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Review

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Circular RNAs: typical biomarkers for bone-related diseases

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Abstract: Bone is a connective tissue that has important functions in the human body. Cells and the extracellular matrix (ECM) are key components of bone and are closely related to bone-related diseases. However, the outcomes of conventional treatments for bone-related diseases are not promising, and hence it is necessary to elucidate the exact regulatory mechanisms of bone-related diseases and identify novel biomarkers for diagnosis and therapy. Circular RNAs (circRNAs) are single-stranded RNAs that form closed circular structures without a 5' cap or 3' tail and polycyclic adenylate tails. Due to their high stability, circRNAs have the potential to be typical biomarkers. Accumulating evidence suggests that circRNAs are involved in bone-related diseases, including osteoarthritis, osteoporosis, osteosarcoma, multiple myeloma, intervertebral disc degeneration, and rheumatoid arthritis. Herein, we summarize the recent research progress on the characteristics and functions of circRNAs, and highlight the regulatory mechanism of circRNAs in bone-related diseases.

Key words: Circular RNA; Bone-related disease; Competing endogenous RNA (ceRNA); MicroRNA

1 Introduction

Bone as a connective tissue is a metabolic entity that performs its function by storing calcium and phosphate, regulating the acid-base balance and supporting hematopoiesis, thereby maintaining movement, support, and protection (Buck and Dumanian, 2012; Florencio-Silva et al., 2015). It mainly consists of cells and extracellular matrix (ECM). Osteoblasts, osteoclasts, osteocytes, and chondrocytes are the four major cell types that play significant roles in regulating bone homeostasis (del Fattore et al., 2012; Florencio-Silva et al., 2015). Under the guidance of genetic and molecular factors and the local microenvironment, bone marrow mesenchymal stem cells (BMSCs) can differentiate into various mature cell types, including osteocytes, osteoblasts, and adipocytes (Discher et al., 2009; Lopes et al., 2020). The skeletal system is in a stable dynamic equilibrium, and its steady state relies on osteoblasts and osteoclasts that are responsible for bone formation and resorption. Osteocytes respond primarily to mechanical stimuli by transmitting signals to cells on the bone surface and adjusting the internal environment, while chondrocytes are mainly found on the surface of joints and play a role in cushioning and protection (Blank and Sims, 2019; Ansari and Sims, 2020) (Fig. 1). The imbalance of cells and ECM regulation leads to bone-related diseases that are difficult to cure completely, and impose a huge socioeconomic and medical burden. Therefore, there is an urgent need to elucidate the molecular regulatory mechanisms and search for new therapeutic targets for bone-related diseases.

Circular RNAs (circRNAs) are a novel type of non-coding RNAs, which were originally thought to be viroids in plants (Sanger et al., 1976). However, with the development of high-throughput RNA sequencing and bioinformatics, circRNAs have been found to be widely distributed in many metazoans (Salzman et al., 2012; Memczak et al., 2013). CircRNAs can be divided into four categories: exonic circRNAs (ecircRNAs) (Chen et al., 2015), intronic circRNAs (ciRNAs) (Zhang et al., 2018), exon-intron circRNAs (EIciRNAs) (Hsiao et al., 2017), and transfer RNA (tRNA) intronic circRNAs (tricRNAs) (Geng et al., 2020). EIciRNAs and ciRNAs are mainly located in the nucleus, suggesting that they may be involved in gene expression (Guo et al., 2014; Li et al., 2015). ecircRNAs are the most abundant circRNAs and are

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found in the cytoplasm (Jeck et al., 2013) (Fig. 2). However, the study of circRNAs in disease is hampered by the limitations of experimental techniques and their own peculiar characteristics.

In this review, we summarize the properties and functions of circRNAs and highlight their regulatory roles in osteosarcoma (OS), osteoarthritis (OA), osteoporosis (OP), multiple myeloma (MM), intervertebral disc degeneration (IDD), and rheumatoid arthritis (RA), to find evidence for the potential clinical value of circRNAs as molecular markers for the diagnosis and treatment of bone-related diseases.

