

Long non-coding RNAs in gallbladder cancer: From mechanisms to therapeutic opportunities (Review)

YINGJIE HE^{1,2*}, XUEZHI DU^{1,2*}, FAN YUAN^{3*}, CAIGU YAN², MING CHEN², LEI HAN¹ and JINJIN SUN²

¹Key Laboratory of Post-Neuroinjury Neuro-repair and Regeneration in Central Nervous System, Ministry of Education and Tianjin, Tianjin Neurological Institute, Tianjin Medical University General Hospital, Heping, Tianjin 300052;

²Department of Hepatopancreatobiliary Surgery, The Second Hospital of Tianjin Medical University, Hexi, Tianjin 300211;

³Institute of Reproductive Medicine, Luoyang Maternal and Child Health Hospital, Luoyang, Henan 471000, P.R. China

Received May 5, 2023; Accepted November 29, 2023

DOI: 10.3892/ijo.2023.5604

Abstract. Due to the lack of specific symptoms, characteristic diagnostic markers and effective comprehensive treatment, gallbladder cancer (GBC) is currently considered one of the most malignant abdominal tumors. With the rapid development of biological technologies, long non-coding RNAs (lncRNAs), once regarded as transcriptional junk, have been demonstrated to participate in almost the whole process of the central dogma of molecular biology. The central dogma deals with the transfer of sequential information at the level of individual residues. lncRNAs have an effect on multiple cancer types. However, evidence of dysregulated lncRNA functions in GBC is limited. In the present review, the regulatory mechanisms of lncRNA function on gene expression were examined, including epigenetic modification, transcriptional regulation and post-translational modulation. These mechanisms are strongly associated with tumor development and metastasis. Next, it was summarized how lncRNAs affect GBC diverse malignant phenotypes through various mechanisms. Moreover, predictions of lncRNA interactions with other functional molecules in malignancies

were made using several valuable databases, including crosstalk between lncRNA and DNA, mRNA, microRNA, and protein. Additionally, several potential therapeutic methods targeting pathological lncRNAs in tumors were identified. Finally, perspectives about lncRNA research and applications in GBC were presented in the current study, including viewpoints of coding potential of lncRNAs and feasible usage of micropeptides encoded by lncRNAs; roles of lncRNAs in tumor cell metabolic reprogramming and tumor microenvironment; and function of lncRNAs as possible biomarkers and therapeutic targets for improving GBC diagnosis, treatment and prognosis.

Contents

1. Introduction
2. Regulatory mechanisms of lncRNAs in cancer, especially in GBC
3. Useful lncRNAs databases for GBC research

Correspondence to: Dr Jinjin Sun, Department of Hepato-pancreatobiliary Surgery, The Second Hospital of Tianjin Medical University, 23 Pingjiang Road, Hexi, Tianjin 300211, P.R. China
E-mail: jsun02@tmu.edu.cn

Professor Lei Han, Key Laboratory of Post-Neuroinjury Neuro-repair and Regeneration in Central Nervous System, Ministry of Education and Tianjin, Tianjin Neurological Institute, Tianjin Medical University General Hospital, 154 Anshan Road, Heping, Tianjin 300052, P.R. China
E-mail: superhanlei@tmu.edu.cn

*Contributed equally

Abbreviations: AGO2, argonaute 2; ASOs, antisense oligonucleotides; ATG, autophagy-related protein; ATPase, adenosine triphosphatase; Cas, CRISPR-associated; CDK1, cyclin-dependent kinase 1; ceRNAs, competing endogenous RNAs; CRC, colorectal cancer; CRISPR, clustered regularly interspaced short palindromic repeats; DNMTs, DNA methyltransferases; DUBs, deubiquitinases; EGFR, epithelial growth factor receptor; EMT, epithelial-to-mesenchymal transition; EZH2, enhancer of Zeste Homolog 2; FDA, Food and Drug Administration;

GBC, gallbladder cancer; GBCDRlnc1, GBC drug resistance-associated lncRNA 1; gRNAs, guide RNAs; H3K27me3, trimethylation of Histone 3 on Lysine-27; HIF1 α , hypoxia inducible factor 1 α ; HMG, high mobility group proteins; IGF2BP3, insulin-like growth factor 2 mRNA-binding protein 3; IL-6, Interleukin-6; IRES, internal ribosome entry sites; JAK, Janus kinase; LNA, locked nucleic acid; lncRNAs, long non-coding RNAs; m6A, N⁶-methyladenosine; miRISCs, miRNA-induced silencing complexes; miRNAs or miRs, microRNAs; MLH1, mutL Homolog-1; MM, multiple myeloma; MRE, miRNA response element; NAT, natural antisense transcript; NHEJ, non-homologous end joining; NONO, non-POU domain containing octamer-binding protein; nt, nucleotides; OC, ovarian cancer; PC, pyruvate carboxylase; PRCs, polycomb repressive complexes; pre-mRNA, precursor mRNA; RBPs, RNA-binding proteins; RISCs, RNA-induced silencing complexes; RNases, ribonuclease enzymes; SFs, splicing factors; shRNAs, short hairpin RNAs; siRNAs, small interfering RNAs; TEAD4, TEA domain family member 4; TFs, transcriptional factors; TME, tumor microenvironment; TNBC, triple-negative breast cancer; TRPs, translation regulatory proteins; TSGs, tumor suppressive genes; USP16, ubiquitin specific peptidase 16

Key words: lncRNAs, GBC, dysregulation, biomarker, therapy

4. Potential therapeutic methods targeting lncRNAs in GBC
5. Conclusions and future perspectives

1. Introduction

Despite representing half of the biliary tract cancer types, gallbladder cancer (GBC) is still regarded as an infrequent malignancy (1). The incidence of GBC is influenced by geographical factors, gallbladder disease history (including gallstones and gallbladder polyps) and autoimmune dysregulation (such as primary sclerosing cholangitis), among other factors (2,3). Anatomically, the gallbladder vein drains into the liver vein directly, promoting the infiltration of GBC to adjacent organs (4). Incipiently, symptoms of GBC are not specific, while the most common symptoms are dyspepsia and abdominal pain. Laboratory tests can identify liver dysfunction, and increased bilirubin and tumor biomarkers such as carbohydrate antigen 19-9 and carcino-embryonic antigen, which is frequent in digestive system tumors (5). In addition, it is difficult to distinguish GBC from lithiasis and cholesterol crystals by imaging methods. Generally, GBC is identified by pathological tests after cholecystectomy for the treatment of gallbladder stones or biliary tract infections (3). As for therapy, surgery is the only curative approach for GBC. However, >50% patients have limited probabilities of undergoing effective treatment at the moment of a clear diagnosis, which leads to a poor 5-year survival rate (6).

Long non-coding RNAs (lncRNAs), characterized by their length exceeding 200 nucleotides (nt) and limited protein-coding potential, have received particular interest among scientists (7). lncRNAs act as multifunctional regulatory factors that participate in gene transcription and epigenetic modifications (8). With the advancements in novel technologies, the expression of lncRNAs has been identified as tissue-specific, thereby laying the foundation for their potential function as disease biomarkers (9). Due to their multifunctional roles and great potential for clinical application, understanding how lncRNAs exert oncogenic or tumor suppressive functions is paramount.

Since Wu *et al* (10) reported in 2014 for the first time that the well-known oncogenic lncRNA, MALAT1, played roles in GBC, researchers have gradually concentrated on the functions of lncRNAs on this lethal malignancy. The present study aimed to summarize the regulatory mechanisms of lncRNAs in cancer, review relevant research of lncRNAs' functions in GBC malignant phenotypes, and summarize current databases and potential therapeutic methods targeting lncRNAs in cancer. The present study is anticipated to furnish valuable insights for enhancing the management of this deadly neoplasm.

2. Regulatory mechanisms of lncRNAs in cancer, especially in GBC

Recently, accumulating studies have revealed various functions of lncRNAs in cancer (11). Since they participate in the regulation of different aspects of gene expression and play important roles in regulating GBC malignant hallmarks via different mechanisms (12,13), detailed roles of lncRNAs are described as follows and summarized in Table I and Fig. 1.

lncRNAs in epigenetic modification. Epigenetic modification is notably relevant to differential gene expression, while

dysregulation in these processes can lead to the development of several cancer types (14). Previous studies clearly showed that lncRNAs participate in this process (15,16) (Fig. 1A).

DNA methylation. Mediated by various DNA methyltransferases (DNMTs), DNA methylation is a basic epigenetic modification to alter gene transcription (17). Phenotypic variations in cancer cells are directly regulated by aberrant DNA methylation, which influences the expression levels of essential oncogenes or tumor suppressor genes (TSGs), thereby impacting cancer progression (18). Numerous studies have identified that lncRNAs could interact with DNMTs and regulate DNMTs-mediated methylation on promoters, particularly on CpG island, thus affecting tumor-related gene expression (19,20) (Fig. 1A-a).

As aforementioned, lncRNAs can be scaffolds or decoys to interact with epigenetic factors, such as enhancer of Zeste homolog 2 (EZH2), DNMT1, to affect gene expression. Cai *et al* (21) found that oncogenic lncRNA UCA1 could promote GBC growth and metastasis by recruiting EZH2 to the promoter of p21 and E-cadherin, and epigenetically regulating their transcription. Similarly, Lin *et al* (22) reported that lncRNA MALAT1 was able to recruit EZH2 to the promoter of ABI family member 3 binding protein, thus inhibiting GBC cell senescence and potentiating cell proliferation. Gao *et al* (23) revealed that lncRNA FOXD2-AS1 could also recruit DNMT1 to the promoter of mutL homolog 1 (MLH1) and promote its methylation, leading to the transcriptional repression of MLH1, which was verified as a TSG involved in the DNA mismatch repair pathway. FOXD2-AS1 affects GBC malignant phenotypes (23). Jin *et al* (24) observed that, with the assistance of EZH2, lncRNA PVT1 recruited DNMT1 to the promoter region of microRNA-18b-5p (miR-18b-5p), and decreased miR-18b-5p transcription epigenetically. As a target of miR-18b-5p, the level of hypoxia inducible factor 1 α (HIF1 α), a well-known cancerous factor, was increased, which promoted GBC growth. Mechanistically, the PVT1/miR-18b-5p/HIF1 α axis facilitated GBC progression in a non-competing endogenous RNA (ceRNA) manner (24). Li *et al* (25) demonstrated that MEG3 could bind to EZH2 and activate EZH2-mediating trimethylation of histone 3 on lysine-27 (H3K27me3) of the CXC motif chemokine ligand 3 (CXCL3) promoter region. Subsequently, MEG3 attenuated GBC cells malignant behavior via inhibition of CXCL3 expression (25).

Histone modification. In addition to DNA methylation, chromatin structure can be altered via histone modifications (26), while lncRNAs have been found to cooperate with histone-modifying enzymes. Generally, lncRNAs function as molecular scaffolds or decoys to affect the recruiting of chromatin remodeling complexes, such as histone modifying enzymes to regulate gene expression in close proximity (*cis*-acting) or distant crosstalk (*trans*-acting) (27), therefore having an impact on tumorigenesis and tumor development (Fig. 1A-b). The most common example is polycomb repressive complexes (PRCs), which functions as a methyltransferase to promote H3K27me3 and leads to chromatin compaction and subsequently transcriptional repression (28,29).

Nucleosome positioning. Nucleosome positioning is another important process in epigenetic modulation because

Table I. Aberrant lncRNAs in GBC.

Mechanisms	LncRNAs	Aberrant expression	Upstream	Downstream	PubMed ID
DNA methylation	UCA1	↑		p21/E-cadherin	28624787
	MALAT1	↑		ABI3BP	31174563
	FOXD2-AS1	↑		MLH1	32917950
	PVT1	↑		miR-18b-5p/HIF1 α	33067424
mRNA stability	MEG3	↓		CXCL3	35188401
	HOTAIR	↑	c-Myc	MiR-130a	24953832
	CCAT1	↑		MiR-218-5p/Bmi1	25569100
	H19	↑		MiR-194-5P/AKT2	26803515
	H19	↑		MiR-343-3p/FOXO1	27716361
	MALAT1	↑		MiR-206/ANXA2, MiR-206/KRAS	27191262
	MALAT1	↑		MiR-363-3p/MCL-1	27420766
	MINCR	↑	MYC	MiR-26a-3p/EZH2	27345740
	LINC00152	↑		MiR-138/HIF1 α	28077595
	TUG1	↑	TGF- β 1	MiR-300	28178615
	PAGBC	↑		MiR-133b/SOX4	28887321
				MiR-511/PIK3R3	
	PVT1	↑		MiR-143/HK2	30825877
	PVT1	↑		MiR-30d-5p	32689767
	GATA6-AS2	↓		MiR-421/TIMP-2	31632058
	HGBC	↑	HuR	MiR-502-3p/SET	31752906
	LINC01694	↑		MiR-340-5p/SOX4	32270853
	DGCR5	↑		MiR-3619-5P	32740494
	SNHG6	↑		MiR-26b-5p	32744686
	GALM	↑		MiR-200 family/ZEB1	33252861
				MiR-200 family/ZEB2	
				MiR-200family/N-cadherin	
				MiR-200 family/IL-1 β	
	OIP5-AS1	↑		MiR-143-3p	33364844
	TTN-AS1	↑		MiR-107/HMGA1	34090483
	FIRRE	↑		MiR-520a-3p/YOD1	34168678
	MYLK-AS1	↑		MiR-217/EZH2	34393514
	TMPO-AS1	↑		MiR-1179/E2F2	34777589
	AFAP-AS1	↑		Hsa-miR-15a-5p/Bcl-2	35404724
	SNHG1	↑		MiR-194-5p/LIF	36261179
Regulation of the ubiquitination and proteasome pathway				MiR-194-5p/PDGFA	
	HOXA-AS2	↑		MiR-6867-5p/YAP1	36299503
	GCASPC	↓	MiR-17-3p	Pyruvate carboxylase	27450454
	MEG3	↓		LATS2	30282996
	GBCDRlnc1	↑		PGK1, ATG5-ATG12 conjugate	30953511
	SSTR5-AS1	↑		NONO	31810606
	LINC01410	↑		STAT5	34322379
Regulation of phosphorylation	MNX1-AS1	↑	TEAD4	USP16/IGF2BP3/TEAD4	35953000
	RP11-147L13.8	↓		c-Jun	34703881
LncRNAs that correlating with signaling pathways	MALAT1	↑		ERK/MAPK pathway	24658096
	LINC00152	↑	SP1	PI3K/AKT pathway	27829993
	HEGBC	↑	STAT3	IL11/STAT3 pathway	30086773
	DILC	↑		Wnt/ β -catenin pathway	30716440
	MEG3	↓		ERS-related proteins/NF- κ B pathway	32633352
Others	LET	↓		p21	25213660
	MEG3	↓		-	26812694

Table I. Continued.

