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Review Article

Circular RNA in osteoarthritis: an updated insight into the pathophysiology and therapeutics

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Abstract: Osteoarthritis (OA) is a common joint disease that mainly results in chronic pain, stiffness and dysfunction in elderly individuals. The molecular mechanisms in the pathogenesis of OA are still unclear, and available treatments are unable to slowdown the development of OA or reverse the tissue damage. Circular RNAs (circRNAs), a novel type of non-coding RNA, are ubiquitous, stable, evolutionally conserved, tissue-specific and functional. An increasing number of studies have revealed that many circRNAs are differentially expressed in OA-affected joint tissues and engage in the pathogenesis of OA by functioning as miRNA sponges. In this review, we briefly introduce the biogenesis, characteristics and functions of circRNAs, and shed light on the important role of circRNAs in the occurrence and progression of OA and their potential diagnostic and therapeutic value in this disease based on the research over the last five years.

Keywords: Circular RNA, osteoarthritis, miRNA sponge, clinical value

Introduction

Osteoarthritis (OA) is one of the most common type of joint diseases and a leading cause of chronic pain and movement limitations in elderly people [1]. OA is primarily characterized by articular cartilage degradation, subchondral bone sclerosis, osteophyte formation and chronic synovitis [2, 3]. Currently, it is universally acknowledged that this disease is multifactorial [4] and involves multiple clinical phenotypes [5] instead of a prototypical degenerative disease. Clinical manifestations of OA include slowly progressive pain, stiffness and joint dysfunction [6], which severely impair the OA patients' quality of life. The main risk factors for OA include age, gender, body-mass index, trauma, and intense sport activities [5, 7, 8]. Cartilage is avascular, and chondrocytes are the single cellular component in cartilage [5, 6] responsible for maintaining the metabolic balance of extracellular matrix (ECM) components [9]. Currently, methods for early diagnosis of OA and etiological therapies are lacking. Paracetamol and non-steroidal anti-inflammatory drugs are crucial for symptom control [10], and arthroplasty surgery is of clinical interest for patients with advanced OA [5]. In addition, the definite molecular mechanisms of OA are still elusive. Thus, the potent pathogenesis and regulatory mechanisms of OA need to be further investigated.

Circular RNAs (CircRNAs) are a large class of non-coding RNAs (ncRNAs) [11] and circularize as a covalently closed loop structure without a 5'-cap structure and 3'-poly (A) tail [11, 12]. In the 1990s, endogenous circRNAs were first discovered and regarded as transcripts with scrambled exons [13]. CircRNAs are usually thought to be byproducts of aberrant splicing or pre-mRNA splicing processes [14, 15]. The advent of high-throughput deep RNA sequencing (RNA-Seq) technology, however, has confirmed that circRNAs exist ubiquitously in eukaryotic cells and tissues [12, 16, 17] with evolutionarily conserved, stable and tissue-specific characteristics [11, 17-19]. Circular

RNAs have numerous functions, such as acting as miRNA sponges [20, 21], regulating transcription [17, 22], interacting with RNA binding proteins (RBPs) [11, 23] and translating into proteins [24, 25]. In recent years, an increasing number of studies have indicated that circRNAs may be involved in the initiation and progression of various diseases, including diabetes [26, 27], cardiovascular diseases [28, 29], malignancies [30, 31], and OA [32-34]. Therefore, illustrating the underlying mechanism of circRNAs in OA may provide new perspectives for us to develop novel biomarkers and therapeutic targets for OA.

In this review, we summarize the biogenesis, characteristics and functions of circRNAs, provide novel insights into the potential role of circRNAs in the occurrence and development of OA based on present research, and illustrate the diagnostic and therapeutic value of circRNAs in OA.