2 Characteristics of circRNAs

CircRNAs, microRNAs (miRNAs), and long non-coding RNAs (lncRNAs) are all non-coding RNAs found mainly in the cytoplasm. Compared to lncRNAs, circRNAs are single-stranded RNAs that form a closed

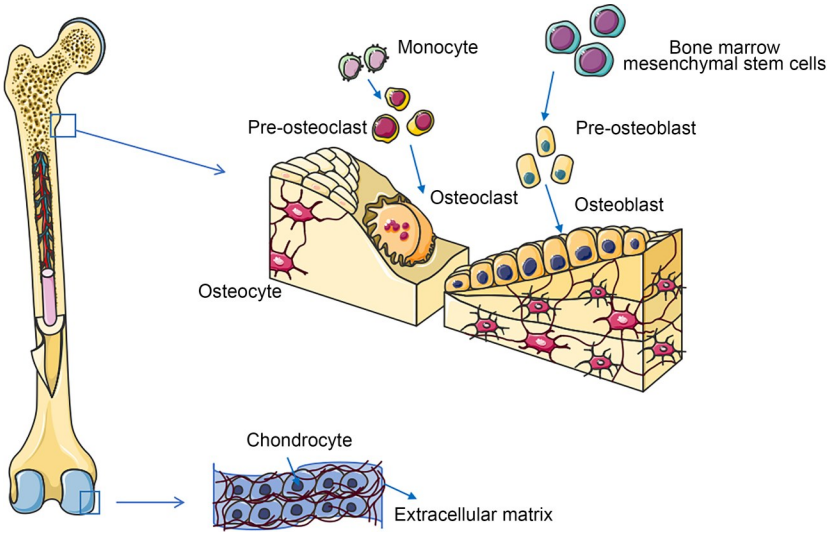

Fig. 1 Microstructure of bone.

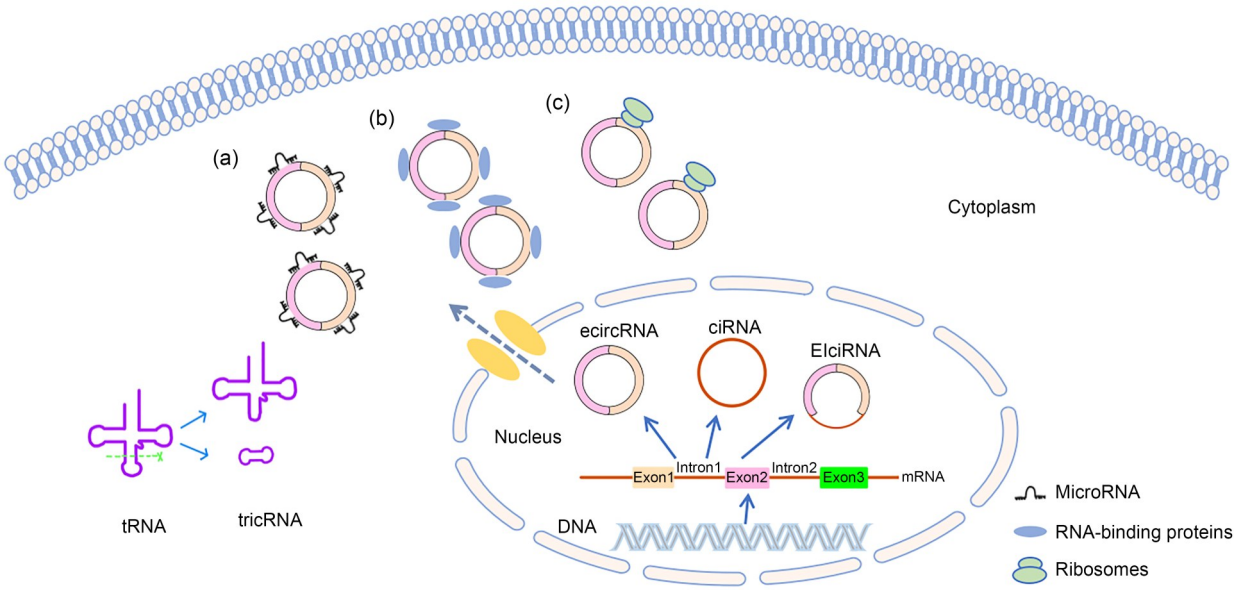

Fig. 2 Functions of different circRNAs. CircRNAs can be classified into four categories: exonic circRNAs (ecircRNAs), intronic circRNAs (ciRNAs), exon-intron circRNAs (EIciRNAs), and transfer RNA (tRNA) intronic circRNAs (tricRNAs). (a) ecircRNAs act as sponges to microRNAs. (b) ecircRNAs combine with RNA-binding proteins. (c) ecircRNAs combine with ribosomes to regulate protein translation.

