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*Review Article*

# Role of long non-coding RNAs in cancer and associated signal transduction pathways

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**Abstract:** LncRNAs have been shown to regulate multiple major biological processes in development processes and differentiation. Accumulating evidence suggests that lncRNAs play an important role in tumorigenesis. Up to now, genetic, epigenetic and transcriptional and posttrancriptional regulatory mechanisms have been clarified to involve in lncRNA disregulation in cancers. However, the detailed mechanisms of most lncRNAs involve in the cancer-associated signal transduction pathways remain largely unknown. In this review, we highlight the recent studies about the biological characteristics of lncRNAs in cancer, and the role of lncRNAs in some conventional caner-associated signaling pathways for clinical application in diagnosis, prognosis and potential treatment.

**Keywords:** Long non-coding RNAs, cancer, signal transduction pathways, regulation, mechanism

## Introduction

RNA was considered as an intermediate between DNA and protein. The central dogma has provided us a simplified framework of how genetic information is translated into diversity of biological process [1]. With the genome-wide sequencing technology and transcriptome analysis the astonishing notion is found that up to 70%-90% of the human genome is transcribed into RNA [2-4]. However, only 1%-2% of the human genome contains the blueprint for protein-coding transcripts, which led to the birth of a new category of transcripts-non-coding RNAs (ncRNAs). The long non-coding RNAs (lncRNAs) are defined as noncoding RNA molecules greater than 200 nucleotides in length according to the size [5]. Many of the lncRNAs are expressed in a tissue-specific and timely restricted manner and show a low level of expression and sequence conservation [6, 7] suggesting a distinguished and regulatory. LncRNA based on their genomic proximity to protein-coding genes, including five types: sense, antisense, bidirectional, intronic and intergenic [8, 9].

The current research has shown that lncRNAs regulate multiple major biological processes in development processes and differentiation, and play a role in human diseases, certainly including cancer [10]. LncRNAs play significant regulatory roles as activators, decoys, guides, or scaffolds for their interacting proteins, such as transcription factors and histone modifiers [11]. Besides these transcriptional and epigenetic regulations, lncRNAs have also been found to be important players in posttranscriptional regulation, such as mRNA editor, mRNA splicing regulators, and reservoirs of small ncRNAs [12].

Accumulating evidence suggests that lncRNAs play an important role in tumorigenesis [13, 14]. However, the detailed mechanisms of most lncRNAs involve in these cancer-associated signal pathways remain largely unknown. In this review, we will overview the recent studies about the biological characteristics of lncRNAs

in cancer, and the role of lncRNAs in some conventional caner-associated signaling pathways.

## Role of lncRNA in cancer

It is not surprising that lncRNAs have been implicated in cancer, considering the wide range of roles that lncRNAs play in cellular networks [15], and the broader involvement of lncRNAs in cancer has been extensively reviewed elsewhere [10, 16, 17]. In particular, several large-scale studies have led to the identification of several lncRNAs-based expression signatures of malignancy [18, 19]. These experimental approaches have suggested that various lncRNAs are indeed involved in cellular transformation, acting as potential tumour suppressors or oncogenes, and leading to tumorigenesis [10]. Up to now, genetic, epigenetic and transcriptional and posttranscriptional regulatory mechanisms have been clarified to involve in lncRNA disregulation in cancers [1].

### *Epigenetic regulation of lncRNA in cancer*

The epigenetics is currently used to refer to the study of heritable changes in gene expression that occur independently of modifications in the primary DNA sequence. The possible mechanism of epigenetic regulation of lncRNA included two types: one kind of actions is directly on lncRNA genes-epigenetic changes during tumorigenesis or contribute to cancer development. The most common epigenetic modifications of cancer-associated lncRNA are loss of imprinting or changed methylation (hypomethylation and hypermethylation). Another is lncRNAs themselves can act as triggers for epigenetic modification of other functional genes and thereby cause or prevent diseases [20]. Generally, these changes can include variable patterns of DNA methylation, nucleosome positioning and histone modifications [21].

*DNA methylation:* DNA methylation affects cytosine residues in CpG dinucleotides concentrated in CpG islands. lncRNAs can recruit DNA methyltransferases, resulting in induced methylation or demethylation, which is commonly associated with silencing of tumor-suppressor genes in many cancer types [22, 23]. A possible mechanism in which lncRNAs affecting DNA methylation is that lncRNAs interacts with a DNA methyltransferase and guides this protein to specific targets, leading to the methylation of the promoters and repression of tumor suppressor genes [21]. A recent study identified 707 potential cancer-related lncRNAs and showed that these lncRNAs tend to exhibit significant differential expression and differential DNA methylation in multiple cancer types [24]. In addition, lncRNA TARID has been proven to activate the tumor suppressor TCF21 expression by inducing promoter demethylation with the GADD45A, a regulator of DNA demethylation [25].

