Advances in the study of antisense long-stranded non-coding RNAs in tumors (Review)

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Abstract. Long-stranded non-coding RNAs (lncRNAs) are RNAs that consist of >200 nucleotides. The majority of lncRNAs do not encode proteins but have been revealed to mediate a variety of important physiological functions. Antisense-lncRNAs (AS-lncRNAs) are transcribed from the opposite strand of a protein or non-protein coding gene as part of the antisense strand of the coding gene. AS-lncRNAs can serve an important role in the tumorigenesis, prognosis, metastasis and drug resistance of a number of malignancies. This has been reported to be exerted through various mechanisms, such as endogenous competition, promoter interactions, direct interactions with mRNAs, acting as 'scaffolds' to regulate mRNA half-life, interactions with 5-untranslated regions and regulation of sense mRNAs. AS-lncRNAs have been found to either inhibit or promote tumor aggressiveness by regulating cell proliferation, energy metabolism, inflammation, inflammatory-carcinoma transformation, invasion, migration and angiogenesis. In addition, accumulating evidence has documented that AS-lncRNAs can regulate tumor therapy resistance. Therefore, targeting aberrantly expressed AS-lncRNAs for cancer treatment may prove to be a promising approach to reverse therapy resistance. In the present review, research advances on the role of AS-lncRNAs in tumor occurrence and development were summarized, with the aim of providing novel ideas for further research in this field.

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Contents

1. Introduction

Malignant neoplasms collectively are the second leading cause of mortality globally, imposing a significant economic burden on public healthcare systems around the world (1). By 2022, China had ~4.82 million new cancer cases, with 3.21 million cases of cancer-associated mortality (2). Compared with USA and UK, China has a lower cancer incidence rate but a higher cancer mortality rate (3). Although there had been a gradual decline in the incidence of gastric cancer (GC), hepatocellular carcinoma (HCC) and esophageal cancers, the morbidity and mortality rates of colorectal cancer (CRC), prostate and breast cancers have seen a progressive rise (4). Although notable advances in surgical, radiotherapeutic chemotherapeutic, targeted therapeutic, immunotherapeutic and multimodality therapeutic methods have all led to significant progress in enhancing treatment efficacy (5), the overall therapeutic effect remains poor in the long-term. Therefore, further studies are required to explore the mechanisms that regulate tumor development and responses to therapy.

Non-coding RNAs form a family that includes microRNAs (miRNA or miR), long non-coding RNAs (lncRNAs) and circular RNAs, which are classified according to their nucleotide length (6,7). In particular, lncRNAs are typically >200 nucleotides in length and can form conserved secondary structures, although the majority of which do not encode proteins (8). lncRNAs are structurally similar to mRNAs, since they also contain promoters and can undergo splicing, capping, polyadenylation and editing (9). In addition, their expression is regulated in a time- and space-specific manner (9). lncRNAs have been reported to regulate gene expression upstream of various biological processes, including cell proliferation and metabolism (10-13). lncRNAs can be classified into the following six categories based on their location on the genome: i) Intergenic lncRNAs, which are transcripts located between two protein-coding genes; ii) intronic lncRNAs, which are located within an intron of a coding gene; iii) bidirectional lncRNAs, which are located within 1 kb of promoters in the opposite direction from the protein-coding transcript; iv) enhancer lncRNAs, which are located in the enhancer regions; v) sense lncRNAs, located in a small segment of a coding gene, which is the overlapping region of one or several introns or exons; and vi) antisense-lncRNAs (AS-lncRNAs), which are transcribed from the antisense strand of protein-coding genes and overlap one or several introns and exons of the sense sequence (14). AS-lncRNAs are transcribed from the opposite strand of a protein or non-protein-coding gene (15). AS-lncRNAs have also been previously observed to serve an important role in the development and progression of malignancies (16-18). In the present review, the mechanism underlying the regulation of target gene expression by AS-lncRNAs was described, before its downstream consequences in tumor occurrence and development were summarized. Finally, the possible association between AS-lncRNA expression and therapy resistance in cancers was reported.

2. Mechanism underlying antisense-long-stranded non-coding RNA (AS-lncRNA)-mediated regulation of gene expression

AS-lncRNAs typically do not translate into proteins that can exert biological effects, but it can control gene expression through other means (8). AS-lncRNAs can mainly regulate the expression of target genes through eight methods (Fig. 1), which are summarized in this section.

Through competing endogenous RNAs (ceRNAs). A number of studies have previously reported that there is a regulatory relationship between AS-lncRNAs and miRNAs. Specifically, AS-lncRNAs can negatively regulate the expression of miRNAs upstream of the occurrence and development of tumors through the ceRNA mechanism (19), namely by serving as an endogenous miRNA sponge (20). Si *et al* (21) found that zinc finger protein (ZNF)561-AS1 expression was increased in tissues from patients with CRC and mediated carcinogenic effects in CRC, which predicted poor prognosis in patients. Serine and arginine rich splicing factor 6 (SRSF6) is a proto-oncogene that was also found to be overexpressed in CRC. In addition, ZNF561-AS1 was found to be an upstream post-transcriptional regulator of SRSF6. Using Starbase and Targetscan bioinformatics analyses, ZNF561-AS1 and SRSF6 were found to have potential binding sites for miR-26a-5p and miR-128-3p. The results of agonaute 2 (ago2)-RNA immunoprecipitation (RIP) assay and luciferase reporter assays revealed that ZNF561-AS1 was a ceRNA of miR-26a-5p and miR-128-3p. Further luciferase reporter assays later found that ZNF561-AS1 knockdown significantly inhibited SRSF6 wild-type plasmid luciferase activity. However, transfection with miR-26a-5p and/or miR-128-3p inhibitors was able to either partially or completely rescue such luciferase activity in CRC cells with ZNF561-AS1 expression knocked down. This led to the conclusion that ZNF561-AS1 can promote the expression of SRSF6 by functioning as a sponge for miR-26a-5p and miR-128-3p, thereby promoting the proliferation of CRC cells. In a different study, Shuai *et al* (22) found that lncRNA motor neuron and pancreas homeobox 1 (MNX1)-AS1 expression was increased in GC tissues, suggesting poor patient prognosis. Subsequent ago2-RIP assay results suggested that MNX1-AS1 may serve as a ceRNA. RNA-sequencing and reverse transcription-quantitative PCR assays found that Bcl-2 expression was significantly decreased in GC cells with MNX1-AS1 expression knocked down. MiRanda prediction then revealed that Bcl-2 was likely to be candidate target to bind to miR-6785-5p. Luciferase reporter gene assay then found miR-6785-5p to bind to the Bcl-2 3'untranslated region (3'UTR), suggesting that miR-6785-5p can target Bcl-2 mRNA. Results from both bioinformatics analyses and luciferase reporter assays suggested that lncRNA MNX1-AS1 can also serve as a ceRNA of miR-6785-5p to upregulate the expression of Bcl-2 in GC cells by sponging miR-6785-5p, thereby promoting GC progression.

Interacting with promoters. A number of pathways that can promote the co-expression of AS-lncRNAs and nearby protein-coding genes have been reported (23,24). On the transcriptional level, one possible mechanism is that AS-lncRNAs share a promoter with neighboring protein-coding genes (25), where they can regulate the H3K4me3 enrichment state in the promoter regions of genes of interest to in turn modulate their expression (26). Bartl *et al* (27) previously reported that the lncRNA hedgehog-interacting protein 1 (HHIP)-AS1 and HHIP share a promoter, whereby promoter activity was negatively regulated by DNA methylation. By contrast, Shuai *et al* (22) found that lncRNA MNX1-AS1 was overexpressed in GC tissues, which was not conducive to GC prognosis. Gene Ontology analysis revealed that the potential targets of MNX1-AS1 are possibly involved in various biological processes, such as signal transduction, cell proliferation and cell death. Chromatin immunoprecipitation (ChIP) experiments subsequently revealed that enhancer of zeste homolog 2 (EZH2) can bind to the promoter region of B-cell translocation gene anti-proliferation factor 2 (BTG2) to induce H3K27me3 modification in GC cells, which inhibits BTG2 transcription. Subsequent rescue experiments revealed that BTG2 can regulate the proliferation, migration and invasion of GC cells induced by MNX1-AS1. These results suggested that lncRNA MNX1-AS1 can suppress the expression of BTG2 in GC through EZH2-mediated H3K27me3 to promote GC progression.

