Long non-coding RNAs: crucial regulators of gastrointestinal cancer cell proliferation

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Abstract
Studies of long non-coding RNAs (lncRNAs) have been prevalent in the field of non-coding RNA regulation in recent years. lncRNAs exert crucial effects on malignant cell processes in the gastrointestinal system, including proliferation. Aberrant lncRNA expression, through both oncogenes and tumor suppressor genes, is instrumental to tumor cell proliferation. Here, we summarize the different molecular mechanisms and relevant signaling pathways through which multifarious lncRNAs regulate cell proliferation and we show that lncRNAs are potential biomarkers for gastrointestinal cancers.

Facts
● Proliferation of gastrointestinal cancers is a consequence of dysregulated signaling pathways and ectopic cellular processes, such as the cell cycle, apoptosis, and angiogenesis.
● lncRNAs play either pro-proliferative or anti-proliferative roles in human gastrointestinal cancers.
● lncRNAs regulate proliferation through interactions with RNA targets, localization to chromatin, or binding to proteins.
● Proliferation-related lncRNAs act on key molecules to activate or inhibit specific signaling cascades.

Open questions
● What cellular processes, e.g., the cell cycle, apoptosis, and angiogenesis, are influenced by lncRNAs to trigger malignant cell proliferation?
● Can lncRNAs from the same gene locus, e.g., 8q24, have similar functions or molecular targets?
● Can lncRNAs be used as biomarkers for gastrointestinal cancer diagnosis or prognosis?

Introduction
A set of transcripts termed long non-coding RNAs (lncRNAs) are some of the most commonly researched non-coding RNA networks. Because of increasingly in-depth studies, it is likely that ~70–80% of human genome can be transcribed into RNAs, and only ~2–3% of these RNAs encode proteins¹. The vast majority of transcripts are actually non-coding lncRNAs². The arbitrary limits of a length of 200 nucleotides and the absence of any detectable open reading frame (ORF) distinguish lncRNAs from other non-coding RNAs³.

Gastrointestinal cancers have high morbidity and mortality rates, which has made them a serious public health problem. They are usually diagnosed in the advanced stages of the disease and there are only limited treatment strategies available. Colorectal cancer (CRC) is the third most common cancer in the world, with ~1.4 million newly diagnosed cases in 2012. Liver cancer is the second leading cause of cancer-related deaths worldwide in men, with an estimated 745,500 deaths. Although less frequent, other gastrointestinal cancers accounted for ~723,100 deaths from gastric cancer (GC) and 400,200 deaths from esophageal cancer (EC) in 2012⁴,⁵.
Tumor cell proliferation is caused by dysregulated cell processes, such as cell cycle progression, apoptosis, and angiogenesis. Normal eukaryotic cells with healthy cell cycles have the ability to control the production and release of growth-promoting signals. The positive control cyclin/cyclin-dependent kinase (CDK) complexes comprise different protein kinases and contribute to the initiation and progression of the cell cycle. CDK inhibitors (CDKIs), such as the ink4 (p15, p16, p18, and p19) and Cip/Kip (p21, p27, and p57) families of proteins, play opposite roles. Ectopic regulation of either the cyclins/CDKs/CDKIs may impinge on cell proliferation and cause malignancy. LncRNAs play highly diverse roles in the regulation of many malignant cell processes, including proliferation. This review summarizes the research progress with respect to the function of lncRNAs in the proliferation of gastrointestinal cancers, highlighting the molecular mechanisms and the recurring signaling pathways involved in these processes.

**Molecular mechanisms of lncRNAs in proliferation**

The function of lncRNAs in the regulation of tumor proliferation is double-sided. On the one hand, some lncRNAs act as oncogene, promoting cell proliferation and survival, whereas, on the other hand, examples exist of lncRNAs that inhibits tumor cell growth. Consequently, lncRNAs are divided into pro-proliferative lncRNAs (Table S1) and anti-proliferative lncRNAs (Table S2). Additionally, some lncRNAs have reversed roles in different gastrointestinal cancers or adverse expression in the same cancer (Table S3). Despite their different functions, lncRNAs have common molecular mechanisms for modulating cell proliferation (Fig. 1).

