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The Roles and Diagnostic Potential of Long Non-Coding RNAs in Some Cancers: A Review

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ABSTRACT

Since their discovery, non-coding RNAs have been known as key regulators of gene expression. Gaining a better understanding about their biogenesis and function may provide valuable knowledge about the heterogeneity of malignancies and contribute to identification of diagnostic, prognostic and therapeutic targets. Long non-coding RNAs (lncRNAs) are a group of RNAs composed of >200 nucleotides that play important regulatory roles in gene transcription, splicing and epigenetics as well as in biological processes involved in cell cycle, development and pluripotency. Generally, the expression levels of lncRNAs are lower than protein-coding genes, but they exhibit more tissue-specific expression patterns. Recent studies have suggested involvement of cancer-specific lncRNAs including HOTAIR, ANRIL, FENDRR, GAS5 and H19 in tumorigenesis, tumor cell proliferation, invasion, migration, apoptosis and angiogenesis. Expression of lncRNAs is tissue-specific and may vary depending on the stage of tumor progression. In this review, we summarize current knowledge on the roles of lncRNAs in some cancers and their potential as diagnostic and prognostic targets.

Keywords: Cancer; lncRNA, Biomarkers

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INTRODUCTION

Cancer is a heterogeneous disease with multiple factors that result in development of malignant tumors. According to the International Agency for Research on Cancer, the global cancer burden is estimated to have risen to 18.1 million new cases and 9.6 million cancer deaths in 2018. The most prevalent types of cancer in box genders combined are lung cancer (11.6% of total cases), female breast cancer (11.6%), prostate cancer (7.1%) and colorectal cancer (6.1%) (1). The discovery of a universal genetic code for protein-coding genes generated countless breakthroughs in understanding the relationship between cancer cells, tumor microenvironments and defense mechanisms involved in cancer development, immune evasion and therapeutic susceptibility (2). Recent advent in the field of RNA biology has shown that noncoding RNAs (ncRNAs) are indeed crucial molecules with diverse roles in cancers. Long non-coding RNAs (lncRNAs) are a group of ncRNAs composed of >200 nucleotides that play important gene regulatory roles including gene transcription, splicing and epigenetics as well as biological processes involved in cell cycle, development and pluripotency (3). Similar to mRNAs, lncRNAs are transcribed by RNA polymerase II, undergo splicing, polyadenylation and 5′-capping. However, lncRNA transcripts are relatively shorter, contain fewer exons and are mainly localized in the nucleus. Generally, the expression levels of lncRNAs are lower than protein-coding genes, but they exhibit more tissue-specific expression patterns (4). Recent studies have suggested involvement of lncRNAs in tumorigenesis, tumor cells proliferation, invasion, migration, apoptosis and angiogenesis. Given the resistance of circulating lncRNAs against RNases, these lncRNAs could serve as potential biomarkers or therapeutic targets for cancer (5). Recently, several cancer-specific lncRNAs such as HOTAIR, FENDRR, GAS5 and H19 have been identified and also characterized as important role players in carcinogenesis events, such as proliferation, apoptosis and metastasis (6). Expression of lncRNAs is tissue-specific and may vary depending on the stage of tumor progression. Given the promising potential of lncRNAs as biomarkers for diagnosis and prognosis of cancer, in this review we summarize current knowledge on the roles of lncRNAs in some cancers.

