138-5p by functioning as a sponge but does not regulate miR-138-5p expression. The effects of circRNA_Atp9b on IL-1β-induced chondrocytes were confirmed to be mediated by targeting miR-138-5p. Thus, the circRNA_Atp9b/miR-138-5p axis may be a part of a potential therapeutic strategy for OA.

The level of MMP13 is increased in chondrocytes induced by tumor necrosis factor (TNF)-α and IL-1β, and the overexpression of MMP13 promotes ECM degradation. circTMBIM6, circRNA-CER, and circRNA.33186 were also upregulated in OA. Wang and colleagues confirmed that circTMBIM6 binds to miR-27a and that the overexpression of circTMBIM6 downregulates miR-27a expression. Ao and colleagues confirmed that circRNA-CER functions as a sponge of miR-27a, and Zhu and colleagues confirmed that miR-127-5p is the only binding target of circRNA.33186. In addition, direct binding of MMP13 to miR-27a, miR-136, and miR-127-5p indicated that MMP13 is downstream of circTMBIM6/miR-27a, circRNA-CER/miR-136, and circRNA.33186/miR-127-5p. The TGF-β, JNK, and ERK pathways target MMP13 and may regulate MMP13 via the circRNA-related pathways. Thus, the mechanisms of chondrocyte apoptosis is essential for the identification of potential approaches to OA treatment. Chondrocyte apoptosis is associated with ECM degradation, cell proliferation, and inflammation, and certain circRNAs play multiple roles, such as circRNF121 and circSERPINE2. Recently, the roles of circRNAs with proapoptotic and antiapoptotic effects in chondrocyte apoptosis in OA were investigated, and the information is presented in the following section.

ROLES OF circRNAs IN APOPTOSIS
Chondrocyte apoptosis plays a key role in the pathogenesis of OA. Several confirmed pathways are involved in chondrocyte apoptosis, such as the FAS/apoptosis antigen 1 (APO-1) pathway, the cysteine-aspartic protease (caspase) family of proteins, and the nitric oxide (NO) pathway. Therefore, investigation of the roles of circRNAs with proapoptotic and antiapoptotic effects in chondrocyte apoptosis in OA was investigated, and the information is presented in the following section.

circRNAs that promote apoptosis
circCDH13 (hsa_circ_0040646) plays proapoptotic and procatabolic roles and is produced by backsplicing of the exon 9 and exon 10 regions of the CDH13 gene on chromosome (chr)16. Upregulated circCDH13 has been detected in OA chondrocytes and in HCs treated with IL-1β and TNF-α. Knocking down circCDH13 downregulated MMP13 and ADAMTS5 and increased COL2A1 and aggrecan; all of these effects were reversed by the overexpression of circCDH13. circCDH13 can bind to miR-296-3p, acting as a sponge, and the downstream targets of circCDH13/miR-296-3p were investigated. The results showed that the 3’ UTR of phosphatase and tensin homolog (PTEN) mRNA is directly targeted by miR-296-3p; the effects of PTEN on MMP13, ADAMTS5, aggrecan, and COL2A1 were consistent with the effects of circCDH13 and were reversed by miR-296-3p mimics. The overexpression of circCDH13 contributed to apoptosis via the miR-296-3p/PTEN pathway.

A pronounced reduction in miR-127-5p and a robust increase in circ_0136474 and MMP13 in OA tissues were revealed by Guan and colleagues. The authors demonstrated that miR-127-5p is...
targeted by circ_0136474 and that overexpression of circ_0136474 can decrease miR-127-5p expression. In addition, miR-127-5p can target MMP13, and the negative correlation of miR-127-5p and MMP13 was confirmed. The overexpression of circ_0136474 or a miR-127-5p inhibitor increased the levels of caspase-3 and BAX but downregulated the expression of Bcl-2, indicating an increase in the apoptosis rate, which can be reversed by si-circ_0136474 and miR-127-5p mimics. In contrast, si-circ_0136474 or miR-127-5p repressed IL-1β, TNF-α, and IL-17, which downregulated MMP13. In addition, miR-127-5p can be targeted by circRNA.33186 and MMP13. In summary, circ_0136474 and circRNA.33186 sponge miR-127-5p to upregulate MMP13 in OA, and the circ_0136474/miR-127-5p/MMP13 axis may provide new therapeutic strategies for OA.

