Antisense Long Non-Coding RNAs in Hepatocellular Carcinoma

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Transcriptome complexity is emerging as an unprecedented and fascinating domain, especially by high-throughput sequencing technologies that have unveiled a plethora of new non-coding RNA biotypes. Several sense–antisense transcript pairs have been recently annotated, especially from mammalian genomes, and an understanding of their evolutionary sense and functional role for human health and diseases is only beginning. Antisense long non-coding RNAs ((lncRNAs) dysregulation is significantly involved in hepatocarcinogenesis, where they can act as oncogenes or oncosuppressors, thus playing a key role in tumor onset, progression, and chemoradiotherapy response. Mechanistically, antisense lncRNAs regulate gene expression by exploiting various molecular mechanisms shared with other ncRNA molecules, and exploit special mechanisms on their corresponding sense gene due to sequence complementarity, thus exerting epigenetic, transcriptional, post-transcriptional, and translational controls.

non-coding RNA antisense lncRNA HCC ceRNET

1. Introduction

As the result of pervasive transcription of the mammalian genome, non-coding RNAs (ncRNAs) represent the majority of the transcriptome. High-throughput sequencing technologies unveiled an unprecedent and fascinating picture of transcriptome complexity, where less than 2% of transcription encodes proteins, and a plethora of ncRNA biotypes are found, in addition to the well-known ribosomal RNAs [1]. The finely regulated expression pattern of ncRNAs, further restricted to specific cell types in comparison to coding RNAs, their role in various physiological processes, and the finding of their dysregulation and involvement in pathological conditions have led to a drastic change in the view of ncRNA world: ncRNAs are no longer considered “evolutionary junk” or “transcriptional noise”, but a valuable resource for greater eukaryote complexity, with molecular mechanisms only beginning to be understood [2][3].

Based on their length, ncRNA molecules can be broadly classified into small or short ncRNAs (from few to 200nt) and long ncRNAs ((lncRNAs) longer than 200nt, with a size up to several kilobases (up to 100 kb)) [4].

Short ncRNAs comprise tRNA (transfer RNA), engaged in translation of mRNA; snRNA (small nuclear RNA), involved in splicing; snoRNA (small nucleolar RNA), involved in ribosomal RNA modification; piRNA (Piwi-interacting RNA), mainly implicated in transposon repression; microRNAs (miRNAs), the most studied group of small ncRNAs, acting as post-transcriptional regulators of gene expression (**Figure 1**). miRNAs work by driving multiprotein complexes on complementary sequences of target transcripts, thus affecting their translation and/or

stability [5]. One miRNA can bind various transcripts, and vice versa one transcript can be targeted by different miRNAs, giving rise to complex regulatory networks controlling more than 30% of protein-coding genes, thus playing key roles in almost all physiological pathways and in the pathogenesis of several diseases [6][7][8].