Circular RNAs

Biogenesis of CircRNAs

RNA circles have various forms, but not all RNA circles are the circular RNAs that we discussed here. CircRNAs can be classified into three basic categories: exonic circRNAs, exon-intron circRNAs (EIciRNAs), and intronic circRNAs [35]. Most of circular RNAs consist of a single or multiple exons and are characterized as single-strand non-colinear molecules [17]. Under normal conditions, linear mRNAs are products generated by pre-mRNA splicing through the canonical splicing. However, genome-wide RNA-sequencing analysis indicates that the bulk of circRNAs are produced by a backsplicing mechanism, which completely reverses the order of canonical splicing [11, 16-18, 36-38]. In brief, canonical splicing of pre-mRNA in eukaryotic cells is catalyzed by the spliceosomal machinery to remove introns and connect exons together, finally generating linear RNA transcripts [39] and lariat RNAs (byproducts of normal RNA splicing) [12]. Unlike canonical splicing, back-splicing can be summarized as splicing a downstream splice donor site with an upstream splice acceptor site, thereby generating an exonic circRNA and a colinear RNA product [39]. At present, three recognized models of exonic circRNA formation have been elucidated: lariat-driven circularization (exon-skipping), intron-pairing-driven circularization (direct back-splicing) and RNA-binding protein (RBP)-driven circularization [40-42]. Intronic circRNAs, they are derived from intron lariats without 3'-tails and contain a distinctive 2',5'-phosphodiester linkage [42, 43]. Their formation depends on GU-rich sequences near the 5'-splice site and C-rich sequences close to the branchpoint site of the intron [44]. Exon-intron circRNAs are formed during the formation of exonic circRNAs, but occasionally, the introns between the exons are retained, thus leading to the appearance of EIciRNAs [23].

Properties of circRNAs

Due to the development of RNA detection methods, numerous properties of circRNAs have been explicitly identified. First, circRNAs are abundant and prevalent in nature. It is estimated that more than 10,000 circRNAs have been uncovered in human cells [17, 40], and the relative percentage of circRNAs, except for rRNAs, accounting for all transcripts approximately varies from approximately 0.1% to 10% of all detectable RNA transcripts [11, 16, 17, 38, 44]. These facts verify that the appearance of circRNAs is not an occasional event and that circRNAs are probably functional. Second, circRNAs are highly stable. Compared with the average 10-hour half-lives of mRNAs in mammalian cells [45], the half-lives of the majority of circRNAs exceed 48 hours [17]. In eukaryotic cells, circRNAs are more stable than corresponding linear RNAs due to their unique structure without 5' and 3' ends; therefore, circRNAs are resistant to RNase R [46]. In addition, some circRNAs are expressed at a relatively higher level than their corresponding linear isoforms, which may also be attributed to their stability [17, 18]. Third, circRNAs are evolutionarily conserved. Several studies have shown that circRNAs detected in humans have orthologous counterparts in mice [11, 16, 47]. In a study, researchers found that 20% of the annotated 635 mouse circRNAs are orthologous to human circRNAs [44], indicating that circular RNAs probably play a functional role in various aspects rather than being byproducts of error splicing or accidental outcomes of mis-splicing [40]. Forth, circRNAs are tissue-specific. Several studies have established that circRNAs

are expressed in specific cell types or tissues [17, 38]. CircRNAs are highly expressed and enriched in the brain and neural tissues of mice, flies and human, especially during the development and aging [48-50]. Fifth, subcellular localization of circRNAs. Exonic circRNAs tend to be enriched in the cytoplasm [16, 17], while intronic and exon-intron circRNAs are abundantly located in the nucleus [23, 44]. These observations suggest that different types of circRNAs may undertake different functions. According to these characteristics, it is reasonable to speculate that circRNAs could function as ideal biomarkers for some diseases (e.g., multifarious cancers [51, 52]) and may serve as novel therapeutic targets.

Functions of circRNAs

The circRNAs' unexpected abundance and the evolutionary conservation imply that these exonic circular isoforms may play a functional role in normal cellular activities, such as functioning as miRNA sponges, regulating gene transcription, interacting with RNA-binding proteins and being translated into proteins.