*Nucleosome positioning:* The positioning and remodelling of the nucleosomes are able to regulate the gene expression by altering the accessibility of regulatory DNA sequences to transcription factors and to the transcriptional machinery [26]. Like the role of lncRNA in DNA methylation in cancer, the participation of nucleosome positioning in tumours is less well understood. A possible participation of lncRNAs in changing the nucleosome positioning is that lncRNAs can interact with a nucleosome remodelling complex, leading to the restructuring or dislocation of the nucleosome in specific genomic regions. An increase in the packing of the nucleosome in a region containing a tumor suppressor gene can lead to its repression [21]. A newly study revealed that dysregulation of lncRNA HNF1A-AS1 participates in oesophageal tumorigenesis mediated, at least in part, by modulation of chromatin and nucleosome assembly as well as by H19 induction, a mechanism essential to cell cycle progression [27].

*Histone modifications:* Histone modifications are catalysed by a large variety of histone-modifying enzymes, which are able to read, add or remove covalent modifications to histone proteins [28]. Histone modification occurs in cis-function, when the lncRNA recruits the histone-modifying enzymes to the genes in the vicinity of the site of lncRNA transcription. And other lncRNAs act in trans-regulation by recruiting the histone-modifying enzymes to different loci away from the lncRNA transcription locus. For example, in prostate cancer, lncRNA CTBP1-AS regulates epigenetic network in response to androgens, acting in cis and in trans [29]. CTBP1-AS was shown to repress the sense CTBP1 mRNA in cis and therefore to be associated with stimulation of cell proliferation. CTBP1-AS acts in trans by participating in the recruitment and influencing the DNA-binding

activity of PSF to genes involved in the cell cycle.

*Transcriptional regulation of lncRNA in cancer*

In addition to regulating gene expression by recruiting epigenetic complexes, lncRNAs can directly affect the process of transcription by influencing the activity of specific transcription factors (TFs) and polymerases due to the wide-spread distribution. The regulation of lncRNAs, in transcriptional level, depends on the relative position and sequence features of the lncRNA and the target gene to regulate gene expression. For instance, lncRNA HOTAIR usually shows overexpressed patterns in early and metastatic breast cancer cells [30]. Mechanically, HOTAIR regulates the gene expression by interacting with polycomb repressive complex 2 (PRC2) and lysine-specific demethylase 1A. Together with these two enzymes, HOTAIR can control methylation and demethylation status of histones [30].

*Posttranscriptional regulation of lncRNA in cancer*

Obviously, lncRNAs, particularly antisense transcripts, can specifically interact with complementary mRNAs via the formation of a RNA dimer via complementary base pairing which can block the binding sites of transcription factors and processing-related factors that affect various processes of posttranscription, such as regulating mRNA splicing, transport, translation and degradation [31, 32]. As for lncRNA MALAT1, a recent study reveals that MALAT1 regulates the alternative splicing of pre-mRNAs by modulating the activation of serine/arginine splicing factors [33], implying that MALAT1 regulates the posttranscriptional processing or modification of RNA.

Besides the genetic and epigenetic changes conferring the dysregulation of lncRNAs in cancer, there are dozens of lncRNAs altered in cancers having been documented to be regulated by specific oncogenic and tumor-suppressor related signals and regulatory factors.

## Role of lncRNAs in cancer-associated signal transduction pathways

The signaling transduction pathways such as Wnt, p53, ERK/MAPK, PI3K/AKT, cAMP/PKA and so on, regulating the cell growth and differention in normal microenvironment, can become disordered and aberrant frequently during the initiation and progression of cancers. As we mentioned above, because of the abroad range of involvement in cellular networks and the huge amount, lncRNAs play an important and wide role in many signal transduction pathways in cancer development. As the potential tumor suppressors and/or oncogenes, lncRNAs are strongly linked with some conventional but aberrant caner-associated signal transduction pathways. In this regard, aberrant lncRNAs can regulate these signal transduction pathways in cell to promote the cancer development through the down-regulation of suppressors or the up-regulation of oncogenes as the regulators. Meanwhile, aberrant transcriptional and expression of lncRNAs in cancers can also be regulated by multiple kinds of signal pathways as the effectors like protein-coding genes or microRNAs. Thus, lncRNAs and cancer-related signal pathways compose together complex regulation networks to participate amount of cancer cell biological activities.

*Role of LncRNAs as regulators in signaling pathways*

Some lncRNAs are capable of directly or indirectly regulating signal transduction pathways in cancer. Although the regulation can occur at the transcriptional or posttranscriptional levels, to data, the evidence of regulation of signaling pathways by lncRNAs is still unclear. Available evidence points of regulation by lncRNAs, which may be able to either activate or suppress the signal transduction pathways.

*Wnt/β-catenin signaling pathway:* The canonical Wnt pathway regulates the stability of the proto-oncogene β-catenin and is aberrantly activated in many cancer types [34]. The Wnt/β-catenin signaling pathway is an evolutionarily conserved pathway which plays an important role in regulating cell proliferation and migration and in controlling tumor progression. Aberrant activation of this pathway, generally caused by genetic and epigenetic alterations, has been linked to several types of tumors [35].