circular structure in which the 5' cap and 3' tail are connected, making the tissue more stable. They are resistant to RNA exonuclease-mediated degradation and may thus be ideal biomarkers for diagnosis or therapeutic targets (Qu et al., 2015; Zhang et al., 2016; Huang S et al., 2017; Huang XQ et al., 2019). CircRNAs are widely expressed in cell activity, embryonic development, neuronal development, and the pathogenesis of various diseases (Guarnerio et al., 2016; van Rossum et al., 2016), and are involved in diseases mainly by regulating cell differentiation, proliferation, migration, invasion, and inflammatory responses (Wan et al., 2016; Luo et al., 2017; Tian et al., 2017; Yuan et al., 2019). Numerous studies have shown that circRNAs can be expressed in a specific form in a variety of organisms (Chen, 2016; Zhao et al., 2019). The expression of circRNAs is tissue-specific. For example, circRNAs are enriched in the nervous system, especially when neurons are developing or undergoing apoptosis (Venø et al., 2015; You et al., 2015).

3 Functions of circRNAs

The functions of circRNAs are directly related to their particular structure. Currently, relevant studies are mainly focused on four mechanisms of circRNAs: (1) They feature the abundance of miRNA-binding sites that can act as molecular sponges for miRNAs to counteract miRNA-mediated messenger RNA (mRNA) inhibition via the competing endogenous RNA (ceRNA) network (Yu et al., 2019; Huang GQ et al., 2020; Xu GY et al., 2020) (Fig. 2a); (2) They can associate with RNA-binding proteins (RBPs) to regulate the post-transcriptional process and influence protein expression and function (Holdt et al., 2016; Zang et al., 2020) (Fig. 2b); (3) They have high sensitivity and extracellular stability, so they can be detected in blood without cellular components, allowing circRNAs to be used as particular biomarkers for diseases (Salzman, 2016; Luo et al., 2018); (4) They can regulate the transcription and alternative splicing of parent genes (Zhang et al., 2013; Conn et al., 2017) (Fig. 2c).

4 Biomarkers for diseases

Due to the unique structure of circRNAs and their resistance to ribonuclease R (RNase R), circRNAs have the potential to be biomarkers and therapeutic targets in diseases (Jeck and Sharpless, 2014). Thus far, extensive studies have demonstrated that circRNAs are ideal biomarkers and have been applied in clinical practice, such as in tuberculosis (Yi et al., 2020), renal cell carcinoma (Chen Q et al., 2020), stroke (Zuo et al., 2020), and chronic obstructive pulmonary disease (Chen SF et al., 2020). Due to their stability and high expression in various diseases, circRNAs are currently the focus of research, significantly advancing the study of disease mechanisms. As bone-related diseases increasingly threaten human health, circRNAs can play important roles as biomarkers.

5 CircRNAs involved in osteoarthritis

OA, a chronic, progressive, and degenerative joint disease, is particularly common among people over 65 years of age (Charlier et al., 2016). Chondrocyte injury and apoptosis, chondrocyte ECM degradation, and mechanical damage to the joint are the three main factors for the occurrence of OA (Wang TF et al., 2020). CircRNAs have a more stable structure, are tissue-specific, and can influence the development of OA. Thus, circRNAs are slowly emerging as a potential diagnostic biomarker and therapeutic target for OA.

5.1 CircRNA and ECM

The degradation process of the ECM is relatively complicated, with the circRNA-miRNA-mRNA network playing a significant role at the post-transcriptional level. CircTMBIM6 and matrix metallopeptidase-13 (MMP-13) were upregulated in interleukin-1β (IL-1β)- and tumor necrosis factor-α (TNF-α)-induced OA, while miRNA-27a (miR-27a) was downregulated. CircTMBIM6 functions as ceRNA to promote ECM degradation (Bai et al., 2020). Wu et al. (2017) showed that hsa_circ_0005105 inhibited the transcriptional activity of miR-26a to enhance the expression of target nicotinamide phosphoribosyl transferase (NAMPT), while promoting the expression of MMP-13 and a disintegrin and metalloproteinase with thrombospondin motifs type 4 (ADAMTS-4), which affected ECM degradation.

Compared to normal cartilage, 71 circRNAs were differentially expressed in OA, of which 16 circRNAs were upregulated and 55 circRNAs were downregulated

(Liu et al., 2016); circRNA chondrocyte extracellular matrix related (circCER) was upregulated in chondrocytes stimulated by IL-1 and TNF-α, and it sponged miR-136 to enhance the expression of MMP-13. The silencing of circCER may promote ECM formation by inhibiting MMP-13 expression.