The interaction between lncRNAs and other RNA targets is of great importance. The competing endogenous RNA (ceRNA)-crosstalk network has become a favorite of researchers over the past few years. CeRNAs are RNA transcripts that have special microRNA-binding sites called miRNA response elements (MREs). Many lncRNAs and mRNAs have MREs, which give them the ability to compete for shared miRNAs. In this case, lncRNAs and mRNAs can regulate each other’s expression. In many gastrointestinal malignancies, lncRNAs may function as ceRNAs to sponge miRNAs, which liberate targeted proliferation-relevant mRNAs at the post-transcriptional level. LncRNAs also engage in RNA metabolism, such as mRNA splicing, transport, translation, and degradation. When localized to nuclear speckles, where abundant spliceosomal proteins and regulatory factors accumulate, lncRNAs coordinate the alternative splicing of pre-mRNA. For instance, SF2/ASF (now called SRSF1) is one of the pivotal factors co-localized with metastasis and associated with lung adenocarcinoma transcript 1 (MALAT1) in nuclear speckles. MALAT1 recruits and changes the specific distribution of SF2/ASF to promote GC proliferation. Complementarily, by direct binding or specific protein induction, cytoplasmic lncRNAs participate in the modulation of either mRNA stability or translation as promoters or inhibitors. In addition, the hybrid duplex between lncRNAs-AS, such as KRT7-AS, and sense mRNAs of their cognate coding genes, have recently been identified in gastrointestinal cancer growth.

Some lncRNAs perform their functions when localized to chromatin. Histone modification plays a central role in epigenetic transcriptional regulation. The acetylation of histones stimulates gene expression, while methylation has dual functions. Transcriptional activation is related to methylation at lysine 4, 36, and 79 of histone 3 (H3K4, H3K36, and H3K79), while silencing is associated with H3K9 and H3K27. Mounting evidence indicates that numerous lncRNAs localized in the nucleus regulate cell cycle progression and proliferation by recruiting chromatin remodeling complexes and specifying histone modification patterns on target genes for their positive or negative expression. The most common remodeling complexes, e.g., methyltransferase polycomb repressive complex 2 (PRC2) and demethylase lysine-specific demethylase1 (LSD1), are regulated by lncRNAs and are responsible for silencing the expression of growth-related genes. Nonetheless, several studies have demonstrated that upregulated zeste homolog2 (EZH2), known as a key component of PRC2, increases cyclin D1 expression and stimulates tumor cell growth, but the exact mechanism is unclear. Gastric cancer-associated lncRNA 1 (GCInc1) is a molecular bridge that connects specific enzyme complexes, e.g., histone methyltransferase (WDR5) and acetyltransferase (KAT2A), with the target gene SOD2. SOD2 promotes proliferation because GCInc1 binds to and guides WDR5 and KAT2A to the SOD2 promoter, upregulating H3K4 trimethylation and H3K9 acetylation to improve its expression.

In addition, lncRNAs actively interact with transcribed gene loci to control the expression of those genes. For instance, lncRNAs transcribed from some active chromatin states have a propensity for modulating the expression of their neighboring genes as enhancer-associated RNAs. By binding directly to the promoter sequences, these enhancer lncRNAs affect the transcription of proximal genes that are correlated tightly with cell proliferation and tumor growth in cis.

Many studies have underscored the significance of crosstalk with diverse proteins. When lncRNAs interact with proteins, they function as scaffolds, guides, decoys, and signals. LncRNA scaffolds with complicated and functional three-dimensional structures serve as a platform to collect regulatory protein partners, such as LSD1 and PRC2, to promoter regions of proliferation-related
genes. Moreover, the formation of the complex including IncRNA and ribonucleoprotein (RNP), e.g., hnRNP-K, suggests that IncRNAs serve as guides that lead proteins to their target sites. Some IncRNAs, such as the UHRF1 protein-associated transcript (UPAT), influence growth by modulating protein ubiquitination and degradation.
LncRNAs inhibit pro-ubiquitination proteins by acting as decoys that prevent them from executing their functions. Additionally, when confronted with various stimuli, some lncRNAs function as molecular signals, exhibiting cell-type-specific expression and regulating biological events involving the cell cycle or apoptosis.

