


Emerging roles of long non-coding RNA in cancer

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Funding information

Japan Agency for Medical Research and Development (AMED; P-CREATE; 17cm0106217h0002); The Uehara Memorial Foundation research grant; The Naito Foundation research grant.

Since comprehensive analysis of the mammalian genome revealed that the majority of genomic products are transcribed in long non-coding RNA (lncRNA), increasing attention has been paid to these transcripts. The applied next-generation sequencing technologies have provided accumulating evidence of dysregulated lncRNA in cancer. The implication of this finding can be seen in many forms and at multiple levels. With impacts ranging from integrating chromatin remodeling complexes to regulating transcription and post-transcriptional processes, aberrant expression of lncRNA may have repercussions in cell proliferation, tumor progression or metastasis. lncRNA may act as enhancers, scaffolds or decoys by physically interacting with other RNA species or proteins, resulting in a direct impact on cell signaling cascades. Even though their functional classification is well-established in the context of cancer, clearer characterization in terms of their phenotypic outputs is needed to optimize and identify suitable candidates that enable the development of new therapeutic strategies and the design of novel diagnostic approaches. The present article aims to outline different cancer-associated lncRNA according to their contribution to tumor suppression or tumor promotion based on their most current functional annotations.

KEYWORDS

epithelial-to-mesenchymal transition, long non-coding RNA, tumor drivers, tumor plasticity, tumor suppressors

1 | INTRODUCTION

For several decades, non-protein-coding DNA was referred to as *junk DNA*, a term that has become obsolete. The large-scale genomic projects FANTOM and ENCODE revolutionized the study of the human genome and elucidated that, in fact, 80% of the genome harbors biochemical marks of active transcription and that solely 2% of the genome is restricted to protein coding.^{1,2} Thereby, the FANTOM and ENCODE platforms highlighted the pervasive way in which the genome is transcribed. Full-length cDNA sequencing profiles revealed new transcripts and new coding genes. Further optimization facilitated the detection of low-abundance transcripts that

corresponded to antisense RNA and long non-coding RNA (lncRNA).³ With the observation of a gradually increased prevalence of non-coding DNA regions in superior organisms, together with recent genome-wide annotations in which 58 648 lncRNA account for 68% of the human transcriptome, the lncRNA class has gained more attention.⁴

Long non-coding RNA, which are defined as transcripts of more than 200 nucleotides that generally do not code for proteins, have been associated with diverse functions. Their biological contributions have been seen in the form of: (i) regulators of transcription in *cis* or *trans*; (ii) modulators of mRNA processing, post-transcriptional control and protein activity; and (iii) organization of nuclear domains.^{5,6}

Despite the elucidation of potential mechanistic roles, the biological relevance of the vast majority of lncRNA remains uncertain. In fact, their intricacy relies not only on their functional switch but also in their ability to be tissue/cell-specific. Furthermore, lncRNA that are detected overall with fewer than 1 copy per cell may appear abundant in certain types of cells or even in specific nuclear compartments, adding yet another layer of complexity.³

Given their sophisticated nature, lncRNA harbor the ability to be tissue-specific, cell-specific or even compartment-specific. As Adriaens et al⁷ clearly describe in their article, lncRNA may be best considered to be *fine-tuners* rather than crucial players. Hence, it is not surprising to find a direct implication of lncRNA in processes such as development or disease. Specifically, in cancer, increasing evidence has strengthened the notion that lncRNA exert cooperative functions to tumor suppression or tumorigenesis. For example, emerging databases, such as Lnc2Cancer (<http://www.bio-bigdata.com/lnc2cancer>), provide an extensive compilation of lncRNA in relation to different types of cancer and vice versa. Thus, this article aims to outline the implication of lncRNA in the landscape of cancer according to their influence in the gain or loss of oncogenic signatures.

2 | THE LONG NON-CODING RNA CODE IN CANCER

The accumulation of genetic and epigenetic alterations results in an extreme form of somatic mosaicism that may lead to cancer.⁸ The history of cancer has been ever-evolving, and the fact remains that cancer is a complex disease that certainly demands a complex understanding. Heretofore, the majority of causative evidence for cancer occurrence and progression has been associated with protein-coding regions. Nonetheless, ultraconserved non-coding sequences are commonly found to be deregulated in cancer.⁹ For instance, single nucleotide polymorphisms (SNP) are among the high-risk alterations associated with cancer occurrence; interestingly, 85% of SNP are annotated in noncoding regions and linked to disease development.¹⁰ These abnormalities have an impact on lncRNA, which display altered expression and disrupted functions with subsequent deregulation of their targets.

