Role of long noncoding RNAs in the regulation of epithelial-mesenchymal transition in osteosarcoma (Review)

ZIHAN LI[1] and YIHAO TIAN[2]

[1]Shengjing Hospital of China Medical University, Shenyang, Liaoning 110004, P.R. China; [2]Department of Pathology, General Hospital of Northern Theater Command, Beifang Hospital of China Medical University, Shenyang, Liaoning 110004, P.R. China

Received September 17, 2024; Accepted December 16, 2024

DOI: 10.3892/or.2025.8868

Abstract. Osteosarcoma (OS) is one of the most widespread malignant bone tissue tumors. However, its early diagnosis is difficult, leading to poor prognoses. Long noncoding RNA (lncRNA) can serve as a molecular marker for the early diagnosis and treatment of OS. lncRNAs regulate the epithelial-mesenchymal transition (EMT) process to control the occurrence and progression of OS. The present review summarizes the studies on lncRNA regulation of OS via the EMT process. A search of the PubMed database yielded 93 published articles since January 2015, of which 73 focused on lncRNA regulation of OS via the EMT process. The present review has classified lncRNAs based on their relationship with tumors (promoting or inhibiting), mechanism of action and naming convention. Most lncRNAs promote OS through EMT and act via microRNA sponging. Previous studies have focused on lncRNAs with known functions, antisense lncRNAs and long intergenic noncoding RNAs. The findings indicated that lncRNAs can regulate the EMT process through various mechanisms to control OS progression. Further studies on specific lncRNAs and their underlying mechanisms will provide insights for the development of strategies for the diagnosis, prevention and treatment of OS.

Correspondence to: Dr Yihao Tian, Department of Pathology, General Hospital of Northern Theater Command, Beifang Hospital of China Medical University, 83 Wenhua Road, Shenhe, Shenyang, Liaoning 110004, P.R. China
E-mail: 18940121470@163.com

Abbreviations: OS, osteosarcoma; EMT, epithelial-mesenchymal transition; lncRNA, long noncoding RNA; lincRNA, long intergenic noncoding RNA; ZEB, zinc finger E-box binding homeobox; ZO-1, zonula occludens-1; ceRNA, competing endogenous RNA; 3'-UTR, 3'-untranslated region; BCRT1, breast cancer-related transcript 1; EBLN3P, endogenous bornavirus-like nucleoprotein three pseudogene; FGF7, fibroblast growth factor 7; PCGEM1, prostate-specific transcript 1; OGT, O-GlcNAc transferase; HCG11, HLA complex group 11; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; NDRG1, N-Myc downstream-regulated gene 1; NEAT1, nuclear enriched abundant transcript 1; HIF-1α, hypoxia-inducible factor-1α; PURPL, p53-upregulated regulator of p53 levels; SNHG, small nucleolar RNA host gene; ITGA6, integrin subunit α6; TUG1, taurine-upregulated gene 1; EZH2, enhancer of zeste homolog 2; XIST, X inactive-specific transcript; CBR3-AS1, carbonyl reductase antisense RNA 1; CDKN2B-AS1, cyclin-dependent kinase inhibitor 2B antisense RNA 1; DDX11-AS1, DEAD/H box protein 11 antisense RNA 1; GPRC5A, G protein-coupled receptor class C group 5 member A; FOXD3-AS1, forkhead box D3 antisense RNA 1; ZCCHC3, zinc finger CCHC-type containing 3; ZFAS1, zinc finger antisense 1; WNT2B, Wnt family member 2B; CASC15, cancer susceptibility candidate 15; CRNDE, colorectal neoplasia differentially expressed; FAL1, focally amplified lncRNA on chromosome 1; GHET1, gastric cancer high expressed transcript 1; HOTTIP, HOXA transcript at the distal tip; MINCR, Myc-induced long noncoding RNA; MSTO2P, pseudogene Minato family member 2; PVT1, plasmacytoma variant translocation 1; lnc-TCF7, long non-coding RNA T-cell factor 7; TDRG1, testis development-related 1; AFAP1-AS1, actin filament-associated protein 1 antisense RNA 1; HNF1A-AS1, hepatocyte nuclear factor 1 homeobox A antisense RNA 1; SPRY4-IT1, sprouty RTK signaling antagonist 4-intronic transcript 1; FER1L4, FER-1 family member 4; GAS5, growth arrest-specific transcript 5; TUSC, tumor suppressor candidate

Key words: antisense, EMT, lincRNA, lncRNA, microRNA, OS

Contents

1. Introduction

Osteosarcoma (OS) is the most common primary malignant bone tumor (1,2), and it substantially impacts bone structure and function (3). Research on OS has increased with continuous development of science and technology. Using the key word 'osteosarcoma', relevant articles were searched in PubMed (https://pubmed.ncbi.nlm.nih.gov/) and it was observed that the number of studies on OS has been increasing annually between 2000 and 2021 (Fig. 1A). Early detection and accurate staging of OS are critical in predicting the clinical prognosis (4,5). Currently, the early diagnosis of OS primarily relies on X-ray imaging and local symptoms (6), and

there are no reliable biomarkers available, leading to untimely diagnosis and a poor prognosis (7,8). Therefore, specific molecular markers, such as long noncoding RNAs (lncRNAs), are required in addition to understanding their biological role. This may lead to the development of strategies that block lncRNAs that promote tumor development while boosting lncRNAs that inhibit tumor development.

lncRNAs are transcripts with a length of >200 nucleotides that do not exhibit protein-coding potential (9). As the most common type of noncoding RNA (10,11), lncRNAs have attracted increasing attention. Using the key word 'lncRNA', relevant articles were searched in PubMed and it was observed that lncRNA research has been increasing annually between 2000 and 2021 (Fig. 1B). The Human Genome Organisation Gene Nomenclature Committee has suggested that lncRNAs should be named based on their function when possible. For genes with unknown function, if there is a closely related protein-coding gene, the name of the lncRNA should begin with the name of the coding gene, followed by a suffix indicating its target location, such as antisense, intronic and opposite strand. Regarding the nomenclature of long intergenic noncoding RNAs (lincRNAs), 'linc' is used as the prefix and numbers as the suffix (12). In some physiological and pathological processes, through regulation of the expression of genes that promote or inhibit tumors, lncRNAs serve an essential role in regulating cell proliferation, apoptosis, invasion, metastasis and epithelial-mesenchymal transition (EMT) (13). lncRNAs act by adsorbing microRNAs (miRNAs/miRs), affecting the expression of downstream target genes (14).

EMT is essential for tumor genesis and development (15-18). Multiple studies have indicated that successful tumor treatment can be achieved through EMT intervention, which may also provide strategies for tumor prevention (19-22). The level of EMT can be determined by measuring the expression levels of a series of related proteins, such as interstitial and epithelial markers (23-25). The upregulation of EMT is manifested through the upregulation of mesenchymal markers [Snail, Zinc finger E-box binding homeobox 1 (ZEB1), ZEB2, vimentin, N-cadherin and fibronectin] and the downregulation of epithelial markers [E-cadherin and zonula occludens-1 (ZO-1)]. The downregulation of EMT is manifested by the downregulation of mesenchymal markers and the upregulation of epithelial markers (23-25).

Using the key words 'osteosarcoma', 'lncRNA' and 'EMT', relevant articles were searched in PubMed and 93 articles published between January 2015 and December 2023 were identified. After further screening, 73 articles that met the review criteria were selected and each article was examined independently. The other 20 articles may be reviews or retrospective clinical studies that only mentioned the aforementioned keywords, and were excluded. Based on the relationship between lncRNAs and OS, lncRNAs were divided into upregulated genes (promoting tumor development) and downregulated genes (inhibiting tumor development). Based on their putative biological effect on downstream genes, the lncRNAs were further divided into two categories: Those affecting downstream genes through adsorption of miRNAs and those affecting downstream genes through other mechanisms. Finally, based on the lncRNA-naming principle, lncRNAs were categorized as lncRNAs with known function, antisense lncRNAs, lincRNAs and intronic lncRNAs.

There are numerous studies on OS, lncRNAs and EMT, as well as the biological roles of lncRNA, and it is necessary to summarize the findings of studies on lncRNA regulation of OS occurrence and development through EMT, examine the underlying regulatory mechanisms, and provide a novel theoretical basis and targets for OS treatment. We hypothesized that the underlying regulatory mechanism is a comprehensive, systematic network rather than a single pathway.