Mechanisms	LncRNAs	Aberrant expression	Upstream	Downstream	PubMed ID
	H19	↑	TGF-β1/IL-6	E-cadherin/Vimentin	27073719
	H19	↑	HHLA2	-	35920182
	ANRIL	↑		-	26812694
	ROR	↑		-	27449039
	AFAP-AS1	↑		E-cadherin/Vimentin	27810781
	SPRY4-IT1	↑		-	27902971
	Loc344887	↑	Nrf2	E-cadherin/N-cadherin/Vimentin	28245089
	HOXA-AS2	↑		-	28388535
	EPIC1	↑		-	34653690
	Linc00261	↓		-	35117219

lncRNA, long non-coding RNA; GBC, gallbladder cancer; ABI3BP, ABI family member 3 binding protein; MLH1, mutL Homolog-1; miR, microRNA; HIF1α, hypoxia inducible factor 1α; CXCL3, CXC motif chemokine ligand 3; FOXM1, Forkhead box M1; ANXA2, Annexin A2; MCL-1, myeloid cell leukaemia-1; EZH2, enhancer of Zeste homolog 2; TGF, transforming growth factor; HK2, hexokinase 2; IL, interleukin; HMGA1, high mobility group proteins A1; LIF, interleukin 6 family cytokine; PDGFA, platelet derived growth factor subunit A; YAP1, yes-associated protein 1; LATS2, large tumor suppressor homolog 2; PGK1, phosphoglycerate kinase 1; ATG, autophagy-related protein; NONO, non-POU domain containing octamer-binding protein; TEAD4, TEA Domain family member 4; USP16, ubiquitin specific peptidase 16; IGF2BP3, insulin-like growth factor 2 mRNA-binding factor 3; SP1, specificity protein 1; ERS, endoplasmic reticulum stress; NF-κB, nuclear factor-κB; HHLA2, human endogenous retrovirus-H long terminal repeat-associating protein 2; Nrf2, nuclear factor (erythroid-derived2)-like 2.

the firm interplay of nucleosomes with histone cores can significantly influence DNA accessibility (30). lncRNAs are known to regulate nucleosome positioning mainly by interacting with adenosine triphosphatase (ATPase) subunits of chromatin remodeling complexes (31). For example, lncRNA PAPAS interacts with the chromodomain helicase DNA-binding 4 subunit of the nucleosome remodeling and histone deacetylation complex. This complex itself plays a role in chromatin remodeling, while the interaction between lncRNAs and ATPase subunits relocates the nucleosome to target regions, such as the transcriptional 'off' position, and finally triggers epigenetic modification (32,33) (Fig. 1A-c).

lncRNAs in transcriptional modification. Transcription is a basic but essential process for gene regulation that changes cell differentiation, cell state and function (34). It has been demonstrated that lncRNAs can regulate transcription in different ways (35) (Fig. 1B). lncRNAs can act as decoys or scaffolds to bind to transcriptional factors (TFs), including transcriptional activators and repressors, subsequently affecting target gene expression (36) (Fig. 1B-a). lncRNAs interact with promoters and influence transcription of target genes by *cis*- or *trans*-acting (37,38) (Fig. 1B-b).

Certain lncRNAs were reported to affect transcription by modulating the local chromatin structure (39). Saayman *et al* (40) demonstrated that lncRNA BGAS interacted with high mobility group proteins (HMG) A1 and HMGB1, as well as the partner of Y14 and within benign gonial cell neoplasm homolog, to regulate local chromatin and DNA architecture of intron 11 of the cystic fibrosis transmembrane conductance regulator gene and thereby affecting its transcription.

lncRNAs in post-transcriptional modification. Since it allows diverse transcripts, post-transcriptional modification remains a key process in controlling protein production. lncRNAs can also control gene expression by acting as post-transcriptional regulators (8,41) (Fig. 1C).

mRNA stability. Affected by endo- or exonucleases, multiple mRNA decay or stabilizing factors, mRNA decapping and mRNA deadenylation, the mRNA stability of oncogenes or TSGs was reported to be regulated by lncRNAs through several mechanisms (42) (Fig. 1C-a). The most common mechanism is that lncRNAs, mainly natural antisense transcript (NAT) lncRNAs, can bind to targeted mRNAs due to sequence complementarity, thus preventing its interaction with different mRNA-decay factors and blocking mRNA degradation (43,44). Apart from this mechanism, lncRNAs can also bind to various RNA binding proteins (RBPs) involved in mRNA turnover or decay, thus affecting mRNA stability (45,46). In particular, lncRNAs can bind to N⁶-methyladenosine (m6A) readers to recognize m6A sites on mRNAs, thus affecting their decay (47-49).

MicroRNAs (miRNAs or miRs) regulate gene expression by binding to a complementary sequence of the target mRNA, which is termed 'miRNA response element' (MRE). According to the level of complementarity, miRNAs can facilitate both mRNA decomposition by argonaute 2 (AGO2) endonuclease in cases of full complementarity, and miRNA-induced silencing complexes (miRISCs)-mediated translational repression in cases of partial complementarity (50). lncRNAs can act as ceRNAs to capture their target miRNAs, releasing the downstream target (generally miRNA-targeted mRNAs) to fulfill its intrinsic function (51,52).

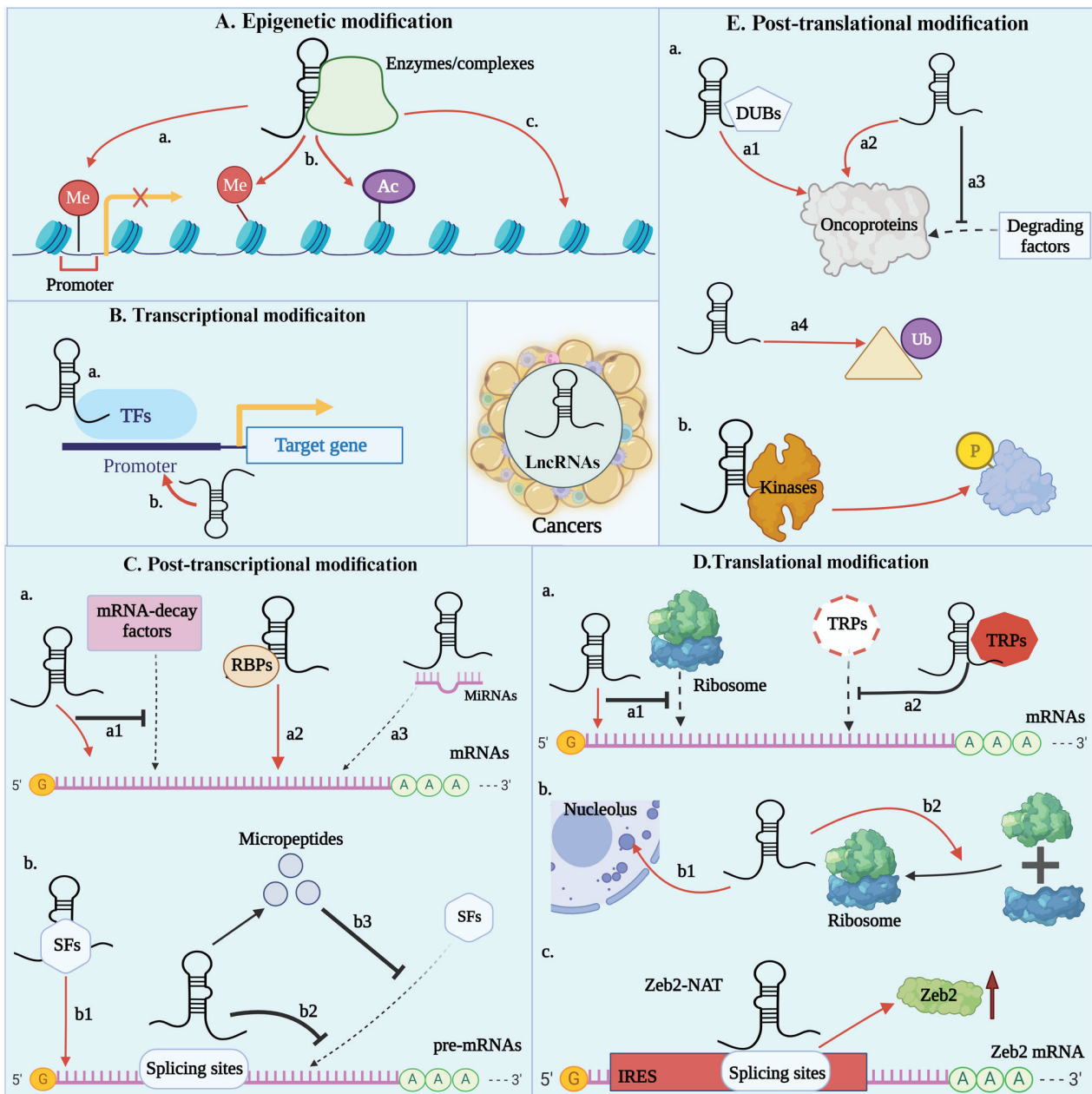


Figure 1. Regulatory mechanisms of lncRNAs in cancer. (A) Epigenetic modification. (A-a) DNA methylation: LncRNAs interact with DNMTs and regulate DNMTs-mediated methylation on promoters. (A-b) Histone modification: LncRNAs cooperate with histone-modifying enzymes to mediate histone modification. (A-c) Nucleosome positioning: LncRNA PAPAS binds to the CHD4 subunit of the NuRD complex to relocate the nucleosome to target regions. (B) Transcriptional modification. (B-a) LncRNAs bind to TFs and affect target gene expression. (B-b) LncRNAs interact with promoters and influence target gene transcription. (C) Post-transcriptional modification. (C-a) mRNA stability. (C-a1) LncRNAs interact with mRNAs to inhibit mRNAs-decay factors function on mRNAs. (C-a2) LncRNAs bind to RBPs to affect mRNAs stability. (C-a3) LncRNAs sponge miRNAs to block miRNA-induced mRNAs degradation. (C-b) Alternative splicing. (C-b1) LncRNAs bind to SFs to decrease the interaction of SFs and pre-mRNAs. (C-b2) LncRNAs interact with pre-mRNAs to block recognition and recruitment of SFs on splicing sites. (C-b3) LncRNAs encode micropeptides to regulate the interaction between SFs and pre-mRNAs. (D) Translational modification. (D-a) mRNA translation. (D-a1) LncRNAs interact with mRNA to decrease ribosome binding sites. (D-a2) LncRNAs interact with TRPs to block the binding of TRPs to target mRNAs. (D-b) Ribosome function. (D-b1) LncRNAs affect nucleolar structures to interfere in ribosome biogenesis. (D-b2) LncRNAs affect the production or maturation of rRNA and/or ribosomal protein to modulate ribosome assembly and activity. (D-c) Translational reprogramming: LncRNA Zeb2-NAT physically binds and masks the splicing site of IRES on Zeb2 mRNA to increase the translation of Zeb2. (E) Post-translational modification. (E-a) Regulation of the ubiquitin-proteasome pathway. (E-a1) LncRNAs recruit DUBs to oncoproteins. (E-a2) LncRNAs interact with oncoproteins physically. (E-a3) LncRNAs bind to oncoproteins competitively to hinder the binding of other degrading factors and subsequent decay. (E-b) Regulation of phosphorylation. LncRNAs bind to kinases to alter their activity. LncRNAs, long non-coding RNAs; DNMTs, DNA methyltransferases; CHD4, chromodomain helicase DNA-binding 4; NuRD, nucleosome remodeling and histone deacetylation; TFs, transcriptional factors; RBPs, RNA binding proteins; miRNAs, microRNAs; SFs, splicing factors; pre-mRNAs, precursor mRNAs; TRPs, translation regulatory proteins; rRNA, ribosomal RNA; IRES, internal ribosome entry site; DUBs, deubiquitinases. Created with BioRender.com.

To date, the majority of studies on the roles of lncRNAs in GBC have focused on their function as miRNAs sponges to

regulate subsequent targets. For example, Wang *et al* (53,54) revealed that H19 had the ability to sponge miR-194-5p or

miR-342-3p separately, thus facilitating AKT2 or forkhead box M1 expression, which contributes to GBC growth. Li *et al* (55) demonstrated that H19 was upregulated in exosomes in bile acid that derived from cholangiocytes under pathological conditions. In addition, two oncogenic lncRNAs were reported to be able to sponge different miRNAs and subsequently modulate the downstream targets, LINC01694 (56) and SNHG6 (57), respectively, which could be detected in serum samples. These results indicated that detection of pathogenic lncRNAs in body fluids may provide more information for the diagnosis and subsequent monitoring of patients with GBC. Wang *et al* (58,59) demonstrated that MALAT1 could function as a ceRNA to sponge miR-206 and miR-363-3p in GBC, thus regulating the expression of annexin a2, KRAS, and myeloid cell leukemia-1, which are known oncogenes in human malignancies. Chen *et al* (60) observed that oncogenic lncRNA PVT1 could act as a ceRNA to sponge miR-143 and upregulate the expression of hexokinase 2, which is considered an oncogene to facilitate glucose utilization. Therefore, PVT1 promoted GBC progression via metabolism reprogramming (60). Similarly, Liu and Xu (61) demonstrated that PVT1 played a tumorigenic role in GBC via directly binding to miR-30d-5p. Notably, overexpression of MALAT1 in GBC tissues was reported to be associated with larger tumor size and positive lymph node metastasis. Furthermore, upregulated PVT1 in GBC tissues was found to be related to higher TNM stage, which predicted poor overall survival of patients with GBC (62). Apart from these well-known lncRNAs, other oncogenic or tumor-suppressive lncRNAs exist, which can sponge targeted miRNAs, as shown in Table I.

