

## OncoLncs: Long Non-Coding RNAs with Oncogenic Functions

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### Abstract

A decade before the discovery of non-coding transcripts, approximately 98% of the human genome was known as “transcriptional noise” or “junk DNA”. However, with the recent findings, non-coding transcripts are continuously turning into functional non-coding RNAs (ncRNA). ncRNAs comprise multiple classes of RNA transcripts that are not transcribed into proteins but have shown to regulate the transcription, stability, or translation of protein-coding genes in the mammalian genome. Nowadays the most studied ncRNAs are called miRNAs. They have been involved in the biogenesis and development of cancer. More recently, long non-coding RNAs (lncRNAs) were discovered and they have been shown not only to play a role in transcriptional and translational regulation, but also be involved in several diseases including cancer. lncRNAs are RNA transcripts longer than 200 nucleotides that do not encode proteins. The accumulating body of evidence suggests that lncRNAs play important roles in a variety of biological processes. They have been reported to be altered in many pathological states including cancer. lncRNAs with oncogenic functions (we may call; OncoLncs) were reported to be overexpressed in cancer cells and involved in the hallmarks of cancer including sustained proliferation, invasion, and metastasis. The field of regulatory RNAs is continuously growing especially the lncRNAs. Thus, in this comprehensive review, we discussed the advances on OncoLncs field in the malignant transformation of cancer and the therapeutics opportunities.

**Keywords:** Cancer; lncRNA; OncoLncs

### Introduction

Cancer is a group of diseases result from survival of defective cells and uncontrolled cell proliferation [1]. In contrast, normal cells have developed multiple mechanisms to efficiently and coordinately regulate cell division, differentiation, and cell death processes [1]. Additionally, several molecular mediators are involved in the regulation of proliferation and differentiation of cells by turning genes on and off [1]. Deregulation of oncogenes and tumor suppressor genes that have been shown to be involved in the physiological cellular processes including regulation of cell cycle and differentiation, forms the molecular basis of carcinogenesis [1]. Cancer cells, unlike normal cells, sustain proliferative signaling to proliferate in an uncontrolled way through various mechanisms [1]. The production and release of growth promoting factors is kept in balance in normal cells in order to maintain the population size stable. On the other hand, cancer cells have deregulated expression of these factors. As cancer cells can produce their own growth promoting factors, they can also stimulate the cells in the tumor microenvironment to produce more growth promoting factors. Furthermore, mutations in signaling pathways, such as B-Raf and Ras, can result in sustain uncontrolled proliferative signaling [1-5].

In fact, cancer arises from a series of genetic abnormalities. Such genetic abnormalities in individual genes lead to deregulation of a gene function. Defects in genes involved in the formation of cancers may either cause hyper- or hypo-activation and these genes are called oncogenes and tumor suppressor genes, respectively [3]. Thanks to the advance of high-throughput DNA sequencing methods, many somatic mutations have been identified in oncogenes and tumor suppressor genes in human tumors. Identified mutations was shown to be frequently associated with the increased production of growth factors and their receptors [6]. Besides growth factors, mutations in genes that control various cellular processes including proliferation, angiogenesis, and cell survival were also identified [7]. Among intracellular signaling pathways, epidermal growth factor receptor (EGFR) is the most abundant and widely reported [7]. EGFR is a receptor tyrosine kinase and member of the human epidermal growth factor receptor HER-erbB family [7]. EGFR was shown to be associated with the pathobiology of

several types of metastatic tumors [7]. For instance, in colorectal cancers (CRC), mutations in EGFR gene are not frequently observed. However, mutations in Kirsten rat sarcoma viral oncogene homolog (KRAS) or Murine Sarcoma Viral (V-Raf) Oncogene Homolog B1 (BRAF), which are important members of MAPK pathway, are more abundant and observed in 32–37% and in 10–17% of the cases, respectively. Mutations in the Phosphatidylinositol-4,5-Bisphosphate 3-Kinase, Catalytic Subunit Alpha (PI3KCA) gene encoding the catalytic subunit of the PI3K are also abundant and were detected in 15% of patients with CRC [8-11]. Oncogenic effect of KRAS protein results from the deregulation of Ras GTPase negative feedback mechanism [8-11].

Besides, many genetic abnormalities also contribute to development of cancer [12]. In this concept, non-coding RNAs have gained much attention by the scientific community. Among non-coding RNAs, miRNAs are well reported in cancer. More recently, the role of long non-coding RNAs is rapidly emerging in cancer and significant involvement of these non-coding RNAs in the growth, invasion, and metastasis of cancer has been reported already.

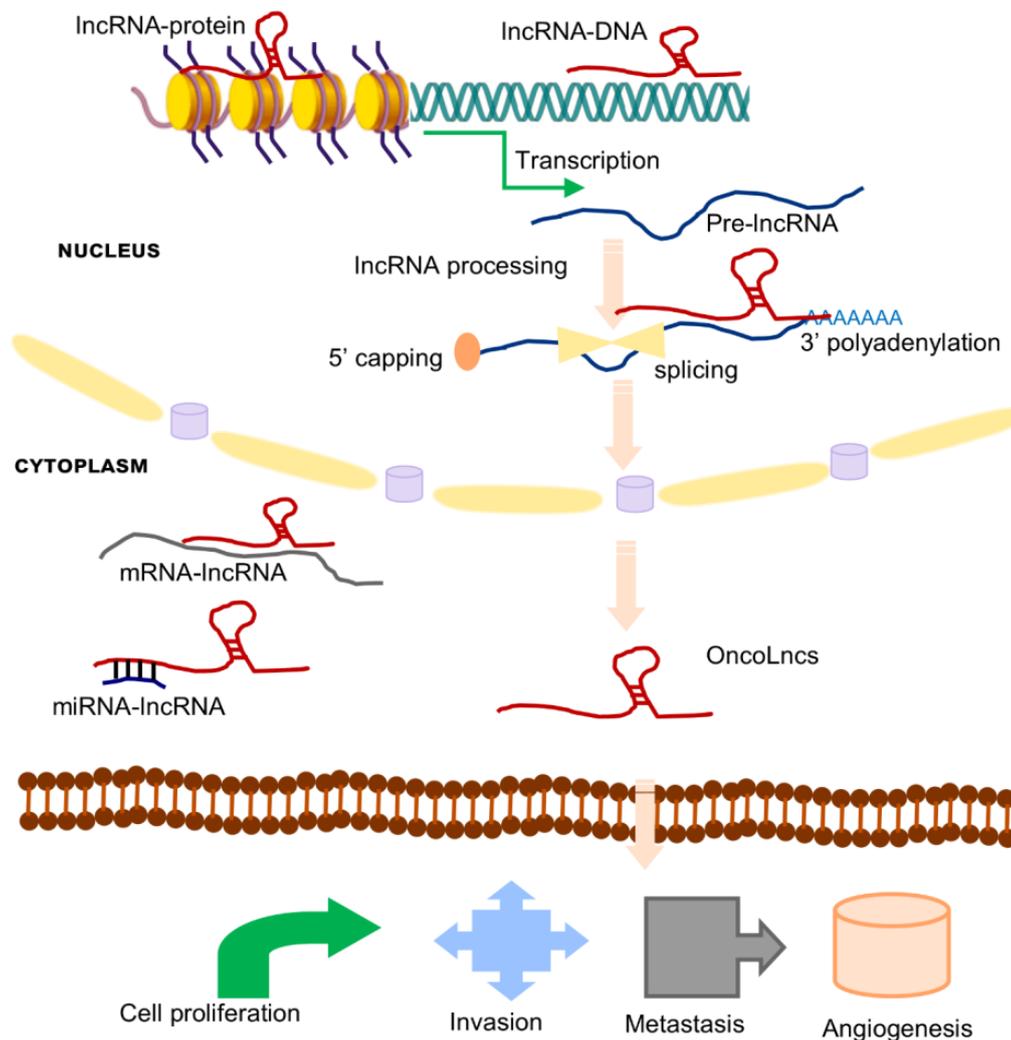
Previously, we all believed that 98% of the human genome was “junk-DNA”. By the completion of the Human Genome and ENCODE projects, this previously believed phenomenon disappeared and now we know that the majority of human genome is encoded into functional transcripts [13]. Accordingly, such functional transcripts were termed as non-coding RNAs (ncRNAs). To date, by using high-throughput approaches such as deep sequencing methods, several non-coding RNA

