

# Role of lncRNAs in GI Cancer

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## Abstract

lncRNAs forms a part of the non coding part of human genome. This term denotes specific non coding RNAs with nucleotide length more than 200. They have been shown to affect various physiological and pathological processes within the human body. Of interest is their role in malignant transformation in several cancers. In this review, the role of lncRNAs in GI cancers namely pancreatic cancer, gastric cancer, hepatocellular cancer and colorectal cancer have been explained in brief. These lncRNAs have shown to be useful as a marker for detection and prognosis of various malignancies. They also have shown to have therapeutic potential. Various relevant lncRNAs in each section has also been mentioned.

## Keywords

lncRNA, Cancer, Pancreatic, Gastric, Hepatocellular, Colorectal

## 1. Introduction

The human genome continues to baffle both scientists and doctors alike. It has been known for a long time that out of the total genome of 3000 Mb only 1% codes for all the proteins [1]. The rest which was earlier thought to be junk DNA is showing to have many previously unknown functions. One among these is the long non coding RNA.

The genome code from DNA is transcribed into RNA in its entirety, but only part of this RNA is translated into proteins. The rest constitutes what is called as non coding RNAs. These include ribosomal RNAs, ribozymes, transfer RNAs, small nuclear RNAs, small nucleolar RNAs and telomere associated RNAs [2] [3]. Non coding RNAs with length more than 200 nt have been termed as long non coding RNAs. Recent studies using microarray technologies have shown that lncRNAs play an important role in several aspects of malignancies. In this

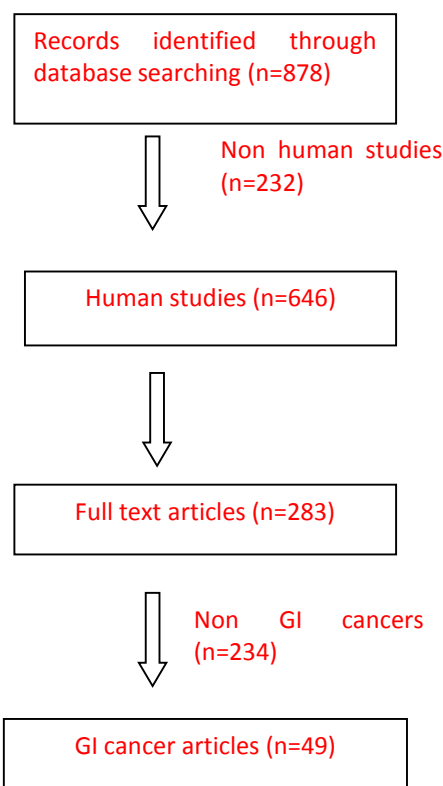
review, we will be looking at the specific actions of lncRNAs and its role in GI cancers, namely pancreatic cancer, gastric cancer, hepatocellular cancer and colorectal cancer.

## 2. Materials and Methods

A literature search was done on PubMed database to check for review article and clinical trials relating to “lncRNA” and “cancer” in the last 5 years. Out of the total 878 articles, non human studies were excluded. The search was further narrowed down to include only full text articles and finally 49 articles, related to GI cancers in this review, were selected. This included 20 articles of gastric cancer, 15 articles of colorectal cancer, 12 articles of pancreatic cancer and 2 articles of hepatocellular cancer (**Figure 1**).

## 3. Classification and Function of lncRNAs

There are many different criteria for classification of lncRNA. One of the earliest was based on genomic location by which it was classified into sense, antisense, intronic, intergenic and bidirectional [4]. Another classification is based on targeting mechanism—signal, decoy, guide and scaffold [5]. With the ongoing research and latest discoveries the list of lncRNAs is evergrowing. However, the classification system results in several overlapping and omissions [6] [7]. An ideal classification system is yet to happen.



**Figure 1.** Flowchart of study selection.

lncRNAs are known to affect diverse processes within the cell. An idea of function can be made based on its subcellular localization [8]. It can be subnuclear, cytoplasmic or both [9] [10]. lncRNA in nuclear position usually affect nuclear function via transcriptional or epigenetic modifications [11] [12] [13] and cytoplasmic lncRNA modulates mRNA stability and translation [13] [14]. The three known mechanisms by which lncRNA affect the cellular processes are epigenetic regulation, transcriptional regulation and post transcriptional regulation [15] [16] [17] [18] [19].