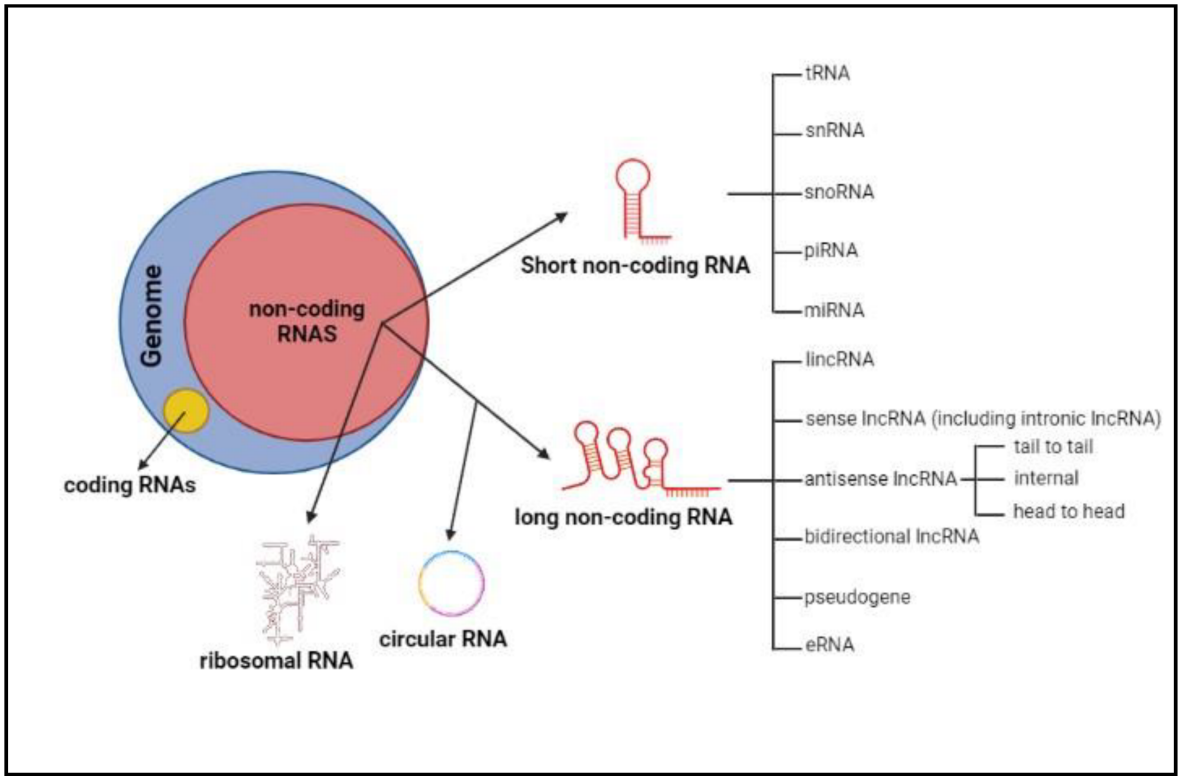

Figure 1. Graphic representation of RNA biotypes' classification in the transcriptome space. ncRNAs represent the majority of the transcriptome. In addition to the well-known ribosomal RNAs, they can be broadly classified into short and long non-coding RNAs; they can be further functionally categorized as indicated. lncRNAs, the largest class of ncRNAs in the mammalian genome, can be classified into subclasses depending on their genomic locations, origins, and transcription direction. Figures created with BioRender.com.

LncRNAs, the largest class of ncRNAs in the mammalian genome, can be further classified into subclasses, depending on their genomic locations, origins, and transcription directions (**Figure 1**): long intergenic ncRNAs (lincRNAs) transcribed from intergenic regions that do not overlap any other gene and have their own regulatory elements; sense lncRNAs, transcribed in the same direction as a coding gene, overlapping one or more exons or embedded in one of the introns without touching any exons (intronic lncRNAs); antisense lncRNAs, transcribed as an antisense strand compared to an overlapping known gene; bidirectional (or divergent) lncRNAs, deriving from promoters with bidirectional activity; pseudogenes, a version of coding genes that lost their protein-coding ability due to mutations; eRNAs (enhancer RNAs), arising from enhancers endowed with an enhancer-like function; circRNAs (circular RNAs), deriving from backsplicing events of protein-coding transcripts that form covalently closed continuous loops [2][4][9][10]. LncRNAs are emerging as key gene expression regulators due to their interaction with DNA, other RNA molecules, and proteins, as detailed in the next paragraph.

The specific name of antisense lncRNAs is derived from their sense gene, with the addition of “-AS”; they can be further categorized according to their localization with respect to sense transcripts, i.e., tail to tail (sense and antisense transcripts overlapping in the 3′ region), internal (antisense lncRNA covering the sense transcript), and head to head (sense and antisense transcripts overlapping the 5′ region) [11].

Sense–antisense gene pairs have been found in a significant proportion in the genome/transcriptome of different species, from prokaryotes to mammals (a higher percentage has been found in mammals); furthermore, sense–antisense gene pairs are generally organized into one coding and one non-coding transcript [12][13][14]. Intriguingly, evolutionary conservation of sense–antisense gene pairs has been reported as low, even between closely related mammals; in particular, only 25% of human pairs have both genomic sequence and gene structure conservation in mice [15]. This evidence, along with the poor evolutionary conservation of lncRNAs’ sequence and their role in gene regulation, lead us to speculate that many interspecies differences could rely on the regulation of protein-coding genes, significantly conserved throughout evolution, by non-conserved antisense lncRNAs. In this regard, it has been inferred that human sense–antisense gene loci may be enriched for primate-specific regulatory functions, and antisense lncRNAs could represent the “linchpins of interspecies distinctions” contributing to evolutionary lineage-specific regulatory outcomes and complexity [15].

It is becoming increasingly clear that antisense lncRNAs play key roles, not only in physiological states, but also in pathological conditions, especially cancer. They can contribute to the onset and progression of different types of tumors, acting as oncogenes, oncosuppressors, or both, depending on the type of cancer. lncRNAs have also been implicated in chemotherapy and radiation therapy resistance.

Antisense lncRNAs are also emerging as novel players in hepatocellular carcinoma (HCC); in particular, one study found that they represent 16% of the newly assembled lncRNAs from HCC patients [16]. HCC is one of the most common aggressive human malignancies. HCC ranks third for cancer-related death and is the fifth most common solid tumor worldwide [17]. Viral hepatitis, metabolic syndrome, alcohol abuse, exposure to carcinogenic agents, and genetic diseases such as Wilson’s disease and hemochromatosis can cause chronic liver diseases, resulting in more than 80% of human HCCs [18]. In addition to the well-known role of protein-driven processes, functional studies have demonstrated the active involvement of ncRNAs in the regulation of key pathways acting in hepatocarcinogenesis [19][20].