Recent study has found the mechanism of lncRNA HOTAIR in esophageal squamous cell carcinoma (ESCC) via Wnt/β-catenin signaling pathway via newly identified HOTAIR/WIF-1 axis

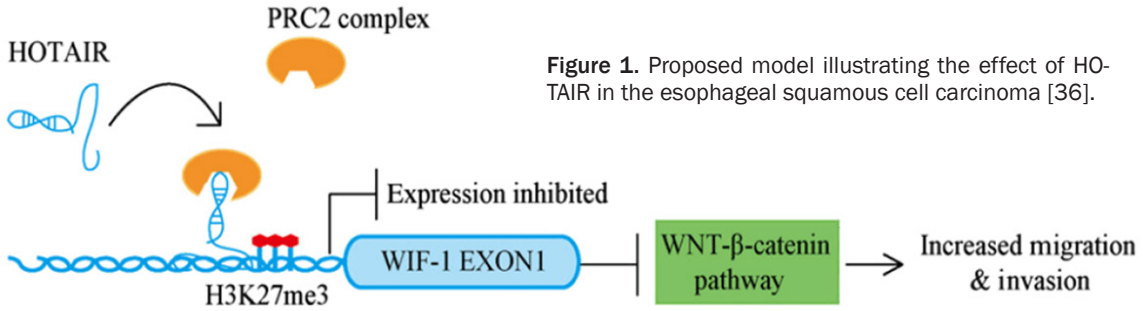


**Figure 1.** Proposed model illustrating the effect of HOTAIR in the esophageal squamous cell carcinoma [36].

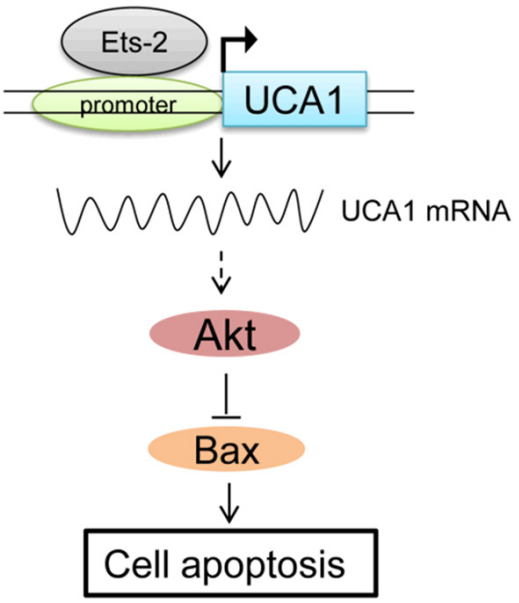


**Figure 2.** Proposed model illustrating the UCA1 regulation by Ets-2 [41].

[36]. The overexpression of HOTAIR, along with PRC2, directly inhibited WIF-1 expression by promoting its histone H3K27 methylation region in the WIF-1 promoter region to activate the Wnt/β-catenin signaling pathway and then induced ESCC cell metastasis (**Figure 1**) [36]. In bladder cancer, associated with enhancer EZH2, LncRNA H19 activates Wnt/β-catenin pathway and subsequently downregulates E-cadherin [37]. Thus, the overexpression of H19 increases bladder cancer metastasis by associating with EZH2 and inhibiting E-cadherin expression. In addition, as for the chemotherapy of bladder cancer, the recent study reveals that lncRNA UCA1/Wnt6 signaling represents a novel pathway regulating chemoresistance [38]. Upregulated UCA1 increases Wnt6 expression and activates Wnt signaling, which results in the cisplatin resistance. And this will be useful for predicting treatment outcome and developing effective chemotherapeutic agents.

*AKT signaling pathway:* The serine-threonine kinase Akt (also known as protein kinase B) is a central convergence node in a broadly influential signaling network. AKT pathway regulates essential cellular functions such as migration, proliferation, differentiation, apoptosis, and metabolism [39].

Just as we mentioned above, lncRNA UCA1 is correlated with cell proliferation and migration in bladder cancer [40]. Another study [41] demonstrated that transcription factor Ets-2 can directly band to the UCA1 promoter region and stimulate UCA1 promoter activity in bladder cancer cells, and Ets-2 knockdown enables to induce apoptosis in bladder transitional cell carcinoma cell lines suggesting that UCA1 may be involved in the activation of AKT signaling pathway by Ets-2 in bladder cancer cells (**Figure 2**). LncRNA H19 also has been proven to play an important role of invasion [42] and carcinogenesis [43] in hepatocellular carcinoma (HCC). A newly study suggested that inhibition of H19 with miR-675 promotes migration and invasion of human HCC cells by activating the AKT/GSK-3β/Cdc25A signaling pathway which may partly explain the molecular mechanism of migration and invasion in HCC [44]. In addition, lncRNA PTENP1 was effectively delivered and ectopicly expressed in HCC cells. Then, the overexpressed PTENP1 repressed the oncogenic PI3K/AKT pathway and elicited pro-death autophagy via sequestering miR-17, miR19b and miR-20a in vitro, and inhibited the HCC tumor growth in vivo, which was accompanied by enhanced apoptosis, autophagy and dampened angiogenesis/neovasculature maturation demonstrating the potentials of modulating PTENP1 for HCC therapy [45]. In non-small cell lung cancer (NSCLC),