CircRNAs function as miRNA sponges

MicroRNAs (miRNAs), a typical class of generally existing ncRNAs, post-transcriptionally regulate gene expression by directly binding to the target messenger RNAs (mRNAs), and then affecting parental gene expression [53]. Currently, two well-known circRNAs, ciRS-7/CDR1as [20, 50] and Sry RNA [20], have been definitely validated to function as miRNA sponges. Antisense cerebellar degeneration-related protein-1 (CDR1as) was the first to prove that circular transcripts can provide target binding sites for specific miRNAs, and reveal a brand-new regulatory mechanism resulting in a positive correlation between circRNAs and their relevant mRNAs [50]. CDR1as harbors over 70 conserved miRNA binding sites for miR-7. CDR1as and miR-7 are co-expressed in the mouse brain and co-localized in various cellular bodies. Overexpression of CDR1as provides more miR-7 binding sites, and then, the number of free miR-7 molecules is decreased. Thus, miR-7 activity is strongly restrained, resulting in the upregulation of miR-7 target genes. In contrast, knockdown of CDR1as or miR-671 overexpression downregulated the expression of miR-7 target genes. These results showed that CDR1as can serve as a miR-7 sponge and that there is a positive correlation between CDR1as and target neural gene expression. Similarly, the circular transcripts derived from the sex-determining region Y (Sry), a testis-specific gene in mouse, contain 16 miRNA binding sites and function as a miR-138 sponge [20]. CircSry overexpression attenuated the miR-138-mediated effects on relevant mRNAs, indirectly regulating the expression of target genes [20]. In summary, these findings indicate that circRNA serving as miRNA sponges is a general phenomenon, and this mechanism might help us to further elucidate the pathogenesis of certain diseases and develop new methods for diagnosis and treatments.

CircRNAs act as transcriptional regulators

CircRNAs also play a regulatory role in the expression of parental genes. For example, ci-ankrd52 is an abundant intronic circRNA in the nucleus. Ci-ankrd52 was shown to plays a regulatory role in the expression level of its parental gene by modulating the transcriptional activity of RNA pol II [44]. Additionally, exon-intron circRNAs, such as circ-EIF3J and circ-PAIP2, can also regulate gene expression [23]. The introns retained between exons can promote the formation of exon-intron circRNA-U1 RNP complexes, which can further interact with RNA polymerase II (Poll II), and thus increase the expression level of the parental gene [23]. The abovementioned experimental results demonstrated that circRNAs enriched in the nucleus, such as intronic circRNAs and EIciRNAs, can function as transcriptional regulators.

CircRNAs interact with RNA-binding proteins

RNA-binding proteins (RBPs) are a large class of regulatory proteins that can specifically bind and interact with RNAs, including circRNAs [54]. RBPs regulate the post-transcriptional activities of various RNAs. It has been reported that circRNAs can stably associate with MBL [36], QKI [55], Argonaute (Ago) proteins [20, 50], RNA Pol II [44] and adenosine deaminases acting on RNA 1 (ADAR1) [47]. RBPs could participate in the biogenesis of circRNAs [55], circRNA-mediated gene transcriptional regulation [56, 57], and translation of circRNAs [58]. However, circRNAs can also be involved in some RBP-related activities; for example, cir-

cRNAs can serve as RBP super sponges [59], and influence the formation of RBPs and the expression of their parental genes [36]. In aggregate, revealing the intricate relationship between various circRNAs and RBPs may help us better comprehend the pathogenesis of diseases and develop new therapeutic methods.

CircRNAs can be translated

CircRNAs were formerly considered byproducts of splicing errors and thought to be nonfunctional and untranslatable. However, an increasing number of studies have found that circRNAs can be translated [24, 60, 61]. Owing to the absence of a 5'-cap structure, the translation of circRNAs depends on the cap-independent mechanism, which is distinct from conventional translation of linear mRNAs [62]. In recent years, several studies have demonstrated that circRNAs containing an open reading frame (ORF) initiated by the internal ribosome entry site (IRES) can be translated into proteins [58, 63]. IRES is a nucleic acid sequence that enables the translational initiation of proteins to be independent of the 5'-cap structure and thus makes it possible to directly initiate translation from the middle part of mRNAs. In addition, many of circRNAs containing N^6-methyladenosine (m^6A) in their 5'UTR can be translated into proteins in a cap-independent fashion [64]. Many studies have shown that circRNAs are translatable, and these discoveries also expand our comprehension of the functions of circRNAs.