circRNA HIPK3 (circHIPK3) was reported to be associated with the occurrence and development of various diseases; low expression of circHIPK3 significantly promotes apoptosis in OA, and miR-124 is significantly downregulated. A dual-luciferase assay confirmed that circHIPK3 binds to miR-124, and their levels are negatively correlated. A decrease in circHIPK3 and the overexpression of miR-124 can enhance chondrocyte apoptosis, increasing the mRNA and protein levels of caspase-3. Considering that miR-124 serves as a sponge of SOX8 in non-small cell lung cancer, Tang and colleagues investigated whether miR-124 also targets SOX8 in OA chondrocytes. The results indicated that miR-124 can directly regulate SOX8 and that the miR-124 level is negatively correlated with SOX8 expression. Overall, circHIPK3 inhibits apoptosis of OA chondrocytes by acting as a sponge of miR-124 via SOX8, and the circHIPK3/miR-124/SOX8 axis provides a novel mechanism for the inhibition of chondrocyte apoptosis in OA therapy.

As noted earlier in this review, circSERPINE2 protects ECM metabolism and regulates the apoptosis of OA chondrocytes. Xia and colleagues found that the overexpression of circSERPINE2 mitigated IL-1β-induced chondrocyte apoptosis by decreasing caspase-3. OA-associated miR-495 has been confirmed as a target of circSERPINE2, and TGF-β receptor 2 (TGFBR2) is targeted by miR-495. These correlations confirm that circSERPINE2 can reduce miR-495 abundance and promote TGFBR2 expression in chondrocytes by competitively binding miR-495. Thus, the circSERPINE2/miR-495/TGFBR2 axis may be a potential target for the prevention of chondrocyte apoptosis in OA.

ROLES OF circRNAs IN PROLIFERATION

In addition to the roles of circRNAs in ECM formation and apoptosis, their effects on the balance of chondrocyte proliferation are involved in the development of OA. Several research groups have recently...
studied the roles of circRNAs in chondrocyte proliferation in OA. In the following section, we summarize recent findings on the effects of circRNAs on chondrocyte proliferation.

circRNAs that promote proliferation

The downregulated expression of hsa_circ_0045714 and the upregulated expression of miR-193b are negatively correlated in chondrocytes treated with TNF-α.48 Insulin-like growth factor 1 receptor (IGF1R) is an important target gene of miR-193b that inhibits IGF1R expression; however, hsa_circ_0045714 notably upregulates IGF1R expression and antagonizes the inhibition of IGF1R expression by miR-193b. IGF1R is a member of the insulin-like growth factor receptor family and has been considered an important target gene affected by miR-193b. Upon IGF1 binding, IGF1R activates the PI3K and mitogen-activated protein kinase (MAPK) signaling pathway and regulates cell proliferation, differentiation, and apoptosis through autophosphorylation. Both hsa_circ_0045714 and IGF1R can promote cell proliferation, whereas miR-193b does not have this effect. In fact, miR-193b can promote apoptosis by silencing hsa_circ_0045714 and thus IGF1R. Moreover, IGF1R siRNA can restrain the function of hsa_circ_0045714, and this effect can be reversed by IGF1R overexpression.48 Thus, hsa_circ_0045714 promotes the proliferation of chondrocytes through the miR-193b target gene IGF1R, and the hsa_circ_0045714/miR-193b/IGF1R axis provides a new possibility for OA treatment based on circRNAs.