LncRNA TUG1, recruiting and binding to polycomb repressive complex 2 (PRC2), is generally downregulated in NSCLC tissues [46]. The recent study reveals that TUG1 can participate in AKT and MAPK pathway through the modulation of HOXB7, by the binding to PRC2, indicating that TUG1 affects NSCLC cell growth at least partly through the epigenetic regulation of HOXB7 [47].

*ERK/MAPK signaling pathway:* The ERK/MAPK pathway impinges on all the functional hallmarks of cancer cells, including immortalisation, growth-factor-independent proliferation, insensitivity to growth-inhibitory signals, ability to invade and metastasis, ability to attract blood vessels, and evasion of apoptosis. Indeed, the pathway is hyperactivated in 30% of all human tumours including prevalent cancers of the colon and lung [48].

LncRNA MALAT1 was found to promote tumor growth and metastasis by activating this signaling cascade [49, 50]. ERK/MAPK pathway was found to be inactivated in the gallbladder carcinoma (GBC) cell lines after MALAT1 knockdown which indicated that MALAT1 might serve as an oncogenic lncRNA that promotes proliferation and metastasis of GBC and activates the ERK/MAPK pathway [51]. In HCC, the recent study was demonstrated that, the levels of a novel lncRNA URHC were significantly increased and it can regulate cell proliferation and apoptosis via ERK/MAPK inactivation by targeting ZAK which is the neighboring gene located near URHC [52]. Thus, the ERK/MAPK pathway inactivation functioned as the downstream of URHC-ZAK axis partially accounted for URHC-ZAK-induced cell growth and apoptosis. Another widely expressed lncRNA, BANCR was confirmed the role in the proliferation of malignant melanoma involved of MAPK pathway in this process [53]. BANCR regulated melanoma proliferation synergistically with ERK1/2 and JNK activation of which are the terminal MAPKs both in vitro and in vivo meaning that BANCR can promote melanoma proliferation via activating ERK1/2 and JNK MAPK pathway [53].

*p53 signaling pathway:* The p53 tumor suppressor pathway is activated in the presence of cellular stress, such as DNA damage and oncogenic signaling, and in turn coordinates the transcriptional response of hundreds of genes [54].

The present studies have shown that lncRNAs are part of the p53 transcriptional network [55, 56]. LincRNA Pint, interacted with PRC2, is a bona fide p53 transcriptional target. The newly study has proven that Pint is downregulated in colorectal cancer, and considered to serve as a novel tumor suppressor, which established a new connection between the tumor suppressor p53 and epigenetic regulation by PRC2 [57]. Another p53-regulated lincRNA p21 has been proposed to act in trans via several mechanisms ranging from repressing genes in the p53 transcriptional network to regulating mRNA translation and protein stability [58]. The findings in the recent study show that p21 acts in concert with hnRNP-K as a coactivator for p53-dependent p21 transcription indicating that p21 as a key modulator of gene expression via influencing the p53 tumor suppressor pathway, by affecting the activation and the chromatin state of hundreds of genes through its cis control of p21 expression [59].

*ATM-CHK2 signaling pathway:* The ATM-CHK2 pathway is an important component of cell cycle regulation, which responds to DNA damage signals, and prevents tumors growing too fast by arresting cell cycle in G2/M stage [60].

In esophageal cancer (ESCC), a newly study showed that [61], ESCC growth is moderated by the ATM-CHK2 pathway which is involved in cell cycle orchestrating. In addition, a negative association between MALAT1 expression and ATM-CHK2 pathway phosphorylation was revealed suggesting that upregulation of MALAT1 may promote ESCC growth by dephosphorylation of the ATM-CHK2 pathway, which may lose the cell cycle arrest. In addtion, another lncRNA CUDR may promote tumorigenesis through upregulating PDGFB in tumorigenesis pathway and downregulating FAS and ATM in cell apoptosis pathway in bladder cancer [62].

*STAT3 signaling pathway:* STAT3 induces progression through the cell cycle, prevents apoptosis and may be associated with cancer development in some cases, which plays an important role in normal development, particularly hematopoiesis [63]. Most cancer cells rely mainly on aerobic glycolysis to generate the energy known as the Warburg effect [64].