3 | TUMOR SUPPRESSORS

Most likely, the most notorious gene in cancer research is the tumor suppressor p53 (p53). It works as a transcription factor and activates the expression of multiple genes related to cell cycle arrest and apoptosis. Cellular stress or oncogenic signaling can trigger the activation of p53 through multiple post-translational modifications, and its consequent accumulation in the nucleus substantially increases its detection; however, at normal conditions, its levels are barely detectable.^{11,12} Several lncRNA are included among the network of p53-transcriptionally activated genes (Table 1).

The lncRNA activator of enhancer domains (LED) has been shown to be involved in a win-win relation with p53. While LED is transcriptionally induced by the same p53, it contributes to the regulation of p53 enhancer-derived transcripts (Figure 1A). Genome-wide characterization showed downregulated expression levels of LED in breast cancer cells, colorectal cancer and androgen-insensitive prostate cancers.^{13,14} Maternally expressed gene 3 (MEG3) is an imprinted maternal gene that does not currently have a defined function. It interacts with the p53 DNA binding domain, stimulating p53-mediated transactivation (Figure 1B).¹⁵ In cervical tumors, MEG3 is conversely related to tumor size and lymphatic metastasis, indicating its strong role as a tumor suppressor and as a potential therapeutic candidate.¹⁶ Likewise, downregulated MEG3 has been associated with autophagy and increased cell proliferation in bladder cancer.¹⁷ CpG methylation assays pinpointed that MEG3 hypermethylation impacts overall survival in patients with acute myeloid leukemia (AML).¹⁸ Another p53-regulated lncRNA is the co-activator of p21 expression, lincRNA-p21. lincRNA-p21 regulates p21 in cis (Figure 1C). Its depletion influences the chromatin status of a few Polycomb target genes that alter the G1/S checkpoint and accelerate cell proliferation.¹⁹ In contrast, overactivation of lincRNA-p21 impairs cell proliferation and cell cycle progression in diffuse large B cell lymphoma (DLBCL) cell lines. Consistently high expression levels in DLBCL patients correlate with progression-free and overall survival, resulting in a new potential prognostic marker.²⁰ Studies in colorectal cancer (CRC) show that lincRNA-p21 enhances sensitivity to radiation by targeting the Wnt/B-catenin pathway and promoting apoptosis. In addition, its low expression levels have been correlated with CRC progression.^{21,22} Not far from the lincRNA-p21 genomic region at approximately 10 kb downstream (3'), we encounter DINO. Its transcription requires p53 to utilize the distinct p53-response elements (p53REs) hosted in the promoter region of CDKN1A. Thereby, DINO is divergently transcribed from CDKN1A, which typically encodes the p21 protein. It participates in optimal activation of the p53 DNA-damage response (DDR) by physically interacting with the C-terminal of p53 (Figure 1D). Consistently, DINO decay impaired the activation of multiple genes of the DDR. Furthermore, preliminary data from colon cancer cell lines showed low expression of DINO at basal conditions and observed differences in expression to drug response.^{23,24}

3.1 | The ambiguity of being a tumor suppressor

One more example of divergent transcription by p53 is the newly found lncRNA GUARDIN. GUARDIN is transcribed from the promoter region of the p53 target gene miR-34a, and it is activated upon DDR, promoting cell survival and controlling genome stability. Its depletion results in telomere fusion, inducing senescence and apoptosis. In addition, GUARDIN acts as a scaffold and integrates a ribonucleoprotein (RNP) complex together with the tumor suppressor breast cancer 1 (BRCA1) and its BRCA-associated ring domain (BRCAD1). The overexpression of wild-type p53 and oncogenic mutant HRAS^{V12} increase the levels of GUARDIN in CRC, lung

