



REVIEW ARTICLE

Comprehensive biological function analysis of lncRNAs in hepatocellular carcinoma

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KEYWORDS

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Abstract Thousands of long non-coding RNAs (lncRNAs) have been discovered in human genomes by gene chip, next-generation sequencing, and/or other methods in recent years, which represent a significant subset of the universal genes involved in a wide range of biological functions. An abnormal expression of lncRNAs is associated with the growth, invasion, and metastasis of various types of human cancers, including hepatocellular carcinoma (HCC), which is an aggressive, highly malignant, and invasive tumor, and a poor prognosis in China. With a more in-depth understanding of lncRNA research for HCC and the emergence of new molecular-targeted therapies, the diagnosis, treatment, and prognosis of HCC will be considerably improved. Therefore, this review is expected to provide recommendations and directions for future lncRNA research for HCC.

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Abbreviations: HCC, Hepatocellular carcinoma; RNA, Ribonucleic acid; mRNA, Messenger RNA; ncRNAs, Non-coding RNAs; lncRNAs, Long non-coding RNAs; miRNAs, microRNAs; ceRNAs, Competing endogenous RNAs; snoRNAs, Small nucleolar RNAs; AASLD, American Association for the Study of Liver Diseases.

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Introduction

Depending on the differences in their structure and function, RNAs have been mainly divided into three categories, namely, messenger RNAs (mRNAs), transport RNAs (tRNAs), and ribosomal RNA (rRNAs). The mRNAs are transcribed according to the DNA in the nucleus, which is a template for the synthesis of proteins. The tRNAs are used to identify the genetic codons on the mRNAs and transport the amino acids. The rRNA is a component of ribosomes, which is a workplace for protein synthesis. In most eukaryotic cells, an abundance of different types of RNAs is different, and the rRNAs account for 80%–85% of the cellular RNA mass roughly, followed by tRNAs and mRNAs.^{1–4} At some stage of germ cell development, these RNA mass ratios might change because of the PIWI-interacting RNA (piRNA) expression.⁵

With the rapid development of molecular biology and molecular diagnostic technology, an increasing number of non-coding RNAs (ncRNAs)⁶ in the human genome have been discovered by gene chip, next-generation sequencing, and/or other methods in recent years, such as long non-coding RNAs (lncRNAs), microRNAs (miRNAs), competing endogenous RNAs (ceRNAs), and small nucleolar RNAs (snoRNAs).⁷ However, the specific molecular mechanisms of lncRNAs, miRNAs, and ceRNAs are unclear. The ncRNAs that have occupied a vast majority of chromosomes are involved in

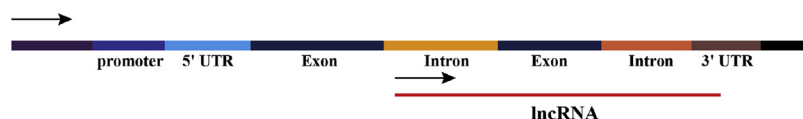
many biological processes and have been increasingly seen as important transcriptional regulators. Initially, they were considered “junk genes” that did not encode proteins; then, they were gradually discovered to play an important regulatory role in various biological processes^{8–14} and perhaps as a regulator of the innate immune cell development and inflammatory gene expressions, biomarkers, and therapeutic targets for liver fibrosis or tumors, particularly in the process of tumor occurrence and development. This could be attributed to the intricate molecular mechanism between the lncRNAs and the other genes, which have rapidly become star molecules in the field of genetic research, particularly in the study of the correlation between lncRNAs and tumors.^{15–19} This article will focus on the latest advances in lncRNA research for HCC.