2. Biogenesis and Functioning of Antisense lncRNAs

Antisense lncRNAs and, generally, lncRNA biogenesis, share various features with coding RNAs and precursor transcripts of miRNAs: they are transcribed, generally, by RNA polymerase II, subjected to 5′-capping, 3′-polyadenylation, and splicing, since they are mainly composed of two exons [2]. In contrast with mRNAs that move to the cytoplasm for translation, antisense lncRNAs can be retained in the nucleus. Similarly to coding RNAs, but even more distinctly, lncRNAs exhibit highly specific cell lineage and restricted spatiotemporal and tissue type expression patterns, although they are detected in lower amounts [3]. It is still challenging to assign a mechanism/role to the increasing numbers of annotated antisense lncRNAs, due to their lower amounts and poor

evolutionary conservation when compared to coding RNAs. In this regard, it should be noted that conservation may be found in secondary structures rather than in sequences; in fact, a crucial feature of lncRNAs is the ability to form thermodynamically stable structures, a structural versatility enabling them to bind to DNA, other RNA molecules, and proteins [21][22]. In addition, an RNA molecule comprising 100nt can capture more than 5 proteins simultaneously, making RNA molecules a more cost-effective scaffold for protein interaction, in comparison to proteins themselves, with well-known modules/motifs dedicated to interactions [23].

In the nucleus and cytoplasm, antisense lncRNAs exploit all the mechanisms of gene regulation known for other lncRNA biotypes. However, antisense lncRNAs can also reroute these mechanisms onto their sense genes. In addition, due to sequence complementary, antisense lncRNAs can play a special role regarding sense genes (**Figure 2**). As a consequence, an efficient manner to obtain clues regarding the main mechanism of action of antisense lncRNAs is to detect their prevailing subcellular localization while taking into consideration a possible shuttling between different compartments under specific physiological or pathological conditions. Then, it is possible to speculate that some of the activities performed in that compartment may involve the regulatory contribution of antisense lncRNAs.