5.2 CircRNA and chondrocytes

Chondrocytes are the only cells in cartilage that are tightly regulated to maintain a dynamic balance between proliferation and apoptosis, which controls the biosynthesis and degradation processes of the ECM under normal physiological conditions (Sandell and Aigner, 2001). CircRNA-9119 was positively related to chondrocyte proliferation; circRNA-9119 and phosphatase and tensin homolog (PTEN) activation decreased cell apoptosis. In contrast, a miR-26a mimic induced cell apoptosis, and the circRNA-9119/miR-26a/PTEN axis was found to be an important regulatory mechanism in the treatment of OA (Chen CJ et al., 2020). PTEN also acts on other signaling pathways, but in a different role. It can inhibit the phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt) pathway, which is the main pathway to promote cell survival, upregulate the levels of MMP-13 and ADAMTS-5, and downregulate the levels of aggrecan and collagen type II α1 chain (COL2A1) to promote cell apoptosis (Yamada and Araki, 2001; Zhou ZB et al., 2021). Yuan et al. (2021) corroborated that circZNF652 was significantly upregulated in lipopolysaccharide (LPS)-induced OA and promoted the mRNA and protein levels of PTEN expression. Huang ZH et al. (2021) revealed the interference with circRNA_0092516 when targeting the miR-337-3p/PTEN pathway to inhibit chondrocyte apoptosis. In addition, the circCDH13/miR-296-3p/PTEN pathway promoted chondrocyte apoptosis and suppressed proliferation (Zhou ZB et al., 2021). Overall, these studies suggested that PTEN is a novel regulatory factor in chondrocyte proliferation and apoptosis.

In the IL-1β-induced chondrocyte model, circRNAs are also involved in the development and progression of OA. CircSEC24A has been positively associated with apoptosis and inflammation; it can attenuate miR-142-5p to promote the expression of sex-determining region Y-box protein 5 (SOX5), thereby exacerbating chondrocyte injury (Shi et al., 2022). Wang QS et al. (2021) showed that circ_0114876 promotes TNF receptor-associated factor 2 (TRAF2) expression by targeting miR-671 in OA tissue. The overexpression of TRAF2 could induce apoptosis and attenuate the effects of high miR-671 expression. Furthermore, the upregulation of circ_0001103 could alleviate the inflammatory response and reduce apoptosis. The circ_0001103/miR-375/silencing information regulator 2-related enzyme 1 (SIRT1) axis has been considered as an important potential mechanism for the treatment of OA (Zhang M et al., 2021).

5.3 CircRNA and mechanical damage

The mechanical damage of cartilage tends to cause inflammation, which is one of the causes of OA. In the anterior cruciate ligament transection (ACLT) mouse model, silencing circSLC7A2 enhanced the inflammatory response by increasing the level of miR-4498 targeting tissue inhibitor of metalloproteinase 3 (TIMP3). The injection of circSLC7A2 into the knee joint can alleviate joint pain and suppress osteophyte formation, slowing the progression of OA (Ni et al., 2021). Yao et al. (2021) also confirmed that circ-0083429 functions as an miR-346 sponge to facilitate Sma- and Mad-related protein 3 (SMAD3), and injecting it into the joint cavities of ACLT mice could alleviate the progression of OA. In addition, circCDK14 was downregulated in an ACLT rabbit model. Moreover, the injection of circCDK14 in vivo inhibited the expression of MMP-3 and MMP-13 promoted the expression of SOX9 and SMAD2 (Shen et al., 2020). The activation of circCDK14/miR-125a-5p/SMAD2 pathway may be a novel therapy to cure OA.

The surgical destabilization of the medial meniscus (DMM) can also cause OA. Zhou et al. (2019) demonstrated that the knockdown of circRNA.33186 inhibited chondrocyte apoptosis in a DMM-induced OA model via the miR-127-5p/MMP-13 axis. CircDE4D is only slightly expressed in OA, and the intra-articular injection of circPDE4D into DMM mice can support cartilage repair. Mechanistically, circPDE4D directly interacts with miR-103a-3p to promote fibroblast growth factor 18 (FGF18) expression (Wu et al., 2021).

In summary, circRNA can exert its effects in ECM, chondrocytes, and inflammation to regulate the progression of OA, and thus may be a promising molecular targeted therapy for OA. The functions of circRNAs and related signaling pathways in OA are shown in Table S1.

6 CircRNAs involved in osteoporosis

OP is a common orthopaedic disease characterized by increased bone absorption and decreased bone formation (Li et al., 2022). The decrease in bone density and damage to its microstructure further increase the fragility of bone tissue, which results in a dramatic rise in the incidence of fractures (Coughlan and Dockery, 2014; Jin et al., 2018). In recent years, research into the pathogenesis of OP has continued to deepen. CircRNAs have been reported to influence the differentiation and function of osteoblasts (Yu and Liu, 2019), osteoclasts (Zhai et al., 2018), and BMSCs (Ren et al., 2019), and are involved in the regulation of bone metabolism (Table S2). Due to the unique ring structure of circRNAs, they have high stability, which makes them potentially useful in the treatment of OP.