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**Figure 1:** Graphical representation of interaction between OncoLncs and various molecular targets and their role in the multistep development of cancers. LncRNAs are shown to interact with mRNAs, miRNAs, proteins and DNA. Also, involvement of OncoLncs in the cell proliferation, metastasis, invasion, and tumor angiogenesis.

molecules were discovered [14]. Yet, there are many of them remaining to be discovered. Moreover, growing evidences suggest that these newly found transcripts play a variety of roles in complex pathologic states, including cancer. Identification and characterization of ncRNAs are of great importance to illuminate the intricate molecular mechanisms undergoing in living cells [15,16].

Although there are several classification parameters for the non-coding RNAs such as function, genomic localization, and expression, they are generally classified according to their sizes. NcRNAs longer than 200 nt are called long ncRNAs (lncRNA) while non-coding RNAs smaller than 200 nt are called small non-coding RNAs (sncRNA), accordingly [17]. Small non-coding RNAs include: microRNA (miRNA), short interfering RNAs (siRNAs), piwi-interacting RNAs (piRNAs), small nuclear RNAs (snRNAs), and small nucleolar RNAs (snoRNAs) subtypes. Long non-coding RNAs include: ribosomal RNA (except 5S rRNA and 5.8S rRNA), antisense RNA (asRNA), long intergenic non-coding RNA (lincRNA), and competing endogenous RNA (ceRNA) [18,19].

In this particular review we aimed to discuss the impact of OncoLncs, oncogenic lncRNA frequently upregulated in cancer, in the

malignant transformation of cancer and their potential therapeutic use in cancer therapy.

### Long non-coding RNAs (lncRNA)

lncRNAs transcripts are longer than 200 nt in length. lncRNA transcripts are known to be transcribed by RNA polymerase II. Similar to protein coding genes, they undergo 5'capping, 3'polyadenylation and splicing modifications. After these modifications, lncRNA can be released and transported to cytoplasmic locations according to their functions [20]. lncRNAs can be classified in several categories according to their genomic localization, interactions with other transcripts, regions overlapping with protein coding genes, regions located within the introns of protein coding genes, and anti-sense orientation to genes [21-25]. Additionally, a lncRNA transcript can be seen in either one or several of these categories. Beside from these, lncRNA can be classified according to their functions. For example; enhancer-RNAs (eRNAs) were shown to interact with enhancer regions [26], and activating ncRNAs (ncRNA-a) were reported to have enhancer-like functions. Globally, lncRNAs were reported to play crucial roles in the regulation of various cellular processes through modulating activation, inhibition, transcription splicing, degradation, and translation of mRNAs [27,28].

## The roles of lncRNAs in cancer

As we all know cancer is a genetic disease formed by the accumulating mutations in oncogenes and tumor suppressor genes. A mass of indication suggests that lncRNAs play significant oncogenic roles in the malignant transformation of cancers [29-31]. Previous studies reported that lncRNAs molecules highly deregulated in several types of cancer (Tables 1 and 2).

## lncRNAs in cancer progression

Unlike normal cells, growth promoting signaling is constantly turned on in cancer cells for continuous uncontrolled growth [32]. A growing body of evidence suggests that several lncRNAs increases the proliferation of cancer cells. Aberrant expression of these lncRNAs was shown to be associated with growth of cancer cells [32]. Of these

