

Research progress regarding the role of long non-coding RNAs in osteosarcoma (Review)

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Abstract. Osteosarcoma is a malignant tumor that occurs in children and adolescents. Although treatments for osteosarcoma have improved, the likelihood of survival remains low for most patients with metastasis and recurrence. Elucidating the mechanism underlying the development of osteosarcoma and chemotherapy resistance will be important to improve diagnosis and treatment. Long non-coding RNAs (lncRNAs), which are longer than 200 nucleotides in length and do not encode for proteins, have been shown to play a regulatory role in the occurrence and development of osteosarcoma, and are expected to serve as biomarkers and molecular targets. This review discusses the progress in the study of the role of lncRNAs in osteosarcoma, and highlights the recent developments in this field.

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1. Introduction

Osteosarcoma (OS) is a malignant tumor that accounted for 15% of all diagnosed malignancies in children and adolescents

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in 2015 that seriously affects the health of these groups of individuals worldwide (1). Epidemiological statistics show that the survival rate of patients with primary OS is only 65-70% and the survival rate after metastasis is only 19-30%; thus, current clinical treatments do not effectively cure OS (2,3). Currently, >90% of patients with OS are treated with limb-preserving surgeries (3). However, the high rates of recurrence, metastasis, and mortality of spinal OS result in an extremely low 5-year survival rate (3). Therefore, identifying novel biomarkers involved in the pathogenesis of OS is of great significance.

Long non-coding RNAs (lncRNAs) are functionally defined as gene transcripts more than 200 nucleotides in length that have no protein-encoding potential. lncRNAs act as major regulatory RNAs, that regulate gene expression at the epigenetic or genetic level. In particular, lncRNAs have been found to play an important role in the occurrence, development and angiogenesis of tumors (4). With the development of next-generation sequencing technology, the OS-associated mutation spectrum has been deciphered, including the expression profiles of lncRNAs. A large number of lncRNAs have been found to play an important role in the occurrence, development and drug resistance in OS (5,6). Further studies on the role of lncRNAs in OS will improve the understanding and ability to treat this disease. This review summarizes current knowledge regarding the function of lncRNAs at the molecular level and the implications for OS research and therapy.

2. Classification and biological function of lncRNAs

lncRNAs are classified as sense lncRNAs, antisense lncRNAs, bidirectional lncRNAs, intron lncRNAs, intergenic lncRNAs, or enhancer lncRNAs, according to the positional association between lncRNAs and protein-coding genes in the genome (7).

At present, the regulation of genes by lncRNAs mainly occurs at the transcriptional and post-transcriptional levels (8). lncRNAs can regulate gene expression through chromatin modification, remodeling, histone modification and nuclear body localization (9). In cooperation with the SWI/SNF complex, lncRNAs can also change the structure of chromosomes, thus directly affecting gene expression (10). lncRNAs can directly induce DNA methylation and damage, which can also affect gene expression (11,12). Finally, lncRNAs can regulate gene expression through complex interactions with microRNAs (miRNAs) (13) (Fig. 1).

3. Promotive role of lncRNAs in the occurrence and development of OS

The occurrence and development of OS is a complex process involving many factors. While the molecular mechanisms of these physiological and biological processes have not been fully elucidated, it is clear that lncRNAs play an important role (5,6,14).

