An update on the roles of circular RNAs in osteosarcoma

Zheng Li1 | Xingye Li2 | Derong Xu3 | Xin Chen1 | Shugang Li1 | Lin Zhang4 | Matthew T. V. Chan4 | William K. K. Wu4,5

1Department of Orthopaedic Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
2Department of Orthopedic Surgery, Beijing Jishuitan Hospital, Fourth Clinical College of Peking University, Jishuitan Orthopaedic College of Tsinghua University, Beijing, China
3Department of Orthopedics, The Affiliated Hospital of Qingdao University, Qingdao, China
4Department of Anaesthesia and Intensive Care, Peter Hung Pain Research Institute, The Chinese University of Hong Kong, Hong Kong City, Hong Kong
5State Key Laboratory of Digestive Diseases, Centre for Gut Microbiota Research, Institute of Digestive Diseases and LKS Institute of Health Sciences, The Chinese University of Hong Kong, Hong Kong City, Hong Kong

Abstract
Osteosarcoma is the most common primary bone malignancy and is a neoplasm thought to be derived from the bone-forming mesenchymal stem cells. aberrant activation of oncogenes and inactivation of tumour suppressor genes by somatic mutations and epigenetic mechanisms play a pivotal pathogenic role in osteosarcoma. Aside from alterations in these protein-coding genes, it has now been realized that dysregulation of non-coding RNAs (ncRNAs), including microRNAs (miRNAs), long non-coding RNAs (lncRNAs) and the recently discovered circular RNAs (circRNAs), is crucial to the initiation and progression of osteosarcoma. circRNAs are single-stranded RNAs that form covalently closed loops and function as an important regulatory element of the genome through multiple machineries. Recently, an increasing number of studies suggested that circRNAs also played critical roles in osteosarcoma. This review summarizes recent development and progression in circRNA transcriptome analysis and their functions in the modulation of osteosarcoma progression.

1 | INTRODUCTION

Osteosarcoma, a neoplasm thought to be derived from the bone-forming mesenchymal stem cells, is the most common primary bone malignancy, predominantly involving metaphyseal regions of the long bones (eg, proximal end of tibia or humerus and distal end of femur) which are the most rapidly growing parts of the skeleton in children and adolescents.1-5 The incidence of osteosarcoma follows a bimodal age distribution with ages between 10 and 30 primarily affected.6-10 The second peak appears in the elderly in which osteosarcoma very often comes as a later cancer secondary to radiation exposure or is associated with Paget disease (a disorder of bone remodelling resulting in structural weakening).11-16 With the advent of neoadjuvant and adjuvant chemotherapy with cisplatin, doxorubicin and high-dose methotrexate and the advances in surgery, the 5-year survival rate of patients with osteosarcoma has improved from ~20% before the 1980s to currently ~70%.17-22 Nevertheless, half of the patients still do not survive for longer than 10 years.23-25 Thus, it is

Li, Li and Xu are the co-first authors.

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important to identify new therapeutic targets for tackling this devastating and potentially fatal disease (Figure 1).

Aberrant activation of oncogenes (eg, COPS3, PIK3CA, CARD11, MYC) and inactivation of tumour suppressor genes (eg, TP53, RB1, ATRX, DLG2, BRCA1/2) by somatic mutations and epigenetic mechanisms play a pivotal pathogenic role in osteosarcoma.26-37 Aside from alterations in these protein-coding genes, it has now been realized that dysregulation of non-coding RNAs (ncRNAs), including miRNAs, long non-coding RNAs (lncRNAs) and the recently discovered circular RNAs (circRNAs), is crucial to the initiation and progression of osteosarcoma.2-38-46 CircRNAs are single-stranded RNAs that form covalently closed loops and function as an important regulatory element of the genome through multiple machineries, including transcription regulation, modulation of alternative splicing, sponging of miRNAs and direct interactions with RNA-binding proteins.47-52 A subset of circRNAs also retains protein-coding capacity and was found to be translated in vivo.53-55

A growing body of evidence now indicates that circRNA expression is dysregulated in most, if not all, types of cancer, including glioma, gastric cancer, bladder cancer, hepatocellular carcinoma, lung cancer, gallbladder carcinoma and renal cell carcinoma, in which circRNA deregulation perturbs cancer-related phenotypes, such as cell survival, proliferation, differentiation, metabolism and invasion/metastasis.49,51,52,54,56-62 Recently, an increasing number of studies suggested that circRNAs also played critical roles in osteosarcoma.63-65 For instance, circLRP6 was shown to promote osteosarcoma progression through inhibiting APC and KLF2 expression.66 Zhao et al also reported that circSAMD4A increased osteosarcoma growth by sponging miR-1244 and thereby derepressing MDM2 expression.67 Previously, Zhang et al elegantly summarized the roles of circRNAs in osteosarcoma. As circRNA research is a rapidly evolving field, over a dozen of original articles related to circRNAs in osteosarcoma have been published since then. It is therefore timely to update the recent progress.