Characteristics of lncRNAs

lncRNAs have been identified as non-protein coding RNA transcripts with a length of approximately more than 200 nt, which have been shown to be involved in diverse molecular functions and pathological processes in epigenetic regulation.²⁰ lncRNAs often have a poly(A) tail structure, which accounts for approximately 80% of the ncRNAs and is regulated by a variety of transcription factors.²¹ At the beginning, researchers thought that lncRNAs

Types of lncRNA

A. Sense lncRNA



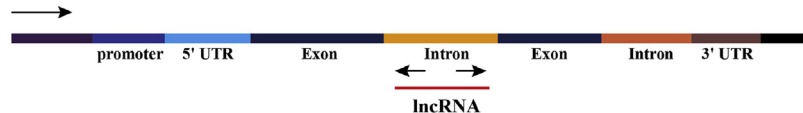
B. Antisense lncRNA



C. Bidirectional lncRNA



D. Intronic lncRNA



E. lincRNA

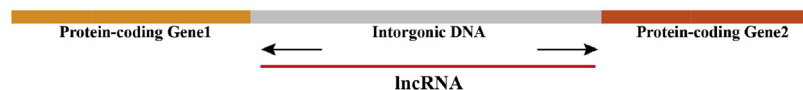


Figure 1 Types of lncRNAs.

were a by-product of RNA polymerase II transcription. With an in-depth understanding of lncRNAs, a number of studies have shown that lncRNAs may have multiple origins: (1) chromatin recombination, (2) replicon concatenation, (3) transposon insertion into the gene, (4) reverse translocation during ncRNA replication, and (5) structural disruption of coding genes.²²

However, currently, there is no unified standard for the classification of lncRNAs. For the classification method, some researchers^{23,24} have suggested that it can be carried out according to the following characteristics: (1) According to the position of the genome, lncRNAs can be divided into five types: sense lncRNAs, antisense lncRNAs, bidirectional lncRNAs, intronic lncRNAs, and intergenic lncRNAs (lincRNAs) (Fig. 1). (2) According to the mode of action based on genes, they can be divided into cis-acting, trans-acting, and so on. (3) According to the functional mechanisms, they can be divided into the transcription level, post-transcription level, translation level, and so on (Fig. 2). (4) According to the mechanism of searching for target genes, they can be divided into the signal mode, molecular decoy mode, guidance mode, molecular framework mode, and so on.

Biological function of lncRNAs

With an in-depth study,^{25–31} it was found that lncRNAs can participate in not only the normal physiological activities of cells but also in the pathophysiological activity of various diseases, particularly tumors, through the modification of chromosomes, splicing, transcriptional activation, mRNA degradation, translation regulation, and so on. The molecular mechanisms of action of lncRNAs can be explained as follows: (1) acting on the promoter regions of the encoding gene, which can interfere with the transcriptional process; (2) forming a double strand with a transcript that can encode the gene by base complementation and then interfere with the cleavage of the mRNA or generate endogenous interfering RNA by using the Dicer enzyme; (3) influencing gene expression by interfering with the activity of RNA polymerase II, mediating chromatin remodeling; (4) playing a biological function by binding to specific proteins; (5) altering the cytoplasmic localization of proteins; and (6) playing a biological function as a structural component of protein or as a precursor molecule of small RNA.

Biological function of lncRNAs in carcinomas

In the initial stage of lncRNA research, some scholars suggested that there is a difference in the expression of lncRNAs between tumor tissues and adjacent normal tissues. An increasing number of studies^{32–65} have shown that lncRNAs may play an important biological role in the regulation of cancer development, as the biological function of lncRNAs in carcinomas is to promote cancer cell proliferation and invasion, suppress cancer cell proliferation and invasion, estimate the prognosis and efficacy, and act as potential biomarkers, as summarized in Table 1.