2. lncRNAs promoting OS

By reviewing and organizing relevant articles on lncRNAs and OS, it was revealed that most lncRNAs promote the EMT process, leading to the occurrence and development of OS.

miRNA sponging. miRNAs induce gene silencing by binding to the mRNA of target genes. lncRNAs regulate gene expression by competitively binding to miRNAs. This process is known as the competing endogenous RNA (ceRNA) mechanism. This section discusses how lncRNAs promote the EMT process through the ceRNA mechanism, resulting in OS progression.

lncRNAs with known functions. Some well-studied lncRNAs, including breast cancer-related transcript 1 (BCRT1) and endogenous bornavirus-like nucleoprotein three pseudogene (EBLN3P), are named based on their known function. The present review discusses some lncRNAs with known functions that promote the occurrence of OS through the ceRNA mechanism.

In addition to inducing EMT, high expression levels of BCRT1 promote OS progression and the cell cycle. Research has indicated that high BCRT1 expression decreased the expression levels of miR-1303 in MG-63 cells. Fibroblast growth factor 7 (FGF7) is a target gene of miR-1303 in OS cells (26). BCRT1 promotes OS cell reproduction by regulating FGF7 expression, and promoting the process of EMT and the secretion of inflammatory mediators (26).

A decrease in miR-200a-3p expression results in the upregulation of its direct target gene O-GlcNAc transferase (OGT), which further promotes EMT in OS cells. The expression of the lncRNA EBLN3P is upregulated in OS. This lncRNA increases the methotrexate resistance of OS cells by downregulating miR-200a-3p expression, promoting EMT and increasing OGT expression (27).

Upregulation of the lncRNA HLA complex group 11 (HCG11) has been reported in OS tissues and cells. The cytoplasmic lncRNA HCG11 increases the expression levels of MMP13 by adsorbing miR-579. Downregulation of HCG11/MMP13 or upregulation of miR-579 suppresses EMT in OS cells (28).

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) expression is upregulated in OS tissues and cells. MALAT1 knockdown induces apoptosis while inhibiting the proliferation, migration, invasion and EMT of OS cells. In OS cells, MALAT1 knockdown upregulates the expression levels of miR-590-3p. MALAT1 inhibits apoptosis, and induces the proliferation, migration, invasion and EMT of OS cells by inhibiting miR-590-3p expression (29).

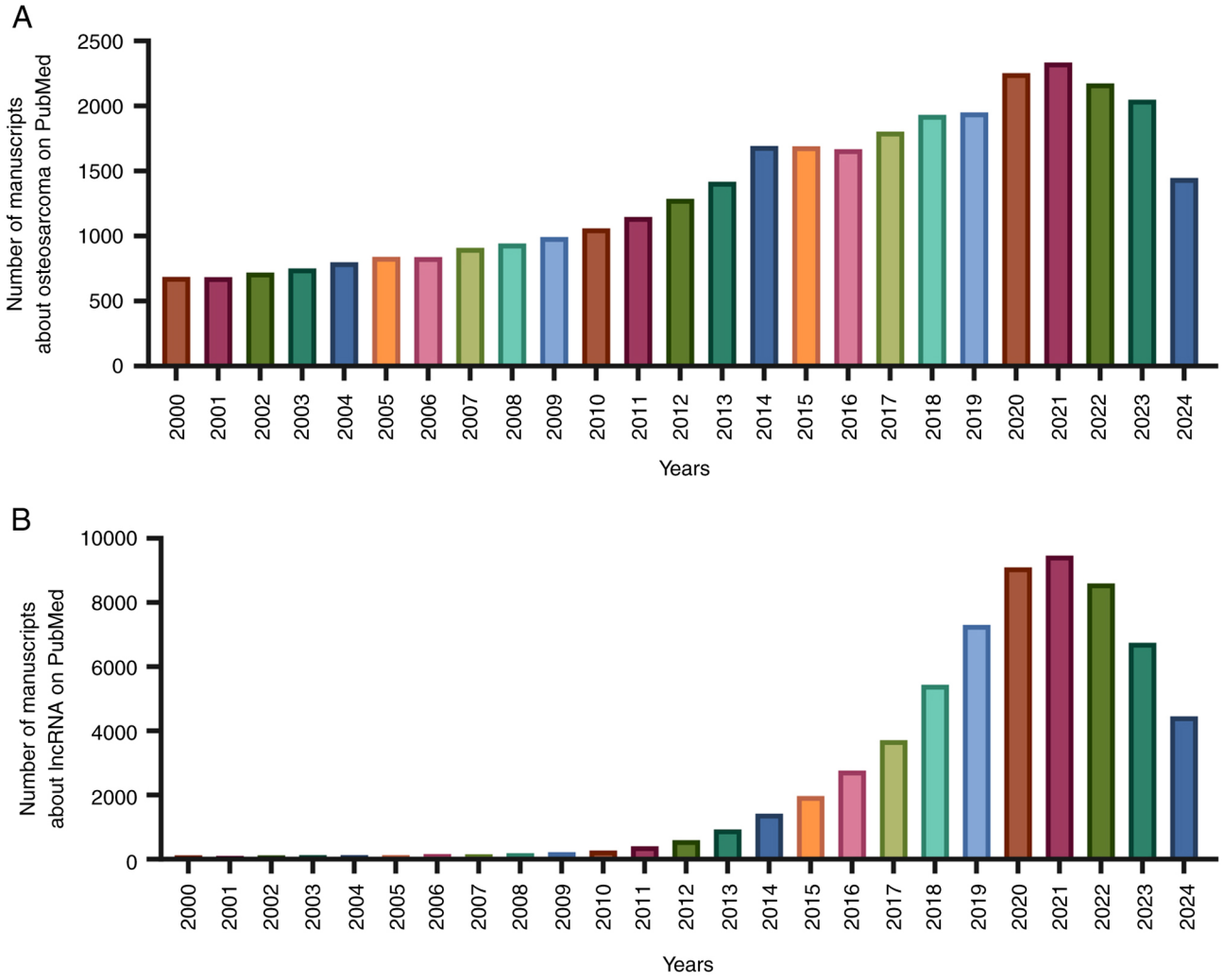

Figure 1. Research trends. (A) Number of articles since 2000 containing the term 'osteosarcoma'. (B) Number of articles since 2000 containing the term 'lncRNA'. lncRNA, long noncoding RNA.

MIR31 host gene expression is upregulated in OS tissues and cells. In OS cells, its upregulation promotes the expression of genes related to the proliferation and metastasis of tumor cells that are downstream of miR-361, including vascular endothelial-derived growth factor, Forkhead box M1 and Twist, resulting in the upregulation of BCL2 and cyclin D1, and EMT (30).

The lncRNA N-Myc downstream-regulated gene 1 (NDRG1) is highly expressed in OS cells and tissues. NDRG1 aggravates OS progression and activates the PI3K/AKT pathway by adsorbing miR-96-5p. This is completed through EMT (31).

Nuclear enriched abundant transcript 1 (NEAT1) is highly expressed in OS tissues and cells. Upregulation of NEAT1 promotes the proliferation, invasion and EMT of OS cells. Furthermore, miR-186-5p is located downstream of NEAT1 in OS cells, and hypoxia-inducible factor-1α (HIF-1α) is a downstream target gene of miR-186-5p. NEAT1 inhibits the expression of miR-186-5p/HIF-1α and serves a tumorigenic role in OS cells (32).

Low expression of miR-483 has been noted in OS tissues and cells. Upregulation of miR-483 suppresses the expression of EMT-related markers in U2OS cells. miR-483 targets the 3'-untranslated region (3'-UTR) of STAT3, thereby inhibiting its expression. NEAT1 increases the expression levels of STAT3, which inhibits STAT1 expression, by adsorbing miR-483, and increases the EMT of OS cells. NEAT1 knockdown disrupts the mesenchymal-epithelial transition at the metastatic site of OS (33).

Prostate-specific transcript 1 (PCGEM1) knockdown inhibits the proliferation, migration, invasion and EMT of OS cells. The lncRNA PCGEM1 is a direct target of miR-433-3p. Research has demonstrated that *OMA1* is a direct target gene of miR-433-3p (34).

Upregulation of p53-upregulated regulator of p53 levels (PURPL) expression promotes the proliferation, migration, invasion and EMT of MG-63 cells. PURPL is a regulator of miR-363 expression and is located upstream of miR-363. miR-363 serves a tumor-suppressive role in OS cells by reducing the expression of PDZ domain containing 2 (35).