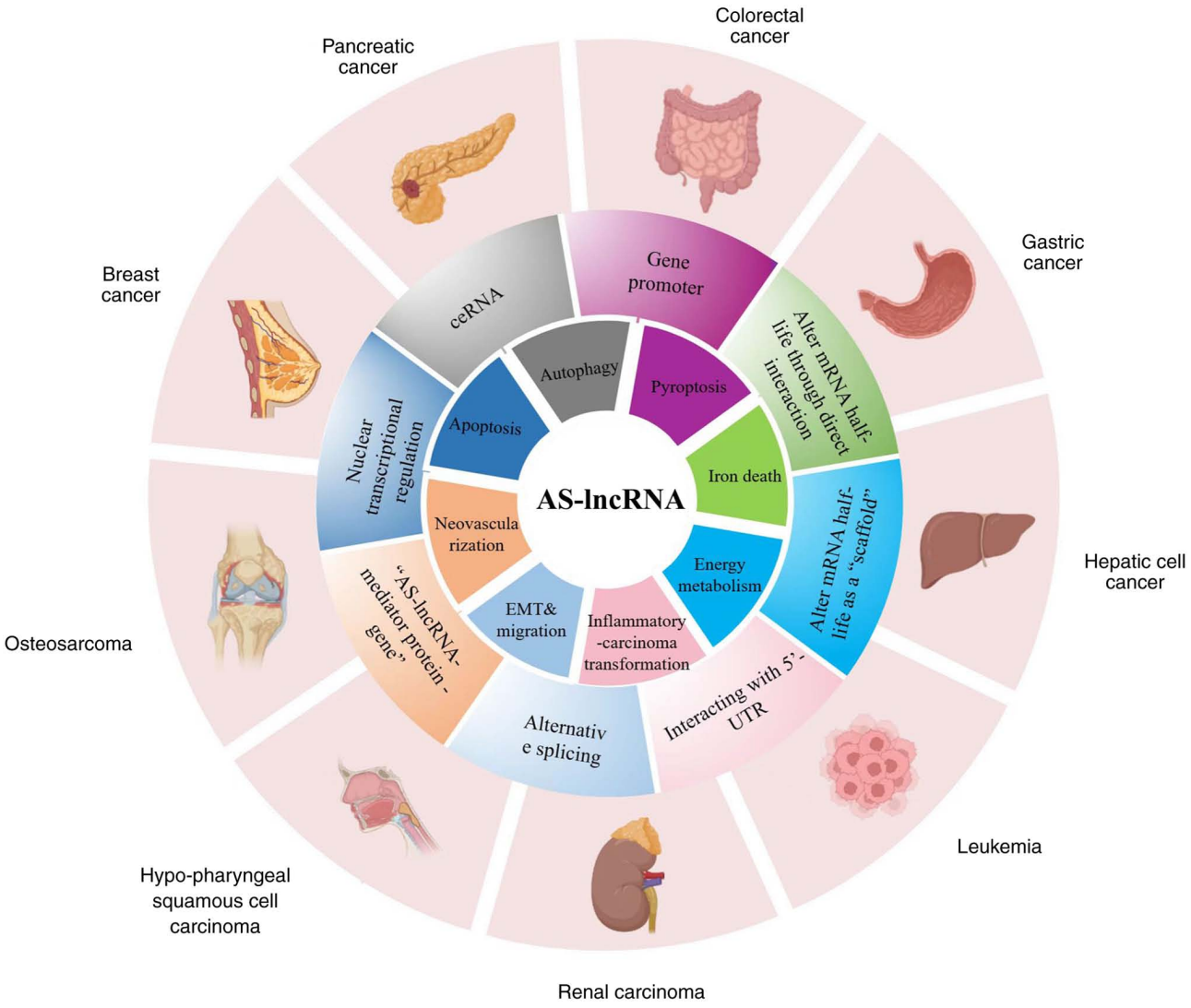

Figure 1. AS-lncRNAs can regulate tumor gene expression through endogenous competition mechanism, promoter interaction, direct interaction with mRNA, acting as 'scaffold' to change the half-life of mRNA, interaction with 5-UTR, regulation of meaningful mRNA, positive feedback loop of 'AS-lncRNA-mediator protein-meaning gene' model, transcriptional regulation in nucleus and so on. AS-lncRNAs can regulate tumor by regulating tumor cell death and proliferation, energy metabolism, inflammatory cancer transformation, invasion and migration, and regulation of tumor neovascularization. AS-lncRNA, antisense-long-stranded non-coding RNA; UTR, untranslated regions; ceRNA, competing endogenous RNA; EMT, epithelial-mesenchymal transition.

Direct interactions alter the half-life of mRNAs. AS-lncRNAs can regulate the stability of sense RNAs by forming RNA duplexes with them (28). Pan and Xie (29) previously observed through subcellular fractionation and fluorescence *in situ* hybridization assays that the lncRNA forkhead box C2 (FOXC2)-AS1 is mainly located in the nucleus where its expression is increased in CRC tissues, which indicates poor patient prognosis. FOXC2 is the closest gene to FOXC2-AS1, where their sequences overlap. The expression of FOXC2 and FOXC2-AS1 in CRC tissues was also found to be positively correlated. FOXC2-AS1 was subsequently found to positively regulate the expression of FOXC2. Reverse transcription-quantitative PCR (RT-qPCR) assay results suggested that FOXC2-AS1 can enhance the stability of FOXC2 mRNA. According to the site and gene structure, exon 1 of FOXC2-AS1 was completely complementary to FOXC2. RNase protection assay then revealed that FOXC2-AS1 and FOXC2 formed a double-stranded RNA structure, which was confirmed by RNA pull-down assay. This resulted in the conclusion that FOXC2-AS1 and FOXC2, and hence AS-lncRNAs and mRNAs, can form double-stranded structures, which enhanced the stability of FOXC2 mRNA (27). In addition, Zhao *et al* (30) found that metastasis-associated in colon cancer protein 1 (MACC1)-AS1 expression was increased in GC tissues, indicating a poor prognosis. MACC1-AS1 was found to promote metabolic plasticity by regulating MACC1 expression, thereby promoting GC progression. Through bioinformatics analysis, it was found that MACC1-AS1 contained the binding site of MACC1 mRNA. MACC1-AS1 was predominantly found to localize in the cytoplasm, allowing for the regulation of mRNA stability. Subsequent RT-qPCR analysis found that MACC1-AS1 significantly reduced the degradation of MACC1 mRNA, whilst affinity pull-down assays confirmed the direct interaction between MACC1-AS1 and MACC1. These findings suggested that MACC1-AS1 promoted mRNA stability through direct binding, thereby promoting GC progression.

Functioning as a 'scaffold' to regulating the half-life of mRNA. AS-lncRNAs can serve as scaffolds to interact with various proteins to form RNA/protein complexes (31). Zhu *et al* (32) found that Rho GTPase-activating protein 5 (ARHGAP5)-AS1 expression was increased in GC cells. Clinical data from The Cancer Genome Atlas (TCGA) database found that higher ARHGAP5-AS1 expression levels were associated with shorter overall survival. m6A modifications were previously found to regulate mRNA stability through RNA-binding proteins (33). Zhu *et al* (32) used RMBase and SRAMP analyses to show that there may be m6A modification in ARHGAP5 mRNA. When ARHGAP5-AS1 was overexpressed, the binding of both m6A modification and methyltransferase 3, N6-adenosine-methyltransferase complex catalytic subunit (METTL3) to ARHGAP5 mRNA were found to be elevated. Taken together, ARHGAP5-AS1 may recruit METTL3 to promote the m6A modification of ARHGAP5 mRNA, thereby stabilizing ARHGAP5 mRNA in the cytoplasm and promoting GC chemoresistance.

