Abstract. Osteoarthritis (OA) is a common disease of the elderly, posing a major personal and socioeconomic burden. OA is characterized by painful degeneration of articular cartilage, and its prevention, diagnosis and treatment remain problematic. Circular RNAs (circRNAs) constitute a large family of non-coding RNAs that are widely distributed, stable, conserved and tissue-specific. circRNAs have been found to be closely associated with OA development and progression, and they may serve as targets for disease prevention and treatment. The aim of the present article was to review the roles of circRNAs in OA and discuss possible treatment strategies.

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1. Introduction

Osteoarthritis (OA) is an atypical degenerative disease of articular cartilage that can lead to progressive pain, joint dysfunction and general disability (1), particularly in the elderly population, and the disease incidence is increasing worldwide along with population aging. OA renders exercise difficult, diminishes the quality of life of those affected (2) and imposes a major socioeconomic burden. The pathogenesis of OA is affected by age, sex, obesity, abnormal osteoclast and chondrocyte activities, and a dysfunctional extracellular matrix (ECM) (3). However, OA prevention, diagnosis and treatment are inadequate. Treatment mainly focuses on pain relief using conventional medications (4), intra-articular steroid injections (5,6) and surgery, but treatment efficacy and patient prognosis remain unsatisfactory. Therefore, new approaches are urgently required. Circular RNAs (circRNAs) serve important roles in OA, and they may provide new research directions in terms of prevention, diagnosis and treatment. The focus of the present review was on the characteristics of circRNAs and their involvement in OA, as circRNA targeting may prove useful as a treatment approach and may also help identify new areas for research.

2. circRNA characteristics

The structure and functions of circRNAs are becoming increasingly understood. circRNAs are abundant and ubiquitous in nature, and >10,000 different circRNAs have been identified in human cells to date (4). The expression levels of some circRNAs are higher compared with those of their linear isotypes (7,8). circRNAs are very stable, with the half-lives of most exceeding 48 h (7), which is longer compared with the half-lives of mammalian mRNAs. circRNAs are covalently closed loops, lacking 5' caps and 3' tails, which makes them resistant to the shearing action of RNA exonuclease and ribonuclease R (9). Compared to linear RNAs, circRNAs are more highly conserved, more tissue-specific and more confined to particular subcellular compartments (10,11). Most exon circRNAs are found in the cytoplasm (12), whereas most intron
and intron-exon circRNAs are found in the nucleus (12-14). circRNAs may serve as therapeutic targets and they may be produced in large amounts if required.

3. circRNA functions

The old view held that the production of circRNAs was merely the result of accidental splicing and had no actual biological function. However, later studies have shown that circRNAs are not products of accidental splicing. Indeed; circRNAs have some specific formation process models, including spliceosomal mediated reverse splicing and linking; processing of exons and flanking introns; the regulatory of RNA binding proteins. circRNAs may act as microRNA (miRNA/miR) sponges (15), interact with transcription regulators and RNA-binding proteins, and they can be translated into proteins. miRNAs are non-coding RNAs ~20 nucleotides in length (16). The binding of miRNAs to the 3’-untranslated regions of mRNAs inhibits translation and, thus, gene expression (17). Certain circRNAs, such as ciRS-7/CDR1as and SRY RNA, have been shown to serve as miRNA sponges (18). The mouse brain ciRS-7/CDR1 circRNA features >70 miRNA-binding sites (19), whereas SRY RNA has 16 binding sites (20). Another miRNA sponge, circHIPK3, has 18 binding sites for miR-124, thus inhibiting the antiproliferative effect of miR-124 in malignant tumors and protecting chondrocytes against OA; in addition, circHIPK3 was shown to bind to miR-30a and miR-558 (21-23). The sponging effects of the circRNA_33186/miR-127-5p combination strongly enhance pathogenicity- circRNA_33186 directly binds and inhibits miR-127-5p, thereby increasing the expression of MPP-13 and contributing to the pathogenesis of OA (24). circRNAs also transcriptionally regulate their parent genes (24). The intron circRNA ci-ankrd52 and the exon-intron circRNAs circ-EIF3J and circ-PAIP2 interact with the RNA encoding Pol II to regulate gene expression (13,14). circRNAs interact with RNA-binding proteins (RBPs), forming RNA-protein complexes that regulate post-transcriptional RNA events (25).