circRNAs that inhibit proliferation

circRNA.33186 is a 536-nt circRNA derived from the Umad1 gene on chr6:8373906→8427185(+) and is significantly upregulated in OA chondrocytes, and silencing circRNA.33186 considerably alleviates OA in vivo.23 Zhu and colleagues23 demonstrated that knocking down circRNA.33186 can reverse a decrease in the proliferation of chondrocytes. Furthermore, the authors confirmed that miR-127-5p was the only binding target of circRNA.33186 and that the level of miR-127-5p was negatively correlated with the expression of circRNA.33186. Then, Zhu and colleagues investigated the interaction between circRNA.33186 and miR-127-5p, and the results showed that a reduction in MMP13 expression caused by silencing circRNA.33186 was significantly restored by a miR-127-5p inhibitor. Thus, circRNA.33186 promotes OA pathogenesis by functioning as a sponge for miR-127-5p. In addition, miR-127-5p functions by regulating MMP13. Overall, the circRNA.33186/miR-127-5p/MMP13 axis can be considered a potential target for OA therapy.
RUN2, were increased. In addition, silencing circPSM3 in OA chondrocytes can significantly promote miR-296-5p expression, which is negatively correlated with the level of circPSM3; subsequent investigation confirmed that circPSM3 may influence the proliferation and differentiation of chondrocytes by acting as a sponge of miRNA-296-5p in OA. Overall, the CircPSM3/miRNA-296-5p axis provides a theoretical basis for OA treatment.

**ROLES OF circRNAs IN INFLAMMATION**

OA is an inflammation-related disease, and the related symptoms include joint swelling and pain; thus, the activation of inflammation is a critical feature of OA pathogenesis. Abnormal increases in inflammatory cytokines can lead to the destruction and degradation of ECM and inhibit the synthesis and repair of chondrocytes, resulting in a vicious cycle of ECM damage, including the role of hsa_circ_0005105. In the next section, we provide a review of the pro-inflammatory and anti-inflammatory roles of circRNAs in OA chondrocytes.

**circRNAs that promote inflammation**

circRNA-UBE2G1 (hsa_circ_0008956), which is derived from the UBE2G1 gene, and HIF-1α were upregulated in the OA tissues, and the levels of both molecules were positively correlated with modified Mankin scores; in contrast, miR-373 expression was downregulated and negatively correlated with modified Mankin scores. Chen et al determined the mechanism of action of circRNA-UBE2G1 in OA and found that miR-373 harbors a binding site for circRNA-UBE2G1. In addition, HIF-1α was identified as an important factor; the results showed that miR-373 mimics significantly reduced HIF-1α expression, and this effect was reversed by miR-373 inhibitors, suggesting that miR-373 is targeted by HIF-1α. Moreover, HIF-1α was positively correlated with circRNA-UBE2G1 and negatively correlated with miR-373, and the overexpression of circRNA-UBE2G1 and HIF-1α or a miR-373 inhibitor can increase the levels of IL-1β, IL-6, and TNF-α. Thus, circRNA-UBE2G1 regulates HIF-1α expression through miR-373 sponging, and the circRNA-UBE2G1/miR-373/HIF-1α axis may be a potential target for the prevention of inflammation for OA treatment.

**circRNAs that inhibit inflammation**

ciRS-7, also known as Cdr1as, is considered an endogenous competitive RNA inhibitor of miR-7 and acts as a “super sponge” of miR-7. In OA chondrocytes, the expression of ciRS-7 was detected in IL-1β-induced chondrocytes by Zhang and colleagues, and miR-26a was inhibited in IL-1β-induced chondrocytes and was negatively correlated with hsa_circ_0005105. In addition, miR-26a can counteract the effects of hsa_circ_0005105. Nicotinamide phosphoribosyltransferase (NAMPT), also known as visfatin or pre-B cell colony-enhancing factor (PBEF), was identified as a target of miR-26a. hsa_circ_0005105 was shown to contribute to the expression of prostaglandin E2 (PGE2), IL-6, and IL-8; however, miR-26a inhibited the expression of these factors, and downregulated NAMPT can reverse this function of hsa_circ_0005105. Thus, hsa_circ_0005105 enhances the expression of inflammatory factors by binding to the miR-26a target NAMPT, thereby aggravating OA progression. Overall, the hsa_circ_0005105/miR-26a/NAMPT axis provides a novel strategy for the prevention of inflammation in OA.
ROLES OF circRNAs IN AUTOPHAGY