In this review, we first summarize circRNA profiling studies on osteosarcoma so as to provide a comprehensive curation of available datasets which may facilitate subsequent studies, followed by in-depth discussion of functions and mechanisms of action of newly discovered osteosarcoma-related circRNAs not covered by the review of Zhang et al.68 The potential diagnostic, prognostic and therapeutic utilities of circRNAs in the clinical management of osteosarcoma are also addressed.

2 | circRNA EXPRESSION PROFILING AND INTEGRATIVE ANALYSIS IN OSTEOSARCOMA

Profiling circRNA expression using microarray or whole-transcriptome sequencing followed by validation with reverse transcription-quantitative PCR (RT-qPCR) is the most frequent method to identify and confirm deregulated expression of circRNAs in specific disease states.69-72 In this connection, attempts have been made to profile circRNAs specific to osteosarcoma or related to its resistance to chemotherapy.

Liu et al65 extracted total RNA from the human osteosarcoma cell lines U2OS, MG63, HOS and 143B and the human normal osteoblast hFOB1.19, and then subjected the RNA samples to digestion with RNase R to remove linear RNAs. The enriched circRNAs were then amplified and transcribed into fluorescent complementary RNA for hybridization onto a human circRNA array. A total of 252 circRNAs were found to be differentially expressed between the human osteosarcoma cell lines and hFOB1.19 (71 upregulated and 181 downregulated in osteosarcoma cell lines). Nevertheless, among the 12 selected differentially expressed circRNAs, only the upregulation of circRNA_103801 and the downregulation of circRNA_104980 were successfully validated in both osteosarcoma cell lines and human osteosarcoma tissues by RT-qPCR.
suggesting a low validity of using cell line models to identify osteosarcoma-specific circRNAs. For the validated circRNA_103801, its expression was found to be strongly correlated with TANC1 (tetractripeptide repeat, ankyrin repeat and coiled-coil containing 1), an oncogene previously reported in rhabdomyosarcoma. In another study, XI et al used the Illumina HiSeq platform to profile circRNA expression in three pairs of osteosarcoma and para-cancerous tissues. A total of 259 circRNAs were found to be differentially expressed (32 upregulated and 127 downregulated in osteosarcoma). Among the five selected differentially expressed circRNAs identified by RNA sequencing, significant upregulation of circ_2137 and circ_20403 and downregulation of circ_32279 and circ_24831 were successfully verified in 10 independent pairs of osteosarcoma and para-cancerous tissues, suggesting an overall high validity of the sequencing findings. Pathway enrichment analysis of genes hosting the differentially expressed circRNAs further indicated the potential involvement of phosphatidylinositol signalling, an oncogenic pathway frequently engaged in tumorigenesis. A recent study used PCR array to profile circRNAs in 30 frozen samples of osteosarcoma and their corresponding adjacent tissues. The authors identified 10 differentially expressed circRNAs (six upregulated and four downregulated in osteosarcoma) with circ_001621 as the top upregulated circRNA.

Qiu et al performed an integrative analysis of publicly available gene expression datasets on osteosarcoma downloaded from the Gene Expression Omnibus (GEO) database. They identified 15 downregulated circRNAs, 136 upregulated miRNAs and 52 downregulated mRNAs in osteosarcoma, among which 14 circRNAs, 24 miRNAs and 52 mRNAs formed a circRNA-miRNA-mRNA network. Pathway analysis revealed these mRNAs were enriched in ‘phosphoinositide 3-kinase-Akt signalling pathway’, ‘proteoglycans in cancer’, ‘cell cycle’ and ‘FoxO signalling pathway’. Importantly, low expression of four mRNAs (ARID5B, ELL2, PHC2 and STAT4) in the circRNA-regulated network was associated with significantly shortened overall survival of osteosarcoma patients.