CircRNAs in OA

CircRNAs modulate metabolic homeostasis in cartilage matrix

The canonical feature of OA is progressive cartilage loss during disease development, although it is now widely accepted that the pathological changes in OA affect the whole joint structures [2, 65]. The predominant structural proteins of cartilage extracellular matrix (ECM) are type II collagen (COL2) and aggrecan, which provide tensile strength and compressive stiffness, respectively [4, 9]. There is a dynamic metabolic equilibrium between anabolism and catabolism in the ECM [9]. In the early stage of OA, the chondrocytes are activated and responsible for repair, such as promoting the synthesis of cartilage matrix and chondrocyte proliferation. However, they also produce and release proinflammatory cytokines, including interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), and matrix catabolic enzymes, such as matrix metalloproteinases (MMPs), a disintegrin and metalloproteinase with thrombospondin-like motifs (ADAMTS) [4, 9]. Aggrecanases (e.g., MMP-3, ADAMTS-5) and collagenases (e.g., MMP-13) can degrade aggrecan and COL2, respectively [2], and cartilage damage cannot be restored if COL2 is lost [66]. Once the lesions occur, the balance between cartilage matrix synthesis and cartilage degradation will be disrupted, and ultimately, the progression of OA will become irreversible.

Cartilage loss is a vital part of the onset and development of OA. An increasing number of studies have found that circRNAs play a regulatory role in the homeostasis of ECM metabolism, and the role of acting as miRNA sponges is regarded as the most common mechanism of circRNA function in OA. The majority of circRNAs promote the expression of MMP-3, MMP-13 and ADAMTS-4 while suppressing the synthesis of COL2 and aggrecan, thus leading to cartilage damage during the progression of OA (**Table 1**). Chondrocyte extracellular matrix (ECM) related circRNA (circRNA-CER) was demonstrated to facilitate the extracellular matrix degradation. In chondrocytes stimulated with IL-1 and TNF-α, circRNA-CER was upregulated, markedly promoting MMP-13 expression and suppressing the expression levels of COL2 and aggrecan by sponging miR-136 [33]. In the following year, the same group of researchers demonstrated that mechanical stress-related circRNA (circRNA-MSR) was also significantly overexpressed in damaged cartilage samples compared with normal samples [67]. CircRNA-MSR can function as a miR-875 sponge to promote TNF-α expression and restrain ECM synthesis, indicating that circRNA-MSR negatively regulates the metabolism in chondrocytes [67]. In another study, it was revealed that in IL-1β-treated chondrocytes, hsa_circ_0005105 could enhance extracellular matrix catabolism by indirectly upregulating the NAMPT expression [68]. Upregulation of hsa_circ_0005105 increased the expression level of nicotinamide phosphoribosyltransferase (NAMPT) by restraining the transcriptional activity of miR-26a.