Alternative splicing. Alternative splicing of precursor mRNA (pre-mRNA) can produce >2 isoforms of the same mRNA, which has an impact on increasing the diversity of proteomics (63). Notably, lncRNAs may be involved in this complex process to support the generation of tumor-related proteins via various mechanisms in cancerous cells (64,65) (Fig. 1C-b). First, lncRNAs can act as decoys and interact with splicing factors (SFs), which results in the physical downregulation of SFs' recruitment to their target pre-mRNAs (66,67). In addition, various lncRNAs contain complementary sequences (named NAT) to be paired with endogenous RNAs, which are able to interplay with *cis*- or *trans*-acting elements of pre-mRNAs via base complementary pairing. Such interplay influences the splicing site recognition and the recruitment of SFs, and results in the dysregulation of splicing isoforms expression (68,69). Furthermore, lncRNAs have a restricted potential to encode some micropeptides. These micropeptides can not only modulate the binding of SFs with targeted pre-mRNAs but also affect the differential expression of splicing isoforms, which can affect tumor growth (70). Moreover, lncRNAs can regulate SF expression in direct or indirect ways in cancer. The best example of direct regulation is MALAT1 in ovarian cancer (OC). Overexpressed MALAT1 leads to upregulation of RNA binding fox-1 homolog 2, which is a vital SF in epithelial-to-mesenchymal transition (EMT)-driven alternative splicing, and ultimately leads to OC aggressiveness (71). As for indirect ways, lncRNAs can affect SF expression via post-translational modification, such as cooperating with certain kinases to enhance the phosphorylation of SFs (72,73).

LncRNAs in translational modification. Regulated translation provides cancerous cells the advantage of rapidly adopting to environmental changes (74). Previous studies have suggested that lncRNAs participate in translational modification via indirect or direct methods (75). The indirect method is the lncRNA-mediated modulation of signaling pathways associated with translation (76,77), while the direct methods are as follows (Fig. 1D).

mRNA translation. Recent research has shown that lncRNAs influence the translation of oncogenes or TSGs mainly through two mechanisms (Fig. 1D-a). Firstly, lncRNAs can bind to mRNA through base complementary pairing, resulting in decreasing binding sites with ribosomes and inhibition of translation (78). Another mechanism involves the interaction of lncRNAs and translation regulatory proteins (TRPs), such as Y-box binding protein-1, subsequently regulating the binding of TRPs to target mRNAs and thereby modulating translation (79).

Ribosome function. Except for the translational modification of mRNA targets, emerging evidence has reported that lncRNAs are capable of modulating ribosome function to affect the translation process (80) (Fig. 1D-b). lncRNAs interfere with ribosome biogenesis in the nucleoli mainly in two ways: By affecting nucleolar structure (81), or by affecting the production (82) or maturation (83) of ribosomal RNA and/or ribosomal protein to modulate ribosome assembly and activity.

Moreover, it could be hypothesized that lncRNAs could be regulators of translation either via recruiting eukaryotic initiation factors to the ribosome, or through regulating other translational stages such as elongation and termination. However, the details of these mechanisms remain unclear.

Translational reprogramming. Compared with normal cells, environmental changes in cancerous cells promote global translation shut down (84), such as decreased cap-dependent translation, while maintaining the biosynthesis of basic proteins for survival via various mechanisms (85). Generally, cap-independent mechanisms include the identification of upstream open reading frames and internal ribosome entry sites (IRES). However, there is little evidence about lncRNA roles in translation reprogramming (86).

For instance, lncRNA Zeb2-NAT physically bound and masked the splicing site of IRES on Zeb2 mRNA, and caused increased translation of Zeb2, which is a transcriptional suppressor of E-cadherin and modulator of EMT (87) (Fig. 1D-c). In this regard, further studies should be conducted to explore the regulatory mechanisms of lncRNAs involved in this dynamic process.

LncRNAs in post-translational modification. Post-translational modifications are essential for almost all aspects of cell function and are frequently implicated in tumors (88-90). Through participating in post-translational modification, lncRNAs can affect the abundance of proteins that impact cancer development (91,92) (Fig. 1E).

Regulation of the ubiquitination and proteasome pathway. Previous studies suggested that numerous oncogenic lncRNAs prevented various oncoproteins from ubiquitination and subsequent proteasomal degradation mainly through three mechanisms, including i) Recruitment of deubiquitinases (DUBs) to oncoproteins (93); ii) direct interaction with

oncoproteins physically (94); and iii) competitively binding to oncoproteins to hinder its degradation mediated by other modulators before (95). Certain oncogenic lncRNAs were found to activate some regulators, which promoted degradation of tumor suppressive factors in a ubiquitin-proteasome-dependent manner, thus releasing the inhibition of tumor growth (96,97).

In contrast to the aforementioned mechanisms, tumor suppressive lncRNAs mediate enhanced ubiquitination and degradation of oncogenic proteins to inhibit tumorigenesis (27). For instance, lncRNA ANCR inhibits aggressive phenotypes of breast cancer by facilitating the interaction between EZH2 and cyclin-dependent kinase 1 (CDK1). CDK1 phosphorylates EZH2 at threonine 345/487, and ultimately increases EZH2 decay via the ubiquitin-proteasome pathway (98) (Fig. 1E-a).

In GBC, studies also reported that several lncRNAs could bind to proteins and modulate protein functions in GBC cells. Ma *et al* (99) demonstrated that ectopic expression of lncRNA GCASPC in GBC cells could bind to pyruvate carboxylase (PC), a key modulator in the Krebs cycle that provides extra energy for cancer cells, and facilitate PC degradation via the ubiquitin-proteasome pathway. Mechanistically, GCASPC acts as tumor-suppressor by blocking energy supply of GBC cells. It was also found that GCASPC is a target for miR-17-3p. Through binding to GCASPC, miR-17-3p recruits miRISCs and promotes GCASPC degradation via an AGO2-dependent manner, and downregulation of GCASPC is correlated with GBC progression (99). Jin *et al* (100) revealed that the tumor-suppressive lncRNA MEG3 is capable of promoting EZH2 ubiquitination, which leads to large tumor suppressor homolog 2 transcription and inhibition of GBC cell proliferation and invasion. Cai *et al* (101) identified an upregulated lncRNA ENST00000425894 named GBCDRlnc1 in doxorubicin-resistant GBC cells. Mechanistically, GBCDRlnc1 could interact with phosphoglycerate kinase 1 and inhibit its ubiquitination in GBC drug-resistant cells, which results in decreased levels of the autophagy-related protein (ATG) 5-ATG12 conjugate. Finally, GBCDRlnc1 mediates the inhibition of autophagy initiation and downregulates sensitivity of GBC cells to doxorubicin (101). Xue *et al* (102) indicated that lncRNA SSTR5-AS1 is overexpressed in gemcitabine-resistant GBC tissues. Mechanistically, SSTR5-AS1 interacts with non-POU domain containing octamer-binding protein (NNO) and strengthens its stability by prohibiting the proteasome-dependent degrading pathway. It has been reported that NNO is capable of forming a subnuclear body by binding to lncRNAs and promoting nuclear retention of RNA, thus regulating the expression of certain genes in differentiated cells. In the study of Xue *et al* (102), an interaction between SSTR5-AS1 and NNO was required for chemoresistance of GBC cells. Liu *et al* (103) identified that lncRNA MNX1-AS1 could serve as a scaffold for the interaction between ubiquitin specific peptidase 16 (USP16) and insulin-like growth factor 2 mRNA binding protein 3 (IGF2BP3). USP16 deubiquitinates IGF2BP3, and stabilized IGF2BP3 could increase TEA Domain family member 4 (TEAD4) expression, which could regulate the Hippo pathway function. Additionally, TEAD4 functions as a transcriptional activator to promote MNXA-AS1 formation. Finally, MNX1-AS1 forms a positive feedback loop with the TEAD4/Hippo pathway with the assistance of USP16 and IGF2BP3 (103).

Regulation of phosphorylation. Protein phosphorylation is regarded as an important post-translational modification to regulate intracellular and transmembrane signal transduction (27). Numerous lncRNAs are considered to modulate the phosphorylation of some critical signaling molecules by direct or indirect methods, thereby affecting hallmarks of cancer (104,105). Direct regulation refers to the fact that lncRNAs alter kinase activity by binding to them directly (73,98) (Fig. 1E-b), while the indirect regulation refers to the fact that lncRNAs affect kinase function through other pathways. Typical examples of indirect regulation include lncRNA interaction with G-protein-coupled receptor and phosphatidylinositol-(3,4,5)-trisphosphate (106), and the influenced targets include Janus kinase (JAK) 2 of the JAK2/STAT3 signaling pathway in breast cancer (107), STAT3 of the interleukin-6 (IL-6)/STAT3 signaling pathway in hepatocellular carcinoma (108) and the PI3K/AKT signaling pathway in medulloblastoma (109).

As aforementioned, Zheng *et al* (110) demonstrated that downregulated lncRNA RP11-147L13.8 was also associated with poor prognosis of patients with GBC. Mechanistically, RP11-147L13.8 can bind to the basic region leucine Zipper of Jun protein, and suppress c-Jun serine 73 phosphorylation by suppressing JNK functions in GBC cells. Therefore, RP11-147L13.8 plays tumor-suppressive roles in GBC (110).

Other potential post-translational modifications regulated by lncRNAs. Besides the regulation of the aforementioned post-translational modifications, other types of post-translational modifications, such as lncRNAs-induced non-histone acetylation have been revealed only in cell proliferation and apoptosis pathways (111,112), which indicates that these modifications may also participate in cancer development.

lncRNAs that correlate with signaling pathways. Previous studies found that aberrant expression of lncRNAs in GBC cells was correlated with certain signaling pathways (Table I), but the regulatory mechanisms involved were unclear. In 2014, Wu *et al* (10) reported for the first time that in GBC tissues, upregulated MALAT1 could promote GBC cell proliferation and metastasis possibly via the ERK/MAPK pathway. Cai *et al* (113) demonstrated that TF specificity protein 1 upregulates lncRNA LINC00152 in GBC and LINC00152 subsequently interacts with the PI3K/AKT pathway and inhibits GBC cell apoptosis. Yang *et al* (114) revealed that lncRNA HEGBC could bind to the promoter of IL-11 and facilitate its expression, thus activating the IL-11/STAT3 signaling pathway. STAT3 could also bind to the promoter of HEGBC and activate its expression. Finally, HEGBC formed a positive feedback loop with the IL-11/STAT3 pathway and exerted oncogenic functions in GBC (114). Liang *et al* (115) demonstrated that lncRNA DILC could facilitate GBC development via the Wnt/ β -catenin signaling pathway.

Regarding tumor-suppressive lncRNAs, Bao *et al* (116) demonstrated that MEG3 is positively correlated with endoplasmic reticulum stress-related proteins. Moreover, downregulation of MEG3 decreases nuclear factor- κ B signaling and suppresses GBC cell proliferation (116).

Others. Previous studies have reported the existence of certain pathogenic lncRNAs in GBC cells (Table I).

Ma *et al* (117) found that downregulation of lncRNA LET is positively correlated with the G₀/G₁ phase arrest marker p21, and LET could suppress GBC proliferation not only via mediating G₀/G₁ arrest but also by promoting GBC cell apoptosis (117). Wang *et al* (118) showed that transforming growth factor- β 1 and IL-6 treatment could induce the upregulation of lncRNA H19 *in vitro*, which is positively associated with GBC lymphatic metastasis and tumor size. Mechanistically, upregulated H19 is able to upregulate Twist1, which could affect the expression of genes related to EMT and tumor invasion, such as E-cadherin and vimentin (118). Similarly to the study by Wu *et al*, Ma *et al* (119) found that another lncRNA, namely AFAP1-AS1 can also interact with Twist1, and upregulate GBC cell EMT in a similar manner. Wu *et al* (120) demonstrated that upregulated lncRNA Loc344887 is able to increase the expression of Twist1, vimentin, and N-cadherin, as well as decrease E-cadherin expression to promote EMT. Ectopic expression of nuclear factor (erythroid-derived2)-like 2 leads to increased Loc344887 expression *in vitro*, which results in GBC cell malignant phenotypes (120). Various pathogenetic lncRNAs are listed in Table I, including ANRIL (121), ROR (122) and Linc00261 (123). However, the functions and regulatory mechanisms of these lncRNAs in GBC cells remain unknown, and require further research.

In summary, the majority of previous studies have focused on the function of lncRNAs as ceRNAs to sponge miRNAs, and certain RBPs that interacted with lncRNAs were also identified. However, studies on other regulatory mechanisms of lncRNAs in GBC are rare. Therefore, further research on the multiple pathogenetic roles of lncRNAs in GBC is needed.

3. Useful lncRNAs databases for GBC research

Thus far, several lncRNAs databases have been established to provide valuable information (124). Therefore, the present study aimed to review and arrange various lncRNA databases according to their usage for improved analysis of the roles of lncRNAs in GBC.

lncRNAs information, including biogenesis, structure and subcellular distribution are essential for functional research. Thus, the present study listed databases with lncRNA comprehensive information in Table SI. Among them, LncAtlas offers the subcellular localization of lncRNAs in human cells based on RNA-seq datasets (125), a tool frequently employed to investigate potential roles of lncRNAs in GBC cells (22,23). Since lncRNAs play vital roles in the whole process of the central dogma, the present study also curated databases to explore the interaction between lncRNAs and DNAs, lncRNAs and other RNAs, and lncRNAs and proteins. For instance, lncRNAs can form triplexes with DNA in the nucleus to affect gene transcription, while the novel Fasim-LongTarget (Table SII) is capable of predicting genome-wide lncRNA/DNA binding (126). lncRNAs can function as ceRNAs, and the Starbase v2.0 (Table SIII) offers comprehensive, experimentally-validated miRNA-lncRNA interaction networks, and develops the ceRNAFunction web servers to predict the function of lncRNAs from miRNA-mediated regulatory networks (127), which is extensively employed for the identification of miRNA targets among pathogenetic lncRNAs in GBC

cells (128,129). Regarding interactions between lncRNAs and proteins, catRAPID omics v2.0 (Table SIV) is important for researchers (130). Previous studies revealed that some lncRNAs are capable of encoding pathological micropeptides; thus, the present study collected several available databases to inquire lncRNAs' encoding potential as shown in Table SIV. For example, the up-to-date LncPep offered annotations for lncRNAs, peptides, supporting evidences, and Basic Local Alignment Search Tool modules for exploring unknown lncRNAs and peptides (131).