Role of lncRNAs in prostate cancer

Prostate cancer (PCa) is the second most common type of cancer and the fifth leading cause of death in men (7). Prostate-specific lncRNA testing has been recently proposed for determining the need for biopsies in PCa. In this regard, PCa–associated transcript 29 (PCAT29) is reported to be suppressed by dihydrotestosterone and upregulated upon castration therapy in a PCa xenograft model. It has been shown that proliferation and migration of PCa cells significantly increase after PCAT29 knockdown, while PCAT29 overexpression controls growth and metastases of prostate tumors. In addition, there was a positive correlation between PCAT29 downexpression in PCa patients and poor prognostic outcomes (8). A recent study reported that transcription of a novel lncRNA called nuclear enriched abundant transcript 1 (NEAT1) is regulated by estrogen receptor alpha (ERα). NEAT1 itself increases expression of PCa genes by changing the epigenetic landscape at target gene promoters. Resistance of both ERα and NEAT1 signaling to inhibitors of androgen receptor (AR) and the absence of AR or ERβ, may stipulate the functional role of the ERα-NEAT1 axis in PCa progression. Although previously proposed as a novel biomarker of disease progression, considering the essential role of NEAT1 in ERα signaling pathway, NEAT1 might pose as a novel therapeutic target for the treatment of PCa (9).

The lncRNA PCa-associated non-coding RNA 1 (PRNCR1), also referred to as PCAT8 and CARLo3, is mapped to 8q24.21 (10). Upregulation of PRNCR1 is associated with PCa development via modulation of AR activity. The impact of

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PRNCR1 polymorphisms on the risk of developing different types of cancers, such as prostate (11), gastric (12) and colorectal cancer (13) has been investigated. A recent study on the impact of PRNCR1 variants on risk of PCa showed that the PRNCR1 rs13252298, rs1456315 and rs7841060 polymorphisms could be used as a biomarker for PCa development (10). Understanding the mechanisms involved in AR activation in the milieu of low androgen may be crucial for favorable treatment of castration-resistant PCa (CRPC). Zhang et al. reported HOTAIR as an androgen-repressed lncRNA, which is significantly overexpressed after androgen deprivation therapies as well as in CRPC. They also demonstrated that overexpression and knockdown of this lncRNA increases and decreases PCa cell growth and invasion, respectively. Overall, such findings clearly elucidate the role of lncRNAs as potential therapeutic targets and drivers of androgen-independent AR activity and CRPC progression (14).

Another important gene for PCa initiation and progression is PCa gene expression marker 1 (PCGEM1) located on chromosome 2q32 (15). Androgen regulates expression of PCGEM1 that suggests a possible role in PCa. Tumor-associated overexpression of PCGEM1 expression has been observed in 84% of patients with PCa (16). Petrovics et al. claim that PCGEM1 overexpression may increase prostate cell proliferation via Rb phosphorylation (17).

Role of lncRNAs in gastric cancer

Despite being among the most common type of cancers and cause of cancer deaths worldwide, gastric cancer is curable if detected early. Majority of patients with GC have poor prognosis because of late diagnosis. Several lncRNAs including HOTAIR, ANRIL, FENDRR, PVT1, HOXA11-AS, GAPLINC and GClnc1 have been well characterized in GC as well as in other types of cancer (18). The *FENDRR* gene located at chr3q13.31 consists of four exons. This lncRNA binds to both polycomb repressive complex 2 (PRC2) and Trithorax group/MLL protein complexes (TrxG/MLL), which are key players in the maintenance of chromatin structure and gene activity. Decreased expression of *FENDRR* has been observed in GC tissues and cell lines. In GC patients, FENDRR underexpresision was correlated with both clinical and pathological characteristics, poor prognosis and lymphatic metastasis. It has been suggested that histone deacetylation could play a role in the downregulation of this gene in GC cells. On the other hand, overexpression of this gene abates GC cell invasion and migration in vitro (19).

The PVT1 is another important lncRNA that acts as an epigenetic regulator with vital roles in tumor development. However, the mechanisms underlying the PVT1 oncogenic functions remain unknown. In a recent study found an association between PVT1 and FOXM1, a key regulator of cancer cell proliferation and metastasis. In GC tissues, lncRNA PVT1 was significantly upregulated, which is accompanied with increased GC cell proliferation and invasion, which ultimately leads to poor prognosis. From a clinical point of view, PVT1 expression can be a suitable biomarker for GC prognosis, and the positive feedback loop of PVT1-FOXM1 could be a therapeutic target in pharmacologic strategies (20). Ding et al. reported that PVT1 expression might be associated with lymph node invasion in GC (21).