In summary, AS-lncRNAs can regulate gene expression through a variety of mechanisms, including ceRNA mechanisms, interaction with promoters and direct interaction or indirect interaction with mRNAs by serving as 'scaffolds' to alter its half-life.

Interacting with 5'-UTRs. Tran *et al* (34) reported an AS-lncRNA, AS-putative RNA-binding protein 15 (RBM15). The sequences of RBM15 and RBM15-AS1 both were first analyzed, which found that exon 1 of RBM15-AS1 coincided with the 5'-UTR of RBM15. The main functional region of lncRNA was then searched further, before full-length and multiple truncated versions were constructed. It was found that the 5-end of RBM15 was the main functional region, which could promote differentiation. The relationship between RBM15-AS1 and RBM15 was then verified experimentally, revealing that the shortest functional region exon 1 of RBM15-AS 1 could promote the translation of RBM15 without significantly affecting its mRNA levels. By constructing a dual-luciferase reporter system with the 5'-UTR of RBM15 and constructs encoding the different truncated versions of the lncRNAs, it was found that the region overlapping the 5'-UTR of AS-RBM15 and RBM15 was responsible for the upregulation of RBM15 protein translation.

Exerting regulatory effects on sense mRNAs. Alternative splicing is a common phenomenon during post-transcriptional regulation, which produces different mRNA variants and unique isoforms of the same protein (35,36). Yuan *et al* (37) previously identified an oncofetal splicing factor, muscleblind-like protein 3 (MBNL3), which promoted HCC tumorigenesis and suggested poor prognosis in patients. Transcriptomic analysis revealed that MBNL3 induced lncRNA PXN-AS1 exon 4 encapsulation. Transcripts of lncRNA PXN-AS1 with exon 4 deleted were found to bind to the coding sequence of PXN mRNA, leading to translation elongation factor separation from the PXN mRNA to inhibit PXN translation. By contrast, exon 4-containing transcripts preferentially bind to the 3' UTRs of PXN mRNA to protect the PXN mRNA from miR-24-ago2 complex-induced degradation, which in turn increases PXN expression. Through this mechanism, MBNL3 was concluded to upregulate PXN expression by promoting exon 4 inclusion, where PXN mediated the pro-tumor effects of MBNL3 in HCC.

Positive feedback loop of 'AS-lncRNA/protein/gene of interest' model. AS-lncRNA/protein/gene of interest can form stable complexes to continuously promote the expression of AS-lncRNAs and sense genes (38). Luo *et al* (39) previously found that zinc finger E-box binding homeobox 1 (ZEB1)-AS1 and ZEB1 expression is increased in triple-negative breast cancer (TNBC), both of which demonstrated direct binding to embryonic lethal, abnormal vision, drosophila, homolog-like 1 (ELAVL1) according to pull-down silver staining and RIP experiments. Specifically, ZEB1-AS1 directed ELAVL1 to the ZEB1 mRNA to protect it from degradation. ChIP experiments then demonstrated that ZEB1 exhibited potent binding affinity to part 1 of the ZEB1-AS1 promoter. ZEB1 could bind to the promoter of ZEB1-AS1 to promote the activation of ZEB1-AS1 expression, which was also verified by luciferase reporter assays. This suggested that ZEB1-AS1 interacted with ZEB1, which then formed a positive feedback loop with ELAVL1 to amplify the promotion of TNBC.

Transcriptional regulation of AS-lncRNAs in the nucleus. AS-lncRNAs can regulate gene expression on a post-transcriptional level by interacting with RNA-binding proteins to regulate mRNA stability (25). Wang *et al* (40) previously found that EGFR-AS1 expression was significantly increased in renal cell carcinoma tissues. Based on literature search results and sequence complementarity between EGFR and EGFR-AS1, the aforementioned study then confirmed that EGFR-AS1 can directly bind to EGFR mRNA to inhibit its degradation. In addition, subsequent RNA pull-down experiments and mass spectrometry analysis revealed that EGFR-AS1 interacted with human antigen R (HuR), which was the reason for the stability of EGFR mRNA. In summary, EGFR-AS1 regulated gene expression on the post-transcriptional level in renal cell carcinoma by enhancing the stability of EGFR mRNA in a HuR dependent manner.

In conclusion, this section mainly summarized the mechanism by which AS-lncRNAs can regulate gene expression.

3. Effect of AS-lncRNAs on tumors and underlying mechanism

Accumulating evidence has revealed that AS-lncRNAs are involved in tumorigenesis and development, where they serve important roles as either tumor suppressors or oncogenes (Table I). They can mediate a variety of processes, including cell proliferation, migration, invasion, epithelial-mesenchymal transition (EMT), apoptosis, drug resistance and immune escape (Fig. 1) (41). lncRNA MBNL1-AS1 and ZNF667-AS1 have been documented to be tumor suppressors (42,43), whilst lncRNA homeobox A11 (HOXA11)-AS, integrin subunit β1-AS1 were reported to be oncogenes (44,45).

Regulation tumor cell death and proliferation. Programmed cell death mainly includes apoptosis, autophagy, pyroptosis and ferroptosis pathways (46,47). Results from several studies

Table I. AS-lncRNAs play a role as tumor suppressor or oncogene.

Tumor	AS-lncRNA	Upregulated	Downregulated
Colorectal cancer	ZNF561-AS1	√	
Colorectal cancer	FOXC2-AS1	√	
Colorectal cancer	SLCO4A1-AS1	√	
Colorectal cancer	RAD51-AS1		√
Colorectal cancer	DNAJC3-AS1	√	
Colorectal cancer	SATB2-AS1		√
Colorectal cancer	STEAP3-AS1	√	
Colorectal cancer	LDLRAD4-AS1	√	
Colorectal cancer	ZNF667-AS1		√
Colorectal cancer	SLCO4A1-AS1	√	
Colorectal cancer	ZEB1-AS1	√	
Colorectal cancer	LOXL1-AS1	√	
Colorectal cancer	DLGAP1-AS1	√	
Colorectal cancer	OIP5-AS1	√	
Colorectal cancer	PGM5-AS1		√
Colorectal cancer	ELFN1-AS1	√	
Colorectal cancer	TTN-AS1	√	
Colorectal cancer	LBX2-AS1	√	
Colorectal cancer	MFI2-AS1	√	
Colorectal cancer	FOXD3-AS1	√	
Colorectal cancer	FGD5-AS1	√	
Gastric cancer	MNX1-AS1	√	
Gastric cancer	MACC1-AS1	√	
Gastric cancer	ARHGAP5-AS1	√	
Gastric cancer	OIP5-AS1	√	
Gastric cancer	ADAMTS9-AS2		√
Gastric cancer	BDNF-AS	√	
Gastric cancer	MACC1-AS1	√	
Gastric cancer	MSC-AS1	√	
Gastric cancer	ELF3-AS1		√
Gastric cancer	MBNL1-AS1		√
Gastric cancer	NKX2-1-AS1	√	
Gastric cancer	HNF1A-AS1	√	
Gastric cancer	SAMD12-AS1	√	
Gastric adenocarcinoma	HAND2-AS1		√
Gastric adenocarcinoma	PGM5-AS1		√
Gastric cancer	CCDC144NL-AS1	√	
Gastric cancer	NUTM2A-AS1	√	
Gastric cancer	VCAN-AS1	√	
Gastric cancer	DLX6-AS1	√	
Gastric cancer	NKX2-1-AS1	√	
Gastric cancer	GATA6-AS		√
Hepatocellular carcinoma	PXN-AS1	√	
Hepatocellular carcinoma	IGF2-AS		√
Hepatocellular carcinoma	GABPB1-AS1		√
Hepatocellular carcinoma	RAB11B-AS1		√
Hepatocellular carcinoma	HMMR-AS1	√	
Hepatocellular carcinoma	KDM4A-AS1	√	
Hepatocellular carcinoma	CCDC144NL-AS1	√	
Hepatocellular carcinoma	MCM3AP-AS1	√	
Hepatocellular carcinoma	CDKN2B-AS1	√	
Hepatocellular carcinoma	BZRAP1-AS1		√

Table I. Continued.