With the development of sequencing technology and bioinformatic analysis, spatial transcriptomics offers information about differential transcriptome at different spatial locations compared with traditional transcriptomics (132). Furthermore, single-cell sequencing technology is a novel and comprehensive method to analyze transcriptomes, which can be a powerful tool for researchers to explore lncRNA functions at the single-cell level (133). Notably, several databases offer single-cell RNA-seq files, such as Colorcells (134) (Table SI). Along with the development of novel methods of detection and analysis, an increasing number of lncRNAs databases are expected to be created for further exploring the vital roles of lncRNAs in GBC, which will provide new ideas for GBC research and clinical management.

4. Potential therapeutic methods targeting lncRNAs in GBC

Due to their tissue-specific expression and multifunctional roles in cancer, lncRNAs appear to be a potential target for clinical cancer management (135). Based on laboratory research, lncRNAs can be targeted probably by different following methods, including promoting transcripts decay, repressing transcription, or inhibiting lncRNA functions such as interacting with other molecules (Fig. 2).

Potential method used in GBC

Small interfering RNAs (siRNAs). In 1998, RNA interfering were identified for the first time, and siRNAs and short hairpin RNAs (shRNAs) are widely used in scientific at present (136). Mechanistically, siRNAs can downregulate specific gene transcription mainly through RNA-induced silencing complexes (RISCs) and AGO2-mediated cleaving (137,138) (Fig. 2A-a). As conserved ncRNAs, oncogenic lncRNAs can be efficiently targeted by well-designed siRNAs to inhibit their roles in carcinogenesis (139,140). However, there are some shortcomings for siRNAs to be applied in clinical treatment. For instance, previous studies found that siRNAs could be decomposed by endogenous ribonuclease enzymes (RNases) and cleared by the kidney (141). Besides, the penetrating efficiency of siRNAs into tumor bulks remains a problem for scientists. To solve these problems, researchers focus on developing nanocarriers to achieve targeted siRNA delivery to tumor cells and prevent them from being degraded by RNases (142,143).

As previously mentioned, investigations into GBC have extensively employed siRNAs or shRNAs to suppress oncogenic lncRNAs, thereby inhibiting the malignant behaviors of GBC cells (24,144). Notably, the Food and

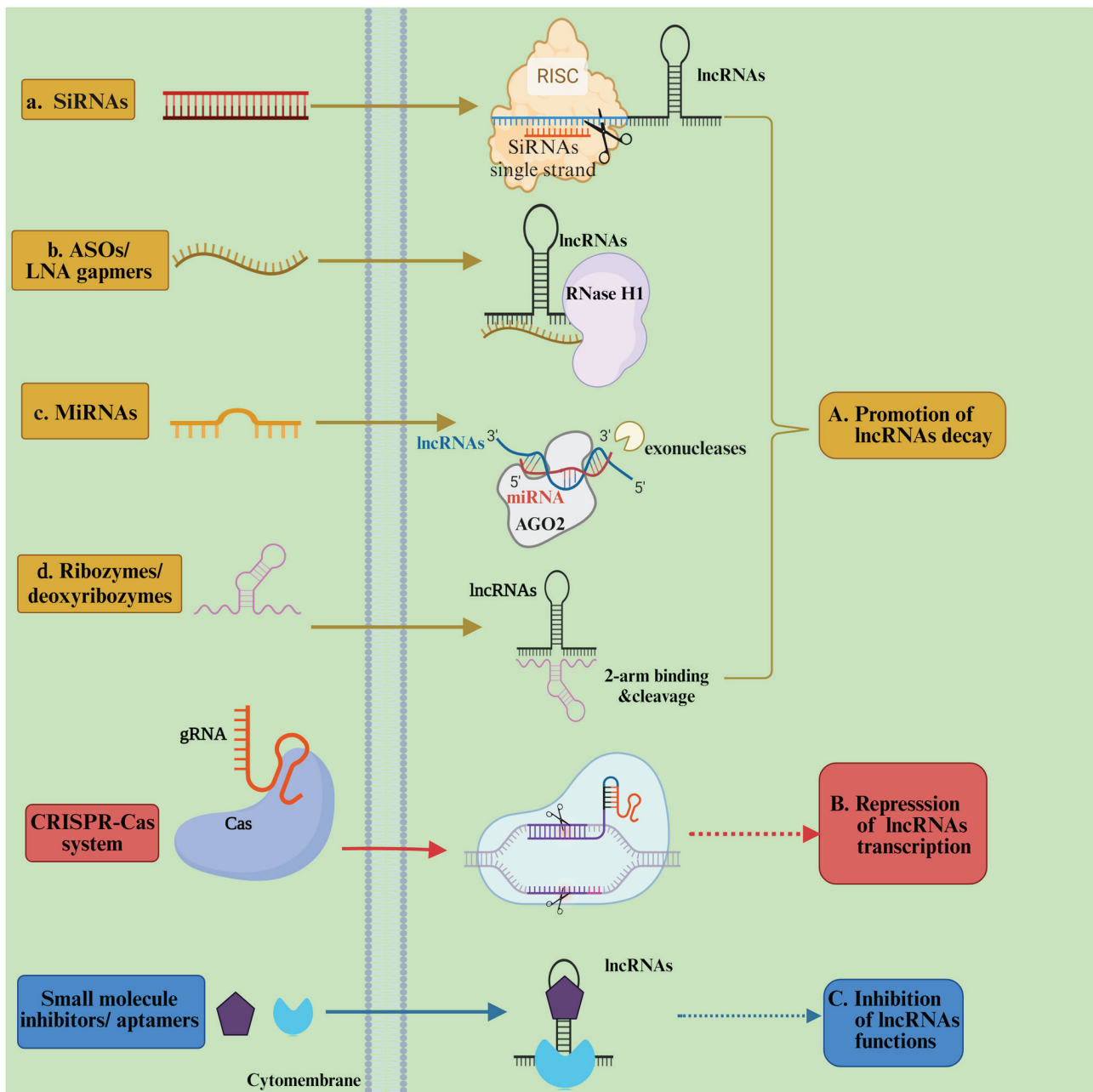


Figure 2. Potential therapeutic methods targeting lncRNAs in GBC. (A) Promotion of lncRNAs' decay: (A-a) SiRNAs are short double-stranded RNAs that target lncRNAs via complementary sequences. After unwinding in the cytoplasm, the single strand of siRNAs assembles into the active RISC to cleave targeted lncRNAs. (A-b) ASOs/LNA gapmers bind to lncRNA transcripts directly via base pairing, and form hybrids to be recognized by endogenous RNase H1, which leads to lncRNAs cleavage. (A-c) MiRNAs can bind to miRNA response elements of lncRNAs to facilitate lncRNAs decay via an AGO2-dependent manner; (A-d) Ribozymes are RNA molecules with catalytic activity. Depending on complementary pairing, two arms of ribozymes bind correctly to target sites in lncRNAs to form a functional catalytic motif and catalyze lncRNAs degradation, while deoxyribozymes have a similar function with ribozymes. (B) Repression of lncRNAs' transcription via the CRISPR-Cas system: With the assistance of designed gRNAs and the catalytic activity of Cas proteins, the CRISPR-Cas system can accurately cleave specific DNA sites that can generate pathogenic lncRNAs. (C) Inhibition of lncRNAs functions: Small molecule inhibitors bind to lncRNAs specific domains to change lncRNAs' spatial structure, or to occupy the docking sites for interactive molecules, thus blocking the interaction between lncRNAs and other functional molecules. For targeting three dimensional structures in lncRNAs, aptamers are short DNA or RNA oligonucleotides or peptides designed to structurally bind to specific lncRNAs to suppress the interactions between lncRNAs and critical factors. lncRNAs, long non-coding RNAs; GBC, gallbladder cancer; siRNAs, small interfering RNAs; RISC, RNA-induced silencing complex; ASOs, Antisense oligonucleotides; LNA, locked nucleic acid; RNase, ribonuclease; miRNAs, microRNAs; AGO2, argonaute 2; CRISPR, Clustered Regularly Interspaced Short Palindromic Repeats; Cas, CRISPR associated; gRNAs, guide RNAs. Created with BioRender.com.

Drug Administration (FDA) approved patisiran for hereditary transthyretin-mediated amyloidosis therapy, which was the first applied drug based on siRNA (145). As for malignancies, phase I/II clinical trials of siG12D local drug eluter combined with gemcitabine for pancreatic

ductal adenocarcinoma treatment are underway (146,147) (ClinicalTrials.gov.; NCT01676259). Overall, siRNA-based therapeutic methods aimed at pathological lncRNAs in clinical trials offer new hope for future breakthroughs in GBC treatment.

Potential methods used in other types of cancer

Antisense oligonucleotides (ASOs). ASOs are ~8-50 nt in length, and are designed short RNA or DNA molecules with a single-stranded structure aiming at specific genes (148). Functionally, ASOs can form a complex with targeted RNAs, and some kinds of RNase can recognize this complex to induce RNA decay (149) (Fig. 2A-b). Compared with siRNAs, ASOs present improved specificity and fewer side effects, and can escape from RISCs degradation (150). It has been demonstrated that ASOs are possible therapeutic alternatives to suppress tumor-related lncRNAs in cancer.

To date, several ASOs have been applied in patients with spinal muscular atrophy, hypercholesterolemia and transthyretin amyloidosis after FDA authorization. In a preclinical animal model, ASOs aiming at MALAT1 suppressed its oncogenic functions in breast cancer (151). Moreover, previous studies revealed that ASOs were capable of replacing PRC2 to bind lncRNAs. Due to the necessary roles of PRC2 for interaction of lncRNAs with chromosomes, ASOs may regulate gene expression in this way (152).

Locked nucleic acid (LNA) gapmers. LNA gapmers are recently employed tools for intractable genes or pathways (153). Structurally, LNA gapmers are able to interact with aimed RNAs using its central DNA gap, which leads to RNase H-mediated degradation (154) (Fig. 2A-b). LNA gapmers exhibit improved stability and efficiency than siRNAs (155). LNA gapmers targeting MALAT1 inhibit multiple myeloma (MM) growth and increase tumor cell apoptosis in an MM patient-derived xenograft model (156). Further studies are needed before LNA gapmers can be applied to clinical practice.

Other potential molecules that promote lncRNA degradation. With the exception of siRNAs, ASOs and LNA gapmers, some molecules can promote lncRNA degradation.

As aforementioned, lncRNAs can act as ceRNAs to sponge miRNAs. Contrarily, miRNAs can also bind to MREs of lncRNAs to regulate their stability (157) (Fig. 2A-c). For example, miRNA let7 upregulation results in lincRNA-p21 decay in an AGO2-dependent manner with the assistance of HuR (158). Nevertheless, disadvantages such as diverse miRNA targets and being easily-cleared *in vivo* limit its application in clinical treatment.

Ribozymes were identified as rare RNA molecules, and their function of degrading specific RNAs drew attention to their potential to target pathological lncRNAs (159). Deoxyribozymes were also found in *ex vivo* selections unexpectedly, which has similar catalytic activity to ribozymes (160) (Fig. 2A-d). Recently, Chen *et al* (161) reported that a ribozyme, termed hominin vlincRNA-located, was able to induce the degradation of its source lncRNAs. However, these kinds of molecule are currently difficult to design for aiming at lncRNAs effectively.

Clustered regularly interspaced short palindromic repeats (CRISPR)-CRISPR associated (Cas) system. Derived from bacteria and archaea, the CRISPR-Cas system guides ribonucleoproteins to specific DNA sites with the assistance of designed guide RNAs (gRNAs) (162). The catalytic activity of Cas proteins then leads to double-stranded breaks, which can be repaired by non-homologous DNA end joining (NHEJ) or homology-directed repair (163,164). Finally, these two repair mechanisms assist to generate needed genome alternation,

such as 'knock-out' or 'knock-in' mutations (165). Due to its specificity and efficiency, the CRISPR-Cas system appears to be a novel method for gene editing, which has great potential for translational medicine (Fig. 2B).

Since NHEJ, the most common repair mode in cells, often results in deletions or frameshift mutations to generate non-functional transcripts (166,167), previous studies suggested that the transcription of specific lncRNAs may be blocked via the CRISPR-Cas9 system. In basic research, CRISPR-Cas9 has been used to explore the functional role of various lncRNAs in neoplasms, examples including lncRNA CCAT2 in colorectal cancer (CRC) (168), and lncRNA LINC-ROR in breast cancer (169). The application of the CRISPR-Cas system is currently limited to *ex vivo* research. Addressing ethical considerations is as important as overcoming technical problems and enabling safety in human subjects. Thus, it can be proposed that the CRISPR-Cas system may be an attractive method for the treatment of patients with GBC.

Small molecule inhibitors. As aforementioned, lncRNAs have multiple functions in cancer mainly via binding to other molecules, including other types of RNA or proteins. Aiming at these interactions, small molecule inhibitors have been developed to suppress the binding of lncRNAs to other cellular components mainly via the following two mechanisms (Fig. 2C): i) Inhibitors bind to target domains of lncRNAs to alter lncRNAs' spatial structure directly (170); or ii) inhibitors occupy the docking sites for DNA, RNA, proteins or lipids to suppress the interaction of lncRNAs with these sites (171).

For instance, the small molecule inhibitor AC1NOD4Q can inhibit the interaction between lncRNA HOTAIR and EZH2 in glioma (172). Isolated from plants, curcumin is a well-known anticancer drug (173), which can downregulate lncRNA ROR and release miR-145 to significantly inhibit prostate cancer development (174). Another compound, 5-azathioprine-2-deoxycytidine, can inhibit the methylation of the imprinted control region of H19 and decrease H19 expression (175). The concomitant use of high throughput technologies and computational analysis to develop specific compounds provides a rationale for the identification of new drugs, and well-designed inhibitors may become important breakthroughs for GBC management.