OncoLncs	Full name	Genomic location	Type of lncRNA
MALAT1	Metastasis-Associated Lung Adenocarcinoma Transcript 1	11q13.1	lncRNA
CCAT1	colon cancer associated transcript 1	8q24.21	lncRNA
CCAT2	colon cancer associated transcript 2	8q24.21	lncRNA
CCAT1-L	CCAT1, the Long isoform	8q.24	lncRNA
HOTAIR	HOX Antisense Intergenic RNA	12q13.13	lincRNA, asRNA
HOTTIP	HOXA distal transcript antisense RNA	7p15.2	NAT, asRNA
H19	imprinted maternally expressed transcript	11p15.5	miRNA primary transcript
CAHM	colon adenocarcinoma hypermethylated (non-protein coding)	Chr:6	lncRNA
XIST	X inactive specific transcript	Xq13.2	lncRNA
TUG1	Taurine up-regulated 1	22q12.2	lncRNA
CNDRE	colorectal neoplasia differentially expressed	16q12.2	lncRNA
UCA1	urothelial carcinoma associated 1	19p13.12	lncRNA
lncRNA-ATB	long noncoding RNA (lncRNA) activated by transforming growth factor (TGF)- $\beta$		lncRNA
lincRN-RoR	long intergenic non-protein coding RNA, regulator of reprogramming	18q21.31	lincRNA
Loc554202	MIR31 host gene	9p21.3	miRNA primary transcript
LINC00472	long intergenic non-protein coding RNA 472	6q13	lincRNA
BCAR4	breast cancer anti-estrogen resistance 4	16p13.13	NAT, asRNA
SPRY4-IT1	SPRY4 intronic transcript 1	5q31.3	lncRNA
LSINCT5	long stress-induced non-coding transcript 5	5p15.33	lncRNA
GHET1	gastric carcinoma proliferation enhancing transcript 1	7q36.1	lncRNA
MALAT2	Metastasis-Associated Lung Adenocarcinoma Transcript 2		lncRNA
PVT1	Pvt1 oncogene (non-protein coding)	8q24	lncRNA
ANRIL	CDKN2B antisense RNA 1	9p21.3	NAT, asRNA
SUMO1P3	Small ubiquitin-like modifier (SUMO) 1 pseudogene 3		Pseudogene
ncRAN	non-coding RNA expressed in aggressive neuroblastoma	17q25.1	lncRNA
SchLAP1	SWI/SNF complex antagonist associated with prostate cancer 1	2q31.3	lincRNA
PCAT1	prostate cancer associated transcript 1	8q24.21	lncRNA
PCAT5	prostate cancer associated transcript 5	10p11.21	lincRNA
PCA3	prostate cancer associated 3	9q21.2	Overlapp
PCGEM-1	PCGEM1, prostate-specific transcript	2q32	lincRNA
CTBP1-AS	CTBP1 antisense RNA	4p16.3	asRNA
HULC	hepatocellular carcinoma up-regulated long non-coding RNA	6p24.3	lncRNA
HNF1A-AS	HNF1A antisense RNA 1	12q24.31	asRNA
AFAP1-AS1	AFAP1 antisense RNA 1	4p16.1	asRNA
LINC01207	long intergenic non-protein coding RNA 1207	4q32	lincRNA
SOX2OT	SOX2 overlapping transcript	3q26.33	Overlapp lncRNA
LINC00635	long intergenic non-protein coding RNA 635	3q13.12	lincRNA
HIF1A-AS1	HIF1A antisense RNA 1	14q23.2	asRNA
DLX6-AS1	DLX6 antisense RNA 1	7q21.3	asRNA
RGMB-AS1	RGMB antisense RNA 1	5q21.1	asRNA
LINC01133	long intergenic non-protein coding RNA 1133	1q23.2	lincRNA
AK001796	MIR4435-2 host gene	2q13	miRNA primary transcript
BCYRN1	brain cytoplasmic RNA 1	2p21	lincRNA
SNHG1	ncRNA small nucleolar RNA host gene 1	11q12.3	small nucleolar RNA primary transcript
SCAL1	lung cancer associated transcript 1	5q14.3	lincRNA
ZFAS1	ZNF1 antisense RNA 1	20q13.13	NAT, asRNA
PANDAR	promoter of CDKN1A antisense DNA damage activated RNA	6p21.2	NAT, asRNA
DANCR	differentiation antagonizing non-protein coding RNA	4q12	lncRNA
OR3A4	olfactory receptor family 3 subfamily A member 4	17p13.3	pseudogene

Table 1: OncoLncs have been reported in cancer.

OncoLncs	Target gene	Cancer process	Clinical findings	Ref
MALAT1	PI3K-AKT pathway, EZH2, PCDH10, ZEB2, AKAP-9	EMT, invasion, metastasis, angiogenesis	overall survival, lymph node metastasis	[67,90, 145-149]
CCAT1	ERK/MAPK pathway, c-Myc, E-cadherin, N-cadherin, BRD4	invasion, metastasis, apoptosis, cell cycle	clinical stage, lymph nodes metastasis, survival time, differentiation grade, TNM stage	[57,61,66, 70,82, 150,151]
CCAT2	WNT signaling, MYC	cell growth, tumor formation, cell proliferation, tumor growth, metastasis, invasion	lymph node metastasis, clinical stage, invasion, overall survival, distal metastasis	[59,152-157]
HOTAIR	c-Myc, TGF- $\beta$ , type I collagen, osteopontin, HER2	Tumor growth, invasion, metastasis, EMT, cell proliferation,	TNM stage, overall survival, lymph node metastasis, poor prognosis, drug resistance	[35, 65, 123, 125, 127, 128, 158-160]
HOTTIP	HOXA genes	cell proliferation, colony formation, cell cycle arrest, apoptosis, tumor growth	clinical stage, distal metastasis, poor prognosis, overall survival	[136, 137, 161-164]
H19	TGFBI, AKT2, c-Myc, miR-138, miR-200a	EMT, cell cycle, cell proliferation, invasion, metastasis	clinical stage, tumor size, overall survival	[48,54, 165,166]
PVT1	MYC, several apoptotic and anti-apoptotic genes, TSHR	cell proliferation, migration, invasion	lymph node metastasis, histological grade, clinical stage, poor prognosis	[87-89, 167-170]
PCAT	c-Myc, BRCA2	cell proliferation, invasion, metastasis, migration	clinical stage, lymph node metastasis, poor prognosis	[32,105-107,171]
UCA1	miR-193a-3p, c-Myc, hsa-miR-145-ZEB1/2-FSCN1 pathway, FGFR1/ERK signaling pathway	cell growth, metastasis, invasion, cell proliferation, colony formation	differentiation, tumor size, invasion depth, clinical stage, overall survival,	[97-99, 172-177]
ncRAN	MYCN	cell proliferation, migration, invasion	stage, tumor origin, differentiation	[102,103, 178]
Loc554202	caspase	cell proliferation, invasion, migration	pathologic stage and tumor size	[50,52]
HULC	SPHK1, IGF2BP1	cell proliferation, invasion, metastasis,	clinical stage, distant metastasis, overall survival, tumor size, vascular invasion.	[133-135, 179-182]
DANCR	CTNNB1	stemness features, intra-/extraliver colonization	clinical stage, histologic grade, lymph node metastasis, overall survival	[183, 184]

**Table 2:** The role of OncoLncs and their target genes in various cancer processes.

lncRNAs, PCAT-1 has been shown to be overexpressed in prostate cancer and its overexpression was significantly associated with increased cell proliferation [32]. In addition, PCGEM-1 is another lncRNA molecule with significant growth promoting effects that was identified to be prostate cancer specific and was shown to be up-regulated in prostate cancer tumors [29-31]. Furthermore, several OncoLncs such as HOTAIR, MALAT1, ncRAN, and CCAT1 were reported to increase the proliferation of cancer cells [29-31].

### The function of lncRNAs in epigenetic modifications

lncRNAs play key roles in epigenetic modifications [33]. lncRNAs were shown to interact with chromatin remodeling enzymes and proteins, and this interaction results in activation/inactivation of target genes [33]. One of the best examples that show the role of lncRNAs in epigenetic regulation is the X-inactive-specific transcript (XIST). XIST transcript is the major effector involved in the inactivation of one of two X chromosomes for the dosage compensation in females. XIST is an lncRNA transcribed from the inactive X chromosome [34]. XIST binds directly to PRC2, which is responsible for H3K27me3 methylation, and allows the inactivation of one X chromosome [34]. HOTAIR lncRNA also interact with the PRC2 and triggers heterochromatin formation in some specific genomic regions and allows epigenetic control of genes located in those regions [35]. In addition to these, H19 is another lncRNA that is shown to participate in epigenetic modifications, H19 knockdown activates SAHH, leading to increased DNMT3B-mediated methylation of an lncRNA-encoding gene Nctc1 within the Igf2-H19-Nctc1 locus [36].