HOXA11-AS is another GC–associated lncRNA that could act as key regulator of GC development and progression. Studies demonstrate that alteration of HOXA11-AS can affect cell proliferation, migration, invasion and apoptosis. Moreover, silencing of this lncRNA changed cell growth and cell–cell adhesion pathways, suggesting new therapeutic directions in GC (22).

GAPLINC is another lncRNA that has be identified in human GC specimens using microarray and in situ hybridization (ISH) analyses. This 924-bp lncRNA is highly expressed in GC tissues. Altered expression of GAPLINC changes cell migration pathways and CD44 mRNA abundance. Nevertheless, suppression of CD44

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expression could neutralize this effect on cell migration and proliferation. ISH analysis of GAPLINC in tissue samples has revealed that overexpression of this lncRNA in GC patients may be linked with poor survival (23).

Sun et al. reported a new lncRNA named GClnc1 that might have a key role in treatment of GC. According to the mentioned study, GClnc1 overexpression is correlated with tumorigenesis, tumor size, metastasis and poor prognosis in GC. Interaction of this lncRNA with WDR5 (a main component of histone methyltransferase complex and KAT2A histone acetyltransferase) consequently changes GC cell biology. Thus, GClnc1 can be regarded as a mechanistic, functional and clinical oncogene for GC (24). Taken together, targeting lncRNAs and their pathway may be beneficial for treating patients with GC.

Role of lncRNAs in colorectal cancer

Colorectal cancer (CRC) is the third most common cancer worldwide, but the molecular mechanisms underlying CRC are to be understood (25). Similar to other cancers, discovering new diagnostic biomarkers and effective therapies is an important aspect of CRC management. Growth arrest specific 5 (GAS5) lncRNA, is overexpressed in numerous types of cancer. GAS5 mRNA expression has been shown to be notably down-regulated in human CRC tissues and cell lines. Downregulation of this lncRNA was correlated with tumor progression and poor survival. Interestingly, GAS5 overexpression can inhibit cell proliferation and survival via induction of G0/G1 cell cycle arrest and apoptosis. However, knockdown of this lncRNA produces opposite effects (26). Moreover, a recent case-control study, the potential role of lncRNA GAS5 and its genetic variation rs145204276 was evaluated in a Chinese CRC population. Results of this study showed that the allele rs145204276 is significantly associated with risk of developing CRC and lymph node metastasis following CRC (27). Altogether, the results of these studies indicate the potential novelty of this lncRNA as a prognostic and diagnostic marker of CRC.

Recently, a study on specimens from CRC patients showed a correlation between lncRNA DANCR upregulation and advanced tumor progression and poor prognosis. This overexpression in CRC tumor tissues was also linked with TNM stage, histologic grade, and lymph node metastasis. Hence, investigating the expression patterns of lncRNA DANCR might be utilized as a novel approach for determining CRC prognosis (28).

The role of lncRNAs in malignancies can be further investigated using small interfering RNAs (siRNAs). In this regard, a recent study exploited a relationship between FOXP4-AS1 lncRNA and colorectal cancer. The study demonstrated that the FOXP4-AS1-specific siRNA transfection can inhibit FOXP4-AS1 expression in CRC tissue samples and CRC cell lines (29). The results depicted upregulation of FOXP4-AS1 in CRC tissues and cell lines, which was correlated with advanced pathological stages and tumor size. In addition, FOXP4-AS1 knockdown had inhibitory effects on cells, while FOXP4-AS1 silencing could inhibit tumor growth *in vivo*.