Aptamers. Previous studies indicated that rigorous folding of the lncRNA secondary structure remains essential for its function. Certain lncRNAs are invalidated to siRNAs, ASOs, and ribozymes due to their complex secondary structures (176). To solve this problem, short DNAs, oligonucleotide RNAs or polypeptides with specific structures were produced as aptamers, which aimed to recognize special structures of lncRNAs and facilitate their degradation or block their interaction with other molecules (177,178) (Fig. 2C). For example, Wang *et al* (179) revealed that chimeric aptamer targeting epithelial growth factor receptor (EGFR) leads to the downregulation of lncRNA HOTAIR in EGFR-expressing triple-negative breast cancer (TNBC) cell and inhibits TNBC cell malignant phenotypes.

Compared with each other, all the aforementioned methods are mainly used *in vitro*. Therefore, breakthroughs are hardly reported without the assistance of a reliable delivery system to facilitate the transport of these targeted molecules to tumor tissues safely and precisely. Although

the CRISPR-Cas system is the most accurate and radical method to knockout pathological lncRNAs, it still requires further investigation to resolve aforementioned problems before being applied in clinical management. To block the interaction of lncRNAs with other functional molecules, aptamers need to be well designed individually, which may be expensive in practice. Small molecule inhibitors are limited at present, but Chinese herbal medicine may shed new light on the research and development of novel drugs. As for methods to promote dysregulated lncRNAs decay, ASOs and LNA gapmers appear to be more specific and safer than siRNAs; however, some drugs based on siRNAs are applied in therapy or in clinical trials. In addition, there are certain disadvantages of miRNAs and ribozymes/deoxyribozymes that cannot be ignored. For miRNAs, numerous studies reported its interaction with lncRNAs, but miRNAs are easily-cleared like siRNAs and are not sufficiently specific. As for ribozymes/deoxyribozymes, they are rare in nature and difficult to design artificially.

As one of the most lethal abdominal tumors, GBC tends to develop resistance to current treatments. Therapy targeting tumorigenesis lncRNAs may provide new opportunities for GBC clinical practice. Although different methods function through various mechanisms, novel therapeutic tools should focus on targeted and rapid delivery systems and avoid their degradation *in vivo* after guaranteeing their safety.

5. Conclusions and future perspectives

In summary, in the present study, multiple lncRNA functions in cancer were reviewed and the role of aberrant lncRNAs in GBC according to different mechanisms were discussed. Different lncRNA databases used for specific purposes were also summarized, and various therapeutic methods targeting pathological lncRNAs were explained, including approaches employed in laboratory tests, preclinical trials and clinical practices. However, further in-depth studies are required for additional clarification.

The classical roles of lncRNAs were previously defined as signal, decoy, scaffold and guide (180). Currently, emerging functions of lncRNAs have attracted attention of researchers. Notably, it has been demonstrated that lncRNAs have coding potential, and various micropeptides encoded by lncRNAs have been shown to be functional in cancer (181). For instance, Huang *et al* (70) found a 159-nt short open reading frame in lncRNA HOXB-AS3, which could encode a 53-aa endogenous peptide named HOXB-AS3. This peptide could inhibit aerobic glycolysis in CRC cell and was associated with favourable prognosis in patients with CRC (70). However, assessment and validation of coding potential of lncRNAs and functions of these micropeptides remain difficult, and further efforts need to be put into revealing the multiple roles of lncRNAs in GBC.

Along with a deeper understanding of tumor cells and their extracellular components, previous studies have highlighted the importance of metabolic reprogramming of tumor cells and its influence on the tumor microenvironment (TME) (182). Increased proliferation, neovascularization and hypoxia of tumor cells lead to increased needs for energy and nutrition, which requires the metabolic reprogramming

of tumor cells (183). Aberrant metabolic pathways cannot only ensure tumor growth, but the metabolites from these pathways also have an effect on cells of the TME, such as inducing metabolic reprogramming of TME (184), modulating functions of immunocytes in TME (185) and influencing expression of immune checkpoints (186). Regarding lncRNA roles in aforementioned spots, previous studies revealed that lncRNAs could interact with metabolic enzymes (101) or modulate metabolic pathways by networks of ceRNAs (187). Additionally, it has been reported that lncRNAs can modulate TME via extracellular vesicles, such as exosomes and microvesicles (188,189). For instance, Ding *et al* (190) demonstrated that EV-lncRNA CAF from oral squamous cell carcinoma activates cancer-associated fibroblasts phenotype in normal fibroblasts by stabilizing IL-33, thus facilitating cancer development. Predictably, oncogenic lncRNAs could either facilitate metabolic reprogramming of GBC and its TME for tumor development, or regulate functions of immunocytes in the TME to promote immune evasion and immunotherapy resistance. However, there is limited research on this topic, and therefore further studies are necessary.

Regarding previous studies aiming to improve clinical practice in GBC management, the application of lncRNAs requires further exploration (191,192). GBC is asymptomatic in the early stage and easily to become resistant to therapy (3). With the development of liquid biopsy (193), specific pathogenetic lncRNAs in blood or other fluids may provide convincing evidence for diagnosis prior to serological or imaging tests, thus monitoring the response of patients with GBC therapy or predicting prognosis of patients. Li *et al* (55) identified that H19 is elevated in diseased cholangiocytes-derived exosomes in the bile acid, which showed the potential of lncRNAs as biomarkers for precise diagnosis or timely monitoring of patients' responses to treatment. Recently, mRNA vaccines for the coronavirus disease 2019 pandemic have drawn interest of scientists in RNA-based therapy (194). As aforementioned, approved siRNA drugs have been applied in clinical practice, and clinical trials targeting oncogenic lncRNAs in tumors are currently underway, which may provide insights for the use of lncRNAs as therapeutic targets. Current problems for this potential type of therapy include patients' tolerability, effective delivery systems, specificity and uncleared off-target effects, which need to be urgently resolved before clinical application.

Acknowledgements

Not applicable.

Funding

The present study was supported by the National Nature Science Foundation of China (grant no. 81773187), the Tianjin high school program for young and middle-aged talents backbone and Tianjin young medical talents program provided by Tianjin Municipal Education Commission and Tianjin Health Commission, Tianjin Health Research Project (grant no. TJWJ2023ZD001), the Tianjin Commission Scientific Research Plan Project (grant no. 2018KJ064) and the Jinan

Clinical Medical Science and Technology Innovation Plan Project (grant no. 202134059).

Availability of data and materials

Not applicable.

Authors' contributions

YH and XD drafted the manuscript. FY completed the visualization. CY and MC performed the literature search and selection and participated in reviewing the paper. LH and JS performed revision of the manuscript and conducted project administration and funding acquisition. All authors read and approved the final manuscript. Data authentication is not applicable.

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.

References

- Piccolo G and Piozzi GN: Laparoscopic radical cholecystectomy for primary or incidental early gallbladder cancer: The new rules governing the treatment of gallbladder cancer. *Gastroenterol Res Pract* 2017: 8570502, 2017.
- Carriaga MT and Henson DE: Liver, gallbladder, extrahepatic bile ducts, and pancreas. *Cancer* 75 (1 Suppl): S171-S190, 1995.
- Ganeshan D, Kambadakone A, Nikolaidis P, Subbiah V, Subbiah IM and Devine C: Current update on gallbladder carcinoma. *Abdom Radiol (NY)* 46: 2474-2489, 2021.
- Sharma A, Sharma KL, Gupta A, Yadav A and Kumar A: Gallbladder cancer epidemiology, pathogenesis and molecular genetics: Recent update. *World J Gastroenterol* 23: 3978-3998, 2017.
- Wang YF, Feng FL, Zhao XH, Ye ZX, Zeng HP, Li Z, Jiang XQ and Peng ZH: Combined detection tumor markers for diagnosis and prognosis of gallbladder cancer. *World J Gastroenterol* 20: 4085-4092, 2014.
- Hundal R and Shaffer EA: Gallbladder cancer: Epidemiology and outcome. *Clin Epidemiol* 6: 99-109, 2014.
- Yao RW, Wang Y and Chen LL: Cellular functions of long noncoding RNAs. *Nat Cell Biol* 21: 542-551, 2019.
- Statello L, Guo CJ, Chen LL and Huarte M: Gene regulation by long non-coding RNAs and its biological functions. *Nat Rev Mol Cell Biol* 22: 96-118, 2021.
- Johnsson P, Lipovich L, Grander D and Morris KV: Evolutionary conservation of long non-coding RNAs; sequence, structure, function. *Biochim Biophys Acta* 1840: 1063-1071, 2014.
- Wu XS, Wang XA, Wu WG, Hu YP, Li ML, Ding Q, Weng H, Shu YJ, Liu TY, Jiang L, *et al*: MALAT1 promotes the proliferation and metastasis of gallbladder cancer cells by activating the ERK/MAPK pathway. *Cancer Biol Ther* 15: 806-814, 2014.
- Ming H, Li B, Zhou L, Goel A and Huang C: Long non-coding RNAs and cancer metastasis: Molecular basis and therapeutic implications. *Biochim Biophys Acta Rev Cancer* 1875: 188519, 2021.
- Perez-Moreno P, Riquelme I, Brebi P and Roa JC: Role of lncRNAs in the development of an aggressive phenotype in gallbladder cancer. *J Clin Med* 10: 4206, 2021.
- lv Y, Yin W and Zhang Z: Non-coding RNAs as potential biomarkers of gallbladder cancer. *Clin Transl Oncol* 25: 1489-1511, 2023.
- Dawson MA and Kouzarides T: Cancer epigenetics: From mechanism to therapy. *Cell* 150: 12-27, 2012.
- Xie M, Zhang L, Han L, Huang L, Huang Y, Yang M and Zhang N: The ASH1L-AS1-ASH1L axis controls NME1-mediated activation of the RAS signaling in gastric cancer. *Oncogene* 42: 3435-3445, 2023.
- Roy L, Chatterjee O, Bose D, Roy A and Chatterjee S: Noncoding RNA as an influential epigenetic modulator with promising roles in cancer therapeutics. *Drug Discov Today* 28: 103690, 2023.
- Huang W, Li H, Yu Q, Xiao W and Wang DO: LncRNA-mediated DNA methylation: An emerging mechanism in cancer and beyond. *J Exp Clin Cancer Res* 41: 100, 2022.
- Sina AA, Carrascosa LG, Liang Z, Grewal YS, Wardiana A, Shiddiky MJA, Gardiner RA, Samaratunga H, Gandhi MK, Scott RJ, *et al*: Epigenetically reprogrammed methylation landscape drives the DNA self-assembly and serves as a universal cancer biomarker. *Nat Commun* 9: 4915, 2018.
- Li D, Feng J, Wu T, Wang Y, Sun Y, Ren J and Liu M: Long intergenic noncoding RNA HOTAIR is overexpressed and regulates PTEN methylation in laryngeal squamous cell carcinoma. *Am J Pathol* 182: 64-70, 2013.
- Song H, Chen L, Liu W, Xu X, Zhou Y, Zhu J, Chen X, Li Z and Zhou H: Depleting long noncoding RNA HOTAIR attenuates chronic myelocytic leukemia progression by binding to DNA methyltransferase 1 and inhibiting PTEN gene promoter methylation. *Cell Death Dis* 12: 440, 2021.
- Cai Q, Jin L, Wang S, Zhou D, Wang J, Tang Z and Quan Z: Long non-coding RNA UCA1 promotes gallbladder cancer progression by epigenetically repressing p21 and E-cadherin expression. *Oncotarget* 8: 47957-47968, 2017.
- Lin N, Yao Z, Xu M, Chen J, Lu Y, Yuan L, Zhou S, Zou X and Xu R: Long noncoding RNA MALAT1 potentiates growth and inhibits senescence by antagonizing ABI3BP in gallbladder cancer cells. *J Exp Clin Cancer Res* 38: 244, 2019.
- Gao J, Dai C, Yu X, Yin XB, Liao WJ, Huang Y and Zhou F: Silencing of long non-coding RNA FOXD2-AS1 inhibits the progression of gallbladder cancer by mediating methylation of MLH1. *Gene Ther* 28: 306-318, 2021.
- Jin L, Cai Q, Wang S, Wang S, Wang J and Quan Z: Long noncoding RNA PVT1 promoted gallbladder cancer proliferation by epigenetically suppressing miR-18b-5p via DNA methylation. *Cell Death Dis* 11: 871, 2020.
- Li DQ, Ding YR, Che JH, Su Z, Yang WZ, Xu L, Li YJ, Wang HH and Zhou WY: Tumor suppressive lncRNA MEG3 binds to EZH2 and enhances CXCL3 methylation in gallbladder cancer. *Neoplasma* 69: 538-549, 2022.
- Chatterjee A, Rodger EJ and Eccles MR: Epigenetic drivers of tumorigenesis and cancer metastasis. *Semin Cancer Biol* 51: 149-159, 2018.
- Barik GK, Sahay O, Behera A, Naik D and Kalita B: Keep your eyes peeled for long noncoding RNAs: Explaining their boundless role in cancer metastasis, drug resistance, and clinical application. *Biochim Biophys Acta Rev Cancer* 1876: 188612, 2021.
- Khalil AM, Guttman M, Huarte M, Garber M, Raj A, Rivea Morales D, Thomas K, Presser A, Bernstein BE, van Oudenaarden A, *et al*: Many human large intergenic noncoding RNAs associate with chromatin-modifying complexes and affect gene expression. *Proc Natl Acad Sci USA* 106: 11667-11672, 2009.
- Laugesen A, Hojfeldt JW and Helin K: Role of the polycomb repressive complex 2 (PRC2) in transcriptional regulation and cancer. *Cold Spring Harb Perspect Med* 6: a026575, 2016.
- Narlikar GJ, Sundaramoorthy R and Owen-Hughes T: Mechanisms and functions of ATP-dependent chromatin-remodeling enzymes. *Cell* 154: 490-503, 2013.
- Bohmdorfer G and Wierzbicki AT: Control of chromatin structure by long noncoding RNA. *Trends Cell Biol* 25: 623-632, 2015.
- Zhao Z, Senturk N, Song C and Grummt I: lncRNA PAPAS tethered to the rDNA enhancer recruits hypophosphorylated CHD4/NuRD to repress rRNA synthesis at elevated temperatures. *Genes Dev* 32: 836-848, 2018.
- Zhao Z, Dammert MA, Grummt I and Bierhoff H: lncRNA-Induced nucleosome repositioning reinforces transcriptional repression of rRNA genes upon hypotonic stress. *Cell Rep* 14: 1876-1882, 2016.