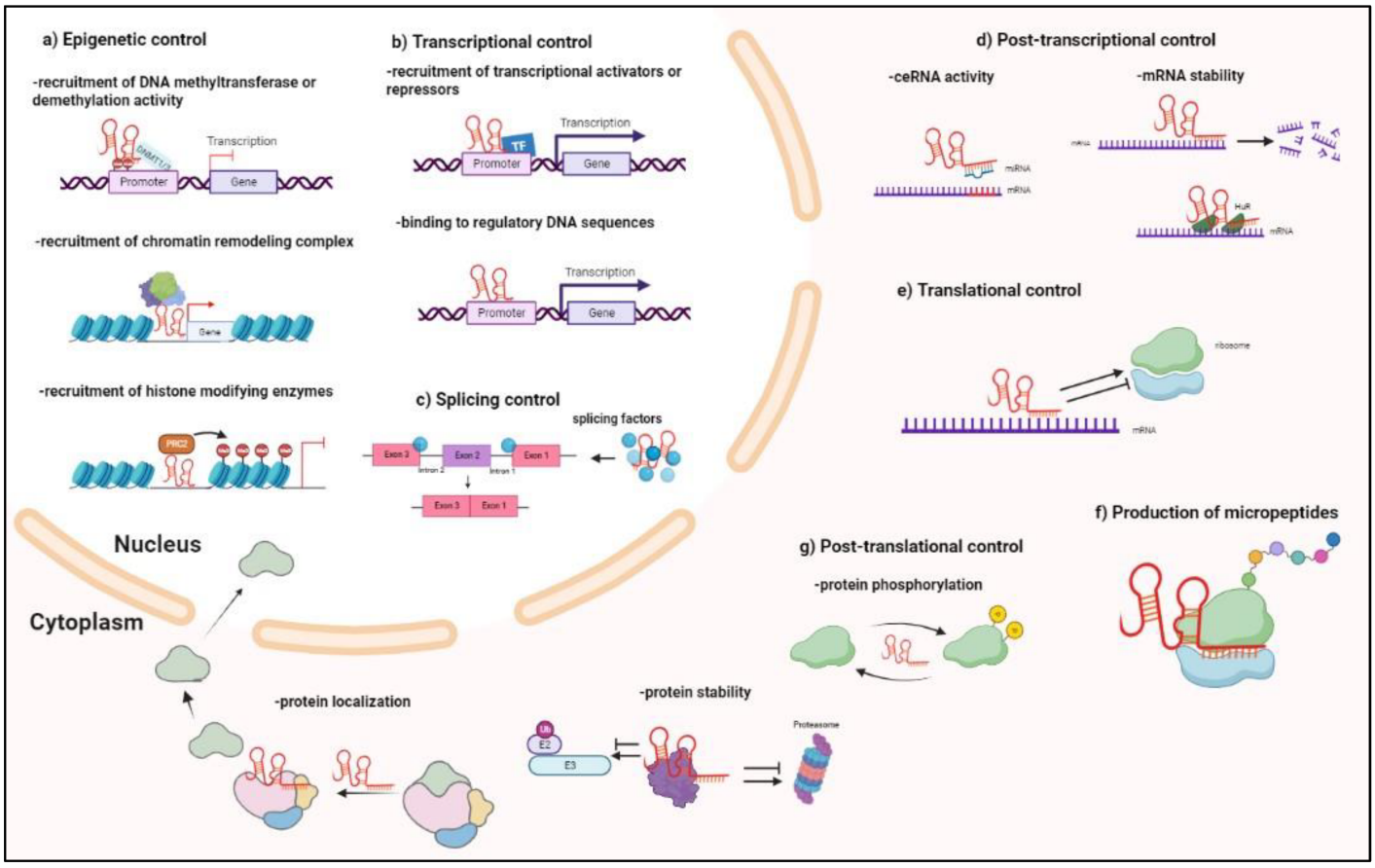

Figure 2. Molecular mechanisms exploited by antisense lncRNAs for gene expression regulation and involved in HCC. Antisense lncRNAs can interact with DNA, RNA, and proteins, thus sharing the mechanisms of gene regulation known for other lncRNA biotypes, and also rerouting them onto their sense genes. Here, the possible mechanisms are represented as compartmentalized between the nucleus and the cytoplasm, with different

sublevels (**a**–**g**) to emphasize the idea that the subcellular localization of a newly annotated antisense lncRNA can provide clues about its prevailing mechanism of action. However, a possible shuttling of antisense lncRNA should be considered in diverse physiological and/or pathological contexts. Many of the illustrated mechanisms are involved in the onset and progression of HCC, as detailed in the text. Figures created with BioRender.com.

In the nucleus, interaction with DNA, chromatin-modifying complexes, histone-modifying enzymes, and/or various transcriptional regulators determines antisense lncRNAs function as epigenetic and transcriptional regulators (**Figure 2**a–c). In particular, antisense lncRNAs can recruit DNA methyltransferases to promoters, thus actively contributing to DNA methylation pattern impacting the expression of a large number of oncogenes or tumor suppressors [24][25]. Antisense lncRNAs can also recruit demethylation enzymatic activities to promoters as has been demonstrated—by RIP (RNA immunoprecipitation) and RNA pull-down experiments—for ZNF667-AS1, able to interact and recruit TET1 to the target gene ZNF667 and E-cadherin to hydrolyze 5′-methylcytosine to 5′-hydroxymerhylcytosine and activate its expression [24][26]. Of note, specific DNA methylation signatures are associated with the HCC stage and patient survival [27][28]. Specific antisense lncRNAs can also interact and recruit chromatin-remodeling complexes and histone-modifying enzymes, such as histone methyltransferase and histone acetyltransferases, that cannot exert their role independently due to a lack of a DNA-binding domain, thus modulating chromatin structure influencing gene expression [11][29][30]. At the transcriptional level, antisense lncRNAs can recruit transcription factors required for promoting or repressing gene expression [31][32]. Although less frequently reported, lncRNAs can also directly bind to genomic DNA to regulate gene expression. An example of this is represented by VIM-AS1 that forms a hybrid DNA:RNA structure, known as R-loop, around the promoter of its head-to-head sense gene VIM, thus triggering an open chromatin structure that favors NF-kB binding and VIM transcription [33]. Another manner of direct lncRNA-DNA interaction is the formation of RNA-DNA triplex, impacting transcriptional induction [34]. Finally, in the nucleus, lncRNAs can also regulate splicing by interacting with splicing factors [20].

In the cytoplasm, by binding proteins and RNA molecules, lncRNAs can regulate gene expression at the post-transcriptional level by sponging miRNAs, regulating mRNA translation and degradation; short open reading frames hidden in the lncRNA sequence could even serve as templates for the synthesis of so-called “micropeptides” up to 100 amino acids long [4][35][36] (**Figure 2**d–g). Currently, many studies are being published on miRNAs sponging activity of antisense lncRNA and ceRNA activity (competing endogenous RNA): the lncRNA can bind a miRNA and, titrating its availability, can endogenously compete with the other miRNA targets, coding or non-coding RNAs, that are resultingly upregulated [37][38]. In this scenario, all RNA biotypes can modulate each other and design regulatory networks (ceRNET, competing endogenous RNA network) governing different pathways, and whose unbalancing can drive carcinogenesis [39][40]. Even at the post-translational level, antisense lncRNAs can exert control of gene expression by binding and modulating the stability of specific proteins, e.g., protecting from or prompting their ubiquitin-proteosome degradation, and modifying their phosphorylation status, or controlling their localization [11][41].