A large number of lncRNAs can function as competitive endogenous RNA (ceRNA) that can block binding of miRNAs to their proper regulatory targets (30). As a ceRNA, CASC2 lncRNA have a crucial impact on CRC pathogenesis, which can be investigated as a promising diagnostic and therapeutic target for cancer. In fact, studies have shown that CASC2 could act as a ceRNA for miR-18a and contribute to PIAS3 overexpression. This results in de-repression of genes downstream of STAT3, thus inhibiting growth of CRC cells and tumors by extending the G_0/G_1-S phase transition. There also may be a significant correlation between CASC2 downexpression in CRC tissues and cells and advanced tumor-node-metastasis (31).

It has been demonstrated that the Myc oncogene and enhancers within the human 8q24 gene form tissue-specific long-range chromatin loops, but the mechanism of chromatin looping regulation at the Myc locus

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is not clear. In this line, a study reported that lncRNA CCAT1-L is transcribed specifically in human CRC from a locus 515 kb upstream of Myc. CCAT1-L is involved in Myc transcriptional regulation and induces long-range chromatin looping. Moreover, the CCAT1-L locus is located within a strong super-enhancer and is spatially close to Myc. CCAT1-L knockdown can decrease long-range interactions between the Myc promoter and its enhancers. Importantly, this LncRNA interacts with CCCTC-binding factor and modify chromatin conformation at these loop regions. Altogether, these findings signify a novel relationship between lncRNA-modulated chromatin organization and Myc expression in a specific human cancer (32).

Role of lncRNAs in breast cancer

Breast cancer (BC) is the most common type of cancer in women. Uncontrolled proliferation and metastasis are the primary causes of death in BC patients**.** Numerous studies have revealed the key regulatory role of lncRNAs in BC progression and metastasis. For instance, Alipoor et al. detected expression of an lncRNA called myocardial infarction associated transcript (MIAT) in various cancer cells and breast tumor tissues. In addition, they revealed MIAT overexpression in high-grade and ER-, progesterone receptor (PR)- and human epidermal growth factor receptor 2 (Her2)-positive tumor tissues. BC cell proliferation via G1 cell cycle arrest following MIAT knockdown and reduced migration of BC cells and induction of apoptosis following MIAT down-regulation suggest that MIAT could be a novel tumor marker candidate for diagnosis and treatment of BC (33).

Estrogen is another critical factor for BC development and progression. In this regard, the screening of 83 disease-related lncRNAs demonstrated overexpression of H19 lncRNA in ER-positive MCF-7 BC cells compared to ER-negative MDA-MB-231 cells. In this study, Sun et al. also revealed that H19 lncRNA knockdown negatively affects cell survival and estrogen-induced cell proliferation, whilst upregulation of this lncRNA induced cell growth. Moreover, H19 is significantly more abundant in ER-positive human BC tissues than in ER-negative counterparts. These findings suggest the potential of H19 as novel biomarker for BC diagnosis and progression (34).

We have previously discussed that lncRNA NEAT1 could be used a potential biomarker in PCa. However, a recent study revealed that this lncRNA could also be involved in in BC progression. Zhang et al. detected NEAT1 overexpression in tissue samples from 40 BC patients. This expression was also intensely correlated with the tumor size, lymph node metastasis and prognosis of BC patients. Interestingly, proliferation and metastasis of BC cells could be repressed through NEAT1 suppression (35).

Urothelial carcinoma-associated 1 (UCA1) lncRNA is a BC-related oncogene that can directly interact with miR-143, a tumor suppressor in BC, and regulate proliferation and apoptosis of cancer cells. In this line, Tuo et al. detected significant UC1 upregulation and significant miR-143 downregulation in BC tumor tissues compared to adjacent normal tissues. They also found that the miRNA recognition sites of UCA1 could directly interact with miR-143. Given that UCA1-modulated miR-143 suppression could regulate BC cell growth and apoptosis, the UCA1-miR-143 axis may be a primary piece of the oncogenic role of UCA1 in BC (36).