### lncRNAs in cancer invasion and metastasis

One of the most important distinguishing characteristics of cancer cells is their capacity to trigger invasion and metastasis processes [1]. Due to the fact that cancer cells must acquire some morphological changes to amend their interactions with other cells and the extracellular environment (ECM-extracellular matrix) [1]. The series

of genetic modifications, which are characterized by the loss of several cell adhesion molecules for the invasion and metastasis of cancer cells, is known as the epithelial to mesenchymal transition (EMT) program [1,37]. MALAT1 is one of the first lncRNA shown to be associated with metastasis of cancers. It was first described in metastatic lung cancer by its significant up-regulation. Later, MALAT1 was reported to be involved in the invasion and metastasis of several other types of cancers [38]. Subcellular localization of MALAT1 was to the nucleus and nuclear speckles [38]. It is implicated as an important regulator in the splicing of mRNAs [39]. Moreover, several of lncRNAs such as HOTAIR, CCAT1, HULC, UCA1, and H19 were shown to be associated with metastasis of cancer. Taken together, these findings prove that alteration of lncRNAs play crucial roles in the metastatic development of cancers.

Furthermore, DNA-interacting lncRNAs can promote mRNA transcription by activating transcription factors and mediating demethylation of promoter regions of transcription factors [23,40,41].

Moreover, lncRNAs can interact with another lncRNAs. In addition, lncRNAs can be transcribed from the anti-sense strand of protein coding genes, accordingly named natural antisense transcripts, or NAT, and regulating the expression of that gene [42]. Also, lncRNAs called 1/2-STAU1-binding site RNAs were reported to be involved in the transactivation of Staufen 1 (STAU1)-mediated messenger RNA decay (SMD) [43]. 1/2-STAU1-binding site RNAs of TINCR, MALAT1, and GHET1 were reported to respectively bind to Kruppel-like factor 2 (KLF2) [44,45], serine/arginine splicing factors (SF2/ASF) [46], and insulin-like growth factor 2 mRNA binding protein 1 (IGF2BP1) in SMD [47].

Additionally, miRNAs regulate gene expression at the posttranscriptional level by mediating mRNA degradation through RNA induced silencing complex (RISC). Several studies suggest that some lncRNAs are the precursors of miRNAs and/or some interact with miRNAs [48,49]. These miRNA precursor lncRNAs are involved in the degradation of mRNAs and include examples such as H19,

ANRIL, Lnc554202, and AK001796, which have been shown to have carcinogenic effects in various types of malignancies [50-54]. In addition, lncRNAs are also precursors of small nucleolar RNAs, and small nucleolar RNA host gene 1 (SNHG1) is one example [55].

HOTTIP lncRNA expression was remarkably increased in GC tissues and cell lines compared with that in the normal control. Clinicopathological analysis revealed that high HOTTIP expression correlated with larger tumor size, deeper invasion depth, positive lymph node metastasis, advanced TNM stage, and shorter overall survival. Multivariate regression analysis identified HOTTIP overexpression as an independent unfavorable prognostic factor in GC patients. Moreover, HOTTIP down regulation by si-HOTTIP transfection impaired GC cell proliferation, promoted cell apoptosis, and reduced cell invasion and migration [56].

Likewise, lncRNAs also interact with RNA binding proteins that can regulate their functions. Moreover, lncRNAs can directly bind to target genes and increase or decrease their expressions. For example, CAT1, CCAT2, CCAT1-L, PCAT1, and PVT1 lncRNA molecules encoded from the MYC genomic desert (8q24 locus) and involved in the regulation MYC oncogene itself [57-61]. Similarly, PCA3 lncRNA has a negative trans-dominant oncogenic role that down-regulates an unrecognized tumor suppressor gene, *PRUNE2* (a human homolog of the *Drosophila* prune gene) thereby promoting malignant cell growth [62,63].

### OncoLncs among the Cancer Types

lncRNAs are frequently overexpressed and associated with the

clinic-pathological characteristics of cancers [64]. Accordingly, lncRNAs that are significantly up regulated in cancers are oncogenic lncRNAs and may be called OncoLncs. In the following section the roles of OncoLncs in the development and progression of cancers are discussed (Table 3).

#### Colorectal cancer (CRC)

In colorectal tumorigenesis, several OncoLncs were identified with important regulatory functions including RNA transcription, post-transcriptional modifications, and chromatin remodeling. Recent studies revealed that aberrant expression of lncRNAs were shown to influence a number of oncogenes and tumor suppressor genes and eventually participate in CRC development. HOX Transcript Antisense RNA (HOTAIR) [65], Colon Cancer Associated Transcript (CCAT) family (CCAT1, CCAT2, CCAT1-L) [59,60,66], and Metastasis-Associated Lung Adenocarcinoma Transcript 1 (MALAT1) [67] were reported to have oncogenic functions and to be frequently up-regulated in CRC. Recently, several lncRNAs were identified in the 8q24 human chromosomal region. Oncogenic MYC gene is also encoded from this region and reported to be regulated in multiple levels including enhancers, transcription factors, and chromatin state [68]. CCAT1 is a lncRNA 2600 nucleotide in length and encoded from the same locus with MYC. CCAT1 was reported as an highly specific marker in colorectal cancer and associated to the clinicopathological characteristics of CRC patients [68,69]. Besides, CCAT1 has been reported to have important roles in the invasion and metastasis of CRC [57,70]. In addition, a 320 nucleotide long novel transcript