The circRNA/RBP effects are very similar to those of miRNA sponges; circRNA binding to RBPs reduces RBP/RNA interactions. For example, circ-like non-coding RNAs [exon-intron circRNAs (ElciRNAs)] specifically interact with RNAs encoding antibodies targeting the U1 small ribonucleoprotein (snRNP), forming ElciRNA-U1-snRNP complexes that recruit RNA Pol II, thus promoting cis-mediated activation (enhanced transcription) of the gene encoding that enzyme (25). RBPs negatively affect RNA cyclization. For example, some adenosine deaminases acting on RNA (ADARs) are in fact RBPs featuring RNA-editing functions that disrupt RNA stem structures and, thus, restrict circRNA formation. ADAR knockdown promotes circRNA expression (26). In addition, circRNAs may be translated into proteins in a manner that differs from the translation of linear mRNAs. circRNAs lack 5’ caps; thus, translation is cap-independent, exploiting open reading frames featuring internal ribosomal entry sites (27) or 5’-untranslated regions that contain N6-methyladenosine (28).

The aforementioned findings may provide some context for circRNA research and applications in the OA context, but the roles played by circRNAs in OA require further clarification.

4. Roles of circRNAs in OA

circRNAs interact with chondrocytes (Fig. 1). Chondrocyte apoptosis (triggered through various pathways) is a crucial feature of OA (29). circRNAs have been reported to regulate chondrocyte apoptosis and proliferation. For example, circADAMTS6 overexpression was shown to inhibit human chondrocyte apoptosis, whereas miR-431-5p overexpression exerted the opposite effect. circADAMTS6 sponges miR-431-5p to create a circADAMTS6/miR-431-5p axis that regulates IL-1β-induced chondrocyte apoptosis (30). circHIPK3 is negatively correlated with miR-124. Promoting miR-124, thus suppressing SOX8 expression, OA chondrocyte apoptosis can be promoted by low-level circHIPK3 expression (31). Therefore, circHIPK3 may exert protective effects on chondrocytes in an osteoarthritic environment. circANKRD36 knockout was shown to promote IL-1β-induced apoptosis and chondrocyte inflammation (32). The zinc-finger-containing transcription factor Casz1 prevents chondrocyte apoptosis and IL-1β-mediated inflammation; the sponging interaction between circANKRD36 and miR-599 upregulated Casz1 expression, in turn preventing chondrocyte apoptosis and inflammation in OA (32). circ_0092516 regulates proliferation and apoptosis of OA chondrocytes by controlling the miR-337-3p/PTEN axis; circ_0092516 binds to miR-337-3p and, thus, modulates the effects of the miR-337-3p/PTEN axis, promoting chondrocyte proliferation, inhibiting chondrocyte apoptosis, and delaying OA progression (33).

However, circRNAs can also damage chondrocytes. For example, circ_0114876 was shown to regulate TNF receptor-associated factor 2 (TRAF2) expression in IL-1β-induced CHON-001 cells by sponging miR-671, thereby controlling the damage of chondrocytes in OA progression and the inflammatory response, and to promote chondrocyte injury by targeting the miR-671/TRAF2 axis that is activated following IL-1β-induced injury (34). Hsa_circ_0005567 can activate autophagy by regulating the miR-495/Atg14 axis, thus inhibiting IL-1β-induced chondrocyte apoptosis (35). Chondrocyte viability is closely associated with the development of OA. The findings presented above suggested that circRNA targeting may enhance chondrocyte proliferation or reduce apoptosis, thereby improving OA.

circRNAs regulate the chondrocyte ECM

circRNAs regulate metabolic homeostasis in chondrocyte ECM. OA is typically accompanied by progressive cartilage loss within the entire joint structure (36,37). The most important components of the ECM are type II collagen (which imparts tensile strength) and aggrecan (which renders cartilage compression-resistant) (3,38). Anabolism and catabolism are in dynamic equilibrium in healthy ECM (38), but not under disease conditions. Early in OA progression, chondrocytes repair damaged cartilage, during which time cartilage matrix synthesis and chondrocyte proliferation are vigorous (39). Some circRNAs promote the synthesis of cartilage matrix proteins. For example, circPDE4D serves as a sponge for miR-103a-3p; as miR-103a-3p directly targets fibroblast growth factor (FGF)18 expression, circPDE4D binding to miR-103a-3p regulates FGF18 synthesis and, thus, protects against OA by maintaining the ECM (40). circCDK14 serves...
as an miR-125a-5p sponge, downregulating Smad2 expression and inhibiting TGF-β signaling, thereby protecting the chondrocyte ECM (41).