**LncRNAs govern proliferation through different signaling pathways**

The malignant proliferation of gastrointestinal tumor cells is always accompanied by the dysregulation of multiple signaling pathways. LncRNAs mediate cell growth by acting on key molecules to activate or restrain specific signaling pathways.

**P53 signaling pathway**

As a canonical suppressor and crucial cell cycle gatekeeper, p53 is capable of suspending the cell cycle when eukaryotic cells suffer from drastic DNA damage or deficient oxygenation. Nonetheless, if the stress signals appear overwhelming and irreparable, p53 tends to induce permanent cell cycle arrest (cellular senescence) or apoptosis instead. The p53 transcriptional response during carcinogenesis and tumor cell proliferation includes the activation and inhibition of various genes. The repressive function of p53 is closely correlated to that of lncRNAs. LncRNAs regulate p53 and are key components of the p53 pathway (Fig. 2).

P53 effectors are those lncRNAs coordinated by p53. There is a reciprocal repression feedback loop between loc285194 (LSAMP antisense RNA 3 or TUSC7) and microRNAs that belong to the ceRNA crosstalk networks, and loc285194 has a consensus response element (p53RE) in its promoter that binds directly to p53. In this way, loc285194 functions as a downstream p53 effector that exerts its anti-proliferative role by binding miR-211 in CRC and miR-23b in GC. Another representative lncRNA is intergenic lincRNA-p21.

When confronted with DNA damage, the activated p53 signal induces lincRNA-p21, which executes suppressive functions at both the transcriptional and post-transcriptional levels. In the nucleus, lincRNA-p21 promotes its neighboring gene p21 as an RNA enhancer and downregulates various p53 target genes to facilitate apoptosis by directly binding to hnRNP-K. In the cytoplasm, however, lincRNA-p21 degrades in an HuR-dependent manner to de-repress Rck, which activates β-catenin and the cell cycle catalyst JunB.

Other lncRNAs also regulate p53. The tumor suppressor role of maternally expressed gene 3 (MEG3) and long non-coding RNA-low expression in tumor (lncRNA-LET) is evident in several gastrointestinal cancers. Data from other studies indicate that the anti-proliferative function of lncRNAs is partially accomplished by activating the p53 pathway. In CRC and hepatocellular carcinoma (HCC), zinc finger antisense 1 (ZFAS1) destabilizes p53 to modulate CDK1 and the expression of its partner, cyclin B1, thus facilitating the G1/S transition, while highly upregulated in liver cancer (HULC) represses its neighboring eukaryotic translation elongation factor 1 epsilon 1 (EEF1E), which is a pivotal p53 activator and this mechanism promotes tumor cell growth.

LncRNA-ROR and lincRNA-H19 can be both regulators and effectors of p53 in gastrointestinal cancer proliferation. Overexpressed ROR increases CRC growth by inhibiting p53. Studies have shown that lncRNA-ROR is under the control of p53 in response to DNA damage. LncRNA-H19 is only activated by p53 through the HIF pathway in HCC but, in GC, it precludes p53 activity and represses Bax expression to avoid apoptosis.

**Akt signaling pathway**

Akt signaling role in tumorigenesis is well established. Activated by growth factors or angiogenesis inducers through receptor tyrosine kinases (RTKs), PI3K phosphorylates PI2 to produce PI3, while the phosphatase and tensin homolog deleted on chromosome 10 (PTEN) inhibits this process. Like RTKs, PI3K is also a direct effector of the Ras protein, which provides crossstalk with the MAPK signaling pathway. Additionally, protein kinase B (PKB/Akt) and mammalian target of rapamycin (mTOR) play crucial roles in cell growth stimulation. By inhibiting the expression of cyclin D1, Bcl-2 antagonist of cell death (Bad), and caspase-9 by increasing their phosphorylation levels, Akt promotes the G1/S transition and prevents tumor cells from undergoing apoptosis. The concomitant activation of HIF-1 and vascular endothelial
growth factor (VEGF) corroborate the involvement of Akt in angiogenesis to indirectly facilitate proliferation (Fig. 3)\(^{54,55}\).