Finally, sequence complementary allows antisense lncRNAs to have a specific effect on their sense gene. In fact, at the post-transcriptional level, antisense lncRNAs can bind their sense transcript, generating an RNA duplex and

affecting the stability of the sense transcript via an RNA interference mechanism; probably the best-known example of this is represented by the pair XIST and TSIX (XIST spelled in reverse order) involved in the X chromosome inactivation, but other examples have been subsequently reported [42][43][44] (**Figure 2**d). An opposite effect to RNAi can also be observed, due to the stabilization of cognate RNA by interaction with antisense lncRNA [37][38][45].

The above mechanisms have been distilled from many studies, detailed in the next section as related to HCC.

3. Antisense lncRNAs Involved in HCC

Antisense lncRNAs are increasingly recognized as mediators of human cancers [11] and, depending on the context, they can act as either oncogenes or tumor suppressors. In the liver, a number of antisense lncRNAs are described as deregulated, thus playing a crucial role in the onset and progression of HCC [16]. In particular, by searching "(antisense lncRNA) AND (HCC)" throughout PubMed, more than 200 articles were retrieved; they were then analyzed and articles concerning antisense lncRNAs were grouped as detailed below. This analysis was also based on information retrieved from https://lncipedia.org (accessed on 3 April 2023) [46].

An extended list of antisense lncRNAs, their dysregulation, and their molecular functions in HCC is provided in **Table 1**.

Table 1. Antisense lncRNAs acting as oncogenes or tumor suppressors in HCC.

Antisense lncRNA	Role	Effect	Molecular Mechanism	Reference
AIRN	Oncogene	Promotes proliferation and inhibits apoptosis	Inhibits CUL4A-mediated ubiquitination of STAT1	[47]
ALKBH3-AS1	Oncogene	Promotes cell invasion and proliferation	Enhances ALKBH3 mRNA stability	[48]
ANRIL	Oncogene	Associated with clinical outcomes; promotes proliferation, migration and invasion; promotes tumor growth and metastasis in vivo; enhances mitochondrial function	Silences epigenetically Kruppel-like factor 2 (KLF2) by binding to PRC2 sponges let-7c-5p to upregulate NAP1L1, thus activating AKT/mTOR pathway; sponges miR-191, inactivating NF-κB and Wnt/β-catenin pathways; sponges miR-153-5p to upregulate	[49][50][51][52][53][54]

Antisense lncRNA	Role	Effect	Molecular Mechanism	Reference
			ARHGAP18 and activate MEK/ERK signaling; sponges miR-199a-5p to upregulate ARL2; sponges miR-122-5p	
BACE1-AS	Oncogene	Promotes cell cycle progression, migration, and invasion	Sponges miR-214-3p to upregulate APLN expression	[55]
BAIAP2-AS1	Oncogene	Promotes proliferation and metastasis	Sponges miR-361-3p to release SOX4	[56]
BSG-AS1	Oncogene	Correlates to hypoxia; promotes proliferation and migration	Enhances the stability of BSG mRNA	[57]
DARS-A1	Oncogene	Correlates with poor prognosis; promotes proliferation, cell invasion, and EMT	Sponges miR-3200-5p to upregulate CKAP2 and activate the FAK/ERK pathway	[58]
DDX11-AS1	Oncogene	Promotes proliferation, migration, invasion and glucose metabolism	Sponges miR-195-5p to upregulate MACC1 expression	[59]
DLG1-AS1	Oncogene	Promotes proliferation, migration, and invasion in HCC and tumor growth in vivo	Induced by MYC; sponges miR-497-5p to upregulare SSRP1	[60]