Table 1. Known circRNAs in the pathogenesis of OA

CircRNA (Circbase ID)	Expression	Sponge miRNA	Target gene	Function	Reference
CircRNA-CER (hsa_circ_0023404)	Upregulated	miR-136	MMP-13	Increase expression of MMP-13 Decrease expression of COL2, aggrecan	[33]
Hsa_circ_0045714	Downregulated	miR-139b	IGF1R	Increase expression of COL2, aggrecan Promote chondrocyte proliferation Suppress chondrocyte apoptosis	[73]
CircRNA-MSR (hsa_circ_0005567)	Upregulated	miR-875	TNF-α	Increase expression of TNF-α Suppress ECM formation	[67]
Hsa_circ_0005105	Upregulated	miR-26a	NAMPT	Decrease expression of COL2, aggrecan Increase expression of MMP-13, ADAMTS-4 Increase expression of PGE2, IL-6, IL-8	[68]
CircRNA_Atp9b (hsa_circ_0002485)	Upregulated	miR-138-5p	/	Increase expression of MMP-13 Increase expression of IL-6, COX-2 Suppress synthesis of COL2	[34]
CircSERPINE2 (hsa_circ_0008365)	Downregulated	miR-1271	ETS-related gene (ERG)	Suppress chondrocyte apoptosis Decrease expression of MMP-3, MMP-13, ADAMTS-4 Increase expression of SOX-9, COL2A1, aggrecan	[74]
Hsa_circ_0032131	Upregulated	miR-16-5p	PRKCH	Overexpression in peripheral blood of OA patients	[90]
CircRNA.33186	Upregulated	miR-127-5p	MMP-13	Increase expression of MMP-13 Decrease expression of COL2A1 Suppress chondrocyte proliferation Promote chondrocyte apoptosis	[70]
CircRNA-9119	Downregulated	miR-26a	PTEN	Promote chondrocyte proliferation Suppress chondrocyte apoptosis	[87]
CircRNA-UBE2G1 (hsa_circ_0008956)	Upregulated	miR-373	HIF-1α	Increase expression of IL-1β, IL-6 TNF-α Promote chondrocyte apoptosis	[81]
CircRNA-CDR1as	Upregulated	miR-641	FGF-2	Increase expression of MMP-13 Increase expression of IL-6 Decrease expression of COL2	[32]
CircGCN1L1 (hsa_circ_0000448)	Upregulated	miR-330-3p	TNF	Promote synoviocyte proliferation Increase expression of TNF-α, p65 Bcl-2, Bax, activated caspase-3 Promote chondrocyte apoptosis Increase expression of MMP-3 MMP-13, ADAMTS-4 Decrease expression of COL2A1	[71, 80]

NAMPT is a catabolic factor in articular chondrocytes that can cause excessive secretion of PGE2, overexpression of ADAMTS-4 and ADAMTS-5, and aberrant formation of MMP-3 and MMP-13 [69]. Recently, Zhang and colleagues established that circRNA-CDR1as can serve as a miR-641 sponge to promote ECM degradation through the FGF-2-mediated MEK/ERK signaling pathway [32]. Furthermore, circRNA-CDR1as expression was elevated in chondrocytes of OA patients, and this increase significantly increased the MMP-13 level while decreasing the COL2 expression, resulting in the disturbance of ECM metabolism and progression of OA [32]. In addition, several other studies also verified that circRNAs participate in the occurrence and development of OA by promoting cartilage matrix degradation. For example, upregulation of circRNA_Atp9b saliently increased MMP-13 expression by sponging miR-138-5p [34]. CircRNA.33186 also elevated the MMP-13 expression by functioning as a sponge of miR-127-5p in IL-1β-treated chondrocytes and destabilized medial meniscus (DMM)-induced OA models [70]. In temporomandibular joint osteoarthritis (TMJOA) synovial tissues and cells, circGCN1L1 can act as a miR-330-3p sponge to enhance the production of matrix-degrading enzymes (MMP-3, MMP-13, ADAMTS-4) while suppressing the synthesis of COL2 by indirectly targeting the TNF-α gene [71]. However, a few circRNAs can promote the synthesis of cartilage matrix proteins. Hsa_circ_0045714 was downregulated in OA patients versus healthy controls, but hsa_circ_0045714 overexpression indirectly increased insulin-like growth factor 1 receptor (IGF1R) gene expression by sponging miR-193b. IGF-1 is known as an important anabolic factor that participates in the proliferation, development and differentiation of chondrocytes and promotes the synthesis of cartilage matrix proteins, including type II collagen and aggrecan [9, 72]. Therefore, hsa_circ_0045714 can enhance cartilage matrix anabolism and have a protective effect on joint tissues [73]. Similarly, circSERPINE2 can promote the synthesis of ECM proteins [74]. CircSERPINE2 was downregulated in OA samples, and circSERPINE2 overexpression increased the levels of COL2, SOX-9 and aggrecan while inhibiting the expression of MMP-3, MMP-13 and ADAMTS-4 by endogenously competing with miR-1271-5p and its target E26 transformation-specific (ETS)-related gene (ERG). The ERG expression level is associated with the expression of catabolic factors and anabolic factors in the articular cartilage of OA patients [75, 76]. Thus, circSERPINE2 expression has a protective effect on OA cartilage by promoting ECM anabolism [74].