Ectopic expression of linc00152 accelerates cell proliferation in many gastrointestinal cancers\(^{56}\). Linc00152 directly binds and activates the epithelial growth factor receptor (EGFR), which is a member of the RTK family\(^{52,57}\). In HCC, linc00152 activates the PI3K/Akt/mTOR cascades by binding directly to its neighbor, then TOR-related gene EpCAM through cis-regulation\(^ {58}\). In gallbladder cancer (GBC), overexpressed linc00152, induced by transcription factor specificity protein 1 (SP1), promotes proliferation via the PI3K/Akt pathway\(^ {56}\). Another lncRNA, urothelial carcinoma-associated 1 (UCA1), is highly expressed in GC. UCA1 elevates cyclin D1 expression and the G1/S transition by binding directly to cyclin D1 promoter and also by activating the AKT/GSK3\(\beta\)/cyclin D1 axis. Furthermore, EZH2 and phosphorylated Akt can influence the expression of each other to form a positive feedback loop. In conclusion, UCA1 stimulates proliferation by increasing EZH2 and activating the Akt pathway\(^ {56}\).

In terms of lncRNA-H19, the expression of the tumor suppressor RUNX1 is downregulated by the lncRNA-H19/miR-675 axis to induce Akt/mTOR signal activation; however, in GBC, lncRNA-H19 acts as a ceRNA for miR-194-5p to liberate Akt\(^ {56-62}\).

Like PI3K, PTEN is a well-known regulator of Akt. The pseudogene-derived lncRNA fer-1-like family member 4 (lncRNA-FER1 L4) is strongly downregulated in GC and induces cell cycle arrest. Because FER1 L4 and PTEN mRNA both target miR-106a-5p and because PTEN is a cell cycle inhibitor, it is likely that the anti-proliferative role of FER1 L4 occurs partially through the PTEN/Akt pathway\(^ {63}\). Upregulated AFAP1-AS1 may mediate GC proliferation and apoptosis by the same mechanism\(^ {64}\). The lncRNAs AB073614 and RP11-708H21.4 are highly expressed in CRC and stimulate proliferation and hamper apoptosis through the Akt signaling pathway, while the exact lncRNA functional molecules warrant further investigation\(^ {65,66}\).

**MAPK signaling pathway**

Mitogen-activated protein kinases (MAPK) are part of the serine–threonine kinase family and they participate extensively in tumorigenesis. Activation of the MAPK pathway, by phosphorylating MAPK kinases, MEK1/2, and extracellular-signal-regulated kinases (ERK1/2), contributes to perpetual cell growth and survival\(^ {53}\). ERKs coordinate the synthesis of cyclin D1 and the degradation of the INK4 proteins, such as CDKN1A (p21) and CDKN2B (p15) (Fig. 3)\(^ {67}\).

MALAT1, which is localized on chromosome 11q13.1, is highly expressed in gastrointestinal cancers. In GBC, the knockdown of MALAT1 significantly impairs the expression of phosphorylated MEK1/2, ERK1/2, and JNK without any changes in quantity, suggesting that this lncRNA is likely to improve GBC proliferation by activating the ERK/MAPK signaling pathway\(^ {68}\). Upregulated zinc finger protein X-linked (ZFX) and cervical carcinoma
expressed PCNA regulatory lncRNA (CCHE1) increase cell cycle progression and decrease apoptosis to stimulate proliferation because of their similar mechanisms in GC and HCC, respectively.69,70 Nevertheless, the direct link between lncRNAs and the MAPK pathway remains enigmatic.