Autophagy represents the ability of the cells to prevent their own death and to protect cells against apoptosis.87 Autophagy is an important trigger of apoptosis and has been reported to be closely associated with the progression of OA. Protective autophagy occurs in the initial degenerative phase of OA and is reduced as cartilage gradually degrades. Activation of the PI3K/AKT/mTOR pathway, which is the fundamental intracellular signaling pathway, can inhibit autophagy.88 Therefore, autophagy-related circRNAs also are worthy of further detailed investigation.

circRNAs that promote autophagy

The expression of circ_0005567 was significantly lower in chondrocytes induced by IL-1β, and circ_0005567 overexpression suppressed the apoptosis induced by IL-1β, an effect that can be abrogated by knocking down circ_0005567.89 Gui and colleagues89 determined the relationship between circ_0005567 expression and chondrocyte autophagy, which is based on the chondroprotective role of autophagy. The results of the study showed that circ_0005567 expression upregulated autophagy-related markers, namely, LC3 and beclin-1, and the ratio of LC3-II/LC3-I. However, an inhibitor of autophagy, 3-methyladenine (3-MA), reversed the promotion of autophagy mediated by circ_0005567 overexpression. In brief, the overexpression of circ_0005567, which is a therapeutic target, attenuated IL-1β-induced chondrocyte apoptosis by restoring autophagy deficiency in OA chondrocytes. circ_0005567 can depress ATG14 expression by functioning as a miR-495 sponge. Thus, the role of circ_0005567 in the promotion of autophagy is mediated by sponging miR-495 to decrease ATG14 expression. Overall, the circ_0005567/miR-495/ATG14 axis can be a promising therapeutic target in the regulation of autophagy in OA therapy.

In addition, Huang and colleagues88 speculated that the regulatory effects of the ciRS-7/miR-7 axis on cartilage degradation and autophagy defects mediated by IL-17A was closely associated with the activation of the PI3K/AKT/mTOR pathway and demonstrated that the ciRS-7/miR-7 axis downregulates IL-17A-mediated PI3K/AKT/mTOR activation, autophagy damage, and ECM degradation.

circRNAs that inhibit autophagy

It was also reported that hsa_circ_0037658 was notably upregulated in OA.90 The correlation between hsa_circ_0037658 and autophagy in CHON-001 cells treated with IL-1β was investigated, and the results showed that knocking down hsa_circ_0037658 can notably attenuate this effect by inducing autophagy.90 A decrease in collagen II and aggregan and an increase in MMP13 induced by IL-1β were reversed by hsa_circ_0037658 shRNAs. LC3 plays regulatory roles in autophagy; the level of LC3 was considerably decreased and the apoptosis rate was obviously increased in CHON-001 cells induced by IL-1β, and both effects were reversed by hsa_circ_0037658 shRNAs. In addition, the expression of ATG5 and beclin-1 was downregulated by IL-1β, and the effect was reversed by hsa_circ_0037658 shRNAs; the expression of p62 and AIF was upregulated by IL-1β and inhibited by hsa_circ_0037658 shRNAs. Thus, knocking down hsa_circ_0037658 inhibited OA progression by inducing autophagy, and hsa_circ_0037658 may serve as a potential target for OA treatment. However, the correlation between hsa_circ_0037658 and miRNAs in OA remains unclear, and the interaction between miRNAs and autophagy-related proteins is poorly understood.

CONCLUSIONS AND PERSPECTIVES

OA is a common arthritis with multifactorial pathogenesis, and it is a serious public health issue with tremendous economic burden worldwide. Cartilage degeneration is the main pathological characteristic, and previous studies have shown that aberrant biological functions of chondrocytes, including ECM formation, apoptosis, inflammation, proliferation, and autophagy, are causally involved in OA pathogenesis. Increasing evidence, as provided in our review, has indicated that circRNAs with regulatory effects are critical for OA pathogenesis. However, it is difficult to select a therapeutic for the prioritization of various classes of non-coding RNAs (miRNAs, lncRNAs, and circRNAs) due to the uncertainty of their importance in OA development.