In short, according to the function of lncRNAs in tumors, lncRNAs can be divided into carcinogenic lncRNAs and anticancer lncRNAs. For example, the lncRNA DANCER can promote the proliferation and invasion of gastric cancer cells, but in the case of knockdown lncRNA DANCER, the migration and invasion of GC cells via the suppression of epithelial–mesenchymal transition (EMT) can be inhibited.⁶⁶ It has been reported that⁶⁷ the lncRNA NEAT1 has emerged as an important participant of the complex transcription network in cancer development. Recently, further studies have shown that⁶⁸ the lncRNA-mediated gene expression can also be at the post-transcriptional level, which includes gene splicing, mRNA stability, protein stability, and nuclear trafficking. Some studies have shown that lncRNAs can act as tumor-promoting factors sometimes but at other times, they can act as tumor suppressors, such as H19. It has been reported that⁶⁹ the level of lncRNA H19 is highly correlated with a higher tumor burden of papillary thyroid carcinoma, which also contributes to the EMT process and then promotes the migration and invasion of papillary thyroid carcinoma cells. However, in the another research,⁷⁰ even in the case of the same type of tumor (papillary thyroid carcinoma), the lncRNA H19 has an opposite effect that can inhibit cell migration and invasion in the thyroid carcinoma cells. Professor Wu⁷¹ reported that the H19-mTOR-4E- BP1 axis can regulate pituitary tumor growth, which may be a potential therapeutic target and be more effective than cabergoline treatment in the suppression of human pituitary carcinomas. The lncRNA H19 can also be used as an important biomarker for prognosis and efficacy evaluation.^{72,73} To date, more than 8000 lncRNAs have been discovered in cancer cells. Their increased number and high expression specificity make these molecules a valuable source of biomarkers and potential therapeutic targets.⁷⁴ As the research progresses, the regulatory network in the tumor by lncRNAs will become more complicated.

Biological function of lncRNAs in HCC

HCC is one of the most common malignancies in the world, and its mortality rate ranks the third among cancer-related deaths.⁷⁵ However, thus far, no effective systematic research has been conducted for the early diagnosis and treatment of HCC. Moreover, the discovery and diagnosis of HCC is often in the late stage of the disease, which may cause a very poor prognosis. The American Association for the Study of Liver Diseases (AASLD) recommends that high-risk patients be regularly screened and monitored.⁷⁶ The past treatments for this disease include liver transplantation, surgical liver resection, chemotherapy, radiotherapy, vascular embolization, and ablation.⁷⁷ The early screening and diagnosis of HCC, particularly with the rapid development of the liquid biopsy technology, will help the prognosis of patients with HCC. Therefore, some researchers have paid more attention to the molecular targets of the HCC treatment and hope to find specific molecular markers for the diagnosis and treatment of HCC. With the deepening of research, many studies have shown that some