Tumor	AS-lncRNA	Upregulated	Downregulated
Hepatocellular carcinoma	F11-AS1		√
Hepatocellular carcinoma	ZFPM2-AS1	√	
Hepatocellular carcinoma	SBF2-AS1	√	
Hepatocellular carcinoma	SLC2A1-AS1		√
Hepatocellular carcinoma	GAS6-AS1	√	
Hepatocellular carcinoma	UPK1A-AS1	√	
Hepatocellular carcinoma	KTN1-AS1	√	
Hepatocellular carcinoma	CACNA1G-AS1	√	
Hepatocellular carcinoma	AGAP2-AS1	√	
Hepatocellular carcinoma	FOXD2-AS1	√	
Hepatocellular carcinoma	FEZF1-AS1	√	
Renal cell carcinoma	EGFR-AS1	√	
Renal cell carcinoma	ENTPD3-AS1		√
Renal cell carcinoma	LOXL1-AS1	√	
Renal cell carcinoma	ZFPM2-AS1	√	
Renal cell carcinoma	FGD5-AS1	√	
Renal cell carcinoma	ZNF582-AS1		√
Renal cell carcinoma	DARS-AS1	√	
Renal cell carcinoma	NNT-AS1	√	
Renal cell carcinoma	DNAJC3-AS1	√	
Renal cell carcinoma	CDKN2B-AS1	√	
Renal cell carcinoma	ITGB2-AS1	√	
Renal cell carcinoma	MSC-AS1	√	
Renal cell carcinoma	ARAP1-AS1	√	
Renal cell carcinoma	TP73-AS1	√	
Renal cell carcinoma	OTUD6B-AS1		√
Renal cell carcinoma	DLX6-AS1	√	
Renal cell carcinoma	ADAMTS9-AS2		√
Renal cell carcinoma	PCED1B-AS1	√	
Triple negative breast cancer	ZEB1-AS1	√	
Triple negative breast cancer	HAND2-AS1		√
Triple negative breast cancer	DLX6-AS1	√	
Triple negative breast cancer	WEE2-AS1	√	
Triple negative breast cancer	HLA-F-AS1	√	
Triple negative breast cancer	FAM83H-AS1	√	
Triple negative breast cancer	LRP11-AS1	√	
Triple negative breast cancer	AFAP1-AS1	√	
Breast cancer	VCAN-AS1	√	
Breast cancer	A1BG-AS1	√	
Breast cancer	CERS6-AS1	√	
Breast cancer	ZBED3-AS1		√
Breast cancer	HNF1A-AS1	√	
Breast cancer	MIF-AS1	√	
Breast cancer	DSCAM-AS1	√	
Breast cancer	ADPGK-AS1	√	
Breast cancer	MCM3AP-AS1	√	
Breast cancer	MBNL1-AS1		√
Breast cancer	OIP5-AS1	√	
Breast cancer	HOXD-AS1	√	
Breast cancer	FBXL19-AS1	√	
Breast cancer	TFAP2A-AS1		√
Breast cancer	MAFG-AS1	√	

Table I. Continued.

Tumor	AS-lncRNA	Upregulated	Downregulated
Breast cancer	CDKN2B-AS1	√	
Leukemia	AS-RBM15	√	
Leukemia	USP30-AS1	√	
Leukemia	SATB1-AS1	√	
Leukemia	CD27-AS1	√	
Leukemia	SBF2-AS1	√	
Leukemia	FBXL19-AS1	√	
Leukemia	GAS6-AS1	√	
Leukemia	MBNL1-AS1		√
Leukemia	TP73-AS1	√	
Leukemia	PRR34-AS1	√	
Leukemia	ITGB2-AS1	√	
Leukemia	LEF1-AS1		√
Leukemia	ZEB2-AS1	√	
Leukemia	LAMP5-AS1	√	
Leukemia	GAS6-AS1	√	
Leukemia	DNAJC3-AS1	√	
Glioma	GATA6-AS	√	
Glioma	FAM181A-AS1	√	
Glioma	PCED1B-AS1	√	
Glioma	FOXD2-AS1	√	
Glioma	DLX6-AS1	√	
Glioma	FLVCR1-AS1	√	
Glioma	GAS5-AS1		√
Glioma	AGAP2-AS1	√	
Glioma	TP73-AS1	√	
Glioma	PSMB1-AS1	√	
Glioma	OIP7-AS5	√	
Glioma	MATN1-AS1	√	
Glioma	HOXD-AS1	√	
Glioma	HOXA11-AS	√	
Glioma	SOX21-AS1	√	
Glioma	ZEB1-AS1	√	
Glioma	TPT1-AS1	√	
Glioma	EGFR-AS1	√	
Glioma	FOXD1-AS1	√	
Glioblastoma	WEE2-AS1	√	
Glioblastoma	UBA6-AS1		
Glioblastoma	TP73-AS1	√	
Squamous cell carcinoma of the hypopharynx	HOXA11-AS1	√	
Squamous cell carcinoma of the hypopharynx	LEF1-AS1	√	
Squamous cell carcinoma of the hypopharynx	MNX1-AS1	√	
Nasopharyngeal carcinoma	DLX6-AS1	√	
Nasopharyngeal carcinoma	SMAD5-AS1	√	
Nasopharyngeal carcinoma	HOXC13-AS	√	
Nasopharyngeal carcinoma	PTPRG-AS1	√	
Nasopharyngeal carcinoma	AFAP1-AS1	√	
Nasopharyngeal carcinoma	TP73-AS1	√	
Nasopharyngeal carcinoma	DLX6-AS1	√	
Nasopharyngeal carcinoma	OIP5-AS1	√	
Nasopharyngeal carcinoma	HOXC-AS1	√	
Nasopharyngeal carcinoma	FEZF1-AS1	√	

Table I. Continued.

Tumor	AS-lncRNA	Upregulated	Downregulated
Nasopharyngeal carcinoma	FOXP4-AS1	√	
Nasopharyngeal carcinoma	FOXD2-AS1	√	
Osteosarcoma	OIP5-AS1	√	
Osteosarcoma	CCDC144NL-AS1	√	
Osteosarcoma	PCED1B-AS1	√	
Osteosarcoma	PGM5-AS1	√	
Osteosarcoma	TTN-AS1	√	
Osteosarcoma	RHPN1-AS1	√	
Osteosarcoma	NR2F1-AS1	√	
Osteosarcoma	DLX6-AS1	√	
Osteosarcoma	C5ORF66-AS1	√	
Osteosarcoma	ASB16-AS1	√	
Osteosarcoma	ADPGK-AS1	√	
Osteosarcoma	AFAP1-AS1	√	
Osteosarcoma	HNF1A-AS1	√	
Osteosarcoma	RUSC1-AS1	√	
Osteosarcoma	FBXL19-AS1	√	
Osteosarcoma	MSC-AS1	√	
Osteosarcoma	LBX2-AS1	√	
Osteosarcoma	FOXD2-AS1	√	
Osteosarcoma	NNT-AS1	√	
Osteosarcoma	DSCAM-AS1	√	

AS-lncRNA, antisense-long-stranded non-coding RNA.

have shown that AS-lncRNAs can regulate tumor cell death and proliferation through the aforementioned pathways (48-51).

Apoptosis. AS-lncRNAs can reduce cell cycle arrest and apoptosis and promote cell proliferation (48). Opa-interacting protein 5 (OIP5)-AS1 overexpression was previously found to downregulate nucleotide-binding oligomerization domain, leucine rich repeat and pyrin domain-containing (NLRP)6 by interacting with EZH2 to promote GC cell proliferation whilst suppressing apoptosis (52). Wang *et al* (53) also reported that OIP5-AS1 can promote cell proliferation by accelerating cell cycle progression in GC cells through sponging miR-641 to increase the expression of cyclin D1 and activation of AKT (53). In a different study, OIP5-AS1 was found to promote GC cell proliferation but inhibited apoptosis by regulating the miR-367-3p/high mobility group AT-hook 2 axis and activating the PI3K/AKT and Wnt/β-catenin pathways (54). In glioma, Liao *et al* (55) found that the expression of GATA6-AS was significantly upregulated, where it promoted proliferation and inhibited apoptosis through taurine upregulated 1.