Small nucleolar RNA host gene (SNHG)1 expression is upregulated in OS tissues and cells. miR-577 acts as a ceRNA of SNHG1 in OS cells. As a direct target gene of miR-577, Wnt family member 2B (WNT2B) activates the Wnt/β-catenin pathway and acts as a carcinogenic factor in OS cells. SNHG1 overexpression promotes the proliferation, migration, EMT and tumor growth of U2OS and MG63 cells (36).

High SNHG7 levels in patients with OS are associated with a high Enneking stage, remote metastasis and shorter overall survival time. Inhibiting SNHG7 expression can restore miR-34a expression in MG63 and SaOS2 OS cells. SNHG7 knockout inhibits the viability, migration, invasion and EMT of OS cells (37).

Compared with those in healthy tissues, SNHG10 levels in OS tissues are increased. SNHG10 can regulate the expression of frizzled class receptor 3 (FZD3) by sponging miR-182-5p. The SNHG10/miR-182-5p/FZD3 axis increases the transfer into the nucleus and accumulation of β-catenin in the nucleus to activate the Wnt signaling pathway. SNHG10 serves an important role in accelerating the proliferation, invasion and EMT of OS cells (38).

The expression levels of SNHG16 and integrin subunit α6 (ITGA6) are increased in OS, while the expression levels of miR-488 are decreased. miR-488 overexpression and SNHG16 knockdown inhibit the migration, invasion and EMT of OS cells. Thus, the effect of SNHG16 on the aforementioned processes depends on miR-488 and ITGA6 (39).

Taurine-upregulated gene 1 (TUG1) knockout inhibits the proliferation, migration and invasion of OS cells, and induces apoptosis. TUG1 regulates miR-144-3p expression through direct binding. Enhancer of zeste homolog 2 (EZH2) is negatively regulated by miR-144-3p and positively regulated by TUG1. *EZH2* overexpression partially weakens the inhibition of the migration and EMT of OS cells induced by TUG1 knockdown or miR-144-3p overexpression (40).

Urothelial carcinoma-associated 1 (UCA1) expression is upregulated in OS tissues and cells. UCA1 increases the expression of cAMP response element-binding protein 1 (CREB1) by acting as a ceRNA of anti-miR-582. UCA1 promotes EMT through the PI3K/AKT/mTOR pathway mediated by CREB1, resulting in metastasis (41).

Compared with matched adjacent nontumor tissues, X inactive-specific transcript (XIST) was highly expressed in 30 pairs of OS tissues. XIST upregulation promotes the invasion, migration and EMT phenotype of OS tissues, and decreases the expression levels of the epithelial marker E-cadherin. However, the interstitial markers fibronectin, Snail and vimentin are upregulated by exogenous XIST (42). XIST downregulates miR-153 directly through a sponging process. The mesenchymal marker snail family transcriptional repressor 1 (SNAI1) is the direct target gene of miR-153. Inhibition of XIST suppresses the EMT of OS cells induced by H_2O_2. XIST promotes the invasion, migration and EMT of OS cells induced by oxidative stress through the miR-153/SNAI1 pathway (42).

XIST is highly expressed in OS tissues and cells, whereas miR-758 expression is low. XIST overexpression and miR-758 inhibitor transfection in OS cells promote the migration, invasion and EMT of tumor cells. By contrast, knockdown of XIST and miR-758 mimic transfection inhibits the aforementioned processes. Furthermore, miR-758 regulates Rab16 expression. XIST promotes the migration, invasion and EMT of OS cells by regulating the miR-758/Rab16 axis (43) (Table I; Fig. 2A).

A total of 16 lncRNAs with known functions that promote the occurrence of OS through the ceRNA mechanism were identified. NEAT1 and XIST were identified twice as 'high-frequency' lncRNAs. NEAT1 promotes EMT through the miR-186-5p/HIF-1α and miR-483/STAT3 axes (32,33), leading to OS progression. XIST promotes EMT through the miR-153/SNAI1 and miR-758/Rab16 axes (42,43), resulting in OS progression.

Antisense lncRNAs. Antisense lncRNAs are transcribed from opposite DNA strands with protein-coding or noncoding functions that contribute to the occurrence and development of OS and other tumors. The present review discusses some antisense lncRNAs that promote the occurrence of OS through the ceRNA mechanism.

Carbonyl reductase antisense RNA 1 (CBR3-AS1) is highly expressed in OS cells, which can enhance the stemness, EMT and proliferation of these cells (44). The lncRNA CBR3-AS1 adsorbs miR-140-5p, recruits DEAD-box helicase 54, and induces the expression of nuclear casein and cyclin-dependent kinase substrate 1, activating the mTOR signaling pathway (44).

Cyclin-dependent kinase inhibitor 2B antisense RNA 1 (CDKN2B-AS1) is upregulated in OS tissues and cells. CDKN2B-AS1 knockout inhibits the proliferation, migration and EMT of OS cells. CDKN2B-AS1 promotes OS progression by adsorbing miR-4458 and enhancing MAP3K3 expression (45).

DEAD/H box protein 11 antisense RNA 1 (DDX11-AS1) is highly expressed in OS cells. Decreased DDX11-AS1 expression inhibits the proliferation, metastasis and EMT of OS cells. DDX11-AS1 induces DDX11 expression in OS by sponging miR-873-5p. DDX11-AS1 maintains DDX11 mRNA levels by binding to insulin-like growth factor 2 mRNA-binding protein 2 in OS cells (46).

High expression levels of DSCAM antisense RNA 1 (DSCAM-AS1) have been reported in OS cell lines. Depletion of DSCAM-AS1 inhibits the proliferation, migration and EMT of OS cells. DSCAM-AS1 is primarily located in the cytoplasm of OS cells and interacts with miR-186-5p. G protein-coupled receptor class C group 5 member A (GPRC5A) is the downstream target of miR-186-5p. GPRC5A is inversely regulated by miR-186-5p but is cooperatively regulated by DSCAM-AS1, which induces GPRC5A expression in OS by chelating miR-186-5p (47).

Increased expression of forkhead box D3 antisense RNA 1 (FOXD3-AS1) is observed in OS tissues and cells. Decreased expression of FOXD3-AS1 inhibits the migration, invasion and EMT of OS cells. FOXD3-AS1 increases zinc finger CCHC-type containing 3 (ZCCHC3) by chelating miR-296-5p. Activated FOXD3-AS1 increases ZCCHC3 expression by adsorbing miR-296-5p, which aggravates the migration, invasion and EMT of OS cells (48).

HOXA-AS2 is upregulated in OS tissues. HOXA-AS2 induces the migration and invasion of OS cells by promoting EMT, and inversely regulates miR-520c-3p expression in OS cells (49).

LMCD1 antisense RNA 1 (LMCD1-AS1) and SP1 are highly expressed in OS tissues and cells. Functionally, silencing of LMCD1-AS1 inhibits the proliferation, migration, invasion and EMT of OS cells. LMCD1-AS1 regulates the survival of OS cells by targeting miR-106b-5p (50).

The lncRNA PGM5 antisense RNA 1 (PGM5-AS1) can competitively bind to miR-140-5p to regulate fibrillin 1 (FBN1). Furthermore, blocking PGM5-AS1 and FBN1 expression or

Table I. lncRNAs with known functions acting as miRNA sponges.