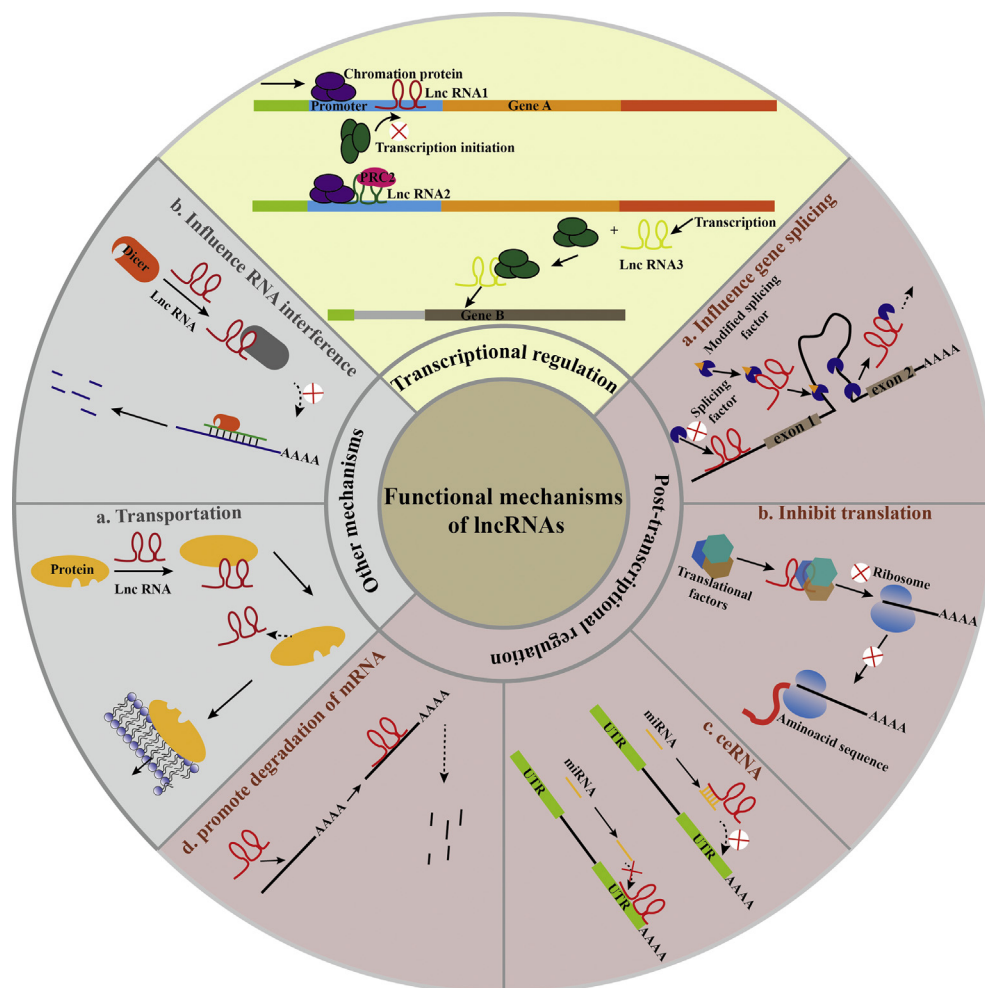


Figure 2 Types of functional mechanisms of lncRNAs.

lncRNAs are directly related to the occurrence and metastasis of HCC.^{78–84} HULC (lncRNA highly upregulated in the cases of liver cancer), the first discovered lncRNA particularly upregulated in HCC, was found to be more highly expressed in HCC tissues than in normal liver tissues, and the expression level of HULC correlated with the prognosis of patients.^{85–87} lncRNAs have complex regulatory effects on the development of HCC; as early as 2010, some researchers showed that CREB could upregulate HULC with miR-372, which was regarded as a ceRNA.⁸⁸ A number of studies have shown that lncRNAs can play an important biological role in the regulation of HCC development; the biological function of lncRNAs in HCC is to promote cancer cell proliferation and invasion, suppress cancer cell proliferation and invasion, estimate prognosis and efficacy, and act as potential biomarkers, as summarized in Table 2.

The lncRNA HOTAIR (which stands for HOX transcript antisense intergenic RNA)⁸⁹ is considered to be a carcinogenic lncRNA involved in the regulation of most human cancers; it is a 2158-nt lncRNA discovered by Howard Chang's group (lncRNA Database, <http://www.lncrnadb.org/>) and is located on human chromosome 12q13.13. Some studies have reported that as a human tumorigenesis regulatory gene, HOTAIR is dysregulated in HCC frequently. Ying⁹⁰ reported that after the inhibition of HOTAIR, there are, in all, 673 transcripts and 293 proteins that can be dysregulated in HCC and promote HCC cell proliferation by regulating the opioid growth factor receptor (OGFr). In the case of knock-down HOTAIR, the HCC cell proliferation can be inhibited dramatically and tumorigenicity can be suppressed by upregulating the miR-122 expression.⁹¹ The expression of HOTAIR⁹² is strongly associated with the prognosis in HCC, which is an indicator of poor prognosis, may be a therapeutic

Table 1 Biological function of lncRNAs in carcinomas.