In addition to canonical catabolic factors, inflammatory cytokines, such as IL-1, TNF, and IL-17, can indirectly cause ECM degradation by promoting the synthesis and release of various matrix-degrading enzymes, repressing chondrocyte proliferation and accelerating chondrocyte apoptosis [77]. Conversely, products of cell death can also evoke the inflammatory response in OA [78]. Therefore, there is a complicated meshwork among matrix degradation, low-grade inflammation and the viability of chondrocytes. Almost all known circRNAs participate in the initiation and progression of OA in many ways rather than through one specific mechanism. Therefore, circRNAs may become novel targets for treating OA.

CircRNAs participate in inflammation in OA

OA was historically regarded as a 'wear and tear' disease or a noninflammatory arthritis, because it lacks of neutrophil infiltration in the synovium and systemic manifestations. However, it is now universally acknowledged that OA is a low-grade inflammatory disease affecting whole articular tissues [79]. Various inflammatory mediators can be found in impaired articular tissues and synovial fluid, such as cytokines (TNF-α, IL-1β, IL-6), chemokines, adipokines, prostaglandins and leukotrienes [9, 78]. Aberrant synthesis and release of pro-inflammatory factors can lead to severe extracellular matrix degradation and cartilage impairments through increased synthesis of matrix catabolic enzymes, suppression of chondrocyte proliferation and differentiation, and induction of chondrocyte apoptosis along with promotion of local inflammation in joints, finally resulting in a vicious cycle between tissue injuries and proinflammatory effects [9, 77, 78]. Thus, inflammation plays a pivotal role in the pathogenesis of OA.

Several circRNAs have been shown to be involved in the inflammatory response of OA, and most of them are related to prototypical inflammatory factors in OA, including IL-1β,

TNF-α, IL-6 and IL-8 (**Table 1**). For instance, hsa_circ_0000448 (circGCN1L1) was proven to promote TNF-α expression in TMJOA synovial tissues [71, 80]. According to the results of a series of assays and bioinformatics analyses, hsa_circ_0000448 was upregulated in TMJOA and can probably bind to miR-330-3p, indirectly facilitating the synthesis and secretion of TNF-α [71, 80]. CircRNA-MSR was also shown to regulate local inflammation of joint tissues by acting as a miR-875 sponge to promote TNF-α expression [67]. In a study, Wu et al. [68] demonstrated that hsa_circ_0005105 can elevate the expression levels of PGE2, IL-6 and IL-8 by functioning as a miR-26a sponge and thus upregulate NAMPT expression. Additionally, circRNA-Atp9b was shown to increase the expression of IL-6 and COX-2 by endogenously competing with miR-138-5p [34], and circRNA-CDR1as facilitated IL-6 expression through the miR-641/FGF-2 pathway [32]. Recently, circRNA-UBE2G1 was demonstrated to enhance the inflammatory response in LPS-induced chondrocytes [81]. In OA tissues, circRNA-UBE2G1 was upregulated and enhanced the production of IL-1β, IL-6 and TNF-α through the miR-373/HIF-α pathway [81].

Inflammation has been shown to be associated with joint pain in OA [82, 83]. Moreover, intermittent and progressive pain is one of the main symptoms of OA, which severely affects patients' quality of life. Hence, pain relief is an important therapeutic goal for OA. At present, symptom-modifying drugs, including NSAIDs, paracetamol and corticosteroids, are universally used in the clinic to alleviate OA-related pain [78], although their role in treating OA-related pain is controversial [84]. CircRNAs may become a new therapeutic target for OA, but this strategy is probably a comprehensive process rather than a simple one-to-one targeted method because the results of previous studies indicated that targeting a single proinflammatory factor will not achieve a satisfactory outcome for OA patients [84, 85].