First author/s, year	lncRNA	Relationship with OS	Relationship with EMT	Action mechanism	(Refs.)
Han *et al*, 2021	BCRT1	Promotes the proliferation and cell cycle of OS cells	Promotes EMT	Reduces the expression levels of miR-1303; FGF7 is the target gene of miR-1303	(26)
Sun *et al*, 2022	EBLN3P	Increases MTX resistance of OS cells	Promotes EMT	Downregulates miR-200a-3p, and then increases the expression levels of OGT	(27)
Wang *et al*, 2020	HCG11	Promotes the progression of OS cells	Promotes EMT	Adsorbs miR-579 and promotes MMP13 expression	(28)
Zhao *et al*, 2022	MALAT1	Inhibits the apoptosis of OS cells, and promotes the proliferation, migration and invasion of OS cells	Promotes EMT	Inhibition of miR-590-3p expression in OS	(29)
Sun *et al*, 2019	MIR31HG	Upregulated expression in OS tissues and OS cell lines	Promotes EMT	Promotes downstream target genes of MIR-361, including VEGF, FOXM1 and Twist	(30)
Wang *et al*, 2022	NDRG1	Aggravates the progression of OS	Promotes EMT	Adsorbs miR-96-5p and activates the PI3K/AKT pathway	(31)
Tan and Zhao, 2019	NEAT1	Promotes the proliferation and invasion of OS cells	Promotes EMT	Inhibits the miR-186-5p/HIF-1 α axis	(32)
Chen *et al*, 2021	NEAT1	Facilitates OS metastasis	Promotes EMT	Adsorbs miR-483, increases STAT3 expression and inhibits STAT1 expression	(33)
Li *et al*, 2023	PCGEM1	Promotes cell proliferation, migration and invasion in OS	Promotes EMT	Directly binds with miR-433-3p; OMA1 is the target gene of miR-433-3p	(34)
He *et al*, 2021	PURPL	Promotes the proliferation, migration and invasion of MG-63 cells	Promotes EMT	PURPL is the upstream regulator of miR-363, which reduces PDZD2 expression	(35)
Jiang *et al*, 2018	SNHG1	Promotes the proliferation, migration and tumor growth of U2OS and MG63 cells	Promotes EMT	miR-577 acts as the ceRNA of SNHG1, WNT2B acts as the target of miR-577 and WNT2B activates the Wnt/β-catenin axis	(36)
Deng *et al*, 2018	SNHG7	Improves the viability, migration and invasion of MG63 and SaOS2 cells	Promotes EMT	Inhibition of miR-34a expression	(37)
Zhu *et al*, 2020	SNHG10	Promotes OS growth and invasion	Promotes EMT	Sponges miR-182-5p to upregulate FZD3 levels, and promotes β-catenin transfer into the nucleus and accumulation in the nucleus to maintain the activation of Wnt signaling	(38)
Bu *et al*, 2021	SNHG16	Promotes the migration and invasion of OS cells	Promotes EMT	Downregulates miR-488 and upregulates ITGA6	(39)
Cao *et al*, 2017	TUG1	Promotes OS cell proliferation, migration and invasion, and inhibits cell apoptosis	Promotes EMT	Directly combines with miR-144-3p; EZH2 is negatively regulated by miR-144-3p	(40)
Ma *et al*, 2019	UCA1	Causes OS metastasis	Promotes EMT	Increases CREB1 expression as an anti-miR-582 ceRNA, thus activating the PI3K/AKT/mTOR pathway	(41)

Table I. Continued.

First author/s, year	lncRNA	Relationship with OS	Relationship with EMT	Action mechanism	(Refs.)
Wen *et al*, 2020	XIST	Induces OS cell invasion and migration	Promotes EMT	Directly downregulates miR-153; SNAI1 is the direct target of miR-153	(42)
Liu *et al*, 2021	XIST	Promotes OS cell migration and invasion	Promotes EMT	Inhibits the miR-758/Rab16 axis	(43)

ceRNA, competing endogenous RNA; EMT, epithelial-mesenchymal transition; lncRNA, long noncoding RNA; miRNA/miR, microRNA; MTX, methotrexate; OS, osteosarcoma.

increasing miR-140-5p expression inhibits the migration, invasion and EMT of OS cells (51).

The expression of RUSC1 antisense RNA 1 (RUSC1-AS1) in U2OS and HOS cells is upregulated compared with that in hFOB1.19 cells. RUSC1-AS1 promotes the EMT of OS cells and directly binds to the 3'-UTR of miR-340-5p to inhibit its expression and activate the PI3K/AKT pathway (52).

RUSC1-AS1 and *Notch1* are upregulated in OS cells and tissues. RUSC1-AS1 knockdown suppresses the proliferation, EMT, lung metastasis, migration and invasion of MG-63 and Saos-2 cells. RUSC1-AS1 acts as a ceRNA. RUSC1-AS1 competitively adsorbs miR-101-3p and upregulates the expression levels of Notch1, interfering with the malignant phenotype. RUSC1-AS1 is a novel carcinogenic lncRNA expressed in OS. RUSC1-AS1 exerts its biological effect via the miR-101-3p-Notch1-Ras-ERK axis (53).

TMPO antisense RNA 1 (TMPO-AS1) is upregulated in OS cells. TMPO-AS1 binds to miR-329, which targets the E2F transcription factor 1 (E2F1) gene. TMPO-AS1 regulates the EMT of OS cells via the miR-329/E2F1 axis (54).

In OS cells, the expression levels of TTN-antisense RNA 1 (TTN-AS1) and transcription factor activating enhancer binding protein 4 (TFAP4) are upregulated, whereas those of miR-16-1-3p are downregulated. Silencing of TTN-AS1 inhibits the proliferation, migration, invasion and tumor growth of OS cells, as well as the expression of N-cadherin and MMP-2 in these cells. TTN-AS1 promotes the proliferation, migration, invasion and EMT of OS cells by inhibiting the miR-16-1-3p/TFAP4 pathway (55).

Depletion of neuropilin and tolloid-like 2 (NETO2) inhibits the proliferation, migration, invasion and EMT of OS cells. NETO2 binds to and is negatively regulated by miR-101-3p, which interacts with TYMS opposite-strand RNA in OS cells (56).

The lncRNA zinc finger antisense 1 (ZFAS1) is upregulated in OS cells. Overexpression of ZFAS1 promotes the proliferation, migration, invasion and EMT of OS cells, while silencing of ZFAS1 has the opposite effect. With regard to its mechanism, ZFAS1 acts as a sponge for miR-520b and miR-50e, while upregulating the expression levels of Ras homolog C (RHOC) (57) (Table II; Fig. 2B).

A total of 14 studies of 13 antisense lncRNAs that promote the occurrence of OS through the ceRNA mechanism were identified. RUSC1-AS1 has been studied twice as a 'high-frequency' lncRNA. RUSC1-AS1 promotes EMT through the miR-340-5p/PI3K/AKT and miR-101-3p-Notch1-Ras-ERK axes (52,53), which results in OS progression.

lincRNAs. lincRNAs are RNAs that contribute to the occurrence of various tumors, including OS. This section discusses some lincRNAs that promote the occurrence of OS through the ceRNA mechanism.

LINC00467 and high-mobility-group A1 (HMGA1) are highly expressed in OS tissues and cells, whereas miR-217 expression is low. Knockout of LINC00467 or miR-217 mimics can induce apoptosis, while inhibiting the proliferation, migration, invasion and EMT of OS cells. LINC00467 directly targets miR-217, whereas HMGA1 is the target of miR-217 (58). LINC00467 upregulates HMGA1 expression by targeting miR-217, and enhances the proliferation, migration, invasion and EMT of OS cells (58).