However, certain circRNAs may promote ECM degradation. For example, circ_DHRS3 increases Gremlin 1 expression by competitively binding miR-183-5p to regulate IL-1β-regulated ECM degradation (42). It was recently demonstrated that circCSNK1G1 upregulation is also associated with ECM degradation. circCSNK1G1 and fucosyltransferase 2 (FUT2) induce ECM degradation and chondrocyte apoptosis; miR-4428 targets FUT2 mRNA to inhibit its expression, reversing the negative effects of circCSNK1G1 and FUT2 (43). CircCSNK1G1 was upregulated in OA affected cartilage, which can induce chondrocyte apoptosis and EMC degradations through sponging mir-4428 targets. miR-4428 conferred a protective effect on OA by inhibiting FUT2 expression. circTMBIM6 promotes cartilage ECM degradation induced by OA via the circTMBIM6/miR-27a/MMP13 axis (44). Thus, circRNAs either promote or inhibit OA occurrence and development; targeting of the aforementioned circRNAs may enhance ECM homeostasis, thereby alleviating OA.

circRNAs regulate ECM inflammation. As OA progresses, the levels of inflammatory mediators, including cytokines, chemokines, prostaglandins and leukotrienes, increase in affected joints and the synovial fluid (38). A number of studies have described the involvement of circRNAs in these processes. Yang et al (45) found that circRSU1 was induced by IL-1β and H2O2, and then modulated oxidative stress-induced inflammation and ECM dysfunction by regulating the MEK/Erk1/Erk2 and NF-κB signaling cascades. The circRSU1/miR-93-5p/MAP3K8 axis increased the oxidative stress involved in OA progression; thus, this axis may serve as a useful therapeutic target (45). circANKRD36 levels are decreased in OA tissues, and circANKRD36 knockout promoted apoptosis and inflammation of chondrocytes that were under IL-1β-induced stress. miR-599 directly targets Casz1 to prevent chondrocyte apoptosis and inflammation caused by IL-1β. circANKRD36 protects against OA by upregulating Casz1 expression through sponging miR-599 (32).

circRNAs are also involved in innate immunity; the circRNA profiles of M1 and M2 macrophages were found to be different (46), suggesting potential roles for circRNAs in macrophage differentiation and polarization. circRasGEF1B has been found to regulate macrophage activation. OA progression reflects activation of the innate immune response (47,48), and various cells of the innate immune system (including monocytes/macrophages and mast cells) become enriched (49). circRNAs may influence these processes, thus modulating the OA course (50); however, this remains conjectural. Inflammation triggers intermittent and progressive joint pain, and the focus of OA treatment is mainly pain relief, which is often ineffective (Table I).

5. circRNAs and OA treatment

As OA progresses, various circRNAs become up- or downregulated and they may serve as prognostic markers or therapeutic targets. The levels of hsa_circ_101178 in serum and synovial fluid were found to be significantly higher in patients with OA compared with those in control patients; the serum level was positively correlated with OA severity, so that level can be used to predict OA development (51). As explained above, targeting
Table I. Roles of circRNAs in osteoarthritis.