Aside from osteosarcoma-specific circRNAs, efforts have been made to identify circRNAs pertinent to chemosensitivity in osteosarcoma. Zhu et al compared the circRNA expression profiles of three chemoresistant osteosarcoma cell lines (MG63/DXR, U2OS/DXR, KHOS/DXR) that were insensitive to cisplatin, doxorubicin and methotrexate with their cognate chemosensitive osteosarcoma cell lines (MG63, U2OS, KHOS) using next-generation RNA sequencing. A total of 80 circRNAs were found to be differentially expressed (57 upregulated and 23 downregulated in chemoresistant cell lines). Validation with RT-qPCR indicated that nine out of 10 selected circRNAs showed consistent direction of deregulation as shown by RNA sequencing. Pathway analyses of the differentially expressed circRNAs and their parental genes revealed biological processes pertinent to chemoresistance, including glycolysis/glucoseonogenesis, ABC transporters, and vascular endothelial growth factor signalling (Table 1).

### FUNCTIONS AND MECHANISMS OF ACTION OF NEWLY DISCOVERED circRNAs IN OSTEOSARCOMA

#### 3.1 Oncogenic circRNAs

#### 3.1.1 CircTCF25

circTCF25 was first identified as an oncogenic circRNA in bladder carcinoma. Wang et al reported that the expression of circTCF25 was significantly higher in osteosarcoma tissues as compared with morphologically normal bone tissues from the same patients. Functionally, enforced expression of circTCF25 promoted osteosarcoma cell proliferation, migration and invasion, accompanied by corresponding alterations of phenotype-related proteins (upregulation of cyclin D1 and CDK6 for increased cell proliferation; upregulation of MMP2, MMP9 and Vimentin and downregulation of TIMP-1 for enhanced cell migration and invasion). Mechanistically, overexpression of circTCF25 reduced the levels of miR-206 in osteosarcoma cells, where transfection of miR-206 mimic abrogated circTCF25-induced pro-tumorigenic phenotypes and the associated protein expression. In this regard, the MEK/ERK and AKT/mTOR pathways were found to be the downstream pathways inhibited by miR-206.

#### 3.1.2 CircPVT1

CircPVT1 is a circRNA derived from the genomic region that also encodes the oncogenic IncRNA PVT1. Liu et al found that circPVT1...
increased the invasiveness and metastatic capacity of osteosarcoma cells in vitro via promoting epithelial-mesenchymal transition through sponging miR-205-5p and thereby derepressing c-FLIP. Yan et al. also showed that circPVT1 played as one oncogene in development of osteosarcoma. These studies suggested that circPVT1 is an oncogenic circRNA in osteosarcoma, where it contributes to metastasis through upregulating c-FLIP.

### 3.1.3 | CircMMP9

CircMMP9 has been shown to promote glioblastoma. Pan et al. found that the expression of circMMP9 was higher in osteosarcoma tissues, where high expression was associated with larger tumours and more advanced TNM staging. The overall survival of osteosarcoma patients with high tumoral expression of circMMP9 was also shorter than those with low circMMP9 expression. Functionally, knockdown of circMMP9 reduced the viability, colony-forming ability, migration and invasion of osteosarcoma cells, suggesting an oncogenic role for circMMP9. The pro-tumorigenic actions of circMMP9 were found to be mediated through sponging of miR-1265 and the subsequent depression of CHI3L1 (chitinase-3-like protein 1).

### 3.1.4 | Circ_001621

Circ_001621 was identified as the top upregulated circRNA in osteosarcoma by PCR array, and its high expression was associated with more advanced TNM staging and shortened overall survival. In this regard, miR-578 was found to be the target of circ_001621 in osteosarcoma where their expression exhibited strong negative correlation. Functional experiments and mechanistic studies revealed that circ_001621 promoted the proliferation and migration of osteosarcoma cells in vitro via attenuating miR-558-mediated repressing of VEGF and the downstream expression of CDK4 and MMP9. Importantly, circ_001621 enhanced the metastatic capacity of osteosarcoma to the lung and liver in vivo accompanied by the upregulating of VEGF, CDK4 and MMP9. Collectively, circ_001621 is an oncogenic circRNA promoting the metastasis of osteosarcoma by regulating the miR-558-VEGF pathway.

### 3.1.5 | Circ-0000285

Circ-0000285 is another circRNA generated from HIPK3. Zhang et al. found that overexpression of circ-0000285 increased the colony-forming ability, proliferation and migration of osteosarcoma cells in vitro and accelerated the growth of osteosarcoma xenografts in vivo whereas knockdown of circ-0000285 produced the opposite effects. Mechanistic investigations suggested that circ-0000285 bound to miR-599 to derepress TGF-β2 (transforming growth factor-beta 2). In this connection, TGF-β signalling is known to contribute to osteosarcoma progression by promoting angiogenesis, bone remodelling, cell migration and immune evasion.