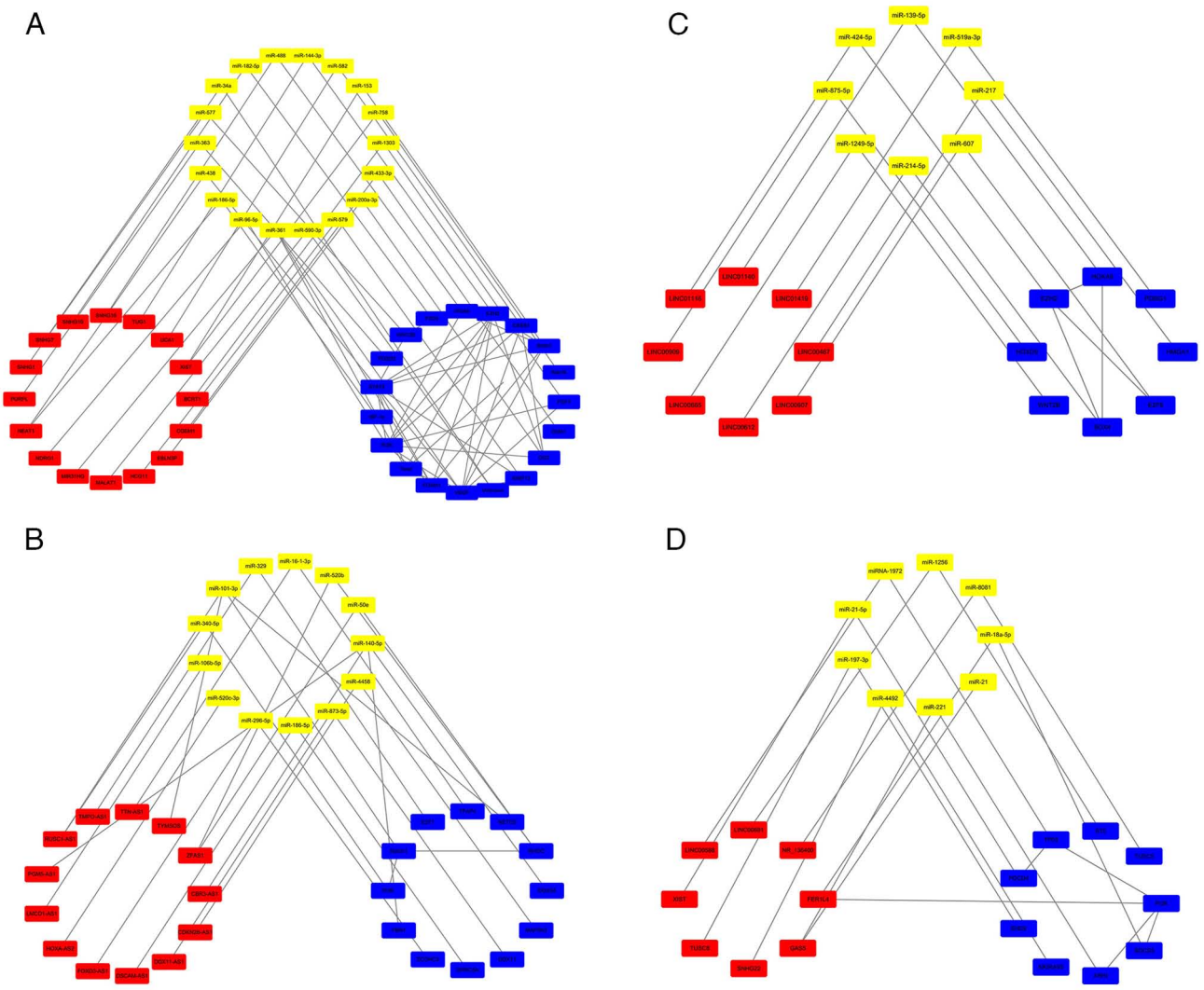

Figure 2. ceRNA network of lncRNAs. (A) ceRNA network of lncRNAs with known functions. (B) ceRNA network of antisense lncRNAs. (C) ceRNA network of lincRNAs and opposite-strand lncRNAs. (D) ceRNA network of lncRNAs inhibiting tumor progression. Red, lncRNA; yellow, miRNA; blue, mRNA. The networks were based on the studies mentioned in the text and were generated using Cytoscape_3.10.0 (https://cytoscape.org/). ceRNA, competing endogenous RNA; lncRNA, long noncoding RNA; miRNA/miR, microRNA; lincRNA, long intergenic noncoding RNA.

LINC00607 promotes the proliferation, migration and invasion of OS cells, as well as the migration and invasion of endothelial cells, thereby simultaneously enhancing EMT. LINC00607 upregulates the expression levels of E2F6 through miR-607, which promotes the proliferation of OS cells (59).

LINC00612 is highly expressed in metastatic OS cells. LINC00612 upregulation regulates EMT by increasing the expression levels of ZEB1, Snail and fibronectin 1, and decreasing those of E-cadherin. LINC00612 overexpression upregulates SOX4 expression by inhibiting miR-214-5p (60).

LINC00665 is highly expressed in OS cells, and its suppression inhibits the proliferation, migration, invasion and EMT of OS cells. LINC00665 acts as a ceRNA to adsorb miR-1249-5p, regulating WNT2B to activate the Wnt pathway, which induces LINC00665 expression, forming a positive feedback loop (61).

LINC00909 expression is upregulated in OS cells and tissues. LINC00909 induces EMT, while contributing to the ongoing metastasis of OS tumors. LINC00909 adsorbs miR-875-5p to exert its biological effect. Homeobox D9 (HOXD9) has been confirmed to be a target gene of miR-875-5p. LINC00909 upregulates HOXD9 expression by binding to miR-875-5p, induces EMT, and promotes the occurrence and metastasis of OS tumors through the PI3K/AKT/mTOR axis (62).

LINC01116 expression in MG-63/Dox cells is higher than that in MG-63 cells. The inhibition of LINC01116 expression impedes the viability, migration and invasion of these cells by upregulating the expression levels of E-cadherin and downregulating those of vimentin, thereby inhibiting EMT. LINC01116 inhibits HMGA2 expression by silencing EZH2-related miR-424-5p (63).

LINC01140 is expressed in OS cells, and its silencing inhibits the proliferation, invasion and EMT of these cells. LINC01140 adsorbs miR-139-5p, which inhibits the invasion, proliferation and EMT of Saos2 and MG63 cells by targeting HOXA9. Silencing of LINC01140 inhibits the invasion, proliferation and EMT of OS cells via the miR-139-5p/HOXA9 pathway (64).

LINC01419 is highly expressed in OS tissues and cells, and enhances the proliferation, metastasis and EMT of OS

Table II. Antisense lncRNAs acting as miRNA sponges.

First author/s, year	lncRNA	Relationship with OS	Relationship with EMT	Action mechanism	(Refs.)
Yao *et al*, 2022	CBR3-AS1	Promotes the stemness of OS cells and the growth of OS	Promotes EMT	Adsorbs miR-140-5p and recruits DDX54 to upregulate NUCKS1, thus activating the mTOR pathway	(44)
Gui and Cao, 2020	CDKN2B-AS1	Promotes cell proliferation and migration in OS	Promotes EMT	Adsorbs miR-4458 and enhances MAP3K3 expression	(45)
Zhang *et al*, 2020	DDX11-AS1	Promotes the proliferation and metastasis of OS cells	Promotes EMT	Sponges miR-873-5p to upregulate DDX11 expression; combines with IGF2BP2 to regulate the mRNA stability of DDX11	(46)
Ning and Bai, 2021	DSCAM-AS1	Promotes cell proliferation and migration in OS	Promotes EMT	Chelates miR-186-5p to enhance GPRC5A expression	(47)
Wang, 2021	FOXD3-AS1	Promotes cell migration and invasion in OS	Promotes EMT	Adsorbs miR-296-5p and increases ZCCHC3 expression	(48)
Wang *et al*, 2018	HOXA-AS2	Promotes OS cell migration and invasion	Promotes EMT	Negative regulation of miR-520c-3p expression	(49)
He *et al*, 2020	LMCD1-AS1	Promotes the proliferation, migration and invasion of OS cells	Promotes EMT	Targets miR-106b-5p	(50)
Liu *et al*, 2020	PGM5-AS1	Promotes the migration and invasion of OS cells *in vitro*	Promotes EMT	Combines with miR-140-5p to upregulate FBN1 expression	(51)
Tong *et al*, 2021	RUSC1-AS1	Upregulated in U2OS and HOS cells compared with hFOB1.19 cells	Promotes EMT	Suppresses miR-340-5p and activates the PI3K/AKT signaling pathway	(52)
Jiang *et al*, 2021	RUSC1-AS1	Enhances the proliferation, growth, lung metas tasis, migration and invasion of MG-63 and Saos-2 cells	Promotes EMT	Via miR-101-3p-Notch1-Ras-ERK pathway	(53)
Liu *et al*, 2020	TMPO-AS1	Upregulated expression in OS cells	Promotes EMT	Via the miR-329/E2F1 axis	(54)
Meng *et al*, 2021	TTN-AS1	Promotes OS cell proliferation, migration and invasion	Promotes EMT	Mediates the miR-16-1-3p/TFAP4 axis	(55)
Zhang *et al*, 2022	TYMSOS	Promotes OS cell proliferation, migration and invasion	Promotes EMT	NETO2 is directly targeted by miR-101-3p, which can be combined with TYMSOS	(56)
Liu *et al*, 2023	ZFAS1	Promotes the proliferation, migration and invasion of OS cells	Promotes EMT	Serves as a sponge for miR-520b and miR-50e, and upregulates RHOC	(57)

EMT, epithelial-mesenchymal transition; lncRNA, long noncoding RNA; miRNA/miR, microRNA; OS, osteosarcoma.

Table III. Long intergenic noncoding RNAs and opposite strand lncRNAs acting as miRNA sponges.