Biological Function	lncRNA	Target Gene/Pathway	Cancer Type	Reference
Promote proliferation, migration, and invasion	LINC00052	miR-608/EGFR	Head and neck cancer	32
	AC009022.1	miR-497-5p	Colorectal cancer	33
	DLGAP1-AS1	miR-486-5p	Hepatocellular cancer	34
	GHSROS	—	Breast cancer	35
	LINC00337	TIMP2/DNMT1	Non-small-cell lung cancer	36
	AK001058	ADAMTS12	Colorectal cancer	37
	FOXD2-AS1	miR-185-5p	Thyroid cancer	38
	LINC00460	—	Colorectal cancer	39
	LINC00908	Sox-4	Hepatocellular cancer	40
	PVT1	Smad3/miR-140-5p	Cervical cancer	41
	RAIN	RUNX2	Breast and thyroid cancer	42
	LINC00673	miR-515-5p/MARK4/Hippo	Breast cancer	43
	TTN-AS1	KLF15	Colorectal cancer	44
	SNHG4	ZIC5	Prostate cancer	45
	SOX2-OT	miR-369-3p/CFL2	Prostate cancer	46
	LINC01559	YAP	Pancreatic cancer	47
	VCAN-AS1	p53	Gastric cancer	48
	OSER1-AS1	miR-372-3p/Rab23	Hepatocellular cancer	49
	ZEB1-AS1	ZEB1	Esophageal cancer	50
	NBAT-1	PKM2	Esophageal cancer	51
	ENST00000489676	MiR-922	Thyroid cancer	52
	CASC2c	ERK1/2, Wnt/ β -catenin	Hepatocellular cancer	53
	GAS5	YAP	Colorectal cancer	54
Suppress proliferation and invasion	ADAMTS9-AS2	CDH3	Esophageal cancer	55
	TCONS_00020456	Smad2/PKC α	Glioblastoma	56
	UCA1, H19	5-fluorouracil	Rectal cancer	57
	ADAMTS9-AS2	FUS/MDM2	Glioblastoma	58
	INCAC112721.1, AL356479.1, LINC00466	hsa-miR-204	Breast cancer	59
	GAS5, HOTAIR, H19, MALAT	—	Colorectal cancer	60
	HOXA-AS3	HOXA3	Non-small-cell lung cancer	61
Estimate prognosis and efficacy	MALAT1	—	Breast cancer	62
	HOTAIR	—	Breast cancer	63
	PURPL, NONHSAT062994	—	Gastric cancer	47
	SNHG11	—	Colorectal cancer	64
	SNHG12	—	Pan-cancer	65
Act as potential biomarkers				

Note: References 32–48 discuss the promotion of cancer cell proliferation and invasion, references 49–56 discuss the suppression of cancer cell proliferation and invasion, references 57–61 discuss the estimation of the prognosis, and references 62–66 discuss efficacy or potential biomarkers.

Table 2 Biological function of lncRNAs in HCC.

Biological Function	lncRNA	Target Gene/Pathway	Reference(s)
Promote proliferation, migration, and invasion	HOTAIR	OGFr, miR-122, SETD2	90–94
	IHS	ERK- and AKT/GSK-3 β	96
	HOXD-AS1	SOX4	97
	PDPK2P	PDK1/AKT/Caspase 3	98
	ATB	autophagy-related protein 5	99
	Ftx	PPAR γ	100
	lncCAMTA1	CAMTA1	101
	SNHG15	miR-490-3p/histone deacetylase 2 axis	102
	RNA LINC00908	Sox-4	103
	MCM3AP-AS1	miR-194-5p/FOXAI axis	104
Suppress proliferation and invasion	GAS8-AS1	GAS8	105
	SVUGP2	MMP2 and 9	106
	uc.134	LATS1	107
	TCONS_00006195	ENO1	108
	EPB41L4A-AS2	miR-301a-5p/FOXL1	109
	FENDRR	miR-423-5p	110
	SchLAH	—	111
	GAS5	miR-182/ANGPTL1	112
	MIR31HG	microRNA-575	113
	MIR22HG	miR-10a-5p/NCOR2	114
Estimate prognosis and efficacy	HOTAIR	—	92
	MIR22HG, CTC-297N7.9, CTD-2139B15.2, RP11-589N15.2, RP11-343N15.5, and RP11-479G22.8	—	115
	MALAT1, HOTAIR, MDIG	Caspase-8/LSD1/H3K9me3/	116
	miR503HG	HNRNPA2B1/NF- κ B	117
	RP11-466I1.1	—	118
Act as potential biomarkers	PVT1, uc002mbe.2	—	119
	UCA1	—	120
	LRB1	—	121
	RP11-486O12.2, RP11-863K10.7, LINC01093 and RP11-273G15.2	—	122
	ELMO1-AS1	—	123