6.1 CircRNAs and bone formation

Osteoblasts and BMSCs play vital roles in regulating the bone formation, which is tightly controlled by a variety of intracellular signaling pathways (Yamaguchi et al., 2000); the role of circRNAs in osteoblast differentiation is currently the focus of research. In a study by Qian et al. (2017), the expression levels of 158 circRNAs in bone morphogenetic protein-2 (BMP2)-induced MC3T3-E1 cells were found to be different from those in the control group. A total of 74 circRNAs were upregulated, the expression levels of circ19142 and circ5846 were significantly increased and 84 were downregulated, suggesting that circRNAs may be involved in the regulation of osteogenic differentiation. Mm9_circ_009056 was upregulated in MC3T3-E1 cells induced by calcitonin gene-related peptide (CGRP), while the expression of miR-22-3p was significantly decreased. The silencing of mm9_circ_009056 was able to increase the occurrence of miR-22-3p and decrease the expression levels of BMP7 and Runt-related transcription factor 2 (Runx2) (Wu et al., 2018). In addition, Wnt/β-catenin was indicated as an important signaling pathway in osteoblasts and OP (Xu ZH et al., 2020). Circ_0024097 promoted the osteogenic differentiation of MC3T3-E1 cells by adsorbing miR-376b-3p as the ceRNA of Yes-associated protein 1 (YAP1) and activating the Wnt/β-catenin pathway (Huang YX et al., 2020). In mesenchymal stem cells (MSCs), hsa_circ_0076906 combined with miR-1305 promoted the expression of osteoglycin (OGN), stimulating the differentiation of BMSCs into osteoblasts (Wen J et al., 2020). Li F et al. (2021) found that the overexpression of circ_0062582 can promote osteoblast differentiation and cell proliferation. Via targeting miR-145, it can affect the expression of core-binding factor subunit β (CBFB) in human BMSCs (hBMSCs). The above results demonstrate that circRNAs can promote osteogenic differentiation and thus prevent and treat OP.

6.2 CircRNAs and bone absorption

Osteoclasts are the only cell type that can absorb the bone matrix, and their excessive activation can lead to OP (Chen et al., 2019). The differentiation of osteoclasts requires the induction of the receptor activator of nuclear factor-κB ligand (RANKL) and colony-stimulating factor 1 (CSF1). In this way, the expression of circRNA_28313 is upregulated. The change in circRNA_28313 expression was positively correlated with osteoclast differentiation, and miR-195a could bind circRNA_28313 and CSF1 to establish a ceRNA network that regulates bone absorption (Chen et al., 2019). CircRNA_009934 is highly expressed during osteoclast differentiation and can bind miR-5107 to promote TNF receptor-associated factor 6 (TRAF6) expression (Miao et al., 2020). TNF-α can decrease osteoblast differentiation and increase osteoclast activity (David and Schett, 2010). Liu ZC et al. (2020) demonstrated that circHmbox1 plays a role in TNF-α-induced osteoclasts. It could intercept miR-1247-5p to promote the expression of B-cell lymphoma 6 (Bcl6) to inhibit osteoclast differentiation, and when exosomes were secreted by osteoclasts that only slightly expressed circHmbox1, osteoblast differentiation was inhibited. Guan et al. (2021) found that hsa_circ_0021739 had lower expression in the OP group than in the control group. The overexpression of hsa_circ_0021739 may inhibit osteoclast differentiation via targeting hsa-miR-502-5p. Overall, data show that in the process of OP, circRNAs are involved in the regulation of osteoclasts.