Autophagy. Autophagy serves a dual role in the physiology of a wide variety of cancer types (56,57). In cancer cells, autophagy can inhibit tumorigenesis by preventing cancer cell survival and inducing cell death (58), but it can also promote tumorigenesis by promoting cancer cell proliferation and tumor growth (59). Wang and Jin (49) previously detected that solute carrier organic anion transporter family member 4A1 (SLCO4A1)-AS1 expression levels in patients with CRC were positively associated with Par-3 family cell polarity regulator (PARD3) expression. PARD3 protein is a key molecule that can trigger autophagy initiation. SLCO4A1-AS1 was also found to promote autophagy and the proliferation of CRC cells both *in vitro* and *in vivo*. Overexpression and knockdown experiments revealed that SLCO4A1-AS1 functioned as a ceRNA to induce autophagy and promote the proliferation of CRC cells by sponging endogenous miR-508-3p, which promoted PARD3 protein expression (47).

Pyroptosis. Pyroptosis is a relatively recently discovered form of programmed cell death mode that is mediated by the gasdermin protein family (60), which also serves a duplicitous role in tumor progression (61). Previous studies have shown that pyroptosis is involved in the growth, differentiation, invasion and late metastasis of cancer (62). Components of pyroptosis have been reported to serve an important carcinogenic role in GC progression (63). Previously, AS-lncRNAs have been found to be key regulators of apoptosis (50). Wang *et al* (64) found that heart and neural crest derivatives-expressed 2-AS1 and phosphoglucomutases (PGM5)-AS1 were independently associated with pyroptosis in GC, where they appeared to participate in the occurrence and development of GC according to co-expression analysis and Kaplan-Meier survival analysis (64). In addition, Ren *et al* (65) found that the overexpression of lncRNA A disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS)9-AS2 inhibited GC

progression by regulating the miR-223-3p/NLRP3 axis-mediated pyroptosis.

Ferroptosis. Ferroptosis is another recently discovered form of cell death that is different from apoptosis, necrosis and autophagy mechanistically (66). In particular, epigenetic mechanisms, such as DNA methylation, histone modifications and AS-lncRNAs, have been reported to serve roles in ferroptosis (67,68). Huang *et al* (51) previously found that reactive oxygen species (ROS), Fe^{2+} and total iron concentrations were decreased after overexpressing brain-derived neurotrophic factor (BDNF)-AS following RT-PCR detection. By contrast, ROS, Fe^{2+} and total iron concentrations were revealed to be increased after BDNF-AS expression was knocked down. A ferroptosis model was then established using erastin and Ras-selective lethal 3 (RSL3), where it was found that the changes in the level of ferroptosis markers induced by erastin were more significant compared with those induced by RSL3. A different previous study also found that erastin can induce ferroptosis by binding to voltage-dependent anion-selective channel protein (VDAC)2/VDAC3 (68). The protein expression profile in GC tissues studied by Huang *et al* (51) revealed that VDAC2/VDAC3 was abnormally expressed in GC samples. However, VDAC3 protein expression was found to be significantly increased when BDNF-AS was overexpressed but was decreased when BDNF-AS expression was knocked down, compared with VDAC2 (49). These results suggested that BDNF-AS can regulate ferroptosis in GC cells through VDAC3. In conclusion, the aforementioned results from previous studies suggested that when BDNF-AS was overexpressed, the degree of ferroptosis in GC cells was reduced, which favored GC invasion and metastasis.

Regulation of energy metabolism reprogramming in tumor cells. In cancer cells, glucose metabolism is reprogrammed to adapt to the increased energy requirements. Unlike in normal cells, the main metabolic process in cancer cells is glycolysis (69). The predominance of aerobic glycolysis is a key metabolic feature of the Warburg phenotype, which is caused by the active metabolic reprogramming required to support the sustained cancer cell proliferation and malignant progression (70). Since the German scientist Otto Warburg put forward the 'Warburg effect' (71), the relationship between aerobic glycolysis and tumorigenesis has become a topic of intense scientific research (72). The mechanism of glucose metabolism in cancer cells can be summarized mainly as follows (70): i) Overexpression of glucose transporters and key glycolytic enzymes, which accelerates the glycolytic flux, followed by the accumulation and transfer of glycolytic intermediates for cancer biomass synthesis; ii) high-speed ATP production to meet the energy demand; and iii) accumulation of lactic acid, which promotes tumor progression, greatly contributing to tumor acidosis. Therefore, the Warburg effect is one of the core factors in underlying the mechanism of cancer progression. Zhao *et al* (30) previously found that in GC cells MACC1-AS1 significantly upregulated the expression of glycolysis components glucose transporter 1 (GLUT1), hexokinase 2 (HK2), glucose-6-phosphate dehydrogenase and lactate transporter monocarboxylate transporter 1 on the mRNA level, whilst significantly upregulating the expression of GLUT1, HK2 and lactate dehydrogenase (LDH) on the protein level. In addition, following 2-NBDG assays, MACC1-AS1 was found to accelerate glucose uptake in GC cells. Under either normal conditions or those of glucose deprivation, MACC1-AS1 also increased the production of ATP and lactic acid, presumably by increasing the activity of key glycolytic enzymes HK2 and LDHA. These results suggested that a potential role of MACC1-AS1 is to promote glycolysis by upregulating the activity and expression of glycolytic enzymes in GC cells. This metabolic transformation may serve to improve cell viability and resistance to apoptosis, which in turn promotes the progression of GC. In a previous study, Li *et al* (73) found that the overexpression of RAD51-AS1 could reduce glucose uptake by CRC cells, which led to a reduction in lactic acid concentrations in CRC cells. Subsequently, through western blotting, it was found that the RAD51-AS1 overexpression led to the reduction in HK2 and GLUT1 levels, suggesting that RAD51-AS1 can inhibit the glycolytic process in CRC cells. In conclusion, these results strongly suggested that RAD51-AS1 serves an important role in maintaining the glycolysis balance, which may affect the proliferation of CRC.

Lipid metabolism reprogramming has also been proposed to be a marker of cancer (74). In rapidly proliferating tumor cells, the re-synthesis of fatty acids is enhanced, such that the expression of key fatty acid synthases, including acetyl-CoA carboxylase (ACC) and fatty acid synthase (FASN), is increased. This subsequently results in the accumulation of a variety of fatty acids (75). Accumulating lipids can promote cell proliferation and tumor progression in a complex tumor microenvironment (76). Previous studies have demonstrated that fibroblasts in the tumor microenvironment express FASN highly (76), which mediates lipid metabolism reprogramming, resulting in the accumulation of various fatty acids to promote the migration of CRC cells (76). EGFR/PI3K/AKT signaling has been shown to activate sterol regulatory element-binding protein-1 cleavage and upregulate the expression of ACC1 and FASN, resulting in increased lipid metabolism (77,78). Tang *et al* (79) previously found that interferon-induced, double-stranded RNA-activated protein kinase inhibitor-AS1 regulated fatty acid synthase through the EGFR/PI3K/AKT/NF-κB signal pathway to promote the progression of CRC. Fatty acid is an important energy source through fatty acid oxidation (FAO), which has been shown to be necessary for the proliferation and survival of cancer cells (80). Inhibition of FAO can inhibit cell stemness and alleviate tumor growth (81). Mesenchymal stem cells (MSCs) have been revealed to promote the dryness of GC cells and predict the poor prognosis of GC. He *et al* (82) found that inhibition of FAO could reverse the MSC-mediated stemness of GC cells, suggesting that FAO is involved in the self-renewal of GC stem cells induced by MSCs, whilst having little effect on non-stem cells.