lncRNA	Function in cancer	Type of cancer	Ref
MALAT1	MALAT1 was shown to be upregulated in various cancer types and associated with the cell proliferation, tumor growth, and metastasis of cancers.	Colorectal cancer, breast cancer, gastric cancer, hepatocellular carcinoma, osteosarcoma, lung cancer, cervical cancer, prostate cancer, clear cell kidney carcinoma, bladder cancer, esophageal squamous cell carcinoma	[185], [186], [90], [187], [145], [188], [146], [147], [148], [173], [189]
CCAT1	CCAT1 was shown to be involved in the development of various type of cancers, especially the CRC. Increased CCAT1 expression was associated with the cell proliferation, invasion, and migration.	Colorectal cancer, breast cancer, hepatocellular carcinoma, gallbladder cancer, gastric cancer	[57, 66, 70], [150], [151], [190], [61]
CCAT2	CCAT2 was shown to be involved in the regulation of MYC oncogene. Also, CCAT2 plays role in the WNT signaling.	Colorectal cancer, cervical squamous cell cancer, breast cancer, esophageal squamous cell carcinoma, gastric cancer, non-small cell lung cancer	[59], [153], [152], [157], [156], [154]
ANRIL	ANRIL was up-regulated in various types of cancers. Increased ANRIL expression was associated with the cell proliferation, invasion, and migration.	Colorectal cancer, bladder cancer, gallbladder cancer, non-small cell lung cancer, cervical cancer, hepatocellular carcinoma	[191], [81], [192], [193], [194]
HOTAIR	HOTAIR was reported as an important prognostic marker in cancers and higher expression was associated with the aggressive carcinogenic characteristics.	Breast cancer, gastric cancer, hepatocellular carcinoma, colorectal cancer, gallbladder cancer, endometrial carcinoma, non-small cell lung cancer, pancreatic cancer,	[35], [195], [196], [65], [123], [159], [128], [197],
HOTTIP	Expression levels of HOTTIP was found to be significantly higher in several types of cancers.	Colorectal cancer, osteosarcoma, lung cancer, pancreatic cancer, hepatocellular carcinoma	[164], [163], [162], [161], [136]
H19	Dual functions of H19 was reported in cancers.	Colorectal cancer, gastric cancer, non-small-cell lung cancer, esophageal cancer	[74], [165], [166], [198]
NcRAN	Up-regulated in various cancer types.	Colorectal cancer, neuroblastoma, bladder cancer	[73], [102], [103]
UCA1	First identified in bladder cancer, and later found to be up-regulated in different types of cancers. Overexpression of UCA1 was associated with the cell proliferation, invasion, and migration of cancers.	Bladder cancer, gastric cancer, breast cancer, cervical cancer, colorectal cancer, hepatocellular carcinoma, lung cancer, tongue squamous cell carcinoma, melanoma	[97-99, 176], [177], [199], [200], [172], [174]
PVT1	Up-regulated in various cancer types. Up-regulation of PVT1 was shown to promote cell proliferation and inhibit apoptosis.	Gastric cancer, ovarian cancer, breast cancer, non-small-cell lung cancer, hepatocellular carcinoma, pancreatic cancer, thyroid cancer	[83, 85], [87], [169], [88], [167], [170]
PCAT-1	PCAT-1 upregulated in prostate tumors and various types of cancers.	Prostate cancer, colorectal cancer, non-small-cell lung cancer, hepatocellular carcinoma, esophageal squamous cell carcinoma	[32], [104], [106], [105], [107]
PCA3	PCA3 is involved in the control of prostate cancer cell survival and frequently up-regulated in prostate cancers. Identified as strong predictive biomarker for prostate cancer diagnosis.	Prostate cancer	[63, 108],
HULC	HULC was identified in HCC by its marked expression. Ectopic overexpression of HULC was associated with increased cell proliferation and tumor burden.	Hepatocellular carcinoma, osteosarcoma, pancreatic cancer, gastric cancer	[133-135], [181], [180], [182]

Table 3: Some of OncoLncs and their functions in cancer.

was also identified from the same locus with CCAT1 and MYC-335 region, called CCAT2 [59]. The expression of CCAT2 was found to be up regulated in invasion and metastasis of CRC and increased expression of this transcript was associated with increased MYC, miR-17-5p, and miR-20a levels [59]. Also, an SNP (rs6983267) found in the CCAT2 was shown to be associated with the CCAT2 expression levels. Particularly, G allele was found to be increased CCAT2 gene [59]. Furthermore, another novel transcript 5200 nucleotide in length located 515 kb upstream to MYC was discovered. This transcript was named CCAT1-L (CCAT1, the Long isoform) and was shown to have regulatory functions in the transcriptional regulation of MYC [60]. Additionally, CCAT1-L was shown to promote long-range chromatin looping and knockdown of CCAT1-L was found to reduce long-range interaction between enhancer and promoter region of MYC [60].

Lnc34a lncRNA is enriched in colon cancer stem cells (CCSCs) and initiates asymmetric division by directly targeting the microRNA miR-34a to cause its spatial imbalance. Lnc34a recruits Dnmt3a via PHB2 and HDAC1 to methylate and deacetylate the miR-34a promoter simultaneously, hence epigenetically silencing miR-34a expression independent of its upstream regulator, p53. Lnc34a levels affect CCSC self-renewal and colorectal cancer (CRC) growth in xenograft models. Lnc34a is up regulated in late-stage CRCs, contributing to epigenetic miR-34a silencing and CRC proliferation [71].

GHET1 lncRNAs expression is significantly increased in the CRC samples compared with adjacent tissues. Furthermore, the cancer tissues had higher GHET1 mRNA levels than their matched adjacent tissues. GHET1 expression was also significantly increased in the CRC cell lines compared with human normal colon epithelial cells. Down-regulation of GHET1 mediated by shRNA suppressed the proliferation, cell cycle arrest, migration, and invasion of colorectal cancer cells *in vitro*. In addition, inhibition of GHET1 reversed the epithelial-mesenchymal transition in colorectal cancer cell lines. GHET1 has potential to be considered as a therapeutic target of colorectal cancer [72].

Colorectal Neoplasia Differentially Expressed (CRNDE) transcript was first identified in CaCo2 and HCT116 colon cancer cell lines using 5'-RACE method [73]. CRNDE was reported to have ten splice variants and all of them (except CRNDE-d) were found to be up regulated in colon cancer biopsies [73].

Taurine Up-regulated Gene 1 (TUG1) has been also reported to be involved in the colorectal carcinogenesis. TUG1 was found to be elevated in primary tumor samples of CRC patients and colon cancer cell lines. In addition, TUG1 was shown to be associated with increased colony formation, migration, and invasion of colon cancer cell lines. In contrast, down-regulation of TUG1 was associated with the reduced colony formation, migration, and invasion [74]. 135 lncRNAs are differentially expressed in HCT116, HCT8, and SW480 colorectal cancer cell lines. A 185-fold increase was reported in AK027294 lncRNA and its down-regulation was associated with reduced cell proliferation and migration, as well as increased apoptosis [75].

### Gastric cancer

lncRNAs were also reported to be differentially expressed in gastric cancers, where they regulate important cellular signaling pathways including Notch, mTOR, NF- $\kappa$ B, and Wnt [76-78]. Gastric Carcinoma High Expressed Transcript 1 (GHET1) is one of the oncoLnc with increased expression levels in gastric cancer. Overexpression of this transcript was shown to be significantly correlated with tumor size, invasion, and poor outcome of gastric cancer patients [79]. Moreover, in gain-of-function and loss-of-function analysis of GHET1 while

overexpression of GHET1 was associated with the increased cell proliferation, knockdown of this transcript was associated with the inhibition of cell proliferation in gastric cancer cell lines [79]. In addition, GHET1 was reported to have direct physical interaction with the insulin-like growth factor 2 binding protein 1 (IGF2BP1) mRNA in pull-down and immunoprecipitation assays.