In a newly study discovered that UCA1 promotes glucose consumption and lactate pro-

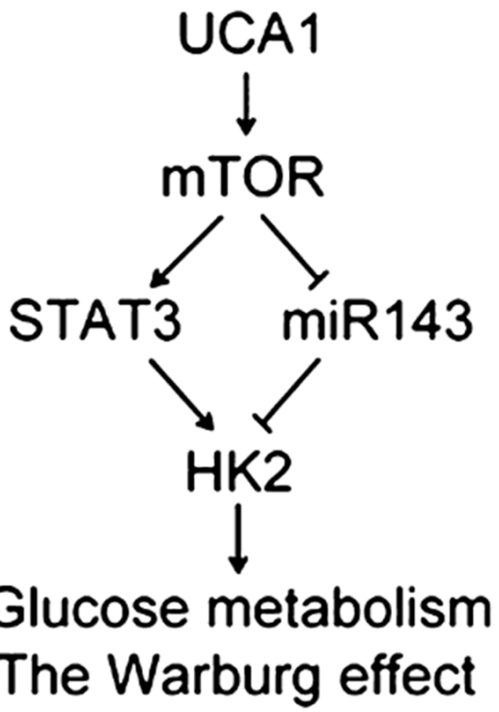


**Figure 3.** Proposed model illustrating the representation of the mechanism for UCA1-regulated metabolic switch [65].

duction in bladder cancer cells revealing a novel UCA1-mTOR-STAT3/miR143-HK2 axis that links lncRNA and glucose metabolism in cancer cells [65]. Two signals control are found in the regulation of HK2 by UCA1 through the mTOR pathway. First, UCA1 facilitates the activation of STAT3, which promotes the transcription of HK2. Second, UCA1 represses miR143 and subsequently restores HK2 expression at the post-transcriptional level. The importance of this dual-control system is reflected by the results that both activation of STAT3 and repression of miR143 are required for UCA1 to accelerate glycolysis in bladder cancer cells. (**Figure 3**).

*Role of LncRNAs as effectors in signaling pathways*

Like protein-coding genes or microRNAs, lncRNAs can also serve as signaling pathways effectors. The transcriptional properties of lncRNAs suppose regulations of lncRNAs are involved in amount of transcription factors which are, furthermore, strongly linked to corresponding with signaling pathways. Profiling experiments probably are the most effective way to identify such lncRNAs. Therefore, the following lncRNAs participate in the signaling pathways network by serving as the effectors.

*Wnt/β-catenin signaling pathway:* As we mentioned, LncRNA MALAT1 involves in the Wnt/β-catenin signaling pathway in cancer initiation and progression which can also be an effector regulated in Wnt signaling pathway.

In endometrioid endometrial carcinoma (EEC), MALAT1 is as the effector through a novel PCDH10- Wnt/β-catenin -MALAT1 regulatory axis which contributes to EEC development and progression [66]. The mechanistic studies uncovered that MALAT1 expression is transcriptionally induced by Wnt/β-catenin signaling through a direct binding site of TCF4 in MALAT1 promoter region and PCDH10 decreased MALAT1 by modulating this pathway (**Figure 4**). In addition, in liver cancer, MALAT1 is a genuine and common target gene of both the Wnt/TCF/β-catenin and Hippo/YAP signaling pathway. And the association between YAP and TCF/β-catenin may synergies in promoting MALAT1 expression [67].

*PI3K/AKT signaling pathway:* LncRNA HOXD-AS1 is encoded in HOXD cluster. A newly study implied that HOXD-AS1 is a subject to morphogenic regulation, which is activated by PI3K/AKT pathway in a human metastatic neuroblastoma model and itself is involved in control of retinoic acid-induced cell differentiation could be regulated via PI3K/AKT pathway by oncogenic BDNF/TrkB axis. And in bladder cancer, through the PI3K/AKT pathway, the expression of lncRNA UCA1 can give rise to cell proliferation and regulate cell cycle progression by activating CREB [68] which is a leucine zipper type transcription factor participating in oncogenesis in many types of cancer [69].

*TGF-β signaling pathway:* The multifunctional cytokine transforming growth factor-β (TGF-β) orchestrates an intricate signaling network to modulate tumorigenesis and progression [70, 71] through inducing cell-cycle arrest and apoptosis, in part by its ability to induce epithelial-mesenchymal transition (EMT) [72, 73].

The newly study found that in HCC, lncRNA ATB is induced through TGF-β signaling pathway, which as effector to reinforce the prometastatic TGF-β response via two distinct mechanisms.