34. Djebali S, Davis CA, Merkel A, Dobin A, Lassmann T, Mortazavi A, Tanzer A, Lagarde J, Lin W, Schlesinger F, *et al*: Landscape of transcription in human cells. *Nature* 489: 101-108, 2012.
35. Zhang Y, Mao Q, Xia Q, Cheng J, Huang Z, Li Y, Chen P, Yang J, Fan X, Liang Y and Lin H: Noncoding RNAs link metabolic reprogramming to immune microenvironment in cancers. *J Hematol Oncol* 14: 169, 2021.
36. Fatma H and Siddique HR: Role of long non-coding RNAs and MYC interaction in cancer metastasis: A possible target for therapeutic intervention. *Toxicol Appl Pharmacol* 399: 115056, 2020.
37. Lingadahalli S, Jadhao S, Sung YY, Chen M, Hu L, Chen X and Cheung E: Novel lncRNA LINC00844 regulates prostate cancer cell migration and invasion through AR signaling. *Mol Cancer Res* 16: 1865-1878, 2018.
38. Zhang J, Li Z, Liu L, Wang Q, Li S, Chen D, Hu Z, Yu T, Ding J, Li J, *et al*: Long noncoding RNA TSLNC8 is a tumor suppressor that inactivates the interleukin-6/STAT3 signaling pathway. *Hepatology* 67: 171-187, 2018.
39. Zhang XZ, Liu H and Chen SR: Mechanisms of long non-coding RNAs in cancers and their dynamic regulations. *Cancers (Basel)* 12: 1245, 2020.
40. Saayman SM, Ackley A, Burdach J, Clemson M, Gruenert DC, Tachikawa K, Chivukula P, Weinberg MS and Morris KV: Long non-coding RNA BGas regulates the cystic fibrosis transmembrane conductance regulator. *Mol Ther* 24: 1351-1357, 2016.
41. Ahmad M, Weiswald LB, Poulain L, Denoyelle C and Meryet-Figuiere M: Involvement of lncRNAs in cancer cells migration, invasion and metastasis: Cytoskeleton and ECM crosstalk. *J Exp Clin Cancer Res* 42: 173, 2023.
42. He RZ, Luo DX and Mo YY: Emerging roles of lncRNAs in the post-transcriptional regulation in cancer. *Genes Dis* 6: 6-15, 2019.
43. Pan K and Xie Y: lncRNA FOXC2-AS1 enhances FOXC2 mRNA stability to promote colorectal cancer progression via activation of Ca(2+)-FAK signal pathway. *Cell Death Dis* 11: 434, 2020.
44. Yuan S, Liu Q, Hu Z, Zhou Z, Wang G, Li C, Xie W, Meng G, Xiang Y, Wu N, *et al*: Long non-coding RNA MUC5B-AS1 promotes metastasis through mutually regulating MUC5B expression in lung adenocarcinoma. *Cell Death Dis* 9: 450, 2018.
45. Di W, Weinan X, Xin L, Zhiwei Y, Xinyue G, Jinxue T and Mingqi L: Long noncoding RNA SNHG14 facilitates colorectal cancer metastasis through targeting EZH2-regulated EPHA7. *Cell Death Dis* 10: 514, 2019.
46. Wang A, Bao Y, Wu Z, Zhao T, Wang D, Shi J, Liu B, Sun S, Yang F, Wang L and Qu L: Long noncoding RNA EGFR-AS1 promotes cell growth and metastasis via affecting HuR mediated mRNA stability of EGFR in renal cancer. *Cell Death Dis* 10: 154, 2019.
47. Barbieri I and Kouzarides T: Role of RNA modifications in cancer. *Nat Rev Cancer* 20: 303-322, 2020.
48. Sun T, Wu Z, Wang X, Wang Y, Hu X, Qin W, Lu S, Xu D, Wu Y, Chen Q, *et al*: LNC942 promoting METTL14-mediated m(6)A methylation in breast cancer cell proliferation and progression. *Oncogene* 39: 5358-5372, 2020.
49. Hou P, Meng S, Li M, Li M, Lin T, Chu S, Li Z, Zheng J, Gu Y and Bai J: LINC00460/DHX9/IGF2BP2 complex promotes colorectal cancer proliferation and metastasis by mediating HMGA1 mRNA stability depending on m6A modification. *J Exp Clin Cancer Res* 40: 52, 2021.
50. O'Brien J, Hayder H, Zayed Y and Peng C: Overview of MicroRNA biogenesis, mechanisms of actions, and circulation. *Front Endocrinol (Lausanne)* 9: 402, 2018.
51. Salmena L, Poliseno L, Tay Y, Kats L and Pandolfi PP: A ceRNA hypothesis: The Rosetta Stone of a hidden RNA language? *Cell* 146: 353-358, 2011.
52. Thomson DW and Dinger ME: Endogenous microRNA sponges: Evidence and controversy. *Nat Rev Genet* 17: 272-283, 2016.
53. Wang SH, Wu XC, Zhang MD, Weng MZ, Zhou D and Quan ZW: Long noncoding RNA H19 contributes to gallbladder cancer cell proliferation by modulated miR-194-5p targeting AKT2. *Tumour Biol* 37: 9721-9730, 2016.
54. Wang SH, Ma F, Tang ZH, Wu XC, Cai Q, Zhang MD, Weng MZ, Zhou D, Wang JD and Quan ZW: Long non-coding RNA H19 regulates FOXM1 expression by competitively binding endogenous miR-342-3p in gallbladder cancer. *J Exp Clin Cancer Res* 35: 160, 2016.
55. Li X, Liu R, Wang Y, Zhu W, Zhao D, Wang X, Yang H, Gurley EC, Chen W, Hylemon PB and Zhou H: Cholangiocyte-Derived Exosomal lncRNA H19 promotes macrophage activation and hepatic inflammation under cholestatic conditions. *Cells* 9: 190, 2020.
56. Liu L, Yan Y, Zhang G, Chen C, Shen W and Xing P: Knockdown of LINC01694 inhibits growth of gallbladder cancer cells via miR-340-5p/Sox4. *Biosci Rep* 40: BSR20194444, 2020.
57. Liu XF, Wang K and Du HC: lncRNA SNHG6 regulating Hedgehog signaling pathway and affecting the biological function of gallbladder carcinoma cells through targeting miR-26b-5p. *Eur Rev Med Pharmacol Sci* 24: 7598-7611, 2020.
58. Wang SH, Zhang WJ, Wu XC, Zhang MD, Weng MZ, Zhou D, Wang JD and Quan ZW: Long non-coding RNA Malat1 promotes gallbladder cancer development by acting as a molecular sponge to regulate miR-206. *Oncotarget* 7: 37857-37867, 2016.
59. Wang SH, Zhang WJ, Wu XC, Weng MZ, Zhang MD, Cai Q, Zhou D, Wang JD and Quan ZW: The lncRNA MALAT1 functions as a competing endogenous RNA to regulate MCL-1 expression by sponging miR-363-3p in gallbladder cancer. *J Cell Mol Med* 20: 2299-2308, 2016.
60. Chen J, Yu Y, Li H, Hu Q, Chen X, He Y, Xue C, Ren F, Ren Z, Li J, *et al*: Long non-coding RNA PVT1 promotes tumor progression by regulating the miR-143/HK2 axis in gallbladder cancer. *Mol Cancer* 18: 33, 2019.
61. Liu K and Xu Q: lncRNA PVT1 regulates gallbladder cancer progression through miR-30d-5p. *J Biol Regul Homeost Agents* 34: 875-883, 2020.
62. Zhong Y, Wu X, Li Q, Ge X, Wang F, Wu P, Deng X and Miao L: Long noncoding RNAs as potential biomarkers and therapeutic targets in gallbladder cancer: A systematic review and meta-analysis. *Cancer Cell Int* 19: 169, 2019.
63. Shi Y: Mechanistic insights into precursor messenger RNA splicing by the spliceosome. *Nat Rev Mol Cell Biol* 18: 655-670, 2017.
64. Ouyang J, Zhong Y, Zhang Y, Yang L, Wu P, Hou X, Xiong F, Li X, Zhang S, Gong Z, *et al*: Long non-coding RNAs are involved in alternative splicing and promote cancer progression. *Br J Cancer* 126: 1113-1124, 2022.
65. Su T, Zhang N, Wang T, Zeng J, Li W, Han L and Yang M: Super enhancer-regulated lncRNA LINC01089 induces alternative splicing of DIAPH3 to drive hepatocellular carcinoma metastasis. *Cancer Res*: Sep 26, 2023 (Epub ahead of print).
66. Huang GW, Zhang YL, Liao LD, Li EM and Xu LY: Natural antisense transcript TPM1-AS regulates the alternative splicing of tropomyosin I through an interaction with RNA-binding motif protein 4. *Int J Biochem Cell Biol* 90: 59-67, 2017.
67. Yap K, Mukhina S, Zhang G, Tan JSC, Ong HS and Makeyev EV: A short tandem repeat-enriched RNA assembles a nuclear compartment to control alternative splicing and promote cell survival. *Mol Cell* 72: 525-540 e13, 2018.
68. Lavorgna G, Dahary D, Lehner B, Sorek R, Sanderson CM and Casari G: In search of antisense. *Trends Biochem Sci* 29: 88-94, 2004.
69. Liu Y, Liu X, Lin C, Jia X, Zhu H, Song J and Zhang Y: Noncoding RNAs regulate alternative splicing in Cancer. *J Exp Clin Cancer Res* 40: 11, 2021.
70. Huang JZ, Chen M, Chen D, Gao XC, Zhu S, Huang H, Hu M, Zhu H and Yan GR: A peptide encoded by a putative lncRNA HOXB-AS3 suppresses colon cancer growth. *Mol Cell* 68: 171-184.e6, 2017.
71. Gordon MA, Babbs B, Cochrane DR, Bitler BG and Richer JK: The long non-coding RNA MALAT1 promotes ovarian cancer progression by regulating RBFOX2-mediated alternative splicing. *Mol Carcinog* 58: 196-205, 2019.
72. Stamm S: Regulation of alternative splicing by reversible protein phosphorylation. *J Biol Chem* 283: 1223-1227, 2008.
73. Hu ZY, Wang XY, Guo WB, Xie LY, Huang YQ, Liu YP, Xiao LW, Li SN, Zhu HF, Li ZG and Kan H: Long non-coding RNA MALAT1 increases AKAP-9 expression by promoting SRPK1-catalyzed SRSF1 phosphorylation in colorectal cancer cells. *Oncotarget* 7: 11733-11743, 2016.
74. Micalizzi DS, Ebright RY, Haber DA and Maheswaran S: Translational regulation of cancer metastasis. *Cancer Res* 81: 517-524, 2021.
75. Karakas D and Ozpolat B: The Role of lncRNAs in translation. *Noncoding RNA* 7: 16, 2021.
76. Hardie DG, Ross FA and Hawley SA: AMPK: A nutrient and energy sensor that maintains energy homeostasis. *Nat Rev Mol Cell Biol* 13: 251-262, 2012.