Note: References 91–105 discuss the promotion of cancer cell proliferation and invasion, References 106–115 discuss the suppression of cancer cell proliferation and invasion, References 93 and 116–119 discuss the estimation of prognosis, and References 120–124 discuss the efficacy or potential biomarkers.

target in HCC, and can promote the HCC cell proliferation by the suppressed RNA binding motif protein 38.⁹³ HOTAIR can promote the malignant growth of HCC stem cells by the downregulation of SETD2.⁹⁴ HOTAIR can also promote the release of exosomes by inducing MVB transport to the plasma membrane, which is regulated by RAB35 and SNAP23.⁹⁵

A number of lncRNAs^{96–104} can promote the progress (such as proliferation, migration, and invasion) of HCC. The lncRNAs HIS, HOXD-AS1, ATB, PDPK2P, ATB, Ftx, lncCAMTA1, SNHG15, RNA LINC00908, and MCM3AP-AS1 can accelerate the proliferation, migration, and invasion of hepatocellular carcinoma. However, some researchers have shown that the lncRNAs^{105–114} can also inhibit the development of HCC. The lncRNA GAS8-AS1 can activate GAS8 epigenetically and then inhibit the malignant transformation of hepatocytes. The progression (such as

proliferation, migration, and invasion) of hepatocellular carcinoma can be suppressed by a mass of lncRNAs, such as lncRNA-SVUGP2, GAS8-AS1, SVUGP2, uc.134, TCONS_00006195, EPB41L4A-AS2, FENDRR, SchLAH, GAS5, MIR31HG, and MIR22HG.

In contrast, the lncRNAs MIR22HG, CTC-297N7.9, CTD-2139B1 5.2, RP11-589N15.2, RP11-343N15.5, RP11-479 G22.8, MALAT1, HOTAIR, MDIG, miR503HG, RP11-466I1.1 PVT1, uc002mbe.2, UCA1, LRB1, RP11-486O12.2, RP11-863K10.7, LINC01093, RP11-273G15.2, and ELMO1-AS1 can estimate the prognosis and efficacy or maybe act as potential biomarkers for the diagnosis or treatment in HCC.^{92,115–123} In the meantime, some researchers^{106,124,125} have also reported that the HCC with different viral causes was regulated by different lncRNAs, and the lncRNAs can regulate the progression (such as proliferation, migration, and