Studies on circRNAs in OA are currently popular, although investigations of the roles of circRNAs in chondrocytes in OA are still at a relatively early stage. Recent studies have confirmed that circRNAs participate in the pathogenesis of OA in chondrocytes, including ECM formation, apoptosis, proliferation, inflammation, and autophagy, providing novel insight into the pathological and mechanistic aspects of OA. Due to the biological characteristics of circRNAs, their roles as biomarkers in OA have been promulgated,13 such as hsa_circ_003213 in peripheral blood and hsa_circ_0104595 in synovial fluid.91 Regarding the therapeutic effects of circRNAs, our review has described the known mechanisms and signaling pathways that may be involved in OA; however, certain challenges remain to be addressed. First, the roles of only a small number of circRNAs have been studied in chondrocytes in OA; thus, additional circRNAs need to be identified and further investigated. Second, in addition to circRNAs themselves, circRNA-related pathways contain other downstream molecules that are directly or indirectly regulated by circRNAs; therefore, the studies need to determine whether circRNA-related pathways should be considered as a whole to achieve clinical therapeutic effects or whether only circRNAs should be targeted. OA is known to involve the entire joint, including subchondral bone and synovium; hence, the roles of circRNAs in osteoblasts, osteoclasts, and synoviocytes deserve additional attention, and more efforts are required to attain a comprehensive understanding of the pathogenesis of OA. Finally, the clarification of the delivery of circRNAs is essential. Previous studies have reported that circRNAs can be highly enriched in exosomes in bodily fluids.12,13 The emerging recognition that circRNAs can be transferred by exosomes suggests a new perspective on the possible transfer of circRNAs through synovial fluid by exosomes; thus, circRNAs in the synovial fluid may be used as biomarkers for the diagnosis of OA. In addition, biotherapy and gene therapy are current research trends in disease treatment, and extracellular vesicles have shown great potential as the vehicle.
to selectively and accurately deliver drugs into a specific site of tissue.\textsuperscript{52} Mesenchymal stem cell (MSC)-derived exosomes have biochemical potential for cartilage regeneration in OA therapy.\textsuperscript{93,94} Therefore, we speculate that transferring protective circRNAs into chondrocytes in OA may be one of the therapeutic mechanisms of MSC-derived exosomes (Figure 8). However, the best way to achieve exosome-specific delivery of circRNA-based therapeutics remains undefined. Moreover, in addition to the diagnostic biomarker and possible therapeutic target of circRNAs, other novel directions need to be explored as well. In summary, further studies are essential to determine whether circRNAs and related pathways can be used to develop clinical therapies.

Current strategies for OA treatment are tiered and palliative; therefore, modifying OA progression, including slowing, halting, and reversing the progression via molecular mechanisms, is essential.\textsuperscript{1} Although exploiting circRNAs for the treatment of OA is premature, circRNAs have been shown to be potential biomarkers and therapeutic targets for novel clinical strategies in OA. Considering the in-depth investigation of circRNAs and the development of biotechnology, treatments for OA may be achieved by restoring the expression of downregulated circRNAs or silencing aberrantly upregulated circRNAs. To the best of our knowledge, the role of circRNAs as miRNA sponges is among the critical functions of circRNAs, suggesting that artificial therapeutic agents mimicking the structures and functions of endogenic circRNA sponges can regulate the downstream miRNA/mRNA pathways in OA. In addition, siRNA and genome-editing tools could be used for suppressing the synthesis of circRNAs, which should be at a low expression state.\textsuperscript{91,95} Moreover, circRNAs are closely associated with gene medicine and translational medicine, both of which are undergoing an upsurge worldwide; hereafter, safer and more effective strategies based on circRNAs and related pathways will be developed.

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AUTHOR CONTRIBUTIONS
X.M. and Y.C. wrote the manuscript, Z.G. retrieved literature, and L.W. and C.X. critically revised the manuscript. All authors have read and approved the final manuscript.

DECLARATION OF INTERESTS
The authors declare no competing interests.

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