77. Liu X, Xiao ZD, Han L, Zhang J, Lee SW, Wang W, Lee H, Zhuang L, Chen J, Lin HK, *et al*: lncRNA NBR2 engages a metabolic checkpoint by regulating AMPK under energy stress. *Nat Cell Biol* 18: 431-442, 2016.
78. Zhuo W, Liu Y, Li S, Guo D, Sun Q, Jin J, Rao X, Li M, Sun M, Jiang M, *et al*: Long Noncoding RNA GMAN, Up-regulated in Gastric Cancer Tissues, Is Associated With Metastasis in Patients and Promotes Translation of Ephrin A1 by Competitively Binding GMAN-AS. *Gastroenterology* 156: 676-691.e11, 2019.
79. Zhao X, Liu Y and Yu S: Long noncoding RNA AWPPH promotes hepatocellular carcinoma progression through YBX1 and serves as a prognostic biomarker. *Biochim Biophys Acta Mol Basis Dis* 1863: 1805-1816, 2017.
80. Verheyden Y, Goedert L and Leucci E: Control of nucleolar stress and translational reprogramming by lncRNAs. *Cell Stress* 3: 19-26, 2018.
81. Jacob MD, Audas TE, Uniacke J, Trinkle-Mulcahy L and Lee S: Environmental cues induce a long noncoding RNA-dependent remodeling of the nucleolus. *Mol Biol Cell* 24: 2943-2953, 2013.
82. Xing YH, Yao RW, Zhang Y, Guo CJ, Jiang S, Xu G, Dong R, Yang L and Chen LL: SLERT Regulates DDX21 rings associated with Pol I transcription. *Cell* 169: 664-678.e16, 2017.
83. Vendramin R, Verheyden Y, Ishikawa H, Goedert L, Nicolas E, Saraf K, Armaos A, Delli Ponti R, Izumikawa K, Mestdagh P, *et al*: SAMMSON fosters cancer cell fitness by concertedly enhancing mitochondrial and cytosolic translation. *Nat Struct Mol Biol* 25: 1035-1046, 2018.
84. Sonenberg N and Hinnebusch AG: Regulation of translation initiation in eukaryotes: Mechanisms and biological targets. *Cell* 136: 731-745, 2009.
85. Liu B and Qian SB: Translational reprogramming in cellular stress response. *Wiley Interdiscip Rev RNA* 5: 301-315, 2014.
86. Leppek K, Das R and Barna M: Functional 5' UTR mRNA structures in eukaryotic translation regulation and how to find them. *Nat Rev Mol Cell Biol* 19: 158-174, 2018.
87. Beltran M, Puig I, Pena C, García JM, Alvarez AB, Peña R, Bonilla F and de Herreros AG: A natural antisense transcript regulates Zeb2/Sip1 gene expression during Snail1-induced epithelial-mesenchymal transition. *Genes Dev* 22: 756-769, 2008.
88. Bernassola F, Chillemi G and Melino G: HECT-Type E3 ubiquitin ligases in cancer. *Trends Biochem Sci* 44: 1057-1075, 2019.
89. Zeng X, Liu C, Yao J, Wan H, Wan G, Li Y and Chen N: Breast cancer stem cells, heterogeneity, targeting therapies and therapeutic implications. *Pharmacol Res* 163: 105320, 2021.
90. Han ZJ, Feng YH, Gu BH, Li YM and Chen H: The post-translational modification, SUMOylation, and cancer (Review). *Int J Oncol* 52: 1081-1094, 2018.
91. Zhang X, Wang W, Zhu W, Dong J, Cheng Y, Yin Z and Shen F: Mechanisms and functions of long non-coding RNAs at multiple regulatory levels. *Int J Mol Sci* 20: 5573, 2019.
92. Gao Z, Xu J, Fan Y, Qi Y, Wang S, Zhao S, Guo X, Xue H, Deng L and Zhao R, *et al*: PDIA3P1 promotes Temozolomide resistance in glioblastoma by inhibiting C/EBP β degradation to facilitate proneural-to-mesenchymal transition. *J Exp Clin Cancer Res* 41: 223, 2022.
93. Chen H, Yang F, Li X, Gong ZJ and Wang LW: Long noncoding RNA LNC473 inhibits the ubiquitination of survivin via association with USP9X and enhances cell proliferation and invasion in hepatocellular carcinoma cells. *Biochem Biophys Res Commun* 499: 702-710, 2018.
94. Bian Z, Zhang J, Li M, Feng Y, Wang X, Zhang J, Yao S, Jin G, Du J, Han W, *et al*: lncRNA-FEZF1-AS1 promotes tumor proliferation and metastasis in colorectal cancer by regulating PKM2 signaling. *Clin Cancer Res* 24: 4808-4819, 2018.
95. Yu J, Han Z, Sun Z, Wang Y, Zheng M and Song C: lncRNA SLCO4A1-AS1 facilitates growth and metastasis of colorectal cancer through β -catenin-dependent Wnt pathway. *J Exp Clin Cancer Res* 37: 222, 2018.
96. Zhao W, Jin Y, Wu P, Yang J, Chen Y, Yang Q, Huo X, Li J, De W, Chen J and Yang F: LINC00355 induces gastric cancer proliferation and invasion through promoting ubiquitination of P53. *Cell Death Discov* 6: 99, 2020.
97. Wang ZQ, He CY, Hu L, Shi HP, Li JF, Gu QL, Su LP, Liu BY, Li C and Zhu Z: Long noncoding RNA UCA1 promotes tumour metastasis by inducing GRK2 degradation in gastric cancer. *Cancer Lett* 408: 10-21, 2017.
98. Li Z, Hou P, Fan D, Dong M, Ma M, Li H, Yao R, Li Y, Wang G, Geng P, *et al*: The degradation of EZH2 mediated by lncRNA ANCR attenuated the invasion and metastasis of breast cancer. *Cell Death Differ* 24: 59-71, 2017.
99. Ma MZ, Zhang Y, Weng MZ, Wang SH, Hu Y, Hou ZY, Qin YY, Gong W, Zhang YJ, Kong X, *et al*: Long Noncoding RNA GCASPC, a Target of miR-17-3p, negatively regulates pyruvate carboxylase-dependent cell proliferation in gallbladder cancer. *Cancer Res* 76: 5361-5371, 2016.
100. Jin L, Cai Q, Wang S, Wang S, Mondal T, Wang J and Quan Z: Long noncoding RNA MEG3 regulates LATS2 by promoting the ubiquitination of EZH2 and inhibits proliferation and invasion in gallbladder cancer. *Cell Death Dis* 9: 1017, 2018.
101. Cai Q, Wang S, Jin L, Weng M, Zhou D, Wang J, Tang Z and Quan Z: Long non-coding RNA GBCDRlnc1 induces chemoresistance of gallbladder cancer cells by activating autophagy. *Mol Cancer* 18: 82, 2019.
102. Xue Z, Yang B, Xu Q, Zhu X and Qin G: Long non-coding RNA SSTR5-AS1 facilitates gemcitabine resistance via stabilizing NONO in gallbladder carcinoma. *Biochem Biophys Res Commun* 522: 952-959, 2020.
103. Liu S, Li H, Zhu Y, Ma X, Shao Z, Yang Z, Cai C, Wu Z, Li M, Gong W and Wu X: lncRNA MNX1-AS1 sustains inactivation of Hippo pathway through a positive feedback loop with USP16/IGF2BP3 axis in gallbladder cancer. *Cancer Lett* 547: 215862, 2022.
104. Liu W, Feng W, Zhang Y, Lei T, Wang X, Qiao T, Chen Z and Song W: RP11-789C1.1 inhibits gastric cancer cell proliferation and accelerates apoptosis via the ATR/CHK1 signaling pathway. *Chin Med J (Engl)*: Oct 25, 2023 (Epub ahead of print).
105. Zhou W, Feng Y, Lin C, Chao CK, He Z, Zhao S, Xue J, Zhao XY and Cao W: Yin Yang 1-Induced Long Noncoding RNA DUXAP9 drives the progression of oral squamous cell carcinoma by blocking CDK1-Mediated EZH2 Degradation. *Adv Sci (Weinh)* 10: e2207549, 2023.
106. Hu Q, Ye Y, Chan LC, Li Y, Liang K, Lin A, Egranov SD, Zhang Y, Xia W, Gong J, *et al*: Oncogenic lncRNA down-regulates cancer cell antigen presentation and intrinsic tumor suppression. *Nat Immunol* 20: 835-851, 2019.
107. Wang S, Liang K, Hu Q, Li P, Song J, Yang Y, Yao J, Mangala LS, Li C, Yang W, *et al*: JAK2-binding long noncoding RNA promotes breast cancer brain metastasis. *J Clin Invest* 127: 4498-4515, 2017.
108. Lin Y, Jian Z, Jin H, Wei X, Zou X, Guan R and Huang J: Long non-coding RNA DLGAP1-AS1 facilitates tumorigenesis and epithelial-mesenchymal transition in hepatocellular carcinoma via the feedback loop of miR-26a/b-5p/IL-6/JAK2/STAT3 and Wnt/ β -catenin pathway. *Cell Death Dis* 11: 34, 2020.
109. Gao R, Zhang R, Zhang C, Liang Y and Tang W: lncRNA LOXL1-AS1 promotes the proliferation and metastasis of medulloblastoma by activating the PI3K/AKT pathway. *Anal Cell Pathol (Amst)* 2018: 9275685, 2018.
110. Zheng B, Wang J, Fan K, Sun W, Wan W, Gao Z, Ni X, Zhang D, Ni X, Suo T, *et al*: lncRNA RP11-147L13.8 suppresses metastasis and chemo-resistance by modulating the phosphorylation of c-Jun protein in GBC. *Mol Ther Oncolytics* 23: 124-137, 2021.
111. Zhao W, Kruse JP, Tang Y, Jung SY, Qin J and Gu W: Negative regulation of the deacetylase SIRT1 by DBC1. *Nature* 451: 587-590, 2008.
112. Chen R, Liu Y, Zhuang H, Yang B, Hei K, Xiao M, Hou C, Gao H, Zhang X, Jia C, *et al*: Quantitative proteomics reveals that long non-coding RNA MALAT1 interacts with DBC1 to regulate p53 acetylation. *Nucleic Acids Res* 45: 9947-9959, 2017.
113. Cai Q, Wang ZQ, Wang SH, Li C, Zhu ZG, Quan ZW and Zhang WJ: Upregulation of long non-coding RNA LINC00152 by SP1 contributes to gallbladder cancer cell growth and tumor metastasis via PI3K/AKT pathway. *Am J Transl Res* 8: 4068-4081, 2016.
114. Yang L, Gao Q, Wu X, Feng F and Xu K: Long noncoding RNA HEGBC promotes tumorigenesis and metastasis of gallbladder cancer via forming a positive feedback loop with IL-11/STAT3 signaling pathway. *J Exp Clin Cancer Res* 37: 186, 2018.
115. Liang C, Yang P, Han T, Wang RY, Xing XL, Si AF, Ma QY, Chen Z, Li HY and Zhang B: Long non-coding RNA DILC promotes the progression of gallbladder carcinoma. *Gene* 694: 102-110, 2019.
116. Bao D, Yuan RX and Zhang Y: Effects of lncRNA MEG3 on proliferation and apoptosis of gallbladder cancer cells through regulating NF- κ B signaling pathway. *Eur Rev Med Pharmacol Sci* 24: 6632-6638, 2020.
117. Ma MZ, Kong X, Weng MZ, Zhang MD, Qin YY, Gong W, Zhang WJ and Quan ZW: Long non-coding RNA-LET is a positive prognostic factor and exhibits tumor-suppressive activity in gallbladder cancer. *Mol Carcinog* 54: 1397-1406, 2015.