7 CircRNAs involved in osteosarcoma

OS is the most prevalent primary malignant bone tumor that occurs mainly in children/adolescents and

adults over 50 years of age (Suehara et al., 2019). It is highly invasive, metastasizes rapidly, and has a high mortality rate and poor prognosis (Li SL et al., 2019; Zhao et al., 2021). OS initially affects the long bones and gradually involves other bones (Zhang ZC et al., 2020). CircRNAs have been studied extensively in OS, and several researchers have conducted one specific circRNA, focusing on its regulatory role in OS reaching a certain level of maturity. Compared with the control group, hsa_circ_0000885 was highly expressed in the serum of OS and could be used as a potential biomarker for OS (Zhu et al., 2019). Chen YX et al. (2020) demonstrated the interaction among circ_0000885, miR-1249, and fibroblast growth factor receptor 1 (FGFR1) in OS by cell transfection. They found that circ_0000885 could target miR-1294 as an OS oncogene to promote FGFR1 expression and thus promoted OS progression. In the tissues and cells of OS, the overexpression of circ_0000285 was positively associated with insulin-like growth factor-binding protein 3 (IGFBP3), enhancing the migration and proliferation of OS through the circ_0000285/miR-409-3p/IGFBP3 axis (Long et al., 2020). Zhang ZC et al. (2020) verified that the other axis via hsa_circ_0000285 could bind miRNA-599 to promote the expression of transforming growth factor β2 (TGFB2). Furthermore, circUBAP2 was significantly increased in OS tissues compared to controls and might be involved in the regulation of OS via the activation of miR-143/Bcl2 axis (Zhang et al., 2017), miR-641/YAP1 axis (Wu et al., 2020), miR-204-3p/high mobility group AT-hook 2 (HMGA2) axis (Ma et al., 2021), and miR-506-3p/SEMA6D axis (Dong and Qu, 2020). The activation of the above signaling pathways may regulate the progression of OS and contribute to the further elucidation of pathogenesis.

However, the results of some circRNA studies need to be further confirmed. CircRNA itchy E3 ubiquitin protein ligase (circITCH) is a circRNA that is downregulated in OS tissues, and it suppresses OS progression through the circITCH/miR-524/RASSF6 axis (Zhou W et al., 2021). However, Li et al. (2020) revealed that circITCH was significantly upregulated in OS; silencing circITCH enhanced miR-7 expression and inhibited epidermal growth factor receptor (EGFR) expression. CircRNA homeodomain-interacting protein kinase 3 (circHIPK3) was associated with various cancers, and circHIPK3 expression may be a sign of accelerated cancer development (Wen JY et al., 2020). CircHIPK3 is derived from exon2 of the *HIPK3* gene and is a research hotspot in OS. It is a molecular sponge that competitively binds miRNA to exert its function (Zhang YL et al., 2020). Ma et al. (2018) first discovered that circHIPK3 had lower expression in OS cells and tissues than in the control group. The overexpression of circHIPK3 in vitro inhibits the development of OS, and hence it can be used as a biomarker for the treatment of OS. However, Huang ZY et al. (2020) took the opposite view and found that circHIPK3 was obviously upregulated in OS cell lines and regulated signal transducer and activator of transcription 3 (STAT3) via miR-637, triggering the occurrence of OS. In another study, Wen Y et al. (2021) also showed that circHIPK3 was highly expressed in OS tissues and cells, and they argued that it exists in the cytoplasm; the circHIPK3 sponge miR-637 was found to positively regulate histone deacetylase 4 (HDAC4) expression, thus facilitating the proliferation, migration, and invasion of OS cells (Table S3).

In conclusion, circRNAs with upregulated expression in OS have been studied extensively. Even though some studies are contradictory, the results suggest that circRNAs are important in the regulation of OS. With the further understanding of circRNA and advances in experimental technology, more studies are expected to verify this notion.

8 CircRNAs involved in multiple myeloma

MM is a hematological malignancy caused by plasma cells that proliferate abnormally in the bone marrow, and by the abundant secretion of monoclonal immunoglobins (Huang H et al., 2020; Luo and Gui, 2020; Zhou et al., 2020). Although bortezomib (BTZ) has shown a good clinical effect and is widely used, some patients are not eligible for it (Fu et al., 2019). Therefore, the search for novel biomarkers is crucial for the diagnosis and targeted treatment of MM.

CircRNAs are novel biomarkers for the regulation of MM; hsa_circRNA_101237 (Liu X et al., 2020), hsa_circ_0007841 (Gao et al., 2019), and hsa_circ_0069767 (Chen F et al., 2020b) were all significantly upregulated in MM. Using cell models with the overexpression or knockdown of circ_0069767, Chen F et al. (2020b) demonstrated that overexpressed

hsa_circ_0069767 can promote cell apoptosis and that knocking down hsa_circ_0069767 increases proliferation, migration, and invasion. Circ_0007841 is a research hotspot, and several studies have shown that it can regulate the process of MM via the hsa_circ_0007841/adenosine triphosphate (ATP)-binding cassette transporters G2 (ABCG2) (Song et al., 2020), circ_0007841/miR-338-3p/bromodomain-containing 4 (BRD4) (Wang Y et al., 2020a), and circ_0007841/miR-129-5p/Jagged1 (JAG1) (Wang Y et al., 2020b) signaling pathways.