## 4. Role of lncRNAs in GI Cancers

### 4.1. Pancreatic Cancer

Pancreatic cancer (PC) is one of the leading causes for cancer related deaths in US and the 5 year survival rate is around 5% [20]. The key to management of PC is early diagnosis and hence it is imperative to have better diagnostic and prognostic markers. The currently used markers include CA19-9, CA242 and CEA [21]. These markers have the down side of not being specific to PC. lncRNA provides a unique opportunity in early diagnosis of PC without invasive testing. The potential lnc markers with relation to PC include HOTTIP-005, XLOC\_006390 and RP11-567G11.1 [22]. Detection of salivary levels of HOTAIR and PVT1 provide an attractive non invasive technique towards detection of PC [23]. Also few lncRNAs have shown to correlate with the clinical characteristics and prognosis of patients. For example increase in levels of HOTAIR has shown to be a negative prognostic factor [24]. Other similar prognostic markers include AFAP1-AS1, BC008363 and MALAT-1 [22] [25] [26].

lncRNAs are breaking new grounds in treatment of PC. Gemcitabine is one of the commonly used drug in therapy of PC. However, few patients have shown to have resistance against this therapy. Study of such patients using microarray have shown that few of lncRNAs are upregulated in these patients. Levels of HOTTIP, PVT1 and MALAT-1 were found to be raised [27] [28] [29]. Therapeutics based on regulating the levels of these lncRNAs could prove vital in making chemotherapy more effective. Another novel therapeutic technique is based on lncRNA H19. Currently in phase 1/2a, BC-819 has been used in patients of unresectable PC. BC-819 is a double stranded DNA plasmid and is injected under CT/USG guidance [30]. A list of lncRNAs found to important in pancreatic cancer is given in the table below (**Table 1**). Out of these lncRNAs HOTAIR and MALAT-1 has been found to be more important with relation to pancreatic cancer.

### 4.2. Gastric Cancer

Of all malignancies, gastric cancer is the fourth most common cancer worldwide. It is also the third most leading cause of deaths caused due to cancer [51]. As in all cancers, early detection has a good prognosis for gastric cancer also because the 5 year mortality for advanced cancer is only 30% - 50% [52]. Of late

**Table 1.** lncRNAs in pancreatic cancer.

LncRNA	Genomic location	Function	Potential targets	References
HOTAIR	12q13.13	Cancer cell invasion, proliferation, progression	PRC2, GDF15	[24] [31] [32] [33] [34]
HOTTIP	7q15.2	Cancer cell proliferation, inhibit apoptosis	AURKA, WDR5, HOXA10, HOXB2	[35] [36]
MALAT-1	11q13.1	Regulate cell cycle, growth, migration	Sox2, E-cadherin, N-cadherin, VEGF	[29] [37] [38]
ENST00000480739	12q13.3	Regulate invasion and migration	OS-9, HIF-1	[39]
AFAP1-AS1	4p16.1	Regulate cell proliferation, migration and invasion	-	[40] [41]
BC008363	5q21.2	-	-	[25]
H19	11q15.5	-	Let-7, HMGA2	[38] [42] [43] [44] [45] [46]
PVT1	8q24.21	-	-	[47] [48]
GAS5	1q25.1	Inhibit cell proliferation	CDK6	[49]
AF339813	13q32	Apoptosis, regulate cell cycle	NUF2, CDK1, CDK4/CDK6	[50]

numerous studies have shown that non coding RNAs play an important part in proliferation, migration and invasion in gastric cancer.

The role of lncRNAs in the pathogenesis of tumor is exactly not known. They are thought to influence the final gene product by several mechanisms like DNA methylation and chromatin modification [53]. LncRNA HOXA11-AS was found to be overexpressed in gastric cancer by doing a microarray profile. Also increased level of HOXA11-AS was associated with poor prognosis [54]. Another finding by Xu *et al.* was that low level of FENDRR was associated with poor prognosis and that elevated levels reduce cancer metastasis [55]. A list of lncRNAs found to important in gastric cancer is given in the table below (**Table 2**). Like many other malignancies, HOTAIR has shown to be important in gastric cancer also. Studies have shown that specific variation in HOTAIR is associated with increased risk for specific cancers. A study by Mulong *et al.* [56] showed that SNP rs4759314 was associated with significantly increased risk of gastric cancer. This could act as a potential bio marker to predict increased susceptibility to cancer.