Previous studies have also reported that IGF2BP1 transcript physically interacted with c-Myc mRNA rescuing it from degradation [47]. Therefore, GHET1 is involved in the development of gastric carcinoma through mediating Myc mRNA stability and expression [79]. ANRIL (CDKN2B Antisense RNA 1) is another oncoLnc 3.8-kb in length and transcribed from opposite direction of INK4B-ARF-INK4A gene cluster. Elevated ANRIL expression was revealed to be interrelated with advanced Tumor, Node and Metastasis (TNM) Classification stage and increased tumor size [80]. Knockdown of ANRIL was also associated with a diminished cell growth in gastric cancer [80]. ANRIL knockdown decreased the expression of MDR1 and MRP1, both of which are MDR related genes; regression analysis showed that the expression of ANRIL positively correlated with the expression of MDR1 and MRP1, respectively. Globally, knockdown of lncRNA ANRIL in gastric cancer cells inhibits the development of MDR, suggesting an efficacious target for reversing MDR in gastric cancer therapy [81].

CARLo-5 long non-coding RNA (renamed as CCAT1) is involved in the malignant transformation of gastric cancers. In particular, CARLo-5 was reported to be up-regulated in gastric cancers and silencing CARLo-5 resulted in G0/G1 cell-cycle arrest and induced apoptosis gastric cancer cells [82].

Also, lncRNA TINCR was shown to be aberrantly overexpressed in human squamous carcinomas. TINCR was found to be up-regulated and increased expression of this transcript was associated with the initiation and progression processes in gastric cancer [45]. While reduced expression of TINCR was correlated with the inhibition of cell proliferation, colony formation and promoted apoptosis, its overexpression stimulated increased cell proliferation in SGC7901 and BGC823 cells [45].

In gastric cancers, 88 differentially expressed lncRNAs that span the 8q24 genomic locus have been described [83]. Among these lncRNAs, PVT1 (Plasma-cytoma Variant Translocation) is oncogenic and is localized to the same genomic region with MYC oncogene [83-85]. PVT1 was identified as a miRNA-coding gene [85]. MiR-205, -206, -207 are encoded miRNAs from the PVT1 gene [86].

In a study conducted in ovarian and breast cancer cell lines, silencing PVT1 resulted in higher apoptosis activation [87]. Also, increased PVT1 expression was associated with invasion and higher TNM stage of gastric cancer [88]. In addition, PVT-1 was shown to be overexpressed in patients resistant to cisplatin and cisplatin-resistant cells. Cisplatin treatment was reported to be more effective inducing apoptosis in gastric cancer cells transfected with PVT-1 siRNA [89].

Metastasis Associated Lung Adenocarcinoma Transcript 1 (MALAT1) was one of the first identified members of lncRNAs with oncogenic functions. MALAT1 is also known as Nuclear-Enriched Abundant Transcript 2 (NEAT2) [38]. MALAT1 was reported to be highly expressed in gastric tumors and gastric cancer cell lines (SGC-7901, MKN-45 and SUN-16) [90,91]. Silencing MALAT1 was shown to inhibit invasion and migration capacity of MKN45 cells. Overexpression of MALAT1 was correlated with overexpression of SF2/ASF in the nucleolus. Knockdown of MALAT1 promoted G0/G1 cell cycle arrest and impaired SGC-7901 cell proliferation [91]. Also,

increased expression of MALAT1 was significantly associated with poor prognosis of advanced stage gastric cancer patients [90].

In a different study, plasma levels of circulating lncRNAs in gastric cancer patients were determined. Interestingly, while the expression levels of H19 were significantly altered, expression changes of HOTAIR and MALAT1 were not significant when compared to control subjects [92]. Furthermore, MALAT2 was also reported to be differentially expressed in gastric cancer patients. MALAT2 overexpression was shown to be associated with advanced TNM stage. In addition, ectopic expression of MALAT2 was shown to induce migration of human GC SGC-7901 cells [93].

Olfactory Receptor, family 3, subfamily A, member 4 (OR3A4) lncRNA is elevated in gastric cancer tissues and associated with the invasion and lymphatic distal metastasis of patients. Moreover, ectopic expression of OR3A4 has been reported to stimulate cell proliferation, angiogenesis, metastasis, and tumorigenesis *in vitro* and *in vivo* [94].

Long Intergenic Non-Coding RNA 152 (LINC00152) is another transcript that was identified to have tumor promoter functions in gastric cancers. LINC00152 was reported to be frequently up-regulated and associated with the clinicopathological characteristics of gastric cancer patients as shown in different studies. Also, increased expression of LINC00152 was reported to increase proliferation of gastric cancer cells as revealed by gene set enrichment analysis. Moreover, ectopic LINC00152 expression was reported to promote proliferation of gastric cancer cells *in vitro* and *in vivo* xenograft models. However, reverse effect was observed in LINC00152 silenced cells. Indeed, LINC00152 was shown to interact with Enhancer of Zeste Homolog 2 (EZH2) and fuel gastric cancer progression through silencing p15 and p21 [95]. In summary, these findings strongly suggest that lncRNAs play key roles in the gastric cancer progression through multiple mechanisms and these RNA molecules can be novel therapeutic targets in gastric cancer therapy.

Small Ubiquitin-like Modifier (SUMO) 1 Pseudo gene 3, (SUMO1P3) is a pseudogene-expressed oncoLnc and its overexpression has been reported in gastric cancer [96].

## Bladder cancer

One of the first lncRNAs discovered in bladder cancer is Urothelial Carcinoma-Associated 1 (UCA1). UCA1 was identified in BLS-211 and BLZ-211 bladder transitional cell carcinoma (TCC) cell lines using 3' and 5' RACE methods [97]. Ectopic expression of UCA1 was associated with increased tumorigenic characteristics in BLS-211 human bladder cancer cells. In addition, tumorigenic capacity of BLS-211 cells was reported to be enhanced by increased UCA1 expression in nude mice [97]. A significant correlation between UCA1 and miR-196a was also reported and expression of these inversely associate with p27kip1, which is frequently down-regulated in bladder cancer [98]. Not surprisingly, UCA1 overexpression was shown to promote gain of mesenchymal type of characteristics in bladder cancer cells by way of activating ZEB1 and ZEB2 transcription factors, activating in turn epithelial to mesenchymal transition program [99].