lncRNAs directly promote the occurrence and development of OS. Dong *et al* (15) revealed that the upregulation of bladder cancer associated transcript 1 (BLACAT1) predicted an unfavorable prognosis for patients with OS. The downregulation of BLACAT1 inhibited cell proliferation and invasion, whereas the upregulation of BLACAT1 accelerated cell proliferation and invasion. More importantly, BLACAT1 accelerated the proliferation and migration of OS cells by regulating the phosphorylation of STAT3. Zhao *et al* (16) showed that HLA complex P5 (HCP5) acts as an oncogene in OS, and the upregulation of HCP5 promoted cell proliferation and invasion, the epithelial-mesenchymal transition (EMT), and the development of OS. Chen *et al* (17) showed that LOXL1 antisense RNA 1 (AS1) predicted the clinical progression and poor prognosis in patients with OS, and functions as an oncogenic lncRNA, regulating cell proliferation, cell cycle, migration, and invasion via the PI3K/AKT pathway. Su *et al* (18), revealed that ELK1-induced upregulation of MIR100HG predicted poor prognosis and promoted the progression of OS by epigenetically silencing large tumor suppressor kinase (LATS1) and LATS2, and inactivating the Hippo pathway. Another study suggested that the lncRNA hepatocellular carcinoma upregulated lncRNA could promote the occurrence of bone tumors by enhancing the proliferation, invasion, migration and expression of EMT-associated factors of OS (19). Meanwhile, nuclear paraspeckle assembly transcript 1 was shown to be significantly upregulated in OS tissue, indicating that it could effectively promote the proliferation and metastasis of OS cells (20). Meanwhile, Gu *et al* (21) confirmed that HOXD-AS1 could interact with enhancer of zeste homolog 2 (EZH2), thereby decreasing the expression of p57 and exacerbating OS. Yang *et al* (22), found that upregulated forkhead box P4-AS1 promoted OS proliferation, migration and the cell cycle, but inhibited apoptosis; this effect was achieved through the interaction with lysine-specific demethylase 1 and EZH2, and further downregulation of LATS1. Yu *et al* (23), demonstrated that antisense non-coding RNA in the INK4 locus (ANRIL) affects OS cell proliferation, invasion and apoptosis by regulating the AKT pathway. Ye *et al* (24), found that nicotinamide nucleotide transhydrogenase (NNT)-AS1 could inhibit the proliferation, migration and invasion of OS cells, as well as tumor growth, by inhibiting the expression of NNT-AS1. Zhang *et al* (25), also demonstrated that prostate cancer-associated transcript 1 could promote cell proliferation, invasion and migration, as well as the EMT, in OS. Li *et al* (26), showed that colorectal neoplasia differentially expressed (CRNDE) plays an oncogenic role in OS cell lines, and CRNDE can act as a carcinogen by regulating Notch1 signaling and the EMT in OS. Overall, lncRNAs

mainly promote the occurrence and development of OS by regulating the proliferation, migration, invasion and EMT of OS cells.

The interaction between lncRNAs and miRNAs promotes the occurrence and development of OS. miRNAs, which have a maximum length of 200 nucleotides, are the most well-known and well-studied non-coding RNAs. Since these molecules appear to play an important role in cellular biology, further investigations are necessary to elucidate their true functions (27).

Jiang *et al* (28), found that the expression of differentiation antagonizing non-protein coding RNA was increased in OS cells, mediated cancer resistance, enhanced AXL invasion and metastasis by competitively binding with miRNA-33a-5p, and targeting AXL degradation by miRNA-33a-5p via the PI3K/AKT pathway. Wang *et al* (29), also demonstrated that DANCR could induce the expression of miRNA-335-5p and miRNA-1972, thereby promoting ROCK1-mediated proliferation and transfer through competing endogenous RNA (ceRNA) networks, and thus the development of OS. Ma *et al* (30), found that UCA1 could act in the ceRNA network of miRNA-582 to positively regulate the expression of CREB1, thereby enhancing the EMT through the PI3K/AKT/mTOR pathway mediated by CREB1, and promoting invasion and metastasis of OS cells. Meanwhile, Liao *et al* (31) demonstrated that small nucleolar RNA host gene 16 might negatively regulate the expression of miRNA-98-5p. This regulation could effectively reverse the inhibitory effects of miRNA-98-5p on the proliferation, migration, invasion, cell cycle and apoptosis of OS cells. Another report showed that distal-less homeobox 6-AS1 could inhibit the proliferation and metastasis of OS cells by targeting the miRNA-641/HOXA9 signaling pathway and acting as a ceRNA (32). Sun *et al* (33), found that MALAT1 could regulate the proliferation and metastasis of OS cells by competitively binding with miRNA-34a/c-5p and miRNA-449a/b. Deng *et al* (34), showed that lncRNA-small nucleolar RNA host gene 1 (SNHG1) plays an oncogenic role in OS. By activating ROCK1, the PI3K/AKT pathway and the EMT, lncRNA-SNHG1 can downregulate the expression of miRNA-101-3p and promote the proliferation, migration and invasion of cancer cells. Wang *et al* (35), also confirmed that SNHG1, acting as an endogenous sponge, inhibits the activity of miRNA-326 by increasing the expression of its target gene Nob1. Dai *et al* (36), confirmed that OIP5-AS1 acts as a miRNA-223 sponge to trigger CDK14 expression, thus promoting OS tumorigenesis. Li *et al* (37), demonstrated that TUG1 could accelerate the proliferation, migration, and invasion of OS cells by competitive diffusion of miRNA-219a-5p, leading to the upregulation of PIK3CA and activation of AKT signaling. Another study showed that TUG1, as a ceRNA of miRNA-132-3p, promoted SOX4 expression and inhibited the expression of miRNA-132-3p, leading to increased proliferation and decreased apoptosis of OS cells (38). Moreover, Wang *et al* (39) found that HOXA-AS2 can promote OS proliferation, migration, invasion and EMT transformation by regulating the expression of miRNA-520c-3p. Deng *et al* (40), demonstrated that SNHG7 inhibits the growth of tumor suppressor