First author/s, year	lncRNA	Relationship with OS	Relationship with EMT	Action mechanism	(Refs.)
Ma *et al*, 2020	LINC00467	Reduces OS cell apoptosis, and promotes OS cell proliferation, migration and invasion	Promotes EMT	Targets miR-217 and upregulates HMGA1	(58)
Zheng *et al*, 2020	LINC00607	Promotes OS proliferation, migration and invasion	Promotes EMT	As a miR-607 sponge, upregulates E2F6 expression	(59)
Zhou *et al*, 2020	LINC00612	Upregulated in OS cells and metastatic OS	Promotes EMT	Upregulates SOX4 by inhibiting miR-214-5p	(60)
Bai *et al*, 2023	LINC00665	Promotes OS cell proliferation, migration and invasion	Promotes EMT	Sponges miR-1249-5p to regulate WNT2B to activate the Wnt pathway	(61)
Liu *et al*, 2022	LINC00909	Helps the occurrence and metastasis of OS	Promotes EMT	By binding with miR-875-5p, it upregulates HOXD9 expression and activates the PI3K/AKT/mTOR pathway	(62)
Li *et al*, 2021	LINC01116	Promotes cell viability, migration and invasion in MG-63/Dox cells	Promotes EMT	Regulates HMGA2 expression by silencing EZH2-related miR-424-5p	(63)
Zhang and Chen, 2022	LINC01140	Promotes the proliferation and invasion of OS cells	Promotes EMT	Targets the miR-139-5p/HOXA9 axis	(64)
Gu *et al*, 2020	LINC01419	Accelerates OS cell proliferation and movement	Promotes EMT	Enhances PDRG1 expression by miR-519a-3p sequestration	(65)

EMT, epithelial-mesenchymal transition; lncRNA, long noncoding RNA; miRNA/miR, microRNA; OS, osteosarcoma.

cells. LINC01419 enhances the expression levels of p53 and DNA damage-regulated gene 1 by inhibiting miR-519a-3p (65) (Table III; Fig. 2C).

A total of eight lincRNAs that promote the occurrence of OS through the ceRNA mechanism were identified. No 'high-frequency' lncRNAs were detected.

miRNA sponging-independent. lncRNAs exert their biological effects not only through ceRNA mechanisms but also through direct regulation of downstream signaling pathways. This section discusses how lncRNAs promote the EMT process through this mechanism, which results in OS progression.

lncRNAs with known functions. Numerous lncRNAs are named based on their known function. The present review discusses some lncRNAs with known functions that promote the occurrence of OS by directly regulating downstream signaling pathways.

lncRNA cancer susceptibility candidate 15 (CASC15) expression is upregulated in OS tissues and cells. CASC15 activates Wnt/β-catenin, which affects the cell cycle and promotes cell proliferation (66). CASC15 causes β-catenin to enter the nucleus through the Wnt signaling pathway, which promotes the EMT of OS cells (66).

Colorectal neoplasia differentially expressed (CRNDE) is highly expressed in OS tissues and cells. Overexpression of CRNDE enhances the activity of Notch1 signaling in MG-63 cells and promotes EMT (67).

Following CRNDE knockdown, the interstitial markers N-cadherin, vimentin and Snail are downregulated, whereas the epithelial markers E-cadherin and ZO-1 are upregulated. CRNDE promotes the phosphorylation of glycogen synthase kinase-3β and the activation of the Wnt/β-catenin pathway (68).

Compared with that in normal control cells, focally amplified lncRNA on chromosome 1 (FAL1) is upregulated in human OS tissues and cells. FAL1 knockdown inhibits the migration and invasion of OS cells by inhibiting the EMT process (69).

lncRNA Ftx expression in OS tissues is higher than that in adjacent nontumor tissues. Upregulated Ftx serves as a biomarker for the progression and prognosis of OS, as Ftx promotes tumor growth through the EMT mechanism. Ftx overexpression decreases the expression levels of E-cadherin, and enhances those of N-cadherin and Snail 1 (70).

Gastric cancer high expressed transcript 1 (GHET1) levels are upregulated in OS tissues compared with those in normal tissues. GHET1 knockout in MG-63 and U2OS cells inhibits the proliferation, invasion, migration and EMT of OS cells (71).

Histocompatibility leukocyte antigen complex P5 expression is upregulated in OS cells, and its silencing suppresses cell invasion and EMT (72).

Overexpression of Hox transcript antisense intergenic RNA enhances the invasion and migration of MG63 and Saos-2 cells. Furthermore, its overexpression induces EMT (73).

The expression of HOXA transcript at the distal tip (HOTTIP) is markedly elevated in OS tissues and cells. Silencing of HOTTIP inhibits the migration, invasion and EMT of tumor cells. c-Myc upregulation increases HOTTIP expression, and HOTTIP promotes the migration and invasion of OS cells by upregulating c-Myc expression. HOTTIP and c-Myc constitute a positive feedback loop that results in OS progression (74).

Downregulation of MALAT1 inhibits the proliferation, migration, invasion and EMT of OS cells. This is related to the 17β-estradiol dose and not to estrogen receptor expression (75).

Myc-induced lncRNA (MINCR) is expressed in OS tissues and cells. The migration and invasion of Saos-2 OS cells are decreased following MINCR knockout, and EMT is inhibited. MINCR controls the growth and metastasis of OS via the Wnt/β-catenin pathway (76).

Knockdown of the pseudogene Minato family member 2 (MSTO2P) results in the inhibition of the proliferation, invasion and EMT of OS cells under hypoxic conditions. Programmed death ligand 1 is a crucial receptor for MSTO2P in the regulation of OS progression under hypoxic conditions (77).

NEAT1 levels are increased in OS tissues and cell lines compared with normal tissues and cell lines. The ectopic expression of NEAT1 also induces EMT. NEAT1 inhibits the expression of E-cadherin through binding to the G9a-DNA methyltransferase 1-Snail compound (78).

Prostate cancer-associated transcript 1 (PCAT1) is upregulated in OS tissues compared with nontumor tissues. High levels of PCAT1 enhance the proliferation, invasion, migration and EMT of MG-63 cells. PCAT1 knockout inhibits the proliferation, invasion, migration and EMT of U2OS cells (79).

Plasmacytoma variant translocation 1 (PVT1) expression is upregulated in OS. Knocking down PVT1 *in vitro* can inhibit the proliferation, migration and invasion of OS cells. Furthermore, PVT1 influences EMT in OS cells (80).

The levels of the lncRNA T-cell factor 7 (lnc-TCF7) in OS tissues are increased compared with those in normal bone tissues. lnc-TCF7 silencing inhibits tumor metastasis in OS by inhibiting the EMT process (81).

Testis development-related 1 (TDRG1) expression is upregulated in OS concomitantly with the upregulation of phosphorylated (p-)PI3K and p-AKT levels. TDRG1 knockout inhibits the proliferation, invasion, migration and EMT of OS cells, while inducing apoptosis, whereas increased TDRG1 levels exert the opposite effect. Inhibiting the PI3K/AKT signaling axis inhibits the proliferation, invasion, migration and EMT of OS cells (82).

Increased TNF and HNRNPL-related immunoregulatory long non-coding RNA (THRIL) expression is associated with increased TNF-α levels in OS tissues and serum. TNF-α signaling is increased in OS cells, whereas THRIL knockout inhibits TNF-α signaling, resulting in decreased viability, increased apoptosis, and reduced invasion and EMT (83).

Silencing of human antigen R (HuR) reduces argonaute 2 (AGO2) expression. HuR enhances AGO2 expression, which is mediated by the lncRNA XIST. *AGO2* knockdown inhibits cell proliferation, migration and EMT. Inhibition of the lncRNA XIST reduces AGO2 expression (84) (Table IV).

A total of 19 studies of 18 lncRNAs with known functions that promote the occurrence of OS by directly regulating downstream signaling pathways were identified. CRNDE was described twice as a 'high-frequency' lncRNA. CRNDE promotes EMT through Notch1 and Wnt/β-catenin signaling (67,68), which results in OS progression.

Antisense lncRNAs. Antisense lncRNAs are transcribed from opposite DNA strands with protein-coding or

Table IV. lncRNAs with known function that do not act as microRNA sponges.