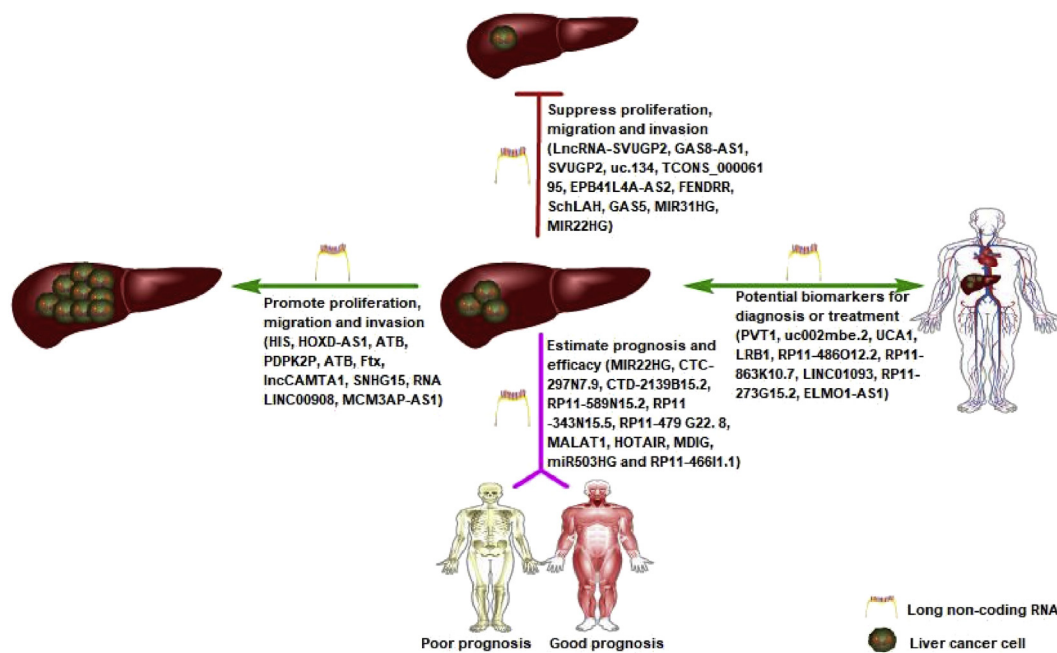


Figure 3 Types of lncRNAs in HCC.

invasion) of hepatocellular carcinoma by regulating various pathways.

Conclusion and perspective

As is known to all, HCC is a type of malignant tumor with high morbidity and mortality in the world. However, there are still some bottlenecks in the early screening and post-operative efficacy of HCC, and the high metastaticity and the lack of the specific molecular-targeted drugs lead to the poor prognosis of liver cancer. At present, the research on lncRNA in HCC is mostly at the level of cell or mouse experiments, the clinical research is relatively little, and the study on the role of lncRNAs in the regulation of gene expression is just the tip of the iceberg, which may seriously restrict the application of lncRNA in HCC. Although some progress and achievements have been made in the research on lncRNAs in HCC, and in fact, the biological function of lncRNAs in HCC is extremely complicated, this article is only a review of the recent research on lncRNAs in HCC; further research on the role of lncRNAs in the regulation of the development of HCC should be conducted more extensively.

This review provides an overall view of lncRNAs in HCC. The lncRNAs have been divided into four categories according to the regulatory mechanisms in HCC (Fig. 3). The biological functions of lncRNAs in HCC are as follows: The first aspect is to promote the proliferation, migration, and invasion of HCC; the second aspect is to suppress the proliferation and invasion of HCC; the third aspect is to estimate the prognosis and efficacy of HCC; the fourth aspect is to act as potential biomarkers that can be used for the diagnosis and treatment of HCC. In fact, the biological function of lncRNAs in HCC is intertwined; most of the

lncRNAs that have been clearly studied belong to the tumor gene activation category, which mainly promotes the occurrence and development of HCC by activating the Wnt, STAT-3, EMT, and other signaling pathways, but these lncRNAs may have the potential to act as tumor markers for clinical diagnosis or treatment.

Although many studies^{126–128} have confirmed that the biological function of lncRNA can be mutually regulated with miRNA, and the regulatory axis of lncRNA-miRNA-mRNA has been proved to exist in other tumors, no complete regulatory network has been established in HCC. In order to fully grasp the regulatory role of lncRNA in the development of HCC, it is important to explore the regulatory network of miRNA-lncRNA-mRNA in HCC and the other undiscovered signaling pathways. The multidimensional regulatory mechanisms of lncRNA in HCC should be further explored and analyzed, and the comprehensive and detailed lncRNA-related databases should be established as soon as possible. There is increasing evidence that an abnormal expression of lncRNAs is associated with diseases, particularly tumors. We need to find specific lncRNAs that are closely related to HCC and study their specific mechanism in depth to carry out more related work and find new directions for HCC diagnosis and treatment. The multidimensional methods of molecular biology, bioinformatics, and other fields should be combined to study the lncRNAs in HCC in order to establish a sophisticated regulatory network successfully. Therefore, this review is expected to be used to provide recommendations and directions for future lncRNA research for HCC.

Conflict of Interests

The authors declare no conflict of interests.

Acknowledgements

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