### 3.1.6 | Circ_0001658

Circ_0001658 was found to be upregulated in osteosarcoma tissues as compared with normal bone tissues. Functional experiments suggested that circ_0001658 promoted the proliferation, migration, and invasion of osteosarcoma cells and impeded apoptosis. These pro-tumorigenic effects were mediated by sponging miR-382-5p and the subsequent depression of YB-1. Taken together, circ_0001658 is an oncogenic circRNA via modulating the miR-382-5p/YB-1 axis.

### 3.1.7 | Circ_0102049

The expression of circ_0102049 was found to be higher in osteosarcoma tissue samples as compared with their paired non-cancerous tissues. In patients with osteosarcoma, high tumoral expression of circ_0102049 was associated with larger tumour size, lung metastasis and shortened overall survival. Gain-of-function and loss-of-function experiments indicated that circ_0102049 acted as an oncogene by promoting osteosarcoma cell proliferation, migration and inhibition apoptosis. Mechanistically, circ_0102049 was found to upregulate MDM2 (an E3 ubiquitin-protein ligase responsible degradation of p53) through sponging miR-1304-5p. To this end, knockdown of MDM2 attenuated the stimulatory effects of circ_0102049 overexpression on osteosarcoma cell viability, migration and invasion, suggesting the miR-1304-5p/MDM2 axis is an effector pathway for the oncogenic action of circ_0102049.

### 3.1.8 | CircEPSTI1

Tan et al. reported that circEPSTI1 was significantly upregulated in osteosarcoma where knockdown of this circRNA suppressed cell proliferation and migration, suggesting an oncogenic role. Mechanistically, circEPSTI1 upregulated the expression of MCL1 (myeloid cell leukaemia 1) via reducing the availability of miR-892b. These data suggested an important role for circEPSTI1-miR-892b-MCL1 axis in the progression of osteosarcoma.

### 3.1.9 | Circ-0060428

Cao and Liu reported that Circ-0060428 was expressed at significantly higher levels in osteosarcoma cell lines (U2OS, 143B, SAOS-2, HOS) as compared with the human normal osteoblast hFOB1.19. Functionally, knockdown of circ-0060428 induced apoptosis of U2OS and HOS osteosarcoma cells, suggesting this circRNA functioned as an oncogenic circRNA. Mechanistic studies found that circ-0060428 bound to miR-375 and thereby depressing RBP1 (a
transcription factor positively regulating Notch signalling). In this connection, miR-375 inhibitor nullified the pro-apoptotic effect of circ-0060428 knockdown.89 These findings suggest that upregulation of circ-0060428 could confer apoptosis resistance to osteosarcoma cells by sponging miR-375. Nevertheless, whether RBPJ is functionally involved in the oncogenic action of circ-0060428 remains unclear. Moreover, the upregulation of circ-0060428 needs to be confirmed in human osteosarcoma tissues.

3.1.10 CircANKIB1

Du et al80 illustrated that circANKIB1 directly sponged miR-19b in the osteosarcoma cell and CircANKIB1 enhanced expression of miR-19b and suppressed SOCS3 expression, which is its downstream gene. Knockdown of miR-19b or circANKIB1 suppressed cell invasion and growth and induced cell apoptosis via modulating STAT3 pathway. These data indicated that circANKIB1 acted as one oncogene and potential treatment target for osteosarcoma.

3.1.11 CircMYO10

Chen et al91 illustrated that miR-370-3p was decreased and circMYO10 was overexpressed in osteosarcoma samples and cells. Inhibition expression of circMYO10 suppressed EMT development and growth through regulating miR-370-3p/RUVBL1/β-catenin/LEF1 axis. These results revealed that circMYO10 played as one oncogene role in progression of osteosarcoma.

3.1.12 CircLRP6

Previous study noted that circLRP6 level was overexpressed in osteosarcoma samples and was correlated with poor overall survival and shorter disease-free survival.92 Knockdown of circLRP6 inhibited cell migration, invasion and growth and induced cell cycle arrested and apoptosis. The interaction between EZH2 and LSD1 with circLRP6 regulates their binding to promoter regions of APC and KLF2. Inhibition expression of circLRP6 decreased binding abilities of EZH2, LSD1 to APC, KLF2. Furthermore, the oncogene effect of circLRP6 on osteosarcoma can be reversed with APC. These data indicated that circLRP6 served as one oncogene through binding to EZH2 and LSD1 to suppress APC and KLF2 expression.