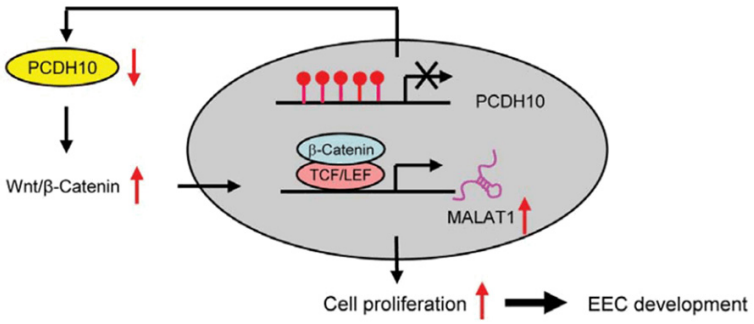


**Figure 4.** Proposed model illustrating PCDH10-Wnt/β-catenin-MALAT1 axis in EEC development [66].

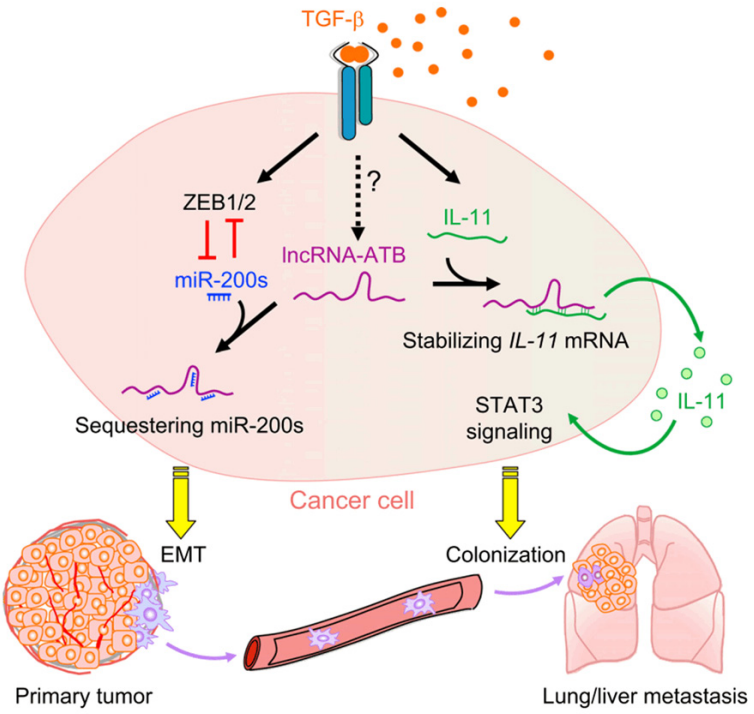


**Figure 5.** Proposed model illustrating the ATB acting downstream of TGF-β to promote different steps of cancer metastasis [74].

First, ATB promotes HCC cell invasion by competitively binding the miR-200 family, upregulating ZEB1/2, and then inducing EMT. On the other hand, ATB promotes HCC cell colonization at the site of metastases by binding mRNA IL-11, increasing IL-11stability, causing autocrine induction of IL-11, and then activating STAT3 signaling (**Figure 5**) [74]. A significant role of lncRNA ANRIL in the occurrence and development of ESCC through TGF-β1 signaling pathways was confirmed in another study [75]. As one of three tumor suppressors encoded by ANRIL, $p15^{INK4b}$ can be induced by TGF-β1 which is a member of the TGF-β family through the canonical TGF-β/Smad signaling pathway.

*cAMP/PKA signaling pathway:* The cAMP/PKA pathway has been reported to stimulate cell growth in many cell types. One cAMP response element binding protein (CREB) binding site within the Hulc proximal promoter region can specifically bind phospho-CREB transcription factors through the PKA pathway. Moreover, phospho-CREB is able to 'open' and maintain the local chromatin structure across the Hulc promoter [76]. LncRNA HULC is identified as a novel mRNA-like lncRNA, highly up-regulated in HCC [77]. Phospho-CREB binding at its binding site through activation of PKA pathway for Hulc promoter activity may involve in the up-regulation of the HULC expression in a cancer-specific manner [76].

*Feedback loop between LncRNAs and signal transduction pathways*

Interestingly, during some development of cancer, we realize that some lncRNAs regulate the signal transduction pathways, and the lncRNA itself can be as the downstream targets in the signal pathways simultaneously forming a positive or negative feedback loop between lncRNAs and signal pathways.

A newly study has found that a novel lncRNA CCAT2 and Wnt signaling pathway could compose a positive feedback loop in colorectal cancer (CRC) [78]. The results suggest that the CCAT2 transcript up-regulates Wnt activity and increases expression levels of Wnt target genes including MYC. This regulation by CCAT2 is possibly through its physical interaction by enhancing transcriptional factors TCF7L2 transcrip-