Regulation of inflammation in cancer. A large number of studies have shown that inflammatory immune cells can serve diverse but key roles in promoting tumorigenesis (83). Tumor-promoting inflammatory cells mainly include macrophages, mast cells, neutrophils, T and B lymphocytes (84). Nie *et al* (85) employed the Gene Set Enrichment Analysis (GSEA) pre-ranking of tumor characteristics to find that there

was a decrease in memory B cells but an increase in naive and effector CD8T cells in the high-risk group, suggesting immune-related regulation. Tumor-infiltrating inflammatory cells have been demonstrated to induce and then maintain tumor angiogenesis (86), stimulate cancer cell proliferation, promote foreign tissue invasion and support cell migration (84,87). AS-lncRNAs have correspondingly been detected to regulate inflammation in tumors and cancer transformation, by regulating the expression of genes associated with the immune response. This was proposed to be exerted through the synthesis of inflammatory factors and inflammatory signaling pathways (88). In addition, AS-lncRNAs have been reported to alter the profile of immune cell infiltration in the tumor microenvironment, mediating a profound impact on tumor invasiveness, progression and prognosis (89). Xu *et al* (90) found that the expression of the CRC tissue-specific lncRNA special AT-rich sequence-binding protein 2 (SATB2)-AS1 was downregulated in CRC tissues, which predicted a favourable prognosis. Transwell and wound healing assays demonstrated that SATB2-AS1 knockdown significantly increased CRC cell migration and invasion ability. The results of GSEA also revealed that the expression of SATB2-AS1 was associated with various immune responses. In addition, it was found that when SATB2-AS1 was negatively associated with the expression of Th1 chemokines C-X-C motif chemokine ligand (CXCL)9 and CXCL10, these chemokines could be induced by IFN-γ and mediated effector T cell transport. In conclusion, these results suggested that SATB2-AS1 is a mediator of the CRC immune response by regulating immune cell density in CRC to inhibit CRC cell metastasis, slowing the progression of CRC.

Regulation of EMT, invasion and migration in tumor cells. One of the key mechanisms for cancer cells to enhance their invasive ability is by detaching from their intercellular adhesion, followed by the acquisition of a more dynamic mesenchymal phenotype as part of the EMT process (91). EMT has been previously considered to be a binary process with two distinct cell groups, namely epithelial cells and mesenchymal cells, characterized by the loss of the epithelial marker E-cadherin and the increased expression of the mesenchymal marker vimentin (92,93). During EMT, epithelial cells lose apical-basal polarity and E-cadherin expression, whilst upregulating the expression of mesenchymal biomarkers, including twist, slug, snail, vimentin and N-cadherin (94,95). EMT has been associated with a number of tumor functions, including tumor initiation, malignant progression, tumor stemness, cell migration and metastasis (92). In addition, EMT is considered to be a key factor on worsening patient prognosis by accelerating the invasion and migration of cancer cells (96).

Yu *et al* (97) previously observed that lncRNA SLCO4A1-AS1 expression was significantly increased in CRC tissues, which was in turn associated with poor patient prognosis and CRC tumor metastasis. By knocking down SLCO4A1-AS1 expression, it was then detected that SLCO4A1-AS1 inhibited the migration, invasion and EMT of CRC cells *in vitro*. In a different study, Zhou *et al* (98) found that SLCO4A1-AS1 activated Wnt/β-catenin signaling in CRC cells, which promoted cell migration and invasion. The authors explored TCGA database for antisense lncRNAs involved in CRC under hypoxic conditions. Among the candidate genes found, lncRNA six-transmembrane epithelial antigen of prostate 3 (STEAP3)-AS1 was reported to be aberrantly transcribed under hypoxic conditions in clinical CRC tissues, where it was positively associated with poor patient prognosis (96). Furthermore, it was revealed that lncRNA STEAP3-AS1 interacted with YTH N6-methyladenosine RNA-binding protein 2 to stabilize STEAP3 mRNA, which increased the expression of the STEAP3 protein. The STEAP3 protein then activated Wnt/β-catenin signaling in an iron-dependent manner to promote cell invasion and migration, in turn accelerating CRC progression (96).

A previous independent study of RNA-sequencing data found that in A549 and HeLa cells, downregulation of E74-like ETS transcription factor 3 (ELF3)-AS1 led to the upregulation of snail family transcriptional repressor (SNAI)2 mRNA expression, suggesting that the negative regulation of SNAI2 expression by ELF3-AS1 may be widespread in cancer (99). In addition, Li *et al* (26) identified 123 lncRNAs regulated by SNAI2 in GC by RNA sequencing, where both the *ELF3* gene and ELF3-AS1 were found to be transcriptionally repressed by EMT-associated transcription factors SNAI2 or SNAI1. In addition, the gene expression profiles produced by SNAI2 overexpression and ELF3-AS1 knockdown were revealed to be highly very similar. These results suggested that knocking down ELF3-AS1 expression cannot only upregulate the expression of SNAI2, but can also activate the downstream signal pathways of SNAI2 in GC. Cell proliferation, Transwell and wound healing experiments revealed that downregulation of ELF3-AS1 promoted the proliferation, migration and invasion of GC cells, indicating poor patient GC prognosis. In conclusion, ELF3-AS1 was suggested to inhibit EMT mainly by inhibiting the SNAI2-mediated transduction of GC-associated transcription factors. Mo *et al* (100) previously found that the higher expression levels of lncRNA low density lipoprotein receptor class A domain-containing 4 (LDLRAD4)-AS1 promoted the progression of CRC, which is associated with poor patient prognosis. Subsequent western blotting and immunohistochemistry results revealed that lncRNA LDLRAD4-AS1 could promote EMT both *in vitro* and *in vivo*. lncRNA LDLRAD4-AS1 was then observed to promote EMT by reducing the expression of LDLRAD4, promoting the process of GC.

The TGF-β/EMT pathway is closely associated with cancer progression (101). In particular, Smad7 is activated by all members of the TGF-β superfamily and has a negative regulatory effect on the TGF-β signal pathway (102). Su *et al* (42) previously reported that MBNL1-AS1 knockdown can increase the proliferation, migration and invasion of GC cells according to *in vitro* experimental results and animal models. MBNL1-AS1 expression was demonstrated to be downregulated in GC tissues and cells, which played a positive role in inhibiting the growth of the GC tumor. Western blotting data demonstrated that MBNL1-AS1 affected the TGF-β/SMAD pathway by regulating the miR-424-5p/Smad7 axis, which inhibited the proliferation of GC.

Collectively, the aforementioned observations strongly suggested that AS-lncRNAs can regulate EMT through the Wnt, SNAI2 and TGF-β signal pathways, serving an important role in the occurrence and development of various tumors.

Regulation of tumor neovascularization. The plasminogen activator system, which includes urokinase type plasminogen activator (uPA), uPA cell receptor and its specific inhibitor plasminogen activator inhibitor-1 (PAI-1), has been reported to serve an important role in tumor progression and angiogenesis (103). The role of PAI-1 in tumor angiogenesis has been extensively studied, the expression of which is essential for tumor angiogenesis (104). Teng *et al* (105) found that the overexpression of NK2 homeobox 1 (NKX2)-1-AS1 and PAI-1 was associated with GC progression and prognosis. Specifically, NKX2-1-AS1 served as a ceRNA of miR-145-5p and promoted tumor progression and angiogenesis, by activating VEGFR2 signaling through PAI-1. Previous studies have shown that the PI3K/AKT signaling pathway is involved in cancer cell invasion and angiogenesis (106,107). Liu *et al* (108) previously detected that hepatic nuclear factor 1 α (HNF1A)-AS1 can promote GC invasion, metastasis and angiogenesis both *in vitro* and *in vivo*. In particular, the high degree of PI3K/AKT signaling pathway activation was found to promote the progression of GC. Results from Transwell migration and matrix-based capillary formation assays revealed that overexpression of HNF1A-AS1 can promote GC angiogenesis *in vitro*. ELISA and rescue experiments confirmed that HNF1A-AS1 exerted its biological function via the PI3K/AKT signaling pathway. The activation of PI3K/AKT signaling in tumor cells could increase the secretion of VEGFA, which serves a role in promoting angiogenesis in human cancers. In conclusion, these aforementioned findings suggested that lncRNA-HNF1A-AS1 can function as a ceRNA of miR-30b-3p to activate PI3K/AKT signaling to increase the secretion of VEGF-A, which promotes angiogenesis and therefore the progression of GC.