3.1.13 CircSAMD4A

Zhao et al67 noted that circSAMD4 was upregulated in osteosarcoma specimens compared with adjacent non-cancerous specimens. Ectopic expression of circSAMD4A induced osteosarcoma cell growth in vitro and in vivo and increased cells stemness characteristics. Moreover, they illustrated that circSAMD4A sponged miR-1244 and identified MDM2 was one direct target gene of miR-1244. Their data illustrated that miR-1244/MDM2/circSAMD4A modulator loop may be one treatment target for osteosarcoma.

3.1.14 Circ-0001785

Previous reference noted that circ-0001785 was overexpressed in cell lines of osteosarcoma.93 Downregulation expression of circ-0001785 inhibited cell growth and enhanced osteosarcoma cell apoptosis. In addition, they showed that circ-0001785 can sponge miR-1200 expression and suppress HOXB2 expression, which is one target gene of miR-1200. They showed that circ-0001785 modulated Bcl-2 pathway and Akt/PI3K signalling in the osteosarcoma. These results suggested that circ-0001785 modulates osteosarcoma pathogenesis via regulating miR-1200 to enhance HOXB2 expression.

3.1.15 CircORC2

Li et al94 illustrated that circORC2 was distributed in cell cytoplasm and overexpressed in several cell lines of osteosarcoma. CircORC2 can sponge miR-19a expression, and knockdown of circORC2 suppressed miR-19a and enhanced its target gene PTEN expression. Knockdown of circORC2 inhibited cell invasion and growth and enhanced cell apoptosis. Thus, they indicated that circORC2 binds with the miR-19a and increased its expression, then enhancing Akt pathway and suppressing its downstream gene PTEN expression to induce cell invasion and growth. These data provided a new oncogene circORC2 for osteosarcoma.

3.1.16 CircRNA_100876

Jin et al95 showed that circRNA_100876 level was overexpressed in osteosarcoma tissues and was associated with differentiation degree and size of tumour. CircRNA_100876 knockdown suppressed tumour growth in vivo and in vitro. Inhibition expression of circRNA_100876 suppressed cell growth and induced cell apoptosis and decreased cell cycle. Moreover, the expression of circRNA_100876 was negatively correlated with miR-136 expression. Knockdown of miR-136 can reverse the inhibition of cell growth induced with silencing circRNA_100876. These data indicate that circRNA_100876 may act as one promising treatment target and biomarker for osteosarcoma.

3.1.17 CircTADA2A

Wu et al96 revealed that circTADA2A was overexpressed in osteosarcoma cells and samples and inhibition of circTADA2A suppressed tumour metastasis and tumorigenesis in vivo and inhibited cell invasion, growth and migration in vitro. Moreover, they noted
that circTADA2A sponged miR-203a-3p expression and enhanced CREB3 expression, which was found as one driver gene of osteosarcoma. CREB3 overexpression or knockdown of miR-203a-3p can reverse circTADA2A silencing-leading impairment of tumour behaviour. These results suggested that circTADA2A acted as one oncogene through regulating miR-203a-3p/CREB3 axis in osteosarcoma.

### 3.1.18 | Circ_0000885

Zhu et al\(^7\) indicated that circ_0000885 expression was upregulated in serum samples and tissue from osteosarcoma patients and higher expression of circ_0000885 was correlated with Enneking stage. Cases with high tumour and serum levels of the circ_0000885 had the lower rates of overall survival and disease-free survival. These


results suggested that circ_0000885 may act as one diagnostic biomarker for the osteosarcoma.

3.2 | Tumour-suppressing circRNAs

3.2.1 | Circ_0021347

The expression of circ_0021347 was lower in human osteosarcoma tissues and cell lines than their normal counterparts. In patients with osteosarcoma, the low expression of circ_0021347 was associated with more advanced tumour-node-metastasis (TNM) staging and shortened overall survival, suggesting circ_0021347 functions as a tumour suppressor.98 Nevertheless, the mechanism of action of circ_0021347 is presently unclear.