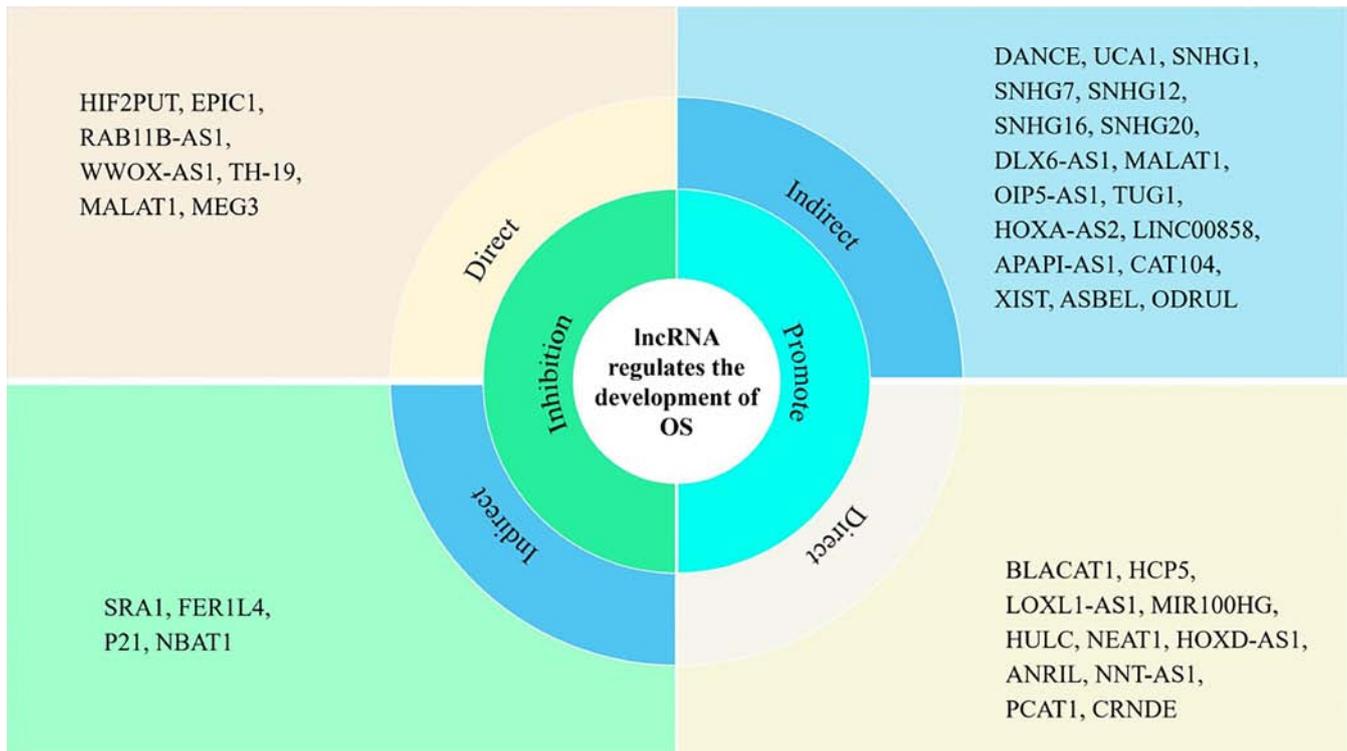


Figure 1. Different lncRNAs play a role in promoting or inhibiting the development of OS, directly or indirectly. Systematic classification of lncRNAs with different effects could provide a basis for application of lncRNAs in the diagnosis and treatment of OS. OS, osteosarcoma; lncRNAs, long non-coding RNAs.