| Relevant context                          | circRNA         | Sponged miRNA | Function                                                                 |
|-------------------------------------------|-----------------|---------------|--------------------------------------------------------------------------|
| Associated with chondrocytes              | circADAMTS6     | miR-431-5p    | circADAMTS6/miR-431-5p axis inhibits apoptosis of human chondrocytes     |
|                                           | (upregulated)   |               |                                                                          |
|                                           | circHIPK3       | miR-124       | Protective effect on chondrocytes in OA                                  |
|                                           | (downregulate)  |               |                                                                          |
|                                           | circ_DHRS3      | miR-337-3p    | miR-337-3p/PTEN axis promotes chondrocyte proliferation                   |
|                                           | (upregulated)   |               |                                                                          |
|                                           | circ_0114876    | miR-671       | miR-671/TRAF2 axis promotes chondrocyte injury                           |
|                                           | (upregulated)   |               |                                                                          |
|                                           | circ_0005567    | miR-495       | miR-495/Atg14 axis activates autophagy and inhibits chondrocyte apoptosis|
| Metabolic homeostasis of the ECM          | circPDE4D       | miR-103a-3p   | Modulates protective role of FGF18                                        |
|                                           | (downregulated) |               |                                                                          |
|                                           | circCDK14       | miR-125a-5p   | Downregulates the expression of SMAD2 and protects the chondrocyte ECM   |
|                                           | (downregulated) |               |                                                                          |
|                                           | circ_DHRS3      | miR-183-5p    | Regulates the degradation of ECM positively regulating the expression of |
|                                           | (upregulated)   |               | gremlin 1 circDHRS3/miR-27a/MMP13 axis degrades chondrocyte ECM           |
|                                           |                 |               |                                                                          |
|                                           | circTMBIM6      | miR-27a       |                                                                          |
|                                           | (upregulated)   |               |                                                                          |
|                                           | circCSNK1G1     | miR-4428      |                                                                          |
|                                           | (upregulated)   |               |                                                                          |
| Inflammation of the ECM                  | circRSU1        | miR-93-5p     | circRSU1/miR-93-5p/MAP3K8 axis regulates oxidative stress in progressive  |
|                                           | (upregulated)   |               | OA                                                                       |
|                                           | circANKRD36     | miR-599       | circANKRD36 upregulates the expression of Cas2 against miR-599           |
|                                           | (upregulated)   |               |                                                                          |
|                                           | circRasGEF1B    | miR-21-3p     | circRasGEF1B can counteract the effect of miR-21-3p, enhancing the innate |
|                                           | (upregulated)   |               | antiviral response                                                        |
| Associated with treatment                 | circ_0083429    | miR-346       | miR-346/Smad3 axis alleviates OA                                          |
|                                           | (upregulated)   |               |                                                                          |
|                                           | circCDH13       | miR-296-3p    | circCDH13/miR-296-3p/PTEN axis promotes OA                                |
|                                           | (upregulated)   |               |                                                                          |

circRNA, circular RNA; ECM, extracellular matrix; FGF, fibroblast growth factor; FUT2, fucosyltransferase 2; miR, microRNA; OA, osteoarthritis; TRAF2, TNF receptor-associated factor 2.

of circ_DHRS3 and circPDE4D may alleviate OA. circ_0083429 regulates Smad3 by sponging miRNA-346, thereby alleviating OA through the miR-346-Smad3 axis (52). circCDH13 promotes OA by sponging miR-296-3p, contributing to OA pathogenesis via the circDH13/miR-296-3p/PTEN axis (53). circRNAs may thus induce the differentiation of cells that target OA. Stem cells (SCs) from the bone marrow or adipose or other potential tissues, such as the umbilical cord, can differentiate into chondrocytes that repair tissue damage (54-56). During such differentiation, the expression levels of several circRNAs are altered. For example, circRNA-CDR1as can maintain human umbilical cord SC (husMSCs) differentiation and proliferation capacities. The knockdown of CDR1as resulted in the down-regulation of the expression of dry transcription factors (STFs), which impaired the osteogenic potential of husMSCs. In addition, circRNA may maintain SC chondrogenic differentiation, thus promoting differentiation that aids bone and joint function (57).

circRNAs can also be loaded into vesicles that are then transported to specific bodily sites (58). Extracellular vesicles are important regulators of cartilage homeostasis and OA; circRNAs within such vesicles may thus exert useful effects. Exosomes are lipid membrane-type extracellular vesicles formed through endocytosis, integration and efflux, and they are found in numerous biological fluids, such as blood, urine, saliva and cerebrospinal fluid (59-61). Recently, exosomes have become favored drug carriers owing to their nanoscale dimensions, low immunogenicity, ability to penetrate biofilms and convenient storage (62). circRNAs can be loaded into exosomes (63), but few relevant studies have been published to date. Yang et al (64) reported that injecting engineered rabies virus glycoprotein-circSCMH1-extracellular vesicles rabies virus glycoprotein-circSCMH1-extracellular vesicles into the brain improved stroke outcomes in mice and monkeys. However, OA data are lacking, as access to OA
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circRNAs in OA focus on metabolic homeostasis, cell apoptosis and inflammation, whereas the effects of circRNAs on chondrocytes and stromal cells, the immune microenvironment and gene regulation require further study. Therefore, circRNAs may serve as OA biomarkers and therapeutic targets, but additional investigation is warranted. OA is a complex disease, and a single anti-circRNA treatment may not be efficacious. Targeting of several circRNAs may be essential when seeking to prevent disease development, arrest progression and improve treatment.

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GC contributed to the investigation and wrote the relevant draft of the manuscript. YP and PLi performed the relevant literature research and revised the manuscript. PLiu, YD, YG and JL contributed to literature searching and processing. XL contributed to the conceptualization of the review. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Not applicable.

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Not applicable.

Competing interests
The authors declare that they have no competing interests.

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