Antisense lncRNA	Role	Effect	Molecular Mechanism	Reference
DLGAP1-AS1	Oncogene	Promotes proliferation	Sponges miR-486-5p to upregulate H3F3B	[61]
DNAJC3-AS1	Oncogene	Correlates with prognosis of patients; promotes proliferation	Suppresses miR-27b maturation	[62]
DLX6-AS1	Oncogene	Promotes cell viability, invasion, and migration	Sponges miR-513c to upregulate Cul4A, thus repressing ANXA10 degradation; sponges miR-424-5p to upregulate WEE1	[63][64]
FAM83H-AS1	Oncogene	Associated with tumor prognosis; promotes proliferation, migration, and invasion	Inhibits the Wnt/β-catenin pathway by reducing β-catenin and WNT1 expression	[65]
FGFR3-AS1	Oncogene	Promotes proliferation, migration, and invasion; promotes tumor growth in vivo	Activates the PI3K/AKT pathway	[66]
FOXP4-AS1	Oncogene	Associated with poor survival, promotes tumor growth in vivo	Recruits EZH2 to the promoter region of ZC3H12D to mediate H3K27me3 methylation, thus inhibiting ZC3H12D expression	[29]
GATA3-AS1	Oncogene	Promotes cell proliferation and metastasis	Suppresses PTEN, CDKN1A, and TP53	[67]
GPC3-AS1	Oncogene	Indicates poor prognosis; proliferation and migration;	Recruits PCAF to the GPC3 gene body region, upregulating GPC3 transcription	[68]

Antisense lncRNA	Role	Effect	Molecular Mechanism	Reference
		Promotes xenograft tumor growth in nude mice		
HOTAIR	Oncogene	Promotes proliferation, migration, invasion, and tumor growth in vivo; regulates the G1/S phase transition; regulates glycolyis; associated with poor survival rates	Increases ATG3 and ATG7 expression; inhibits RBM38; activates Wnt/β-catenin pathway, increases CCND1 expression and STAT3 signaling; binds STAT3 andP300 to upregulate FUT8 and MUC1; upregulates GLUT1, upregulating mTOR; sponges miR-130a-3p to upregulate HIF1A regulated by FOXC1; sponges miR-1; sponges miR-214-3p to upregulate FLOT1	[32][69] [70][71] [72][73] [74][75] [76]
HOXA11-AS1	Oncogene	Promotes proliferation, invasion, and self-renewal	Suppresses the transcription of HOXA11 by recruiting DNMT1 to the promoter activating Wnt/ βcatenin pathway	[25]
HOXA-AS2	Oncogene	Promotes cell migration and invasion by inducing EMT	Sponges miR-520c-3p to upregulate GPC3	[77]
HOXD-AS1	Oncogene	Promotes proliferation and invasion; regulates cell cycle progression	Sponges miR-miR-326 to upregulate SLC27A4, induces MEK/ERK signaling pathway	[78][79]
KCNQ1OT1	Oncogene	Correlates with liver cirrhosis, an advanced TNM stage, and a large tumor size; promotes	Sponges miR-504 to regulate GSK3β/β-catenin/Bcl-2 signaling pathway	[80]

Antisense lncRNA	Role	Effect	Molecular Mechanism	Reference
		proliferation and tumor growth in vivo		
KTN1-AS1	Oncogene	Associated with poor survival, promotes proliferation	Sponges miR-23c to upregulate ERBB2IP	[81]
LASP1-AS	Oncogene	Associated with poor prognosis, enhances proliferation and migration	Upregulates LASP1	[82]
LEF1-AS1	Oncogene	Promotes proliferation, invasion, angiogenesis, and tumor growth in vivo	Sponges miR-136-5p to regulate WNK1 espression, recruits CEBPB to promote CDCA7/EZH2 expression	[30][83]
LOXL1-AS1	Oncogene	Promotes proliferation, migration, and invasion	Sponges miR-3614-5p to upregulate YY1	[84]
MACC1-AS	Oncogene	Increases stemness; promotes cell proliferation, EMT, and invasion	Sponges miR-145 to regulate Nanog, Oct4, and Sox9; regulates PAX8	[85][86]
MAFG-AS1	Oncogene	Promotes proliferation, invasion, and migration	Sponges miR-6852	[87]
MAPKAPK5-AS1	Oncogene	Associated with poor clinical features and prognosis, promotes growth and metastasis	Sponges miR-154-5p to upregulate PLAGL2, thus activating EGFR/AKT signaling and regulating HIFA	[88]
MCM3AP-AS1	Oncogene	Correlated with poor prognosis, promotes cell	Sponges miR-194-5p to upregulate FOXA1	[89]