First author/s, year	lncRNA	Relationship with OS	Relationship with EMT	Action mechanism	(Refs.)
Wang and Zhang, 2021	CASC15	Influences OS cell cycle, thus promoting OS cell proliferation	Promotes EMT	Activation of the Wnt/β-catenin pathway	(66)
Li *et al*, 2018	CRNDE	Upregulated expression in OS tissues and cell lines	Promotes EMT	Enhances Notch1 signal transduction activity	(67)
Ding *et al*, 2020	CRNDE	High expression in OS tissues and cell lines	Promotes EMT	Promotes GSK-3β phosphorylation and activates the Wnt/β-catenin axis	(68)
Wang *et al*, 2018	FAL1	Promotes the migration and invasion of OS cells	Promotes EMT	Reduces the level of p21 and promotes GSK-3β phosphorylation	(69)
Li *et al*, 2018	Ftx	Increased expression in OS	Promotes EMT	Via the Snail pathway	(70)
Yang *et al*, 2018	GHET1	Promotes MG-63 and U2OS cell proliferation, invasion and migration	Promotes EMT	-	(71)
Zhao *et al*, 2019	HCP5	Induces OS cell invasion	Promotes EMT	-	(72)
Wang *et al*, 2019	HOTAIR	Promotes the invasion and migration of MG63 and Saos-2 cells	Promotes EMT	-	(73)
Tang and Ji, 2019	HOTTIP	Promotes OS cell migration and invasion	Promotes EMT	Increases c-Myc expression	(74)
Fang *et al*, 2015	MALAT1	Promotes OS cell proliferation, migration and invasion	Promotes EMT	17β-estradiol dose-dependent and estrogen receptor-independent	(75)
Bai *et al*, 2022	MINCR	Increases migration and invasion of Saos-2 cells	Promotes EMT	Via the Wnt/β-catenin signaling pathway	(76)
Shi *et al*, 2020	MSTO2P	Increases proliferation and invasion of OS cells	Promotes EMT	PD-L1 is the key effector	(77)
Li and Cheng, 2018	NEAT1	Increased expression in OS tissues and cell lines	Promotes EMT	Inhibition of E-cadherin expression by binding with G9a-DNMT1-Snail	(78)
Zhang *et al*, 2018	PCAT1	Enhances MG-63 cell proliferation, invasion and migration	Promotes EMT	-	(79)
Xun *et al*, 2021	PVT1	Promotes the proliferation, migration and invasion of OS cells	Promotes EMT	-	(80)
Gao *et al*, 2017	lncTCF7	Facilitates OS metastasis	Promotes EMT	Increases MMP-2 and MMP-9 expression	(81)
Huang *et al*, 2020	TDRG1	Promotes OS cell proliferation, invasion and migration	Promotes EMT	Promotes the PI3K/AKT signaling pathway	(82)
Xu *et al*, 2020	THRIL	Increases the viability of OS cells	Promotes EMT	Promotes TNF-α expression	(83)
Liu *et al*, 2021	XIST	Promotes cell proliferation and migration in OS	Promotes EMT	Mediates the increase of AGO2 expression	(84)

EMT, epithelial-mesenchymal transition; lncRNA, long noncoding RNA; OS, osteosarcoma.

Table V. Antisense lncRNAs, long intergenic noncoding RNAs and intronic lncRNAs not acting as microRNA sponges.

First author/s, year	lncRNA	Relationship with OS	Relationship with EMT	Action mechanism	(Refs.)
Shi *et al*, 2019	AFAP1-AS1	Promotes OS cell proliferation, migration, invasion and angiogenesis	Promotes EMT	Via the RHOC/ROCK1/p38MAPK/Twist1 signaling pathway	(85)
Luo *et al*, 2020	CDKN2B-AS1	Upregulated in OS tissues and cell lines	Promotes EMT	Promotes CDK4 and cyclin D1 expression	(86)
Cai *et al*, 2017	HNF1A-AS1	Promotes OS cell proliferation, G_1/S phase transition, migration and invasion	Promotes EMT	-	(87)
Yang *et al*, 2020	ZEB2-AS1	Promotes the migration and invasion of OS cells *in vitro*	Promotes EMT	-	(88)
Jiang and Luo, 2020	LINC01354	Promotes the invasion and infiltration of OS cells	Promotes EMT	Increases integrin β1 expression	(89)
Xu *et al*, 2016	SPRY4-IT1	Promotes the migration and invasion of OS cells	Promotes EMT	-	(90)

EMT, epithelial-mesenchymal transition; lncRNA, long noncoding RNA; OS, osteosarcoma.

noncoding properties. They serve an important role in the occurrence and development of OS and other tumors. The present review describes several antisense lncRNAs that promote the occurrence of OS by directly regulating downstream signaling pathways.

Actin filament-associated protein 1 antisense RNA 1 (AFAP1-AS1) is expressed in human OS tissues and cell lines. AFAP1-AS1 knockout suppresses the proliferation, migration, invasion, angiogenesis and EMT of OS cells (85). AFAP1-AS1 serves a carcinogenic role in OS through the RHOC/Rho-associated coiled-coil containing protein kinase 1/p38MAPK/twist family bHLH transcription factor 1 axis (85).

CDKN2B-AS1 is upregulated in OS tissues and cells. CDKN2B-AS1 knockout in OS cells inhibits CDK4 and cyclin D1 expression, as well as EMT. This is evidenced by an increase in E-cadherin levels, and a decrease in vimentin and N-cadherin levels (86).

Hepatocyte nuclear factor 1 homeobox A antisense RNA 1 (HNF1A-AS1) is upregulated in human OS tissues and cells, and is positively associated with distant metastasis and tumor stage. HNF1A-AS1 knockout using small interfering RNA inhibits cell proliferation and G_1/S phase transition, simultaneously inhibiting the migration and invasion of cells by obstructing the EMT process (87).

Zinc finger E-box binding homeobox two antisense RNA1 (ZEB2-AS1) is associated with tumor size, distant metastasis and prognosis. ZEB2-AS1 knockout inhibits the migration, invasion and EMT of tumor cells (88) (Table V).

A total of four antisense lncRNAs that promote the occurrence of OS by directly regulating the downstream signaling pathways involved were identified. No 'high-frequency' lncRNAs were detected.

lincRNAs. lincRNAs can contribute to the development of various tumors, including OS. The lincRNA LINC01354 promotes the occurrence of OS by directly regulating downstream signaling pathways (89). LINC01354 is highly expressed in OS tissues, serum and cells (89). Upregulation of LINC01354 promotes the invasion, EMT and integrin β1 expression of OS cells. However, downregulation of LINC01354 suppresses the aforementioned processes in OS cells. Furthermore, LINC01354 promotes EMT and invasion of OS cells (89) (Table V).

Intronic lncRNAs. Intronic lncRNAs are located in the intronic region of protein-coding genes and do not overlap with any exons in the transcript. The lncRNA sprouty RTK signaling antagonist 4-intronic transcript 1 (SPRY4-IT1) promotes the occurrence of OS by directly regulating downstream signaling pathways (90). SPRY4-IT1 is upregulated in OS cells. The promoting effect of SPRY4-IT1 on cell migration and invasion is partially related to EMT (90) (Table V).

3. lncRNAs inhibiting OS

As aforementioned, lncRNAs can promote the EMT process, leading to the occurrence and development of OS. They can also inhibit the occurrence and development of OS by suppressing the EMT process.

miRNA sponge-dependent mechanism. This section describes how lncRNAs inhibit the EMT process through the ceRNA mechanism to prevent the occurrence of OS.

Table VI. Antitumor lncRNAs acting as miRNA sponges or via other mechanisms.

First author/s, year	lncRNA	Relationship with OS	Relationship with EMT	Action mechanism	(Refs.)
Ye *et al*, 2019	FER1L4	Reduction of FER1L4 in OS tissues and cell lines	Suppresses EMT	Promotes SOCS5 and inhibits the PI3K/AKT signaling pathway by downregulating miR-18a-5p	(91)
Wang *et al*, 2021	GAS5	Reduces the migration and invasion of U2OS cells	Suppresses EMT	Reduces miR-21 expression	(92)
Ye *et al*, 2017	GAS5	Inhibition of OS cell proliferation and migration	Suppresses EMT	Via regulation of the miR-221/ARHI pathway	(93)
Zheng *et al*, 2020	SNHG22	Inhibits the progression of OS	Suppresses EMT	Directly interacts with miR-4492 and upregulates NKIRAS2 expression	(94)
Fan *et al*, 2020	TUSC8	Inhibits the proliferation, migration and invasion of OS cells	Suppresses EMT	Via the miR-197-3p/EHD2 axis	(95)
Zhang and Xia, 2017	XIST	Inhibition of OS cell invasion and migration	Suppresses EMT	Blocks miR-21-5p to maintain PDCD4 expression	(96)
Zhou *et al*, 2020	LINC00588	Inhibition of OS cell proliferation, viability, migration, invasion, endothelial cell function and tumor growth	Suppresses EMT	Downregulates miRNA-1972 expression, while miRNA-1972 inhibits TP53 expression	(97)
Wan *et al*, 2020	LINC00691	Decreased levels in OS cells	Suppresses EMT	Combines with miR-1256 to regulate ST5 expression	(98)
Liu *et al*, 2020	NR_136400	Downregulated in OS cells	Suppresses EMT	Combines with miR-8081, and then upregulates TUSC5 expression	(99)
Ma *et al*, 2019	FER1L4	FER1L4 expression is low in MG63 cells	Suppresses EMT	Via activation of the PI3K/AKT pathway	(100)

EMT, epithelial-mesenchymal transition; lncRNA, long noncoding RNA; miRNA/miR, microRNA; OS, osteosarcoma.