Triple-negative BC (TNBC) is a complex BC subtype characterized by the absence of ER, PR and Her2 (37). The involvement of ANRIL lncRNA in tumorigenesis has been demonstrated in several cancers and is thought to be exerted through regulation of its adjacent tumor suppressors CDKN2A/B via epigenetic mechanisms (38). In an in-depth study of the impact of ANRIL expression and regulation on TNBC tumorigenesis, Xu et al. revealed ANRIL upregulation in TNBC tumor tissues and cell lines, which was closely linked to poor prognosis (37). In addition, ANRIL knockdown was able to significantly suppress TNBC cells proliferation, promote apoptosis and block tumor growth. The authors believed that ANRIL overexpression

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modulates TNBC tumorigenesis by acting as molecular 'sponge' for miR-199a. These findings shed light of the potential of this lncRNA as a therapeutic target for TNBC (37).

Dysregulation of the lncRNA CCAT2 has been demonstrated in different types of cancer. However, a study by Cai et al. proposed the possible involvement of this lncRNA in BC tumor growth. In this study, high levels of CCAT2 were observed in BC tissues and BC cell lines. Furthermore, CCAT2 silencing could decrease in vitro cell proliferation and in vivo tumor formation. Altogether, the findings revealed that the abnormal expression of CCAT2 could affect BC tumor growth via Wnt signaling pathway (39), introduing this lncRNA as another potential therapeutic target for this cancer.

CONCLUSION

In the last decade, the scientific community has beheld a marked development of knowledge about lncRNAs and their crucial involvement in disease development and in various biological processes. In this review, we presented the aberrant overexpression of a number of lncRNAs, including HOTAIR, PVT1, GAS5 and H19 in some cancers (Table 1). It is well understood that lncRNAs can act as key regulators of gene expression, which undoubtedly can be beneficial for uncover the underlying molecular mechanisms involved in development of cancer, thereby providing novel strategies for cancer therapy. In this regard, the functional analysis of cancer-related lncRNAs seems more crucial today than ever before.

Table 1. List of some cancer-related lncRNAs

Cancer Type	lncRNA	Mechanism	Alteration	Reference
Prostate cancer	PCAT29	Cell proliferation	Downregulation	(8)
	NEAT1	Transcriptional and Post transcriptional regulation	Upregulatation	(9)
	PRNCR1	Activates AR regulated genes	Upregulatation	(10)
	HOTAIR	Mediate AR activation	Upregulatation	(14)
	PCGEM1	Activates AR regulated genes	Upregulatation	(16)
Gastric cancer	FENDRR	Histone modification	Upregulatation	(19)
	PVT1	Interacts with p53	Upregulatation	(40)
	HOX11-AS	Cell proliferation and cell–cell adhesion pathways	Upregulatation	(22)
	GAPLINS	Cell proliferation	Upregulatation	(23)
	GClnc1	Histone modification	Upregulatation	(24)
Colorectal cancer	GAS5	G0/G1 cell cycle arrest and apoptosis	Downregulation	(26)
	DANCR	Cell proliferation	Upregulatation	(28)
	FOXP4-AS1	G0/G1 cell cycle arrest	Upregulatation	(29)
	CASC2	G0/G1-S phase transition	Downregulation	(31)
	CCAT1-L	Regulates Myc by long range chromatin loops	Upregulatation	(32)

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Breast cancer	MIAT	Regulates cell cycle	Upregulatation	(33)
	H19	Imprinting	Upregulatation	(41)
	UCA1	Regulates cell cycle through CREB	Upregulatation	(42)
	ANRIL	Regulates CDKN2A/2B locus by recruiting PRC1/PRC2	Upregulatation	(37)
	CCAT2	Involved in Microsatellite stability	Upregulatation	(43)

AR: androgen receptor, CREB: cAMP response element-binding protein, PRC: polycomb repressive complex, CDKN: cyclin dependent kinase inhibitor

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