miRNA-34a and upregulates its target gene, which could induce cell proliferation, cell cycle arrest and apoptosis. Gu *et al* (41), revealed that LINC00858 regulates the OS phenotype by acting as a ceRNA of miRNA-139 to enhance CDK14 expression. Li *et al* (42), found that actin filament-associated protein 1-AS1 promoted the proliferation and invasion of OS cells by inhibiting miRNA-4695-5p and activating Tcf4- β -catenin signaling. Xia *et al* (43) confirmed that inhibition of CAT104 could significantly inhibit the proliferation, migration and invasion of OS cells by regulating the expression of miR-381 and the downstream ZEB1, JNK, and Wnt/ β -catenin pathways. Yang *et al* (44) showed that X inactive specific transcript (XIST) was upregulated in OS tissues and cells. XIST affected the proliferation, invasion and EMT of OS cells by regulating miRNA-195-5p/Yes-associated protein signaling. Zhao *et al* (45) found that ASBEL could induce PI3K/AKT/GSK3 β and MEK/ERK signaling, as well as the activation, proliferation, migration, and invasion of OS cells by inhibiting the expression of miRNA-21. Zhou *et al* (46) found that SNHG12 regulated Notch expression by acting as a molecular sponge of miRNA-195-5p, thereby activating Notch signaling in OS and playing a regulatory role in the occurrence and progression of OS. Zhu *et al* (47) showed that the lncRNA osteosarcoma doxorubicin-resistance related up-regulated lncRNA could effectively absorb miRNA-3182 by upregulating MMP2. This regulation directly led to the loss of the inhibitory effects of miRNA-3182 on OS proliferation, migration, invasion and tumor growth, and indirectly promoted the progression of OS. The experimental data of another study showed that the lncRNA SNHG20/miRNA-139/RUNX family transcription

factor 2 (RUNX2) axis promoted the occurrence and apoptosis of OS cells through the mitochondrial apoptotic pathway (48). Overall, lncRNAs and miRNAs act as crucial regulators in the occurrence and development of OS by acting as a ceRNA.

4. Inhibitory effect of lncRNAs on the development of OS

Although most members of the lncRNA family promote the occurrence and development of OS, a number of lncRNAs have been shown to actively inhibit the development of cancer. After systematically collating and analyzing the results described in this review, a number of lncRNAs have been found to have significant inhibitory effects on the occurrence and development of OS.

lncRNAs directly inhibit the occurrence and development of OS. Zhao *et al* (49) showed that the lncRNA HIF2PUT could inhibit the proliferation and migration of OS cells, and the self-renewal of OS stem cells, by upregulating HIF-2 α . Zhao *et al* (50) showed that upregulation of EPIC1 could promote ubiquitin-mediated degradation of myocyte-specific enhancer factor 2, an oncogene important in the development of OS. Therefore, EPIC1 can effectively inhibit the occurrence and progression of OS. Chen *et al* (51) showed that RAB11B-AS1 expression was negatively correlated with RAB11B expression, and thus, RAB11B-AS1 could significantly inhibit the occurrence and development of OS. The results of Qu *et al* (52) showed that lncRNA WW domain containing oxidoreductase (WWOX)-AS1 inhibited the proliferation, migration and invasion of OS cells. The overall survival rate of the high WWOX-AS1 group was higher compared with

Table I. Expression and association of lncRNAs in osteosarcoma.

Chemotherapeutic drug	lncRNA	Deregulation	Genes/proteins affected	Signaling pathway	(Refs.)
Gemcitabine	PVT1	Up	microRNA-152	c-MET/PI3K/AKT	(61)
	KCNQ1OT1	Up	DNMT1/Kcnq1	-	(62)
	TUG1	Up	-	MET/Akt	(63)
CDDP	OIP5-AS1	Up	miR-340-5p/LPAAT β	PI3K/AKT/mTOR	(64)
	ANRIL	Not analyzed	miR-125a-5p	STAT3	(65)
	HOTTIP	Up	-	Wnt/ β -catenin	(69)
	SNHG12	Up	miR-320a/MCL1	-	(66)
DXR	FOXC2-AS1	Up	FOXC2/ABCB1	-	(67)
methotrexate	LUCAT1	Up	miR-200c/ABCB1	-	(68)

Drug resistance of osteosarcoma is one of the most important problems in the clinical treatment of osteosarcoma. Different lncRNAs play an important role in the chemoresistance of osteosarcoma, which is expected to be a breakthrough point to solve this problem. lncRNA, long non-coding RNA; miR, microRNA.