Antisense lncRNA	Role	Effect	Molecular Mechanism	Reference
		growth		
MFI2-AS1	Oncogene	Promotes invasion and metastasis of HCC cells in vitro and vivo	Sponges miR-134 to upregulate FOXM1 expression	[90]
MKLN1-AS	Oncogene	Promotes proliferation, migration, invasion, and tumor growth in vivo; associated with poor prognosis	Sponges miR-22-3p to upregulate ETS proto-oncogene 1, sponges miR-654-3p to upregulate HDGF	[91][92]
MYLK-AS1	Oncogene	Associated with poor prognosis; promotes cell invasion, migration, proliferation, and angiogenesis	Sponges miR-424-5p to upregulate E2F7 and activate VEGFR2 signaling; increases EGFR, pEGFR, HER2 and RAF1 expression	[93][94]
NNT-AS1	Oncogene	Decreases CD4 lymphocyteinfiltration, promotes proliferation in vitro and tumor growth in vivo	Enhances TGF-β signaling pathway, sponges miR-363 to upregulate CDK6 expression	[95][96]
NPSR1-AS1	Oncogene	Promotes proliferation and glycolysis	Regulates MAPK/ERK pathway	[97]
NR2F1-AS1	Oncogene	Induces glycolysis under hypoxia and promotes migration	Sponges miR-140 to upregulate HK2	[98]
OTUD6B-AS1	Oncogene	Promotes proliferation and invasion	Sponges miR-664b3-p to induce GSKIP/Wnt/β-catenin signalling	[99]

Antisense lncRNA	Role	Effect	Molecular Mechanism	Reference
PCNA-AS1	Oncogene	Promotes tumor growth in vitro and in vivo	Stabilizes PCNA transcripts	[100]
PITPNA-AS1	Oncogene	Promotes proliferation, migration, and EMT	Sponges miR-876-5p to upregulate WNT5A	[101]
PRKAG2-AS1	Oncogene	Associated with poor survival rates; promotes proliferation, migration, and invasion	Sponges miR-502-3p to upregulate BICD2	[102]
PRR34-AS1	Oncogene	Promotes proliferation migration, invasion, and EMT; enhances tumor growth in vivo	Sponges miR-296-5p to upregulate E2F2 and SOX12, activating Wnt/βcatenin pathway; interacts with DDX3X to regulate the stability of Rab27a mRNA and promote the exosome secretion of VEGF and TGF-β; sponges miR-498 to upregulate TOMM20 and ITGA6	[103][104][105]
RBM5-AS1	Oncogene	Promotes cell proliferation and invasion	Sponges miR-132/212 via recruiting PRC2 complex	[106]
RHPN1-AS1	Oncogene	Correlated with prognosis of patients; promotes proliferation and metastasis; associated with the occurrence of lymphatic metastasis and a higher level	STAT1 induces overexpression of RHPN1-AS1, sponges miR-485 to upregulate CDCA5, sponges miR-596 to upregulate IGF2BP2	[107][108]

Antisense lncRNA	Role	Effect	Molecular Mechanism	Reference
		of serum AFP; correlated with poor survival		
RNF185-AS1	Oncogene	Correlated with advanced TNM stage, distant metastasis and a poor survival rate; promotes proliferation, migration, and invasion	Sponges miR-221-5p to upregulate ITGB5	[109]
SBF2-AS1	Oncogene	Correlated with poor prognosis, promotes proliferation and tumor growth in vivo	Sponges miR-140-5p to upregulate TGFBR1 expression	[110]
SNAI3-AS1	Oncogene	Promotes proliferation and metastasis	Sponges miR-27-3p/34a-5p	[111]
SOX9-AS1	Oncogene	Promotes proliferation, migration, and invasion; Promotes tumor growth and metastasis in vivo	Sponges miR-5590-3p to upregulate SOX9, thus activating Wnt/b-catenin pathway	[112]
SPACA6P-AS	Oncogene	Promotes cell proliferation	Sponges miR-125a/Let7a to upregulate Lin28b, MMP11, SIRT7, Zbtb7a, Cyclin D1, CDC25B, HMGA2	[113]
ST8SIA6-AS1	Oncogene	Promotes proliferation, migration, and invasion	Sponges miR-338-3p to upregulate NONO expression, sponges miR-5195-3p to regulate HOXB6 expression	[114][115]

Antisense lncRNA	Role	Effect	Molecular Mechanism	Reference
TMPO-AS1	Oncogene	Associated with poor prognosis, promotes proliferation and EMT	Sponges miR-126-3p to upregulate LRP6, inducing Wnt/β-catenin signalling; sponges miR-329-3p to upregulate FOXK1, inducing AKT/mTOR signaling pathway; sponges miR-320a to upregulate SERBP1	[116][117][118]
TP73-AS1	Oncogene	Correlated with poor prognosis, promotes proliferation	Sponges miR-200a to induce HMGB1/RAGE pathway	[119]
TRG-AS1	Oncogene	Promotes proliferation, migration, invasion, and EMT progress	Sponges miR-4500 to modulate BACH1	[120]
TRIM52-AS1	Oncogene	Promotes proliferation and EMT	Sponges miR-514a-5p to upregulate MRPS18A	[121]
TTN-AS1	Oncogene	Promotes proliferation, migration, and EMT	Sponges miR-139-5p to upregulate SPOCK1 expression	[122]
UNC5B-AS1	Oncogene	Promotes proliferation, migration, and EMT	Sponges miR-4306 to upregulate KDM2A expression	[123]
UPK1A-AS1	Oncogene	Correlated with poor prognosis, promotes proliferation and cell cycle progression	Interacts with EZH2; sponges miR-138-5p	[124]
USP2-AS1	Oncogene	Increases proliferation, migration, and invasion under	Interacts with YBX1 to increase the protein translation of HIF1a	[125]