CircRNA chromodomain Y-like (circCDYL) and circ_0000142 exacerbated the progression of MM by activating the circCDYL/miR-1180/YAP axis (Chen F et al., 2020a) and circ_0000142/miR-610/RAC-γ serine/threonine-protein kinase (AKT3) axis (Liu et al., 2021). However, circRNAs were also involved in MM. Circ_0000190 was downregulated in tissues of MM and peripheral blood, and it can intercept miR-767-5p to enhance mitogen-activated protein kinase 4 (MAPK4) expression, to inhibit the growth and progression of MM (Feng et al., 2019). BTZ is a typical chemotherapeutic drug in MM, but BTZ chemoresistance is a challenge to be solved (Gonzalez-Santamarta et al., 2020). Fang et al. (2021) showed that the knockdown of circRNA arginine-glutamic acid dipeptide repeats (circRERE) attenuated BTZ chemoresistance, with circRERE acting mechanically through the miR-152-3p/cluster of differentiation 47 (CD47) axis. In contrast, the overexpression of circITCH can block BTZ resistance in MM. Moreover, circITCH binds miR-615-3p to upregulate protein kinase C-δ (PRKCD), thereby increasing BTZ sensitivity (Liu JH et al., 2020) (Table S4).

9 CircRNAs involved in intervertebral disc degeneration

Cells of the nucleus pulposus (NP) can secret ECM to maintain the homeostasis of intervertebral discs. The aberrant function of NP cells will lead to IDD through three main mechanisms, namely cell senescence, apoptosis, and ECM degradation (Li Z et al., 2019; Chang et al., 2021). The IDD of the lumbar spine is closely associated with low back pain, which severely affects patients' quality of life and increases the economic burden on society (Xu GY et al., 2020). CircRNAs are crucial transcription regulatory factors in IDD.

CircRNAs are capable to simultaneously regulate cell apoptosis and ECM degradation. Silencing circRNA glucuronic acid epimerase (circGLCE) could enhance the apoptosis of NP cells and matrix-degrading enzyme expression, and overexpression of circGLCE inhibited miR-587 to increase signal-transducing adaptor family member 1 (STAP1) expression (Chen ZH et al., 2020). In this respect, circGLCE acts as a therapeutic target for IDD via the miR-587/STAP1 axis. CircRNA involved in compression-induced damage of NP cells (circRNA-CIDN) is a negative regulator of IDD, as it promoted the expression of SIRT1 by targeting miR-34a-5p in loading-induced NP cells to slow the onset of IDD (Xiang et al., 2020). However, Cui and Zhang (2020) revealed that circ_001653 was positively related to the severity of IDD, and may serve as a sponge for miR-486-3p to upregulate cell migration-inducing protein (CEMIP) expression. Therefore, it can be regarded as a promising diagnostic biomarker for IDD.

Currently, an increasing pool of researches have evidenced that circRNAs are widely involved in the regulation of IDD, and most of them involved circRNAs that are downregulated in IDD. CircRNA derived from vacuolar ATPase assembly factor 21 (circ-VMA21) (Cheng et al., 2018), circRNA PBX/knotted 1 homeobox 1 (circPKNOX1) (Huang YZ et al., 2021), circRNA growth factor receptor bound protein 10 (circGRB10) (Guo et al., 2020b), hsa_circ_0059955 (Kong et al., 2020), circRNA ADP ribosylation factor-like GTPase 15 (circARL15) (Wang HB et al., 2021), circRNA semaphorin 4B (circSEMA4B) (Wang et al., 2018), and circRNA ERCC excision repair 2 (circERCC2) (Xie et al., 2019) all notably ameliorated the progression of IDD by inhibiting cell apoptosis and ECM degradation. All of them could establish a ceRNA network that mediates the regulation of IDD, such as circPKNOX1/miR-370-3p/KIAA0355 (Huang YZ et al., 2021), circARL15/miR-431-5p/disrupted in schizophrenia 1 (DISC1) (Wang HB et al., 2021), and circERCC2/miR-182-5p/SIRT1 (Xie et al., 2019). Nevertheless, there are also upregulated circRNAs in IDD. For instance, Li YJ et al. (2021) demonstrated that circRNA family with sequence similarity 169 member A (circFAM169A) was overexpressed in degenerative NP tissues, while miR-583 was negatively

related to circFAM169A and SOX9. Another study suggested that β-transducin repeat-containing E3 ubiquitin protein ligase (*BTRC*) is also the target gene of miR-583, and that the circFAM169A/miR-583/BTRC pathway is a therapeutic option for IDD (Guo et al., 2020a). CircRNA_104670 and circITCH modulated the progression of IDD via the miRNA-17-3p/MMP-2 axis and the miR-17-5p/SOX4 axis (Song et al., 2018; Zhang F et al., 2021), respectively (Table S5).