the low WWOX-AS1 group. Therefore, WWOX-AS1 may be associated with the occurrence and development of OS. Furthermore, the molecular mechanism underlying the inhibition of OS by WWOX-AS1 is associated with genes activated by RUNX2. Moreover, Zhao and Ma (53) found that TH19 expression affected the migration and invasion of OS cells by activating the NF- κ B pathway. Zhang *et al* (54), showed that metastasis associated lung adenocarcinoma transcript 1 (MALAT1) inhibited the occurrence and progression of OS by enhancing the expression of angiogenic factors, such as vascular endothelial growth factor A and fibroblast growth factor 2, via positive regulation of the MALAT1/mTOR/hypoxia-inducible factor-1 α pathway. Zhang *et al* (55) and Sun *et al* (56) found that MEG3 could inhibit the growth and metastasis of OS cells by inhibiting the Notch and TGF- β signaling pathways. Overall, lncRNAs directly inhibit the occurrence and development of OS by regulating the proliferation, angiogenesis, and metastasis of OS cells.

The interaction between lncRNAs and miRNAs inhibits the occurrence and development of OS. Guo *et al* (57) found that the lncRNA steroid receptor RNA activator 1 plays an anti-tumor role in OS, via the sponge miRNA-208a, since it decreases cell migration, invasion and proliferation, and promotes apoptosis. Fei *et al* (58) demonstrated that fer-1 like family member 4 inhibits the proliferation, colony formation, migration and invasion of OS cells by regulating the miRNA-18a-5p/PTEN pathway. Han *et al* (59) showed that lncRNA-p21 decreased the proliferation of OS cells *in vivo* and *in vitro*, by inhibiting the expression of miRNA-130b, thus enhancing the anti-tumor effects of PTEN/pAKT. Yang *et al* (60) showed that the expression of lncRNA-neuroblastoma associated transcript 1 (NBAT1) is downregulated in OS tissues and cell lines. The downregulated expression of NBAT1 in OS is closely associated with the clinical stage, lymph node metastasis, and prognosis. In addition, NBAT1 was shown to inhibit OS tumor growth and metastasis *in vivo* by binding miRNA-21. Overall, lncRNAs and miRNAs may inhibit the occurrence and development of OS, by acting as a ceRNA.

5. The role of lncRNAs in OS resistance

At present, the treatment of OS is primarily based on chemotherapy following surgical excision of lesions. In recent decades, with the overall improvement in human health and the development of clinical imaging technology, lesions in some patients with OS are detected early and surgery can be performed before metastasis occurs. However, most patients still require chemotherapy, which contributes to the rapid development of resistance. Chemotherapy resistance of OS is the primary reason for treatment failure at present; determining the intrinsic mechanism of resistance has become an important avenue of research. In addition to their role in the occurrence and development of OS, lncRNAs have also been shown to mediate OS resistance (Table I).

Sun *et al* (61), demonstrated that the lncRNA plasmacytoma variant translocation 1 (PVT1) could enhance the resistance of OS to gemcitabine by directly targeting and downregulating activation of the c-MET/PI3K/AKT pathway by miRNA-152. These results demonstrated that PVT1 not only promotes the occurrence and development of OS, but also enhances the resistance of patients to conventional chemotherapy drugs. Qi *et al* (62), found that knockdown of the lncRNA KCNQ1OT1 inhibited the proliferation, migration and invasion of OS cells, and upregulated potassium voltage-gated channel subfamily Q member 1 through DNA methyltransferase 1, to promote apoptosis and chemosensitivity to cisplatin (DDP). Therefore, KCNQ1OT1 may be an important promoter of the occurrence, development and chemotherapy resistance of OS. Zhou *et al* (63), demonstrated that TUG1 also promoted DDP resistance and inhibited DDP-induced cytotoxicity and apoptosis of Saos-2/DDP and MG-63/DDP cells. Song *et al* (64), showed that opa interacting protein 5 (OIP5)-AS1 silencing led to the accumulation of miR-340-5p and thus inhibited mRNA translation, decreased the protein expression of lysophosphatidic acid acyltransferase β (LPAAT β), and inactivated the PI3K/AKT/mTOR signaling, resulting in decreased cisplatin resistance in OS. In conclusion, OIP5-AS1 induced LPAAT β /PI3K/AKT/mTOR signaling by mutagenizing miRNA-340-5p, resulting in cisplatin resistance in OS. Li and