3.2.2 | Circ_0000190

Circ_0000190 has been shown to inhibit the progression of multiple myeloma through sponging miR-767-5p. Li et al reported that circ_0000190 was expressed at significantly lower levels in human osteosarcoma tissues and cell lines as compared with para-cancerous normal tissues and hFOB1.19 normal osteoblasts, respectively.99 Enforced expression of circ_0000190 suppressed osteosarcoma cell proliferation, migration and invasion. Mechanistically, circ_0000190 bound to miR-767-5p and thereby derepressing the downstream target TET1. The levels of circ_0000190 in extracellular nanovesicles isolated from plasma of osteosarcoma patients were also significantly lower than those from healthy subjects, suggesting the potential diagnostic use of circulating circ_0000190. In this regard, low abundance of
circ_0000190 in extracellular nanovesicles could distinguish cases from controls with an AUROC of 0.8894.99

3.2.3 | Circ-LARP4

Hu et al.100 showed that circ-LARP4 level was decreased in osteosarcoma tissues compared to non-tumour samples and circ-LARP4 was associated with Enneking stage. Patients with high circ-LARP4 level indicated enhanced tumour cell necrosis rates to chemotherapy after resection. The higher expression of circ-LARP4 was associated with prolonged overall survival and disease-free survival. Ectopic expression of circ-LARP4 enhanced MG63 cells chemosensitivity to doxorubicin and cisplatin but not the methotrexate. Moreover, overexpression of miR-424 decreased the chemosensitivity effect in circ-LARP4 overexpression handled MG63 cells. Their data suggested that high expression of circ-LARP4 was associated with prolonged survival profiles and decreased Enneking stage and overexpression of circ-LARP4 enhanced chemosensitivity to doxorubicin and cisplatin through sponging miR-424 in development of osteosarcoma.

3.3 | Circ-ITCH, a circRNA with an ambiguous role

Circ-ITCH was found to act as a tumour-suppressing circRNA in esophageal squamous cell carcinoma,101 colorectal cancer102 and lung cancer.103 In contrast with its inhibitory role in these cancer types, Li et al.104 reported that circ-ITCH was expressed at significantly higher levels in a panel of osteosarcoma cell lines as compared with hFOB1.19 normal osteoblasts. Importantly, enforced expression of circ-ITCH promoted osteosarcoma cell proliferation, migration and invasion whereas knockdown of circ-ITCH produced the opposite effects. The oncogenic action of circ-ITCH was mediated by the sponging of miR-7 and the subsequent enhancement of epidermal growth factor receptor (EGFR) expression and activation the downstream MEK-ERK cascade. To this end, erlotinib (an EGFR tyrosine kinase inhibitor) nullified the pro-migratory and pro-invasive effects of circ-ITCH.104 Ren et al.105 also found that circ-ITCH played as a tumour suppressor in progression of osteosarcoma by modulating miR-22 (Tables 2 and 3; Figures 2 and 3).

4 | CONCLUSIONS AND FUTURE PERSPECTIVES

Osteosarcoma is one multi-factor and multi-step comprehensive disease, pathogenesis mechanism is still unclear, and more efforts are in urgent need. CircRNAs function as an important regulatory element of the genome via several machineries, including transcription regulation, modulation of alternative splicing, sponging of miRNAs and direct interactions with RNA-binding proteins. CircRNAs may play as tumour suppressors or activators in tumour and have been applied in modulating cancer metastasis and chemoresistance. As summarized in our review, circRNAs are acting critical roles in many biological processes in the procedures in the progression and development of osteosarcoma including cell apoptosis, invasion, growth, differentiation, migration, drug resistance and cachexia. As one crucial biomarker for prognosis and diagnosis of osteosarcoma, circRNA is one potential target for therapy of osteosarcoma. This use of circRNAs as therapeutics has vast tremendously and may supply a new method to treat osteosarcoma.

Here are some future suggestions for circRNAs study. Firstly, more exact mechanisms about how circRNAs participated in progression of osteosarcoma need to further research, potentially via using online databases. Secondly, further study on circRNAs in osteosarcoma needs to use non-invasive specimens such as saliva, urine and blood. Thirdly, since the purpose of circRNA study is to
use circRNAs for clinical application for osteosarcoma, generous clinical markers experiments and cell function mechanism studies are required in future.

CONFLICT OF INTEREST
The authors declare that they have no competing interests.

AUTHORS’ CONTRIBUTIONS
ZL, XYL, DRX, XC and SGL collected the related paper. ZL, XYL and DRX drafted and wrote the manuscript. LZ, MTVC and WKKW revised the manuscript. SGL participated in the design of the review and helped to draft and revise the manuscript. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT
Research data are not shared.

ORCID
Zheng Li  https://orcid.org/0000-0001-6024-0194
Shugang Li  https://orcid.org/0000-0002-1737-9796

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