CircRNAs regulate chondrocyte apoptosis

Apoptosis is a programmed process of cell death. Apoptosis can be initiated by not only psychological but also pathological stimuli, and by specific morphological changes [86]. Dysregulation of apoptosis is involved in the occurrence and development of various diseases, including OA.

In addition to regulating extracellular matrix metabolism and inflammation in OA, circRNAs also modulate the proliferation and apoptosis of chondrocytes (**Table 1**). CircSERPINE2 overexpression reduced the apoptotic rate of chondrocytes in human chondrocytes and animal models of OA [81], while circRNA-UBE2G1 promoted chondrocyte apoptosis via the miR-373/HIF-α axis [81]. CircRNA.33186 was shown to inhibit the chondrocyte proliferation and enhance chondrocyte apoptosis by endogenously competing with miR-127-5p [70]. In addition, Chen et al. [87] revealed that circRNA-9119 has protective effects on chondrocytes. CircRNA-9119 upregulation can suppress chondrocyte apoptosis and enhance chondrocyte growth via the miR-26a/PTEN pathway. Recently, it was revealed that circGCN1L1 promoted synoviocyte proliferation and saliently elevated the expression level of NF-κB-related apoptotic factors, including TNF-α, p65, Bcl-2, Bax and caspase-3, leading to chondrocyte apoptosis [71].

In the same way, apoptosis or cell death is the result of cartilage injury, while products of chondrocyte breakdown in OA can also activate inflammation in turn, causing cartilage matrix degradation and joint tissue damage. Hence, chondrocyte apoptosis is positively correlated with matrix catabolism and local inflammation, collectively influencing the pathogenetic process of OA. Targeting circRNAs to control chondrocyte proliferation and apoptosis may be a promising strategy for OA treatment.

In the light of the available studies, many circRNAs contribute to the pathogenesis of OA. Most of them promote the progression of OA, while a few circRNAs have protective effects on chondrocytes. Unfortunately, none of them has been applied in the clinic. However, it is foreseeable that circRNAs will have broad prospects for diagnosing OA in an early stage and providing an alternative treatment modality for OA patients.

CircRNAs in clinical practice

Although many circRNAs have been found to participate in the occurrence and progression of OA, now none of these studies clearly dem-