### 4.3. Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the second leading cause mortality due to cancer in the world [72] and the incidence rate is on an increase. Delay in diagnosis is the major factor affecting mortality. It is imperative that newer biomarkers be found for early diagnosis and prognostic assessment of HCC. An exact understanding of pathogenesis of the tumor will help to evolve new

**Table 2.** lncRNAs in gastric cancer.

lncRNA	Function	Potential target	Reference
LINC00673	Proliferation, invasion and metastasis	KLF2, LATS2	[57]
SNHG5	Proliferation and migration	miR-32	[58]
LincRNAFEZF1-AS1	Proliferation, tumor growth and apoptosis	p21	[59]
PVT1	Proliferation and metastasis	FOXM1	[60]
lncRNA-GHET1	Proliferation	c-Myc	[61]
TINCR	Proliferation and apoptosis	KLF2	[62]
ANRIL	Proliferation	miR-99a/miR-449a	[63]
LincHOTAIR	Invasion and metastasis	miR34a	[64]
GAPLINC	Proliferation and invasion	miR211-3p	[65]
FENDRR	Migration and invasion	FN1	[55]
H19	Proliferation, migration and metastasis	ISM1	[38]
FERIL4	Proliferation and cell cycle	PTEN	[66] [67]
GAS5	Cell cycle	YBX1	[68]
nc886	Proliferation	FOS, MYC	[69]
HOXA11-AS	Proliferation, migration, invasion and apoptosis	EZH2, LSD1	[54]
GClnc1	Proliferation, migration and invasion	WDR5, KAT2A	[70]
BC032469	Proliferation	hTERT	[71]

treatment and diagnostic methods. lncRNAs has emerged as an interesting prospect for same. It has been found that epigenetic changes are more common in HCC than in other cancers [73]. Also lncRNA is one of the main culprits responsible for these epigenetic alterations.

Major HCC related lncRNAs are H19, HOTAIR, HULC and HOTTIP. They have been shown to be involved in various functions like proliferation, apoptosis, invasion and metastasis. H19 has shown to act like an oncogene and enhances the tumorigenic potential of HCC cells [74]. However, there are other studies showing that H19 acts as a tumor suppressor [45]. Without any doubt H19 has shown to be closely involved with HCC progression and also it has a linear correlation with AFP levels [75]. It can be used as a marker in addition to AFP levels.

Another marker shown promise is HOTAIR. It regulates silencing of HOX locus [31] and has been found to be overexpressed in HCC tissues [76] [77]. The specific expression of these lncRNAs allow for its detection in bodily fluid. An example is elevated levels of HULC in HCC patients as compared to control [78]. A list of lncRNAs found to be important in hepatocellular cancer is given in the table below (Table 3). Another lncRNA which has been found to be more

**Table 3.** lncRNAs in hepatocellular cancer.

LncRNA	Genomic location	Function	Potential target	References
H19	11p15.5	Proliferation and inhibit migration	IGF2, AFB1	[74] [80]
HOTAIR	12q13.13	Proliferation	PRC2, H3K27, P16, P14	[77]
HOTTIP	7p15.2	Proliferation	HOXA13	[35]
HULC	6p24.3	Proliferation	PPARA, ACSL1, YB-1	[81]
MALAT1	11q13.1	Invasion	Sp1/3, SRSF1	[82]
MVIH	10q22-q23	Proliferation, invasion and metastasis	miR-199a	[83]
MEG3	14q32.2	Inhibit cell growth	p53	[84]
Lnc-FTX	Xq13.2	Proliferation and cell cycle progression	miR-374a, miR-545	[85] [86]

specific for HCC is LINC01225. In a study conducted by Wang *et al.* [79], this specific lncRNA was found to be overexpressed in cases of HCC and was also confirmed by in vivo animal studies. LINC01225 acts by increasing level of epidermal growth factor receptor (EGFR) and its level can be measured in serum, thus making it an attractive future biomarker.