SUMO1P3 was also shown to be significantly overexpressed in bladder cancer tissues and its expression was well-correlated with the histological grade and TNM stage of bladder cancer patients. It has been shown that knockdown of SUMO1P3 reduced proliferative and migratory capacity and significantly induced apoptosis in bladder cancer cells. Postulating that SUMO1P3 can be taken into account in the future therapeutic attempts as a novel molecular target in bladder cancer therapy [100].

LOC572558 is one of the most deregulated lncRNAs in bladder cancer. A large cohort of human bladder cancer tissue samples with benign controls, as well as established human bladder cancer cell lines, has been examined for the expression of LOC572558. Using a high-throughput phospho-proteome array, it has been identified proteins that were ectopic phosphorylated in bladder cancer cells where LOC572558 expression was up regulated. In this study they also demonstrated that LOC572558 expression was markedly decreased in bladder cancer tissues and bladder cancer cell lines. Moreover, ectopic expression of LOC572558 inhibited cell proliferation and motility, induced S phase arrest of the cell cycle and promoted cell apoptosis in T24 and 5637 bladder cancer cell lines. Further studies verified that overexpression of LOC572558 was associated with dephosphorylation of AKT, MDM2 and phosphorylation of p53 protein. The data demonstrated that LOC572558 is a tumor suppressor and regulates the p53 signaling pathway in bladder cancer [101].

NcRAN is another novel OncoLncRNA that was first described in neuroblastoma and was reported to be associated with the aggressive behavior of tumor cells and poor outcomes of patients [102]. Expression levels of ncRAN were also found to be increased in bladder cancers. In consistent with these, its expression was also reported to be elevated in aggressive bladder cancer cells. Ectopic expression of NcRAN was shown to be overexpressed tumorigenic characteristics of RT4 bladder cancer cells. Moreover, reducing the expression of ncRAN in 5637 cells diminished chemotherapeutic resistance [103].

## Prostate cancer

OncoLncs play significant roles in the development of prostate cancers and several molecular targets with diagnostic, prognostic, and therapeutic potentials were identified. Encoding gene of Prostate Cancer-Associated ncRNA Transcripts 1 (PCAT-1) was initially postulated as a molecular biomarker in prostate cancers [32]. PCAT-1 was shown to be involved in the metastasis of prostate cancer tumors and associated with increased cell proliferation in these tumors [32].

Recent studies showed that PCAT-1 have significant impact on the development of various of types of cancer including colorectal cancer [104], hepatocellular carcinoma [105], non-small cell lung cancer (NSCLC) [106], and esophageal squamous carcinoma [107].

Besides PCAT-1, Prostate-specific transcript 1 (PCGEM1) is another prostate cancer specific OncoLnc and revealed to be an androgen-dependent non-coding RNA. PCGEM1 was shown to be markedly expressed in prostate cancer tumors [31]. Ectopic expression of PCGEM1 increased the cell number and colony forming potential of LNCaP and NIH3T3 prostate cancer cell lines [30]. Moreover, this ectopic expression interfered with doxorubicin (DOX) induced apoptosis [29].

Furthermore, significant up regulation of Differential Display Code 3 (PCA/DD3) lncRNA was reported in prostate cancer [108]. In clinical trials, PCA3 is accepted as an early sign of prostate cancer and considered as an important risk factor in addition to serum PSA levels. Studies also reported that expression of PCA3 is elevated in prostate cancer cell lines and tumor samples [109]. Thus, accumulating findings suggest that PCA3 is a most specific prostate cancer biomarker [110-114]. PCA3 was identified as an intronic long noncoding RNA in the PRUNE2 gene locus and was shown to regulate expression of PRUNE2. Also, PCA3 and PRUNE2 were reported to have inverse relationship in tumor formation *in vivo* tumor models. Thus, PRUNE2 was recently postulated as a novel tumor suppressor in prostate cancer cells [63].

The expression of lncRNAs in several prostate cancer exosomes and

their parental cell lines has been characterized. In this study they show that certain lncRNAs are enriched in cancer exosomes with the overall expression signatures varying across cell lines. These exosomal lncRNAs are themselves enriched for miRNA seeds with a preference for *let-7* family members as well as miR-17, miR-18a, miR-20a, miR-93 and miR-106b. The enrichment of miRNA seed regions in exosomal lncRNAs is matched with a concomitant high expression of the same miRNA. In addition, the exosomal lncRNAs also showed an over representation of RNA binding protein binding motifs. The two most common motifs belonged to ELAVL1 and RBMX. Given the enrichment of miRNA and RBP sites on exosomal lncRNAs, their interplay may suggest a possible function in prostate cancer carcinogenesis [115].

Lastly, LOC400891 is another oncoLnc identified to have relevance in the development of prostate cancers. LOC400891 was reported to be overexpressed in prostate tumors and cancer cell lines and Kaplan-Meier analysis showed that PCa patients with high LOC400891 expression had a significantly shorter biochemical recurrence-free survival time than those with low LOC400891 expression and associated with the clinical characteristics of patients [116]. Functional analysis revealed that silencing of LOC400891 inhibits cell proliferation, migration, and invasion capabilities of prostate cancer cells [116].

### Breast cancer

Several lncRNAs were implicated to have significant roles in developing breast tumors, some of the examples discussed here. lincRNA-RoR was discovered to be one the oncoLnc which is significantly overexpressed in breast cancer tumors including triple-negative breast cancer (TNBC) [117]. lincRNA-RoR was first identified to be involved in the regulation of pluripotency [118]. Its ectopic expression was also shown to activate EMT program and increase migration and invasion of mammary epithelial cells. In contrast, knockdown of lincRNA-RoR was associated with the less breast tumor burden and metastasis *in vivo* [119].

A well reported OncoLnc in breast carcinogenesis is MALAT1. Aberrant expression of MALAT1 has been reported in breast cancer. Silencing of MALAT1 in breast cancer cells significantly reduced cell proliferation and cell cycle progression both *in vitro* and *in vivo*. Besides, tumor suppressor miR-124, was identified as one of the targets of MALAT1 as overexpression of MALAT1 inhibit miR-124 expression in breast cancer [120].

Moreover, it has been identified lncRNA in non-homologous end joining (NHEJ) pathway 1 (LINP1), which is overexpressed in human triple-negative breast cancer. It was found that LINP1 enhances repair of DNA double-strand breaks by serving as a scaffold linking Ku80 and DNA-PKcs, thereby coordinating the NHEJ pathway. Importantly, blocking LINP1, which is regulated by p53 and epidermal growth factor receptor (EGFR) signaling, increases the sensitivity of the tumor-cell response to radiotherapy in breast cancer [121].