**Wnt/β-catenin signaling pathway**

The Wnt signaling pathway can be categorized as either canonical or non-canonical based on its downstream components. Here, we focus on the former because of its important role in gastrointestinal cancer initiation and progression. The activation of the canonical Wnt pathway, accurately termed the Wnt/β-catenin/TCF signaling pathway, mainly depends on translocation of the central oncogene, β-catenin. Both negative mutation of adenomatous polyposis coli (APC) or axin and positive mutation of β-catenin itself can lead to cytoplasmic accumulation of free β-catenin and its translocation to the nucleus to bind to T cell factors (TCFs). Consequently, a series of downstream targets, including c-MYC, cyclin D1, MMP7, and ITF-2, undergo transcriptional activation. LncRNAs interact with critical components of the canonical Wnt pathway and are therefore involved in the regulation of cell proliferation (Fig. 4).

LncRNA colorectal neoplasia differentially expressed (CRNDE) is upregulated in CRC and can act as ceRNA for different miRNAs to promote tumor proliferation. Han et al. demonstrated that β-catenin and TCF4 are targets of miR-181a-5p, which inhibits their expression. Similarly, miR-217 modulates transcription factor 7-like 2 (TCF7L2). Because overexpressed CRNDE hampers specific miRNAs that inhibits β-catenin, TCFs, c-MYC, and cyclin D1, its pro-proliferation function is partially exerted through the Wnt/β-catenin pathway.

In addition to inducing miRNA expression, proteins can also serve as bridges between lncRNAs and key components of the Wnt pathway. HnRNP-K, a protein with a nuclear shuttling domain (KAS), interacts with β-catenin and TCF4 to facilitate the import and nuclear accumulation of β-catenin. A positive feedback loop between CASC11 and hnRNP-K provides an alternative explanation for how the upregulation of CASC11 activates the Wnt/β-catenin pathway to stimulate CRC growth through the induction of hnRNP-K. c-MYC, an important target of β-catenin, increases CASC11 expression through epigenetic regulation.

LncRNAs stimulate the Wnt signaling pathway through direct physical interactions with key effectors. Ling et al. confirmed that CCAT2 increases TCF7L2 transcriptional activity without affecting its quantity in CRC. Furthermore, CCAT2 is likely to be a downstream target of the Wnt pathway because of the TCF7L2-binding element within its SNP loci. This positive feedback loop supports the function of highly expressed CCAT2 in CRC growth. Similarly, the combination of lincRNA-p21 and its mRNA target, CTNNB1, precludes the translation of β-catenin, which suggests that the anti-proliferative role of lincRNA-p21 in CRC is accomplished through the canonical Wnt pathway. The snoRNA host gene 16 (SNHG16) is regulated by Wnt targets, including TCF1, TCF4, and c-MYC, and its knockdown promotes CRC cell death and apoptosis. This presents the possibility that upregulated SNHG16 may stimulate tumor proliferation via the Wnt pathway. Data from Wang et al. demonstrate that the expression of lncRNA UCA1 is reduced in esophageal squamous cell carcinoma (ESCC) and overexpressed UCA1 decreases the levels of the active form of nuclear β-catenin. So, UCA1 may inhibit ESCC growth through the Wnt/β-catenin signaling pathway.

**MYC signaling pathway**

The proto-oncogene MYC is frequently upregulated in gastrointestinal cancers, and its gene product is a transcription factor that can accelerate cell proliferation by regulating the expression of genes involved in cell cycle progression. It upregulates the expression of cyclin D and cyclin E, which both promote cell cycle progression. Myc also hampers expression of crucial cyclin/CDK inhibitors, such as CDKN2B (p15), CDKN1A (p21), and CDKN1B (p27). MYC lies at the crossroads of the pathways involved in regulating cellular proliferation. It is a downstream target of the Wnt, Akt, MAPK, and TGF-β signaling cascades and activates the p53 and ARF checkpoints, which makes it even more important to cell growth regulation (Fig. 5b). LncRNAs both support and repress the pro-proliferative function of MYC by...
regulating the MYC-target cell cycle modulator genes (Fig. 5a).