Zhu (65), demonstrated that ANRIL mediated the proliferation, apoptosis and cisplatin resistance of OS cells by targeting miRNA-125a-5p/STAT3. Zhou *et al* (66), demonstrated that SNHG12 could enhance OS resistance to doxorubicin (DXR) by inhibiting the expression of miRNA-320a and promoting the expression of MCL1. Knockdown of MCL1 could enhance the sensitivity of OS cells to DXR. In addition, the upregulation of MCL1 could attenuate the sensitivity to DXR induced by the knockdown of mimic RNA-320a and SNHG12. Zhang *et al* (67), showed that forkhead box C2 (FOXC2)-AS1, and in particular its FOXC2-overlapping region, exerted these functions by forming RNA-RNA double strands with FOXC2, further increasing the RNA and protein levels of FOXC2 and promoting the expression of ATP binding cassette subfamily B member 1 (ABCB1), a classical multi-drug resistance gene, ultimately resulting in OS resistance to doxorubicin. Han and Shi (68), revealed that lung cancer associated transcript 1 enhances OS resistance to methotrexate by modulating the miRNA-200c ABCB1 pathway. A study by Li *et al* (69), showed that HOXA distal transcript antisense RNA, which is overexpressed in OS, plays an important role in OS proliferation, accelerating cell cycle progression and inducing chemoresistance via the Wnt/ β -catenin pathway. Therefore, the drug resistance of OS is one of the most important problems in the clinical treatment of OS. Different lncRNAs play an important role in the chemoresistance of OS, which are expected to be a breakthrough point to solve this problem.

Resveratrol is a natural antitoxin that has previously been reported to have selective anti-tumor effects on a variety of tumor cells, including OS. Hu *et al* (70), showed that taurine up-regulated 1 (TUG1) was abnormally upregulated in adriamycin-resistant OS cells. Resveratrol can inhibit the proliferation, and promote the apoptosis, of drug-resistant OS cells by inhibiting AKT signaling mediated by TUG1.

6. Summary and prospects

As described in this review, there is ample evidence to support the view that lncRNAs play an important role in the occurrence, growth, invasion, metastasis and drug resistance of OS. Furthermore, it is apparent that different members of the lncRNA family play different roles in OS. Therefore, at present, lncRNAs cannot be defined as cancer initiators or anticancer agents in OS. This will require an understanding of the common mechanisms of lncRNA regulation through exploring the single regulatory roles of different lncRNAs in detail, and determining their associations and mechanism of internal feedback regulation. In this way, important laboratory results can be translated into clinically feasible treatments.

However, it is also important to recognize that current research on the role of lncRNAs in OS is still at the exploratory stage, and there is insufficient evidence to support its use for clinical applications. Nevertheless, it is believed that the current experimental results support lncRNAs as future biomarkers and therapeutic targets in the diagnosis and prognosis of OS.

lncRNAs are used as biomarkers for early diagnosis of OS. lncRNAs play an important regulatory role in OS

tumorigenesis, tumor cell proliferation, invasion, migration, apoptosis and angiogenesis. lncRNAs can be secreted and circulated in bodily fluids. As lncRNAs secreted in the circulation are resistant to RNase, PCR could be used to clinically detect the presence of lncRNAs. Recent reports have indicated lncRNAs as good candidates for tumor markers with high specificity, sensitivity and non-invasive characteristics (71,72).

It is believed that the detection of lncRNAs using readily available clinical specimens, such as blood and articular puncture fluid, could revolutionize the early diagnosis of OS. If early diagnosis of OS can be made, the efficacy of early clinical treatments will be improved.

lncRNAs serve as a molecular target for OS biotherapy. Cancer treatment based on biological targeting technology has been gradually accepted and promoted by clinicians. This type of precise cancer treatment, which shows good therapeutic effects and fewer side effects, represents an important breakthrough. lncRNAs can be targeted using small interfering RNA, antisense oligonucleotides, ribozymes, aptamers and miRNAs; these methods have long been used to target important cancer-associated genes, and are at different stages of clinical trials (73,74). Overall, lncRNAs, which regulate the development of OS, may be a molecular target for OS biotherapies.

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Authors' contributions

YZ and YP conceived the review. YZ, ZL, and JW wrote the review. ZL and HW revised the review. YP proofread the manuscript and revised the manuscript for important intellectual content. All authors have read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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