118. Wang SH, Wu XC, Zhang MD, Weng MZ, Zhou D and Quan ZW: Upregulation of H19 indicates a poor prognosis in gallbladder carcinoma and promotes epithelial-mesenchymal transition. *Am J Cancer Res* 6: 15-26, 2015.
119. Ma F, Wang SH, Cai Q, Zhang MD, Yang Y and Ding J: Overexpression of LncRNA AFAP1-AS1 predicts poor prognosis and promotes cells proliferation and invasion in gallbladder cancer. *Biomed Pharmacother* 84: 1249-1255, 2016.
120. Wu XC, Wang SH, Ou HH, Zhu B, Zhu Y, Zhang Q, Yang Y and Li H: The NmrA-like family domain containing 1 pseudogene Loc344887 is amplified in gallbladder cancer and promotes epithelial-mesenchymal transition. *Chem Biol Drug Des* 90: 456-463, 2017.
121. Liu B, Shen ED, Liao MM, Hu YB, Wu K, Yang P, Zhou L and Chen WD: Expression and mechanisms of long non-coding RNA genes MEG3 and ANRIL in gallbladder cancer. *Tumour Biol* 37: 9875-9886, 2016.
122. Wang SH, Zhang MD, Wu XC, Weng MZ, Zhou D and Quan ZW: Overexpression of LncRNA-ROR predicts a poor outcome in gallbladder cancer patients and promotes the tumor cells proliferation, migration, and invasion. *Tumour Biol* 37: 12867-12875, 2016.
123. Niu JZ, Liang XC, Xu ZW, Li ZH, Li J, Meng Y and Sun ZW: Long non-coding RNA Linc00261 as a novel potential diagnostic and prognostic biomarker for gallbladder cancer. *Transl Cancer Res* 9: 6078-6085, 2020.
124. Li Q, Li Z, Feng C, Jiang S, Zhang Z and Ma L: Multi-omics annotation of human long non-coding RNAs. *Biochem Soc Trans* 48: 1545-1556, 2020.
125. Mas-Ponte D, Carlevaro-Fita J, Palumbo E, Hermoso Pulido T, Guigo R and Johnson R: LncATLAS database for subcellular localization of long noncoding RNAs. *RNA* 23: 1080-1087, 2017.
126. Wen Y, Wu Y, Xu B, Lin J and Zhu H: Fasim-LongTarget enables fast and accurate genome-wide lncRNA/DNA binding prediction. *Comput Struct Biotechnol J* 20: 3347-3350, 2022.
127. Li JH, Liu S, Zhou H, Qu LH and Yang JH: starBase v2.0: decoding miRNA-ceRNA, miRNA-ncRNA and protein-RNA interaction networks from large-scale CLIP-Seq data. *Nucleic Acids Res* 42(Database issue): D92-D97, 2014.
128. Li Y, Tian M, Zhang D, Zhuang Y, Li Z, Xie S and Sun K: Long Non-Coding RNA Myosin light chain kinase antisense 1 plays an oncogenic role in gallbladder carcinoma by promoting chemoresistance and proliferation. *Cancer Manag Res* 13: 6219-6230, 2021.
129. Lin Z, Li Y, Shao R, Hu Y and Gao H: LncRNA TTN-AS1 acts as a tumor promoter in gallbladder carcinoma by regulating miR-107/HMGAI axis. *World J Surg Oncol* 19: 163, 2021.
130. Armaos A, Colantoni A, Proietti G, Rupert J and Tartaglia GG: catRAPID omics v2.0: Going deeper and wider in the prediction of protein-RNA interactions. *Nucleic Acids Res* 49(W1): W72-W79, 2021.
131. Liu T, Wu J, Wu Y, Hu W, Fang Z, Wang Z, Jiang C and Li S: LncPep: A resource of translational evidences for lncRNAs. *Front Cell Dev Biol* 10: 795084, 2022.
132. Li JSY, Raghubar AM, Matigian NA, Ng MSY, Rogers NM and Mallett AJ: The utility of spatial transcriptomics for solid organ transplantation. *Transplantation* 107: 1463-1471, 2022.
133. Zhao X, Lan Y and Chen D: Exploring long non-coding RNA networks from single cell omics data. *Comput Struct Biotechnol J* 20: 4381-4389, 2022.
134. Zheng LL, Xiong JH, Zheng WJ, Wang JH, Huang ZL, Chen ZR, Sun XY, Zheng YM, Zhou KR, Li B, *et al*: ColorCells: A database of expression, classification and functions of lncRNAs in single cells. *Brief Bioinform* 22: bbaa325, 2021.
135. Aprile M, Costa V, Cimmino A and Calin GA: Emerging role of oncogenic long noncoding RNA as cancer biomarkers. *Int J Cancer* 152: 822-834, 2023.
136. Fire A, Xu S, Montgomery MK, Kostas SA, Driver SE and Mello CC: Potent and specific genetic interference by double-stranded RNA in *Caenorhabditis elegans*. *Nature* 391: 806-811, 1998.
137. Robb GB, Brown KM, Khurana J and Rana TM: Specific and potent RNAi in the nucleus of human cells. *Nat Struct Mol Biol* 12: 133-137, 2005.
138. Kanojia D, Garg M, Martinez J, M T A, Luty SB, Doan NB, Said JW, Forscher C, Tyner JW and Koeffler HP: Kinase profiling of liposarcomas using RNAi and drug screening assays identified druggable targets. *J Hematol Oncol* 10: 173, 2017.
139. Gupta RA, Shah N, Wang KC, Kim J, Horlings HM, Wong DJ, Tsai MC, Hung T, Argani P, Rinn JL, *et al*: Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. *Nature* 464: 1071-1076, 2010.
140. Gutschner T, Hämmerle M, Eissmann M, Hsu J, Kim Y, Hung G, Revenko A, Arun G, Stentrup M, Gross M, *et al*: The noncoding RNA MALAT1 is a critical regulator of the metastasis phenotype of lung cancer cells. *Cancer Res* 73: 1180-1189, 2013.
141. Wang T, Shigdar S, Shamaileh HA, Gantier MP, Yin W, Xiang D, Wang L, Zhou SF, Hou Y, Wang P, *et al*: Challenges and opportunities for siRNA-based cancer treatment. *Cancer Lett* 387: 77-83, 2017.
142. Delfi M, Sartorius R, Ashrafizadeh M, Sharifi E, Zhang Y, De Berardinis P, Zarrabi A, Varma RS, Tay FR, Smith BR and Makvandi P: Self-assembled peptide and protein nanostructures for anti-cancer therapy: Targeted delivery, stimuli-responsive devices and immunotherapy. *Nano Today* 38: 101119, 2021.
143. Ashrafizadeh M, Delfi M, Hashemi F, Zabolian A, Saleki H, Bagherian M, Azami N, Farahani MV, Sharifzadeh SO, Hamzehlou S, *et al*: Biomedical application of chitosan-based nanoscale delivery systems: Potential usefulness in siRNA delivery for cancer therapy. *Carbohydr Polym* 260: 117809, 2021.
144. Sui Z and Sui X: Long non-coding RNA TMPO-AS1 promotes cell proliferation, migration, invasion and epithelial-to-mesenchymal transition in gallbladder carcinoma by regulating the microRNA-1179/E2F2 axis. *Oncol Lett* 22: 855, 2021.
145. Gonzalez-Duarte A, Berk JL, Quan D, Mauermann ML, Schmidt HH, Polydefkis M, Waddington-Cruz M, Ueda M, Conceição IM, Kristen AV, *et al*: Analysis of autonomic outcomes in APOLLO, a phase III trial of the RNAi therapeutic patisiran in patients with hereditary transthyretin-mediated amyloidosis. *J Neurol* 267: 703-712, 2020.
146. Zoré Khvalevsky E, Gabai R, Rachmut IH, Horwitz E, Brunschwig Z, Orbach A, Shemi A, Golan T, Domb AJ, Yavin E, *et al*: Mutant KRAS is a druggable target for pancreatic cancer. *Proc Natl Acad Sci USA* 110: 20723-20728, 2013.
147. Springfield C, Jäger D, Büchler MW, Strobel O, Hackert T, Palmer DH and Neoptolemos JP: Chemotherapy for pancreatic cancer. *Presse Med* 48 (3 Pt 2): e159-e174, 2019.
148. Bennett CF and Swayze EE: RNA targeting therapeutics: Molecular mechanisms of antisense oligonucleotides as a therapeutic platform. *Annu Rev Pharmacol Toxicol* 50: 259-293, 2010.
149. Dhuri K, Bechtold C, Quijano E, Pham H, Gupta A, Vikram A and Bahal R: Antisense oligonucleotides: An emerging area in drug discovery and development. *J Clin Med* 9: 2004, 2020.
150. Pandya G, Kirtonia A, Sethi G, Pandey AK and Garg M: The implication of long non-coding RNAs in the diagnosis, pathogenesis and drug resistance of pancreatic ductal adenocarcinoma and their possible therapeutic potential. *Biochim Biophys Acta Rev Cancer* 1874: 188423, 2020.
151. Arun G, Diermeier S, Akerman M, Chang KC, Wilkinson JE, Hearn S, Kim Y, MacLeod AR, Krainer AR, Norton L, *et al*: Differentiation of mammary tumors and reduction in metastasis upon Malat1 lncRNA loss. *Genes Dev* 30: 34-51, 2016.
152. Matsui M and Corey DR: Non-coding RNAs as drug targets. *Nat Rev Drug Discov* 16: 167-179, 2017.
153. Maruyama R and Yokota T: Knocking down long noncoding RNAs using antisense oligonucleotide gapmers. *Methods Mol Biol* 2176: 49-56, 2020.
154. Orafidiya F, Deng L, Bevan CL and Fletcher CE: Crosstalk between Long Non Coding RNAs, microRNAs and DNA damage repair in prostate cancer: New therapeutic opportunities? *Cancers (Basel)* 14: 755, 2022.
155. Lennox KA and Behlke MA: Cellular localization of long non-coding RNAs affects silencing by RNAi more than by antisense oligonucleotides. *Nucleic Acids Res* 44: 863-877, 2016.
156. Hu Y, Lin J, Fang H, Fang J, Li C, Chen W, Liu S, Ondrejka S, Gong Z, Reu F, *et al*: Targeting the MALAT1/PARP1/LIG3 complex induces DNA damage and apoptosis in multiple myeloma. *Leukemia* 32: 2250-2262, 2018.
157. Yoon JH, Abdelmohsen K and Gorospe M: Functional interactions among microRNAs and long noncoding RNAs. *Semin Cell Dev Biol* 34: 9-14, 2014.
158. Yoon JH, Abdelmohsen K, Srikantan S, Yang X, Martindale JL, De S, Huarte M, Zhan M, Becker KG and Gorospe M: LincRNA-p21 suppresses target mRNA translation. *Mol Cell* 47: 648-655, 2012.
159. Yokobayashi Y: High-Throughput analysis and engineering of ribozymes and deoxyribozymes by sequencing. *Acc Chem Res* 53: 2903-2912, 2020.

160. Silverman SK: Catalytic DNA: Scope, applications, and biochemistry of deoxyribozymes. *Trends Biochem Sci* 41: 595-609, 2016.
161. Chen Y, Qi F, Gao F, Cao H, Xu D, Salehi-Ashtiani K and Kapranov P: Hovlinc is a recently evolved class of ribozyme found in human lncRNA. *Nat Chem Biol* 17: 601-607, 2021.
162. Jinek M, Chylinski K, Fonfara I, Hauer M, Doudna JA and Charpentier E: A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity. *Science* 337: 816-821, 2012.
163. Mali P, Yang L, Esvelt KM, Aach J, Guell M, DiCarlo JE, Norville JE and Church GM: RNA-guided human genome engineering via Cas9. *Science* 339: 823-826, 2013.
164. Nishimasu H, Ran FA, Hsu PD, Konermann S, Shehata SI, Dohmae N, Ishitani R, Zhang F and Nureki O: Crystal structure of Cas9 in complex with guide RNA and target DNA. *Cell* 156: 935-949, 2014.
165. Paquet D, Kwart D, Chen A, Sproul A, Jacob S, Teo S, Olsen KM, Gregg A, Noggle S and Tessier-Lavigne M: Efficient introduction of specific homozygous and heterozygous mutations using CRISPR/Cas9. *Nature* 533: 125-129, 2016.
166. Hustedt N and Durocher D: The control of DNA repair by the cell cycle. *Nat Cell Biol* 19: 1-9, 2016.
167. Wang H, La Russa M and Qi LS: CRISPR/Cas9 in genome editing and beyond. *Annu Rev Biochem* 85: 227-264, 2016.
168. Yu Y, Nangia-Makker P, Farhana L and Majumdar APN: A novel mechanism of lncRNA and miRNA interaction: CCAT2 regulates miR-145 expression by suppressing its maturation process in colon cancer cells. *Mol Cancer* 16: 155, 2017.
169. Peng WX, Huang JG, Yang L, Gong AH and Mo YY: Linc-RoR promotes MAPK/ERK signaling and confers estrogen-independent growth of breast cancer. *Mol Cancer* 16: 161, 2017.
170. Winkle M, El-Daly SM, Fabbri M and Calin GA: Noncoding RNA therapeutics-challenges and potential solutions. *Nat Rev Drug Discov* 20: 629-651, 2021.
171. Shi Y, Parag S, Patel R, Lui A, Murr M, Cai J and Patel NA: Stabilization of lncRNA GAS5 by a small molecule and its implications in diabetic adipocytes. *Cell Chem Biol* 26: 319-330 e6, 2019.
172. Ren Y, Wang YF, Zhang J, Wang QX, Han L, Mei M and Kang CS: Targeted design and identification of ACINOD4Q to block activity of HOTAIR by abrogating the scaffold interaction with EZH2. *Clin Epigenetics* 11: 29, 2019.
173. Termini D, Den Hartogh DJ, Jaglanian A and Tsiani E: Curcumin against prostate cancer: Current evidence. *Biomolecules* 10: 1536, 2020.
174. Liu T, Chi H, Chen J, Chen C, Huang Y, Xi H, Xue J and Si Y: Curcumin suppresses proliferation and in vitro invasion of human prostate cancer stem cells by ceRNA effect of miR-145 and lncRNA-ROR. *Gene* 631: 29-38, 2017.
175. Zhao XM, Ren JJ, Du WH, Hao HS, Wang D, Liu Y, Qin T and Zhu HB: Effect of 5-aza-2'-deoxycytidine on methylation of the putative imprinted control region of H19 during the in vitro development of vitrified bovine two-cell embryos. *Fertil Steril* 98: 222-227, 2012.
176. Watrin M, Dausse E, Lebars I, Rayner B, Bugaut A and Toulme JJ: Aptamers targeting RNA molecules. *Methods Mol Biol* 535: 79-105, 2009.
177. Famulok M, Hartig JS and Mayer G: Functional aptamers and aptazymes in biotechnology, diagnostics, and therapy. *Chem Rev* 107: 3715-3743, 2007.
178. Keefe AD, Pai S and Ellington A: Aptamers as therapeutics. *Nat Rev Drug Discov* 9: 537-550, 2010.
179. Wang YL, Chang LC, Chen KB and Wang SC: Aptamer-guided targeting of the intracellular long-noncoding RNA HOTAIR. *Am J Cancer Res* 11: 945-954, 2021.
180. Wang KC and Chang HY: Molecular mechanisms of long noncoding RNAs. *Mol Cell* 43: 904-914, 2011.
181. Pan J, Wang R, Shang F, Ma R, Rong Y and Zhang Y: Functional micropeptides encoded by long non-coding RNAs: A comprehensive review. *Front Mol Biosci* 9: 817517, 2022.
182. Eisenberg L, Eisenberg-Bord M, Eisenberg-Lerner A and Sagi-Eisenberg R: Metabolic alterations in the tumor microenvironment and their role in oncogenesis. *Cancer Lett* 484: 65-71, 2020.
183. Sun L, Suo C, Li ST, Zhang H and Gao P: Metabolic reprogramming for cancer cells and their microenvironment: Beyond the Warburg Effect. *Biochim Biophys Acta Rev Cancer* 1870: 51-66, 2018.
184. Wei F, Wang D, Wei J, Tang N, Tang L, Xiong F, Guo C, Zhou M, Li X, Li G, *et al.*: Metabolic crosstalk in the tumor microenvironment regulates antitumor immunosuppression and immunotherapy resistance. *Cell Mol Life Sci* 78: 173-193, 2021.
185. Watson MJ, Vignali PDA, Mullett SJ, Overacre-Delgoffe AE, Peralta RM, Grebinoski S, Menk AV, Rittenhouse NL, DePeaux K, Whetstone RD, *et al.*: Metabolic support of tumour-infiltrating regulatory T cells by lactic acid. *Nature* 591: 645-651, 2021.
186. Lv H, Lv G, Chen C, Zong Q, Jiang G, Ye D, Cui X, He Y, Xiang W, Han Q, *et al.*: NAD(+) metabolism maintains inducible PD-L1 expression to drive tumor immune evasion. *Cell Metab* 33: 110-127 e5, 2021.
187. Qi X, Zhang DH, Wu N, Xiao JH, Wang X and Ma W: ceRNA in cancer: Possible functions and clinical implications. *J Med Genet* 52: 710-718, 2015.
188. van Niel G, D'Angelo G and Raposo G: Shedding light on the cell biology of extracellular vesicles. *Nat Rev Mol Cell Biol* 19: 213-228, 2018.
189. Hu W, Liu C, Bi ZY, Zhou Q, Zhang H, Li LL, Zhang J, Zhu W, Song YY, Zhang F, *et al.*: Comprehensive landscape of extracellular vesicle-derived RNAs in cancer initiation, progression, metastasis and cancer immunology. *Mol Cancer* 19: 102, 2020.
190. Ding L, Ren J, Zhang D, Li Y, Huang X, Hu Q, Wang H, Song Y, Ni Y and Hou Y: A novel stromal lncRNA signature reprograms fibroblasts to promote the growth of oral squamous cell carcinoma via lncRNA-CAF/interleukin-33. *Carcinogenesis* 39: 397-406, 2018.
191. Khandelwal A, Malhotra A, Jain M, Vasquez KM and Jain A: The emerging role of long non-coding RNA in gallbladder cancer pathogenesis. *Biochimie* 132: 152-160, 2017.
192. Rana V, Parama D, Khatoon E, Girisa S, Sethi G and Kunnumakkara AB: Reiterating the emergence of noncoding RNAs as regulators of the critical hallmarks of gall bladder cancer. *Biomolecules* 11: 1847, 2021.
193. Dey Ghosh R and Guha Majumder S: Circulating long non-coding RNAs could be the potential prognostic biomarker for liquid biopsy for the clinical management of oral squamous cell carcinoma. *Cancers (Basel)* 14: 5590, 2022.
194. Anand P and Stahel VP: Review the safety of Covid-19 mRNA vaccines: A review. *Patient Saf Surg* 15: 20, 2021.