10 CircRNAs involved in rheumatoid arthritis

RA is a chronic systemic autoimmune disease with synovial hyperplasia, cartilage destruction, and bone erosion, leading to systemic inflammatory response (Bombardieri et al., 2011; Zheng et al., 2017; Taheri et al., 2020). Approximately 1% of the global population is affected by RA, while the pathogenesis and etiology of RA remain elusive (Nemtsova et al., 2019). In recent years, studies have gradually focused on the biomarkers of circRNAs in RA (Wen JT et al., 2021).

Two studies have explored the mechanisms of circRNA fragile mental retardation 2 (circAFF2) in RA tissues. CircAFF2 has a high expression level in RA fibroblast-like synoviocytes (RAFLSs). The increased expression of circAFF2 can enhance the proliferation, inflammatory response, and migration of RAFLSs. However, upregulated miR-650 reversed circAFF2-mediated effects in RA. 2',3'-Cyclic nucleotide 3'-phosphodiesterase (*CNP*) was the target gene of miR-650 (Qu et al., 2021). Another study showed that circAFF2 exacerbated the extent of RA via the miR-375/TAK1-binding 2 (TAB2) axis (Zhi et al., 2021).

CircPTPN22, hsa_circ_0002715, hsa_circ_0035197, and hsa_circ_0044235 in peripheral blood mononuclear cells have been identified as novel biomarkers for the diagnosis and treatment of RA (Luo et al., 2018, 2019; Jiang et al., 2021), while the relevant regulatory mechanisms need further investigation. Furthermore, Cai et al. (2021) demonstrated that circ_0088194 was upregulated in RAFLSs and bound to miR-766-3p. MMP-2 was positively related to circ_0088194, which promoted the migration and invasion of RAFLSs. The overexpression of miR-766-3p alleviated the promoting effect of circ_0088194, and MMP-2 expression was also inhibited. In addition, circRNA absent-small-homeotic-2-like protein (circASH2L), circMAPK9, and hsa_circ_0088036 were involved in promoting the growth and inflammation of RAFLSs by regulating the miR-129-5p/homeodomain-interacting protein kinase 2 (HIPK2) axis (Li X et al., 2021), miR-140-3p/protein phosphatase magnesium-dependent 1A (PPM1A) axis (Luo et al., 2021), and miR-140-3p/SIRT1 axis (Zhong et al., 2020), respectively (Table S6).

11 Conclusions

Bones are fundamental parts of the body with vital functions; the occurrence of bone-related diseases places a great burden on society. CircRNAs were demonstrated to act as molecular regulators of bone-related diseases and closely associated with disease development and severity. Although our understanding of circRNAs is still at the preliminary stage, we believe that circRNAs have good prospects as targets in disease regulation. The different expression of circRNAs between control and diseased groups indicates that they are involved in disease occurrence. Due to their high specificity and stability, circRNAs could be used as biomarkers for bone-related diseases. The fact that the overexpression or knockdown of circRNAs can influence the expression of mRNAs by sponging miRNAs and thus alleviate the disease process confirms that circRNAs can act as therapeutic targets.

Currently, circRNAs are a relatively new subject of research. Due to their unique and stable structure, they are involved in the regulation of a variety of diseases. Currently, studies mainly focused on the function of circRNAs as a miRNA "sponge" by developing a ceRNA network to explore the regulatory roles of circRNAs in controlling gene expression and influencing disease progression. However, the functions of circRNAs to regulate parental gene transcription and alternative splicing have been less frequently studied, and the comprehensive functions of circRNAs remain to be elucidated. As our understanding of circRNAs further deepens, they are expected to provide a broader perspective on the diagnosis and treatment of bone diseases.

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Author contributions

Linghui HU: study development, data curation, writing – original draft, writing – review and editing. Wei WU: writing – review and editing. Jun ZOU: funding acquisition, supervision, writing – review and editing. All authors have read and approved the final manuscript.

Compliance with ethics guidelines

Linghui HU, Wei WU, and Jun ZOU declare that they have no conflict of interest.

This review does not contain any studies with human or animal subjects performed by any of the authors.

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Supplementary information

Tables S1–S6