4. AS-lncRNAs in the diagnosis, prognosis and treatment of tumors

AS-lncRNAs have the potential to assist in tumor diagnosis and prognosis. A number of previous studies have demonstrated that AS-lncRNAs have significant potential as a biomarker for both cancer diagnosis and prognosis (10). Guo *et al* (109) previously found that overexpression of muskelin 1, intracellular mediator containing Kelch motifs-AS enhanced the stability of Yes-associated protein 1 mRNA, which promoted carcinogenic effects. This was proposed to facilitate the diagnosis and prognosis of HCC. In a different previous study, El-Ashmawy *et al* (110) revealed that family with sequence similarity 83-member H (FAM83H)-AS1 was involved in the progression of various malignant tumors. Coincidentally, it was found to be particularly dysregulated in cancers, potentially serving a crucial role in their diagnosis and prognosis (110). Supporting this, Da *et al* (111) demonstrated that FAM83H-AS1 may serve a prognostic and diagnostic role in GC.

AS-lncRNAs in the treatment of cancer. AS-lncRNAs have been documented to not only have the potential for cancer diagnosis and prognosis, but may also facilitate the design of treatment strategies for patients with cancer (41). AS-lncRNAs are increasingly becoming biomarkers for the treatment of tumors (45,64,112,113).

Activation of tumor suppressors. Tumor suppressors refer to a large number of molecules that can reliably control cell division, promote apoptosis and inhibit metastasis (114). The loss of tumor suppressor functions may lead to uncontrolled cell division malignant transformation (115). Tumor suppressors mainly exert their roles through the following four main mechanisms: i) Inhibition of cell division; ii) induction of apoptosis; iii) repair of DNA damage; and iv) inhibition of metastasis (116). Lu *et al* (113) previously observed that the expression of sterile α motif domain-containing 12 (SAMD12)-AS1 was increased in human GC tissues and cell lines. SAMD12-AS1 was then detected to exert its biological role in GC through direct interactions with DNA methyltransferase 1 (DNMT1), which inhibits p53 signaling to promote the malignant transformation of GC cells. Silencing SAMD12-AS1 expression restored p53 signaling to reverse the progression of GC, suggesting that SAMD12-AS1 may serve as a potential diagnostic and therapeutic target for GC. Liu *et al* (117) previously reported that the expression of HNF1A-AS1 was significantly upregulated in GC tissues. Similar to the function of HNF1A-AS1, the overexpression of early growth response 1 (EGR1) was reported to enhance cell proliferation and promote GC cell cycle progression. The RT-qPCR assay showed that EGR1 promotes the expression of HNF1A-AS1. EGR1 and HNF1A-AS also inhibited the expression of the antibiotic growth factor p21 by promoting cell division cycle 34-mediated ubiquitination and p21 degradation. It was then suggested that the inhibition of EGR1-activated HNF1A-AS1 and the subsequent upregulation of anti-growth factors could inhibit the development of GC. In another study, Zhuang *et al* (43) previously observed that the lower expression levels of ZNF667-AS1 predicted poorer prognosis and were associated with the progression of CRC. Upregulation of ankyrin 2 by the overexpression of ZNF667-AS1 was then found to inhibit the proliferation, migration and invasion of CRC cells, which hindered the development of CRC progression.

In conclusion, AS-lncRNA could regulate tumor development by activating tumor suppressor factors, which may be exploited as a target for tumor therapy.

Inhibition of oncogene expression. SLCO4A1-AS1 is highly expressed in CRC cells and tissues, which is associated with poor patient prognosis (118). Zhang *et al* (118) previously documented that SLCO4A1-AS1 increased the expression of CDK2 by enhancing the interaction between CDK2 and heat shock protein 90 (HSP90) and activating c-MYC signaling. This increase in CDK2 expression downstream of SLCO4A1-AS enhanced tumor growth by promoting the phosphorylation of c-Myc at the Ser6 site, activating this protein (115). Downregulation of SLCO4A1-AS1 inhibited the proliferation of CRC cells *in vivo* and *in vitro*. Ni *et al* (119) reported that the expression of ZEB1-AS1 in CRC was significantly upregulated, which was associated with poor prognosis in patients with colon adenocarcinoma. Specifically, ZEB1-AS1 promoted the expression of p21 Protein (Cdc42/Rac)-activated kinase 2 (PAK2) by sponging miR-455-3p, which advanced the proliferation and metastasis of colon adenocarcinoma cells. Knocking down ZEB1-AS expression was then observed to increase the expression of miR-455-3p and decreased the expression of PAK2, which suppressed the proliferation

and metastasis of cancer cells. It would be of significance to identify novel therapeutic targets for patients with colon adenocarcinoma. Wu *et al* (120) previously found that the expression of lysyl oxidase homolog 1 (LOXL1)-AS1 was upregulated in CRC, which then increased the expression of target gene *CD44* by sponging miR708-5p. This in turn promoted the expression of EGF to facilitate CRC progression. Knocking down LOXL1-AS1 expression was found to reverse this upregulated CD44/EGFR signaling pathway to inhibit the progression of CRC, providing another potential novel pathway to explore the treatment strategy of CRC.

In conclusion, these previous findings aforementioned suggested that knocking down AS-lncRNAs can regulate tumor development by inhibiting the expression of oncogenes, which may become a novel method for tumor therapy.

Activation of antitumor immunity. Possibly the biggest natural antagonist of cancer development is the host immune system, especially T cells, which can initiate an antitumor response by expressing specific receptors of tumor antigens (121). To prevent immune hyperactivation, effector lymphocytes express immune checkpoints, which are mainly receptor proteins expressed on the cell surface (122). Several tumors, including liver cancer, exploited this by expressing corresponding ligands to these checkpoints (123). After ligand binding, the activity of effector lymphocytes becomes impaired. Programmed cell death protein 1 (PD-1) was one of the main such co-inhibitory receptors (124), whereas programmed death ligand (PD-L)1 is one of the ligands for PD-1 (125). As a co-suppressor molecule during cancer development, PD-L1 is expressed on T lymphocytes and promotes immune escape (126). Fan *et al* (127) previously found that PC-esterase domain-containing 1B (PCED1B)-AS1 enhanced the expression and function of PD-L1 and PD-L2 by sponging miR-194-5p, which induced immunosuppression by HCC. Therefore, PCED1B-AS1 was a potential therapeutic target for HCC. In cancer, the PD-1/PD-L1 pathway is responsible for T cell activation, proliferation and cytotoxic secretion, leading to the degeneration of the antitumor immune response (128). Zhou *et al* (129) reported that in hypopharyngeal squamous cell carcinoma there was a positive regulatory relationship between HOXA11-AS1 and PD-L1. In particular, downregulation of HOXA11-AS1 inhibited PD-L1-mediated immune escape and metastasis by reducing the association between polypyrimidine tract binding protein 1 and FOS-like 1 in hypopharyngeal squamous cell carcinoma. Results from the aforementioned study provided a preliminary basis for applying HOXA11-AS1 as a potential target for the immunotherapy of hypopharyngeal squamous cell carcinoma. In addition, AS-lncRNAs can regulate the expression of genes associated with immune responses, changing the status of immune cell infiltration in the tumor microenvironment and profoundly dictate tumor invasiveness, progression and prognosis (88,130). Nie *et al* (85) performed an integrative analysis using publicly available gene expression datasets from TCGA project and the Genotype-Tissue Expression project from various GC patients' cohorts and a novel pairing algorithm to identify and validate 13 immune-related lncRNA pair signatures. This may provide novel insights into the role of AS-lncRNAs in tumor immunity and to facilitate the development of antitumor immunotherapeutic methods.

In conclusion, AS-lncRNAs can regulate gene expression related to immune response, thereby regulating antitumor immunity to regulate tumor development, and it may become a novel target for tumor therapy.