### Lung cancer

HOTAIR is transcribed from the antisense of HoxC gene and is 2,158 nucleotides in length. It is reported to be spliced and polyadenylated and comprises 6 exons [122]. HOTAIR was reported as an important prognostic factor in several types of malignancies [123]. Distinctive higher expression of HOTAIR was found in small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) [124]. HOTAIR regulate genes involved in differentiation, proliferation, and invasion of lung cancer cells [124]. HOXA5 gene was listed as an important target of HOTAIR due its pivotal roles in the lung cancer formation [125]. Elevated expression of HOTAIR was also reported to

be associated with the poor clinical outcomes and poor survival of lung cancer patients [126,127]. Moreover, significant correlation between HOTAIR expression and brain metastasis in NSCLC patients has been reported [128].

Knockdown of TATDN1-1 by shRNA significantly inhibited cell proliferation, adhesion, migration and invasion in 95D cells. Further mechanism study showed that TATDN1 knockdown suppressed the expression of E-cadherin, HER2,  $\beta$ -catenin and Ezrin. Moreover, knockdown TATDN1 also inhibited tumor growth and metastasis in a 95D mouse model *in vivo* by inhibiting  $\beta$ -catenin and Ezrin [129].

The lncRNA PVT1 is 1716 nt in length and located in the chr8q24.21 region, which also contains the myelocytomatosis (MYC) oncogene. Previous literature demonstrated that MYC promotes PVT1 expression in primary human cancers. However, the expression pattern and potential biological function of PVT1 in non-small cell lung cancer (NSCLC) it was not clear yet. Until was demonstrated that PVT1 was up-regulated in human NSCLC tissues. High expression of PVT1 was associated with a higher TNM stage and tumor size, as well as poorer overall survival. Functional analysis revealed that knockdown of PVT1 inhibited NSCLC cell proliferation and induced apoptosis both *in vitro* and *in vivo*. RNA immunoprecipitation (RIP) and Chromatin immunoprecipitation (ChIP) assays demonstrated that PVT1 recruits EZH2 to the large tumor suppressor kinase 2 (LATS2) promoter and represses LATS2 transcription. Ectopic expression of LATS2 increased apoptosis and repressed LAD cell proliferation by regulating the Mdm2-p53 pathway [130].

SOX2 Overlapping Transcript (SOX2OT) was reported to harbor in the intronic region of the SOX2 gene locus [126]. SOX2OT4 and SOX2OT7 transcription variants of SOX2OT oncoLnc were reported to be significantly up-regulated in NSCLC tumors. SOX2OT silencing significantly decreased colony formation in lung cancer cells, yet not induced apoptotic cell death in these cells. Conversely, SOX2OT silencing was reported to induce cell cycle arrest at G2/M checkpoint and associated with reduced migration capacity [131,132].

### Liver cancer

Highly Upregulated in Liver Cancer (HULC) is the novel transcript with prominent expression levels in hepatocellular carcinoma (HCC) and showing mRNA-resembling characteristics. siRNA-mediated silencing of HULC impaired the expression of several genes in two different HCC cell lines. Indicating potential gene expression-regulating role of HULC at post-transcriptional level [133]. Furthermore, increased expression of HULC oncoLnc was significantly linked to positive hepatitis B (HBV) infection and associated with the higher Edmondson grades [134].

HULC is involved in tumor angiogenesis by targeting and increasing SPHK1 (Sphingosine Kinase 1) expression in HCC. HULC expression was shown to be well-correlated with the expression levels of SPHK1 and the SPHK1 gene product, Sphingosine-1-Phosphate (S1P), in HCC [135].

Lastly, HOXA distal transcript antisense RNA (HOTTIP) was discovered from the HOXA locus and was reported to be targeted by miR-125b [136]. Expression levels of HOTTIP were found to be significantly higher in patients with HCC and was shown to be involved in the HCC development by targeting its adjacent protein coding genes [137].

### Lnc RNAs and Therapeutic Tools

There have been major advances understanding LncRNAs and is clear their significant involvement in the development of cancer.

Moreover, it has been shown the prognostic value of several lncRNAs as well as their diagnostic and therapeutic potentials. More recently, many of the non-coding RNAs were shown to be novel molecular targets in cancer therapy due their strong predictive and specific expression patterns. lncRNAs have critical roles in cancer and regulating their functions and/or levels have shown promising anti-cancer effects. There are several possible approaches for targeting lncRNAs such as silencing, functional blockage, and structure disruption [138]. More recently, nucleic acid-based methods come up with targeting RNAs either by modulating the level of lncRNAs in cancer cells or modifying their structures [139]. In several types of cancers, knockdown of OncoLncs were shown to inhibit tumor progression and metastasis in cancer cells and tumor xenograft studies [140]. lncRNAs expression signatures either alone or in combination with other types of markers such as miRNAs, siRNAs, mRNAs, proteins, and small inhibitors have been used to predict outcome or treatment follow-up to develop the therapeutic care of cancer patients. Therefore, siRNA-mediated silencing of OncoLncs seems to be an important therapeutic strategy to fight against cancer. siRNAs are complementary to their target lncRNAs, leading to their degradation in RISC complex, results in controlling the activity of these transcripts by decreasing their levels [141]. For instance, distal metastasis in breast cancer was reported to be diminished through siRNA-mediated silencing of HOTAIR [35]. Also, both miR-145 transfection and siRNA-mediated silencing of PCGEM-1 significantly reduced proliferation, invasion, and metastasis in prostate cancer cells [142]. In addition, similar to siRNA-mediated silencing, the use of complementary longer antisense oligonucleotides seems to be an alternative therapeutic strategy in cancer therapy. These longer antisense oligonucleotides are complementary to the target lncRNAs and promote their degradation by RNase H [141]. Besides OncoLncs, miRNA-based therapeutics has received overwhelming volume of attraction. In particular, miRNA mimics and inhibitors are highly attractive for novel therapeutic intervention to cancer therapy. Replacement of the down-regulated miRNA via miRNA mimic or depletion of the up regulated miRNA via miRNA inhibitors (Anti-miRs) is a novel strategy [143]. The first miRNA-based medication is miR-34 mimics and replacement therapy to miR-34 tumor suppressor microRNA and is in phase I clinical trials [144]. All of these approaches may be adapted to target lncRNA transcripts.

lncRNA-based therapeutics have not been used for targeting lncRNAs in clinics yet, however there are three different clinical trials related to detect lncRNA levels in patients with Acute Pancreatitis, Chronic Kidney Disease, and triple-negative breast cancer.

lncRNAs may play crucial roles in the regulation of many pathophysiological processes in cancer development and may be therapeutically targeted. In the near future, non-coding-based cancer therapeutics seems to be promising to fight against cancer and will be soon available to patients.

#### Conflict of Interest

The authors have no potential conflicts of interest to disclose.

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