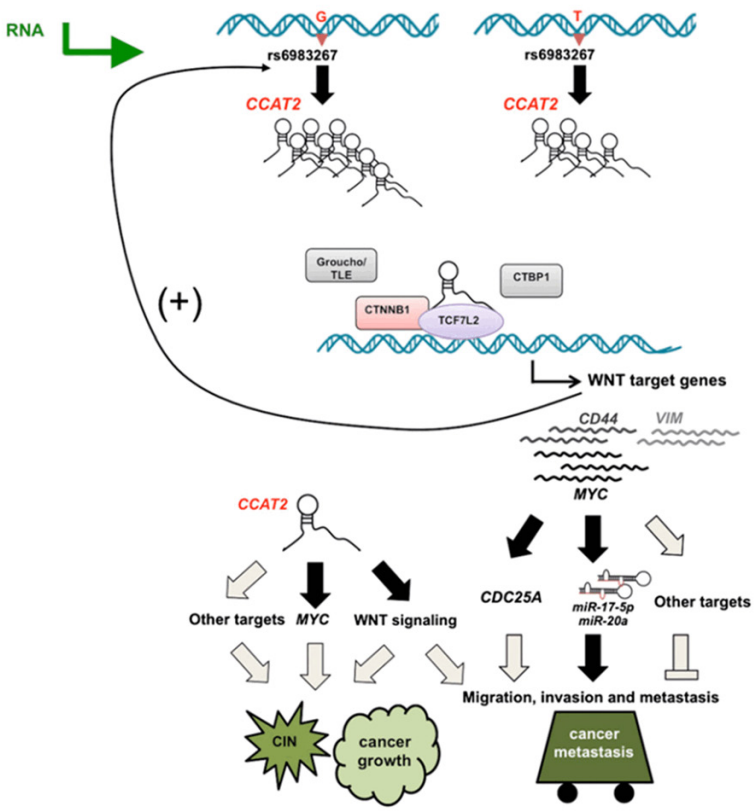


**Figure 6.** Proposed model illustrating CCAT2 locus involvement in CRC [79].

tional activity. On the other hand, CCAT2 expression is regulated by TCF7L2, meaning that CCAT2 itself is a Wnt downstream target indicating a positive feedback loop between CCAT2 and Wnt signaling (**Figure 6**). Another feedback loop found in CRC is between lncRNA CRNDE and insulin/IGF signaling pathways. LncRNA CRNDE was originally discovered as an upregulated gene in colorectal adenomas and cancers [79]. In CRC, insulin/IGFs repress CRNDE intronic transcripts via the two signaling pathways, PI3K/AKT/mTOR pathway and Raf/MAPK pathway. The elevated levels of CRNDE nuclear transcripts in CRC cells increase glucose metabolism, lactate secretion and lipid synthesis. Meanwhile, CRNDE nuclear transcripts also feedback on upstream insulin/IGF signaling pathways, but the extent to which these pathways can be attenuated likely depends on whether constitutively activating mutations are present. And there appears to be potential for both positive and negative feedback on upstream signaling molecules, in addition to the likelihood that CRNDE mediates a subset of insulin/IGF's downstream effects. (**Figure 7**) [80].

In gastric cancer (GC), there is a positive feedback loop between lncRNA ANRIL and mTOR and CDK6/E2F1 signaling pathway. A recent study [81] demonstrated that ANRIL was up-regulated in GC tissues and could be served as an independent predictor for overall survival in GC. In addition, ANRIL could epigenetically silence miR-99a/miR-449a by binding to PRC2 to regulate mTOR and CDK6/E2F1 pathway. Interestingly, the silenced miR-449a by ANRIL releases E2F1 expression, then, upregulated E2F1 promotes ANRIL expression, thus forming a positive feedback loop, continuing to promote GC cell proliferation.

The DNA damage response (DDR) is an important anticancer barrier to maintain genome integrity against intrinsic and extrinsic genotoxic stresses. The ATM-mediated phosphorylation of downstream target proteins triggers a cascade of signals to activate cell cycle checkpoints and DNA repair [82]. The recent data [83] revealed that ATM-induced E2F1 transcriptionally activates ANRIL, and the elevated ANRIL consequently suppresses the expression of INK4B-ARF-INK4A which is INK4 family members to alleviate p53 and pRB signaling pathways at the late-stage of the DDR, forming a negative feedback loop to the DDR. The cell will eventually return to normal at the completion of the DDR. The feedback loop demonstrates that ATM-E2F1 signaling regulates the expression of ANRIL, furthermore, to affect DNA repair efficiency, which provide novel mechanistic insights into the DDR and a novel layer of regulation in gene expression program (**Figure 8**).

## Conclusions and perspectives

In this review, we highlight characterized oncogenic and tumor-suppressor lncRNAs described to have a functional role in cancer-associated signaling transduction pathways. As represent a significant new vista in cancer, aberrant