Colon cancer-associated transcript 1 (CCAT1), CASC11, plasmacytoma variant translocation 1 (PVT1), and PCAT-1 are IncRNAs that are all localized on the gene desert of chromosome 8q24 and interact with MYC. Among them, CCAT1 and CASC11 can be induced by MYC due to the presence of an E-box Myc-responsive element in their promoters75,82–84. In CRC, the PVT1 expression correlates with c-MYC expression levels. Similarly, MYC-related IncRNAs MYCLos are overexpressed in CRC and sustain MYC-driven tumorigenesis. Indeed, MYCLo-1 represses p21, whereas MYCLos-2 (CCAT6) represses p15 by interacting with the HuR and hnRNP-K proteins, respectively79. By binding to the promoter of LncRNA-H19 in GC or of HOTAIR in GBC, c-MYC increases their expression43,85. In some instances, MYC can also restrict IncRNA expression. For example, IncRNAs MYCLo-4, -5, and -6, with known tumor-suppressive roles in CRC, are repressed by MYC86.

Notably, MYC can be characterized as a downstream effector of IncRNA. For instance, IncRNA gastric carcinoma high expressed transcript 1 (GHET1) was found to be upregulated in GC. By binding to insulin-like growth factor 2 mRNA-binding protein 1 (IGF2BP1), GHET1 increases the physical interaction between c-Myc mRNA and IGF2BP1, therefore improves the stability of c-Myc mRNA and upregulates its expression. The expression of GHET1 and c-Myc are strongly associated and link with malignant progression in GC87.

Other signaling pathways

The distribution of regulatory T cells (T-regs) is highly necessary in immune processes and tumorigenesis. T-reg differentiation, TGF-β recruitment, and the subsequent increase in phosphorylated SMAD3 and SMAD2 induced by linc-POU3F3, result in a pro-proliferative role in GC88. Takahashi et al. reported that knockdown of PVT1 in CRC could activate several genes of the TGF-β signaling pathway, including SMAD4 and ROCK1. These genes are capable of inducing apoptosis and invasion89. Moreover, a feedback loop between TGF-β and PVT1 in HCC has been suggested, as PVT1 can not only be induced by TGF-β but, in turn, it also activates the TGF-β signaling pathway90.

The hypoxia-inducible factor-1 (HIF-1) sustains cell proliferation and survival, and angiogenesis in hypoxic tumor areas. A crosstalk between the HIF-1 pathway and IncRNA network exists5,44. LncRNA-ROR sponges miR-145 to increase HIF-1α expression and therefore expression of its downstream target VEGF49. lncRNA-LET stabilizes NF90 (a double-stranded RNA-binding protein) to improve HIF-1α mRNA stability in GBC, while p53 increases H19 expression through the HIF signaling pathway in HCC43,45,51.

The previously discussed IncRNA MALAT1, which is overexpressed in ESCC, induces dephosphorylation of the ATM/CHK2 pathway thereby overcoming the G2/M cell cycle checkpoint91. In addition, MEG3 and lncRNA-p21 contribute to apoptosis and growth inhibition through endoplasmic reticulum (ER) stress pathways in ESCC and
HCC, respectively. In GC, IncRNA gastric cancer-associated transcript 3 (GACAT3) works as a downstream target of I6/STAT3 signaling pathway to accomplish its function.

Conclusions

Although advancements in surveying the molecular mechanisms underly the actions of proliferation-associated IncRNAs have broadened our ability to annotate these tumor-related transcripts, the exact signaling pathways in which many IncRNAs participate remain unclearly defined. The major signaling cascades and specific functional sites reviewed here may provide a foundation upon which new IncRNAs involved in gastrointestinal tumor proliferation can be identified and may motivate an increased focus on understanding the signaling pathways, which remain enigmatic. Malignant cell growth can be non-comprehensive because it can be caused by any of several dysregulated cellular processes, such as the cell cycle, apoptosis, angiogenesis, and cell senescence; it is likely that the IncRNAs described here are important regulators of these pathophysiological processes. Consequently, IncRNAs characterized as oncogenes or tumor suppressors that modulate proliferation may be promising biomarkers and therapeutic targets in gastrointestinal cancers.
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