To sum up, tumor gene therapy is currently a topic of intense research, with main fields including the activation of tumor suppressor factors, inhibiting oncogene expression and inducing antitumor immune activation, which can all be regulated by AS-lncRNAs according to the aforementioned previous findings.

Enhancing chemoradiotherapy and chemotherapy by interfering with tumor drug resistance. Radiotherapy and chemotherapy form the core of all treatment strategies for cancer; however, the majority of patients will develop drug resistance, which is a major obstacle to the long-term efficacy of radiotherapy and chemotherapy (131,132). The mechanisms underlying drug resistance are complex, which can involve a wide array of factors, such as drug efflux, DNA damage repair, apoptosis and target mutations (133,134). Since AS-lncRNAs have been reported to be aberrantly expressed in tumors, they regulate chemoradiotherapy resistance (135-138).

5-Fluorouracil resistance. In a previous study, Zhou *et al* (135) found the lncRNA transmembrane protein 44 (TMEM44)-AS1 to be associated with resistance to 5-FU by GC cells. TMEM44-AS1 was observed to function as a ceRNA, which upregulated protein phosphatase 1 regulatory subunit 13-like expression and inhibited the p53 pathway, finally promoting resistance to 5-FU. To combat this, Zhou *et al* (129) developed the nano-carrier chitosan-gelatin epigallocatechin gallate to deliver small interfering RNA-TMEM44-AS1 to knock down TMEM44-AS1 expression, which effectively reversed 5-FU resistance, specifically by observing a significant enhancement in the therapeutic effects of 5-FU in xenograft mouse models of GC. Gui *et al* (137) recently observed that FEZ family zinc finger (FEZF1)-AS1 was upregulated in 5-FU chemically resistant GC tissues. RIP then revealed that FEZF1-AS1 increased the chemical resistance of GC cells through directly targeting autophagy-related 5 ganglion autophagy. By contrast, knocking down FEZF1-AS1 expression was documented to increase the sensitivity to 5-FU in GC cells *in vivo*. In a recent study, Qu *et al* (136) revealed that lncRNA discs large homolog associated protein 1 (DLGAP1)-AS1 promoted the progression of CRC. Subsequently, functional assays revealed that silencing DLGAP1-AS1 expression enhanced the chemosensitivity of cells to 5-FU, suggesting that silencing DLGAP1-AS1 expression may be a promising therapeutic target for CRC.

Cisplatin resistance. Ren *et al* (65) found that lncRNA ADAMTS9-AS2 overexpression inhibited the progression of GC and promoted cisplatin chemosensitivity by regulating the pyroptosis process mediated by the miR-223-3p/NLRP3 axis. This molecular mechanism underlying the drug resistance in GC to cisplatin provided a novel therapeutic target for the clinical treatment of GC. Song *et al* (139) previously reported that OIP5-AS1 was highly expressed in cisplatin-resistant (CR) osteosarcoma cells. Silencing OIP5-AS1 expression promoted the apoptosis in CR osteosarcoma cells, suggesting that the

downregulation of OIP5-AS1 can significantly reverse cisplatin resistance in osteosarcoma cells. These results deepened the understanding into the role of OIP5-AS1 in cisplatin resistance in osteosarcoma, possibly providing a novel therapeutic target for patients with CR osteosarcoma. Wu *et al* (140) previously revealed that upregulation of FOXD1-AS1 increased the resistance of GC cells to cisplatin. FOXD1-AS1 promoted FOXD1 translocation through PIK3CA/PI3K/AKT/mTOR signaling, which increased the progression of GC and chemotherapy resistance. These findings provided a novel target for the treatment of patients with CR GC.

Oxaliplatin resistance. Recent studies have demonstrated that lncRNAs are involved in the regulation of oxaliplatin resistance (141-143). Liang *et al* (144) previously found that OIP5-AS1 expression was upregulated in CRC tissues, whilst that of miR-137 was downregulated. Therefore, there was a negative association between the expression of OIP5-AS1 and miR-137. OIP5-AS1 was subsequently found to directly target miR-137, such that silencing OIP5-AS1 expression reversed the resistance of CRC cells to oxaliplatin by promoting the expression of miR-137. Furthermore, Hui *et al* (145) reported that overexpression of PGM5-AS1 inhibited the proliferation of oxaliplatin-resistant colon cancer cells by using colony formation assays, Cell Counting Kit-8 analysis and EdU assays. Transwell analysis revealed that compared with those in the control group, the overexpression of PGM5-AS1 inhibited the invasion and migration of oxaliplatin-resistant colon cancer cells. These results suggested that PGM5-AS1 overexpression can render colon cancer cells more sensitive to oxaliplatin. Hui *et al* (136) also found that PGM5-AS1 and oxaliplatin could enter colon cancer cells through engineered exosomes to effectively reverse drug resistance. Li *et al* (143) previously observed that extracellular leucine rich repeat and fibronectin type III domain-containing 1 (ELFN1)-AS1 interacted with the promoter region of meis homeobox 1 (MEIS1) to inhibit the expression of MEIS1. By contrast, MEIS1 can enhance the sensitivity of CRC cells to oxaliplatin. This resulted in the conclusion that the combination of oxaliplatin and ELFN1-AS1 ASO can reverse oxaliplatin resistance in CRC, highlighting the potential of targeting ELFN1-AS1 as a treatment method oxaliplatin resistance.

Radiotherapy resistance. Zou *et al* (138) previously found that lncRNA OIP5-AS1 and dual specificity tyrosine-phosphorylation-regulated kinase 1A (DYRK1A) were downregulated in radiation-resistant CRC cell lines. Specially, overexpression of OIP5-AS1 can regulate DYRK1A expression through miR-369-3p, damage the survival of cell clones and promote apoptosis after radiotherapy, suggestive of the reversal of radiation resistance in CRC cells.

5. Conclusion

Malignant tumors are one of the main causes of mortality worldwide. As the second leading cause of mortality in China, cancer seriously threatens the lives of the population and restricts social and economic development. lncRNAs are RNAs that contain >200 nucleotides. Although the majority of lncRNAs do not encode proteins, they can mediate a variety of important physiological functions. AS-lncRNAs are part of the antisense chains of coding genes that are transcribed from the opposite strands of protein or non-protein coding genes. Accumulating evidence has shown that AS-lncRNAs can serve an important role in tumorigenesis, metastasis, prognosis and drug resistance. AS-lncRNAs can regulate gene expression in tumors through endogenous competition mechanisms, promoter interactions, direct interactions with mRNA, acting as 'scaffolds' to regulate the half-life of mRNA, interactions with 5'-UTR, regulation of mRNAs of interest, positive feedback loop of 'AS-lncRNA/mediator protein/gene of interest' model and transcriptional regulation in the nucleus. Over the past decade, AS-lncRNAs have been found to mediate a variety of molecular functions, such as the regulation of cell proliferation, invasion, migration and apoptosis. In addition, they have been shown to regulate tumor energy metabolism, inflammation and tumor neovascularization. Although the discovery of AS-lncRNAs has only been relatively recent, their possible application in tumor treatment has been widely studied. AS-lncRNAs can potentially serve as markers of tumor therapy, as they may activate tumor suppressor factors, inhibit oncogene expression and induce antitumor immune activation. In addition, there is evidence that AS-lncRNAs can regulate the mechanism underlying tumor treatment and drug resistance. To conclude, AS-lncRNAs are likely to serve a role in tumor gene expression, the mechanisms regulating tumors physiology and tumor response to treatment. Treatment of abnormally expressed AS-lncRNAs in tumors is a promising method. The study into AS-lncRNAs has opened up a new era for the exploration, diagnosis and treatment of tumors.

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Authors' contributions

YS wrote the manuscript, searched the literature and prepared the table. YD, YL and YC was involved in the design of the study, and revised the manuscript. YL prepared the figure. JZ, ZL, CC and XY provided article ideas, modified the tables and revised the manuscript. QL, SZ, WT, ZC, YW, LH, ZQ, KW and ZM performed literature research and collected relevant articles. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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