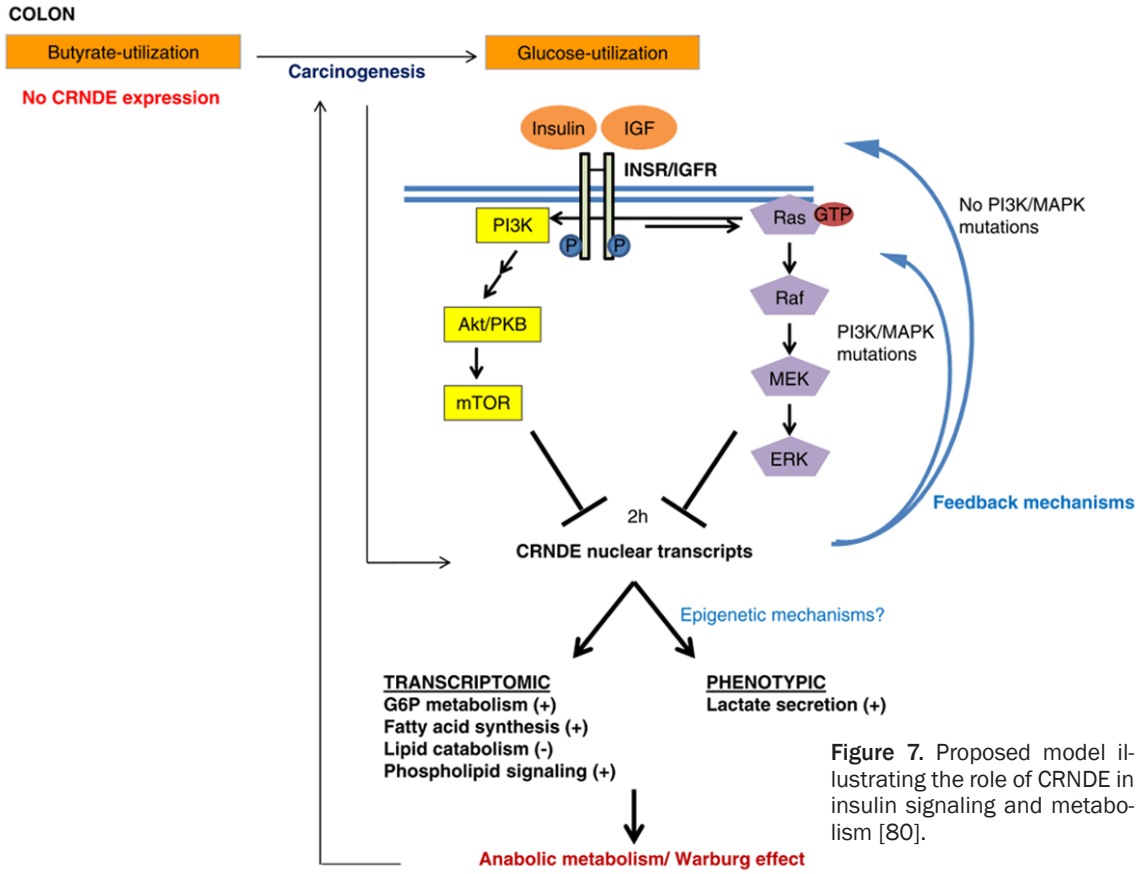


**Figure 7.** Proposed model illustrating the role of CRNDE in insulin signaling and metabolism [80].

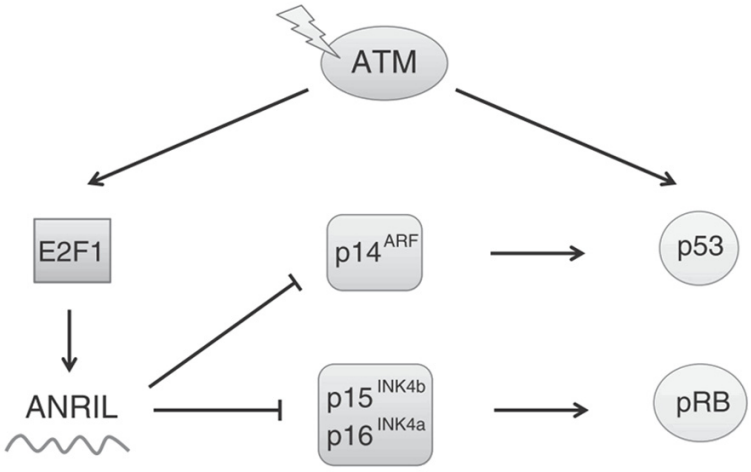


**Figure 8.** Proposed model illustrating the working role of ANRIL in the DNA damage response [83].

lncRNA expression participates in carcinogenesis by disrupting major biological processes involved in signaling transduction pathways as regulators, effectors or forming feedback loops. The signaling transduction pathways, regulating the cell growth and differention in cellular microenvironment, play an import role in cancer initiation and progression. Despite the fast progress in the lncRNA field and we have a deeper understanding of their roles in cancers, overall, lncRNA studies are still at a primary stage. To better understand the lncRNA-cancer-associated signaling network, we still need to solve several issues. For instance, a much more systematical and detailed relations between lncRNAs and cancer-associated signaling pathways are needed to be identified because current studies are still scattered. A more systematic and clear screen may be able to provide a more comprehensive relations of lncRNAs and cancer-associated signaling pathways. We can take a hypothesis that

studies elucidating exact molecular functions and mechanisms in cancer will continue to emerge. Therefore, we need to make much endeavor to fully elucidate the diverse regulatory mechanisms of the detailed lncRNAs involved in how they confer cancer cell associated signaling transduction pathways would ultimately pave novel strategies for cancer diagnosis and therapy.

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## Disclosure of conflict of interest

None.

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