#### 4.4. Colorectal Cancer

Colorectal carcinoma (CRC) has been known to be affected by epigenetic and genetic mutations as classically described in the adenoma-carcinoma sequence by Fearon and Vogelstein [87]. The adenoma carcinoma sequence describes the orderly progression of normal epithelium to carcinoma. Each step is associated with specific mutations involving specific pathways. Each of these pathways has shown to have specific lncRNAs associated with it. The first lncRNA shown to have a role in CRC was endogenous H19 gene reported by Hibi *et al.* [88].

lncRNA may be the future biomarkers for screening, diagnosis, prognosis and also therapy for CRC [89]. One of the promising methods for susceptibility screening is to check for single nucleotide polymorphism (SNP) in lncRNA region. For example lncRNA CCAT2 maps to genome 8q24. A SNP rs6983267 is related to this genome and is linked to CRC oncogenesis, progression and prognosis [90].

Another role for lncRNA is in the early diagnosis of CRC. The modality of choice at present is periodic screening by colonoscopy which is both invasive and time consuming. A non invasive blood test could be helpful in easy screening of CRC. lncRNA (LIT1/KCNQ1OT1) was found to be increased in tumor samples as compared to normal tissue [91]. Other potential biomarkers include elevated level of hypomethylated CAHM in plasma and elevated CCAT1 in fecal and blood samples [92].

lncRNA is also being looked upon to be a prognostic marker. lincRNA-p21, ncRAN and Loc285194 has shown to be useful for this purpose [93] [94] [95].

**Table 4.** lncRNAs in colorectal cancer.

lncRNA	Location	Function	Reference
CCAL	3q29	Suppress AP-2 $\alpha$	[99]
CCAT1	8q24.21	-	[100] [101] [102]
CCAT1-L	8q24.21	Regulate chromatin interaction	[103]
CCAT2	8q24.21	Upregulate Wnt signalling	[90]
CRNDE	16q12.2	Respond to EGFR signalling	[104] [105]
E2F4 antisense	16q21-22	Reduces level of E2F4	[106]
HOTAIR	12q13.13	Correlate to PRC2 function	[34]
HULC	6p24.3	-	[107]
KCNQ1OT1/LIT1	11p15.5	Participates in mesenchymal transition	[91] [108]
lncRNA-ATB	14q11.2	Activated by TGF- $\beta$	[109]
MALAT1	11q13.1	Promotes mesenchymal transition	[37]
ncNRFR	1p13.2	Inhibit function of let-7	[110]
PCAT1	8q24.21	-	[111]
PVT1	8q24	Antiapoptotic activity	[112]
uc.73A	2q22.3	Decrease apoptosis	[113]
CUDR	19p13.12	-	[114]
BANCR	9q21	Suppress cell proliferation	[115]
CAHM	6q26	-	[92]
lncRNA-LET	15q24.1	Contributes to metastasis	[116]
LincRNA-p21	6p21.2	Transcriptional co activator of p53	[93]
Loc285194	3q13.31	Inhibit tumor cell growth	[95] [117]
MEG3	14q32.2	Induces accumulation of p53	[118] [119]
ncRAN	17q25.1	-	[94]
PTENP1	9p13.3	Regulates cellular level of PTEN	[120]
BA318C17.1	20p12.1	-	[121]
H19	11p15.5	Decrease RB expression, promotes mesenchymal transition	[42] [122] [123]
PRNCR1	8q24	CRC related SNP	[119]
XIST	Xq13.2	-	[124] [125]

All these markers were significantly lesser expressed in tumor sample as compared to normal tissue. The most interesting prospect is the use of lncRNA as a therapeutic modality. BC-819 is a treatment targeting H19 and has shown to decrease tumor growth in vivo [96] [97]. A list of lncRNAs found to be important in colorectal cancer is given in the table below (Table 4). Among these lncRNAs, MALAT1 has shown to be useful for targeted therapy against colorectal carcinoma. A study by Qing *et al.* [98] explored the effects of resveratrol on colorectal cancer. It was found to inhibit invasion and metastasis by down regulating

MALAT1 which in turn caused decreased Wnt/ $\beta$ -catenin signalling. Further studies are required before it can be established as a therapeutic agent.

## 5. Conclusion

The future of lncRNA holds much promise. It could be the key in understanding the pathogenesis of various tumors. It will definitely play a major part in diagnosis and prognostication of various cancers as has been evident in the review above. We have just scratched the surface when coming to the therapeutic utilization of lncRNAs. Several developments are required to further this study of lncRNA like high throughput RNA seq, RNA imaging and a better understanding of the interaction of lncRNA to RNA and DNA. Further in depth studies and analysis is required to truly unlock the potential of lncRNAs.

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