Compared with those in normal bone or hFOB1.19 cells, FER-1 family member 4 (FER1L4) levels in OS tissues and cells are reduced (91). Overexpression of FER1L4 promotes the expression of suppressor of cytokine signaling by interacting with miR-18a-5p and inhibiting EMT and PI3K/AKT pathways (91).

Compared with those in healthy volunteers (n=10), the expression levels of growth arrest-specific transcript 5 (GAS5) in patients with OS (n=24) were generally downregulated. Compared with that of patients without lung metastasis (n=13), GAS5 expression in those with lung metastasis (n=11) was more downregulated. GAS5 downregulation increases cell migration and invasion, and upregulates EMT. This is demonstrated by the downregulation of E-cadherin, and upregulation of vimentin, ZEB1 and ZEB2. The downregulation of GAS5 expression results in an increase in miR-21 levels, and a decrease in the elevated miR-21 expression reverses the effect of GAS5 silencing (92).

As a ceRNA of miR-221, the lncRNA GAS5 inhibits the proliferation and EMT of OS cells through the miR-221/ARHI axis (93).

SNHG22 is downregulated in OS cells, and increased SNHG22 expression suppresses OS progression. Furthermore, SNHG22 overexpression prevents the EMT of OS cells. SNHG22 interacts with miR-4492 and upregulates NK-κB inhibitor-interacting Ras-like 2 (94).

Tumor suppressor candidate (TUSC)8 is downregulated in OS tissues and cells. TUSC8 overexpression suppresses the proliferation, migration, invasion and EMT of OS cells. TUSC8 acts as a sponge to adsorb miR-197-3p, the target gene of which is EH domain 2 (EHD2). As a ceRNA, TUSC8 inhibits the proliferation and EMT of OS cells via the miR-197-3p/EHD2 pathway (95).

XIST maintains the expression levels of programmed cell death 4 by blocking miR-21-5p expression, thus slowing the progression of OS. XIST overexpression inhibits cell invasion and migration by inhibiting the EMT process (96).

LINC00588 is downregulated in OS. Increased levels of LINC00588 appear to suppress the proliferation, viability, migration, invasion, endothelial cell function, EMT and tumor growth of OS cells. This lincRNA serves a vital role in OS progression by downregulating the levels of miRNA-1972, the target gene of which is *TP53* (97).

Compared with that in normal cells, LINC00691 expression is downregulated in OS cells. LINC00691 regulates ST5 levels by directly interacting with miR-1256. Excess LINC00691 expression suppresses the EMT process by upregulating E-cadherin expression, and suppressing ZEB1, Snail and fibronectin expression (98).

NR_136400 is downregulated in OS cells, which promotes the EMT process by inhibiting E-cadherin expression, and boosting ZEB1, Snail and fibronectin expression. NR_136400 binds to miR-8081 and upregulates TUSC5 levels (99) (Table VI; Fig. 2D).

Due to a lack of studies on lncRNAs inhibiting OS compared with those on lncRNAs promoting OS, lncRNAs were not further classified based on the type of lncRNA. A total of 10 studies of eight lncRNAs that inhibit the occurrence of OS through the ceRNA mechanism were identified, and GAS5 was identified twice as a 'high-frequency' lncRNA. GAS5 inhibits EMT through miR-21 and the miR-221/ARHI axis (92,93), leading to the prevention of OS.

miRNA sponge-independent mechanism. This section describes how lncRNAs inhibit the EMT process through this mechanism to prevent the occurrence of OS.

FER1L4 exhibits decreased expression in OS cells, particularly MG63 cells. Increased FER1L4 expression inhibits the EMT process, as evidenced by an increase in E-cadherin expression, and a decrease in vimentin and fibronectin expression. FER1L4 serves an important role in preventing OS tumors by activating the PI3K/AKT pathway (100) (Table VI; Fig. 2D).

A lncRNA, FER1L4, which inhibits the occurrence of OS by directly regulating downstream signaling pathways, was identified. Due to the lack of studies on lncRNAs inhibiting OS compared with those on lncRNAs promoting OS, lncRNAs were not further classified based on the type of lncRNA. Currently, there is relatively little research in this area, although future studies are warranted.

4. Discussion

By examining the literature on the relationship between lncRNAs and EMT in OS, the present review indicated that the developmental direction of EMT and OS is consistent. In other words, enhancing EMT can promote the occurrence and progression of OS, whereas inhibiting EMT has the opposite effect. Furthermore, some lncRNAs promote the occurrence and progression of OS by promoting the EMT process, whereas others exhibit opposite biological effects.

Different lncRNAs regulate the EMT process through various mechanisms to regulate the occurrence and progression of OS. Of these, the most common and widely studied molecules are lncRNAs that act as miRNA sponges to interact with downstream molecules through the ceRNA mechanism. Furthermore, several lncRNAs regulate the expression of downstream RNAs or proteins to fulfill their biological roles by regulating signaling pathways.

For lncRNAs that promote the EMT process through the ceRNA mechanism, the studies were reviewed by focusing on lncRNAs with known functions, antisense lncRNAs and lincRNAs. For lncRNAs that promote the EMT process through direct regulation of downstream signaling pathways, the discussion was further divided into four parts: lncRNAs with known functions, antisense lncRNAs, lincRNAs and intronic lncRNAs. For lncRNAs that inhibit the EMT process, the discussion was divided into two parts: lncRNAs involved in ceRNA mechanisms and those directly participating in the regulation of downstream signaling pathways.

Studies on lncRNAs are increasing. Previous research has considered RNA molecules that cannot encode proteins as ineffective; however, studies have indicated that these RNA molecules can encode small open reading frame-derived peptides. With the development of ribosome profiling, mass spectrometry and sequencing technologies, increasing research on lncRNAs has emerged. These findings are important for the development of clinical diagnostic biomarkers, prognostic biomarkers and targeted drugs (101-103). lncRNAs participate in the occurrence and development of OS, other tumors and

other nontumor diseases through this mechanism (101-103). Only one lncRNA that regulates the occurrence and development of OS by encoding a small peptide (LINC00665) has been described. In OS, this lncRNA encodes an 18-amino acid-long peptide (LINC00665_18aa) that inhibits the proliferation and migration of OS cells by suppressing CREB (104). Since the EMT process was not specified in the aforementioned study (104), this appears unrelated in the context of the present review. However, the lncRNA was identified in a study included in the present review (61). lncRNAs regulate the occurrence and development of a disease through a complex network pathway rather than a single pathway. Thus, based on the aforementioned studies (61,104), lncRNAs likely regulate EMT by encoding small peptides, thereby regulating the occurrence and development of OS. This is expected to become a research focus in future studies.

By studying and summarizing relevant articles, evidence that lncRNAs regulate OS through the EMT process was obtained. The vast majority of lncRNAs increase the occurrence of OS by promoting the EMT process. Regarding the underlying mechanism, most lncRNAs exert their biological effects of promoting or inhibiting OS through miRNA-dependent pathways. Of these, MALAT1 (29,75), NEAT1 (32,33,78), XIST (42,43,84,96) and CDKN2B-AS1 (45,86) promote the EMT process, and the occurrence and development of OS through the miRNA and non-miRNA sponge methods. Notably, XIST enhances the EMT process to promote the occurrence and development of OS (42,43,84). XIST also inhibits the EMT process to suppress the occurrence and development of OS (96). This will be the focus of future research.

5. Conclusion

Based on the present review of the literature, lncRNAs regulate the EMT process in OS in complex ways, thus regulating its occurrence and development. Future studies should focus on the identification of these lncRNAs and actively explore their underlying mechanisms. This will become an innovative field of study in OS and other tumor types. It will also provide a basis for the early screening, prevention, diagnosis and treatment of OS.

Acknowledgements

Not applicable.

Funding

The present study received funding from the Liaoning Natural Science Foundation Project (grant no. 2023-BS-035).

Availability of data and materials

Not applicable.

Authors' contributions

YT contributed to the conception and design of the study. ZL performed literature collection and review, tabulation and drawing, and wrote and edited the manuscript. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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