Antisense lncRNA	Role	Effect	Molecular Mechanism	Reference
		hypoxia	under hypoxia	
VPS9D1-AS1	Oncogene	Facilitates cell proliferation, migration, and stemness	Sponges miR-491-5p to upregulate SEC61A1	[126]
WEE2-AS1	Oncogene	Positively correlated to HBV infection; increases proliferation, migration, invasion, and cell cycle progression	Upregulates FERMT3 expression and activates PI3K/AKT/GSK3b signaling	[127]
ZEB1-AS1	Oncogene	Promotes proliferation and invasion, associated with bone metastasis	Sponges miR-229-3p to upregulate E2F1 expression, sponges miR-23c, sponges miR-302b to increase PI3K-AKT pathway activation and EGFR expression	[128][129] [130]
ZEB2-AS1	Oncogene	Associated with large tumor volume, increased tumor-node-metastasis (TNM) stage, and positive lymph node metastasis; promotes proliferation, migration, invasion, and suppressed apoptosis	Sponges miR-582-5p to upregulate FOXC1	[131]
ZFAS1	Oncogene	Associated with worse prognosis and survival; promotes proliferation, migration, and invasion	Sponges miR-624 to upregulate MDK-mediated ERK/JNK/AKT signaling pathway	[132]

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Antisense lncRNA	Role	Effect	Molecular Mechanism	Reference
ZFPM2-AS1	Oncogene	Correlated with advanced TNM stage, distant metastasis, and a poor survival rate; promotes proliferation, migration, invasion, and tumor growth in vivo	Sponges miR-1226-3p to upregulate ITGB1, sponges miR-3065-5p activity to regulate XRCC4, sponges miR-139 to upregulate GDF10, sponges miR-653 to upregulate GOLM1	[133][134] [135][136]
ZSCAN16-AS1	Oncogene	Correlated with poor clinical outcomes; promotes proliferation, migration, and invasion	Sponges miR-451a to increase ATF2 expression; sponges miR-181c-5p to upregulate SPAG9, activating JNK	[137][138]
ADORA2A-AS1	Tumor suppressor	Inhibits proliferation, migration, and invasion; represses xenograft growth and metastasis in vivo	Competitively binds HuR decreasing FSCN1 transcript stability, thereby repressing the AKT pathway	[139]
CADM1-AS1	Tumor suppressor	Inhibits proliferation, migration, invasion, and tumor growth in vivo	Regulates the AKT/GSK-3β signaling pathway	[140]
F11-AS1	Tumor suppressor	Suppresses proliferation, migration, and invasion	Sponges miR-221-5p to upregulate NR1I3	[141]
HHIP-AS1	Tumor suppressor	Downregulation of HHIP-AS1 correlates with larger tumor size, metastasis, and advanced TNM stage; inhibits proliferation, migration, and invasion; induces apoptosis	Facilitates HHIP mRNA stability by promoting HuR binding to HHIP mRNA	[45]

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Antisense lncRNA	Role	Effect	Molecular Mechanism	Reference
HNF1A-AS1	Tumor suppressor	Suppresses proliferation, migration, and invasion; inhibits tumorigenesis and metastasis in vivo	Interacts and activates SHP-1	[142]
MAGI2-AS3	Tumor suppressor	Inhibits proliferation in vitro and tumor growth in vivo	Sponges miR-519c-3p to increase TXNIP, decreases RCGAP1 expression by facilitating histone demethylation of the RACGAP1 promoter by recruiting KDM1A	[143][144]
TMEM220-AS1	Tumor suppressor	Suppresses proliferation and invasion	Increases TMEM220 expression to regulate Wnt/β-catenin pathway	[145]
UCHLAS1	Tumor suppressor	Inhibits proliferation and migration	Enrichment analysis reveals that HRAS, BMP4, and CALM3 are hub genes of HCC, related to UCHLI-AS1	[146]
WT1-AS	Tumor suppressor	Promotes cell apoptosis	Inhibits JAK2/STAT3 and MAPK signaling, regulates WT1 by binding promoter region	[147]
WWOX-AS1	Tumor suppressor	Decreases cell proliferation, migration and EMT	Sponges miR-20b-5p to upregulate WWOX expression	[148]

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