onstrated that circRNAs can be applied in clinical diagnosis or treatment and obtained the expected results. Multiple studies have reported that circRNAs have a latent capacity in clinical practice. On the one hand, circRNAs can probably function as prospective biomarkers for OA. In a previous study, Yu et al. [88] found that some circRNAs may become novel biomarkers for OA. In the synovial fluid of OA patients, hsa_circ_0104873, hsa_circ_0104595 and hsa_circ_0101251 were significantly elevated. According to ROC and AUC analyses, they have diagnostic value for OA. Furthermore, the levels of hsa_circ_0104873, hsa_circ_0104595 and hsa_circ_0101251 in synovial fluid had a positive correlation with radiographic severity and WOMAC scores, indicating that these circRNAs can serve as latent biomarkers for severity of OA. In addition, Wang et al. [89] identified that hsa_circ_0032131 could potentially be used as a diagnostic biomarker for OA in peripheral blood. It was discovered that 1380 circRNAs were differentially expressed in OA chondrocytes compared with the controls, and among them, 215 circRNAs were upregulated and 1165 circRNAs were downregulated. Based on the results of qRT-PCR verification and microarray analysis, hsa_circ_0032131 was screened out. Further bioinformatics analysis demonstrated that the parental genes of these differentially expressed circRNAs were functionally related to chondrocyte development, extracellular matrix components, collagen fibrils and skeletal disease. The researchers also identified 10 potential target miRNAs of hsa_circ_0032131, and speculated that PRKCH is the final target gene of hsa_circ_0032131. Following that, they established that in the peripheral blood of OA patients, the hsa_circ_0032131 levels were significantly increased compared with that in healthy controls, and hsa_circ_0032131 can probably act as a relatively convenient and safe diagnostic biomarker for OA [90]. In another study, Wang et al. [91] found that hsa_circ_0020014 in peripheral blood potentially functioned as a biomarker for differential diagnosis of Kashin-Beck disease (KBD) and OA. On the other hand, circRNAs may function as an available treatment option for OA in the future. Currently, a few animal experiments have demonstrated that circRNAs can be used to treat OA in vivo. For instance, circSERPINE2 overexpression was shown to promote ECM anabolism and alleviate OA in rabbit models [74]. In this study, WT adeno-associated virus (AAV) circSERPINE2 was intra-articularly injected into the anterior cruciate ligament transection (ACLT)-induced rabbits models of OA. Consequently, intra-articular injection of adeno-associated virus-circSERPINE2-WT partially restored the cartilage surface in ACLT-induced OA rabbits, lowered the OARSI scores, reduced osteophyte formation on CT images and suppressed cartilage matrix degradation while promoting ECM anabolism. Additionally, Zhou et al. [70] observed that inhibition of circRNA.33186 in vivo markedly mitigated cartilage damage and the imbalance between anabolic and catabolic factors in the DMM-induced mouse models of OA. Similarly, downregulation of circGCN1L1 has also been shown to attenuate cartilage matrix degradation in TMJOA rat models [71]. In occlusal-induced TMJOA, shcircGCN1L1 injection suppressed the expression of MMP-3 and MMP-13 and proteoglycan loss, elevated the COL2A1 level, and lowered OARSI scores, indicating that knockdown of circGCN1L1 can reduce cartilage loss and attenuate TMJOA in vivo.

In addition to the theoretical clinical value for OA, most of circRNAs have been predicted as promising biomarkers or therapeutic targets, such as circ-CER [33], circ-MSR [67], and hsa_circ_0005105, have been predicted as promising biomarkers or therapeutic targets [68]. These studies have provided us with a new insight into the diagnosis and management for OA.

However, there are still some limitations in clinical application of circRNA. First, obtaining circRNAs from impaired joint tissues is more complicated than traditional methods, and the operation may cause trauma to patients. Second, detecting circRNA in OA tissues is more expensive compared to current examinations before it can be widely used. Third, the reliability and accuracy of circRNAs in diagnosing and treating OA need further authentication. Fourth, it is unknown whether other irrelevant genes are affected or not when circRNAs serve as miRNA sponges or therapeutic targets. Currently, owing to a dearth of practical application of circRNAs in OA patients, the diagnostic and therapeutic value of

OA-specific circRNAs is still elusive and needs to be further studied and discussed.

Conclusions

OA is a widespread joint disease that severely affects the quality of life of patients. However, there is no effective drug or therapeutic method to treat OA. Current studies have established that circRNAs abundantly exist in eukaryotic cells and have various functions; thus, circRNA has become a novel frontier in the pathogenetic and clinical research fields of various diseases, including OA. In this review, we briefly summarized the biogenesis, general characteristics and functions of circRNAs with emphasis on their role in the pathophysiologic processes and the clinical application of OA. CircRNAs act as miRNA sponges to participate in the multifaceted pathogenesis of OA, including metabolic imbalance in cartilage matrix, local inflammation in joint tissues, and the viability and apoptosis of chondrocytes. Among them, most circRNAs promote the occurrence and progression of OA. Moreover, a few circRNAs were found to function as biomarkers for the diagnosis of OA in synovial fluid and peripheral blood. In addition, some animal experiments have demonstrated the therapeutic value of circRNAs. Although OA-related circRNAs are known the mere visible parts of an iceberg, the discovery of more circRNAs and verification of their latent roles in OA will probably facilitate the early-term diagnosis and etiological treatment for OA in the future.

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Disclosure of conflict of interest

None.

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