TABLE 1 Tumor suppression-associated lncRNA

LncRNA	Cancer type	Function	Aberrant phenotype
LED ^{13,14}	Breast cancer CRC Androgen-insensitive prostate cancer	G1 checkpoint arrest Activation of p53-RER and p53-FER	Enhanced cell proliferation
MEG3 ^{15,18}	Cervical cancer Bladder cancer AML	Induces p53-mediated transactivation	Increased cell proliferation Autophagy
Linc-p21 ¹⁹⁻²²	DLBCL CRC	Regulation in cis of p-21	Altered G1/S checkpoint Accelerated cell proliferation
DINO ^{23,24}	CRC	Transcription of p53 Activation of p53-induced genes	Drug-resistance Impaired DNA-damage response
GUARDIN ²⁵	CRC Lung adenocarcinoma Osteosarcoma Breast cancer	DNA-damage response Integrates RNP complex BRCA1-BRCAD1	Promotion of cell survival and proliferation
NEAT1 ²⁶⁻³¹	CRC Breast cancer PanIN lesions	Nuclear paraspeckles assembly Transcription and RNA processing	Cell growth Enhanced malignancy
PTENP1 ³²⁻³⁷	Colon cancer Melanoma Prostate cancer HCC Breast cancer	Decoy of PTEN-targeting oncomirs	Tumor growth Activation of PI3K/AKT pathway

Long non-coding RNA (lncRNA) with a role in tumor suppression are shown in white, whereas lncRNA displaying ambiguous phenotypic outputs are highlighted in grey.

adenocarcinoma and osteosarcoma cell lines. Moreover, whereas GUARDIN expression is visibly diminished in p53-mutant tumors of CRC, its depletion may induce senescence, apoptosis and abrogate xenograft growth formation.²⁵ Collectively, GUARDIN may be considered to be a good target in p53-mutant tumors; however, further studies are required regarding the ambiguous phenotype that it may present in distinct types of tumors.

The activation of p53 stimulates the formation of paraspeckles, a class of sub-nuclear RNP bodies that participate in transcription and RNA processing. The formation and maintenance of these nuclear complexes depends on their interaction with nuclear enriched abundant transcript 1 (NEAT1).^{26,27} NEAT1 is a direct target gene of p53 that induces the formation of paraspeckles upon stress. Interestingly, paraspeckles are present in the early stages of cancer. Studies on NEAT1-paraspeckle complexes and tumor formation showed that *Neat1* KO mice did not develop chemically-induced skin cancer.²⁸ Likewise, higher expression correlated with unfavorable prognosis in CRC patients.²⁹ However, intriguingly, depletion of NEAT1 inhibited cell growth in breast cancer cells.³⁰ Furthermore, loss of *Neat1* in *Kras*^{G12D} murine models promoted pancreatic precursor lesions and enhanced fibroblast malignant transformation.³¹ Therefore, the biological relevance of NEAT1 in tumorigenesis should be clarified before it can be considered to be a therapeutic target.

The PTENP1 locus is selectively deleted in colon cancer and melanoma tissues, and its restoration results in the growth inhibition of

prostate cancer cells.^{32,33} Transfection of PTENP1-expressing Sleeping Beauty-based hybrid baculovirus (SB-BV) vectors into mice bearing hepatocellular carcinoma (HCC) tumors mitigates tumor growth and intratumoral cell proliferation by suppressing the oncogenic PI3K-AKT pathway. PTENP1 is a pseudogene of the tumor suppressor PTEN, which functions as a decoy for PTEN-targeting oncomirs miR-17, miR-19b and miR-20a.^{34,35} Nonetheless, similar to NEAT1, a recent report uncovered a divergence in the activity of PTENP1 linked to the breast cancer phenotype. Whereas overexpression of PTENP1 in estrogen receptor (ER)-negative breast cancers shows its tumor suppressor activity, inhibiting cell growth and enhancing PTEN levels, in ER-positive breast cancers, PTEN expression is decreased, and cell growth is potentiated. Furthermore, in a cohort of 318 patient samples, the presence of PTENP1 was not revealed to have a prognostic impact on human breast cancer.^{36,37}

4 | TUMOR DRIVERS

The metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), also called NEAT2, is an abundant and highly conserved lncRNA across vertebrates. It was first described as a prognostic marker for lung adenocarcinoma.^{38,39} MALAT1 is recruited to nuclear speckles, which are dynamic compartments destined to processes of mRNA alternative splicing.^{40,41} Importantly, *Malat1* knockout mice develop normally and have a normal life span, showing that MALAT1 is dispensable for

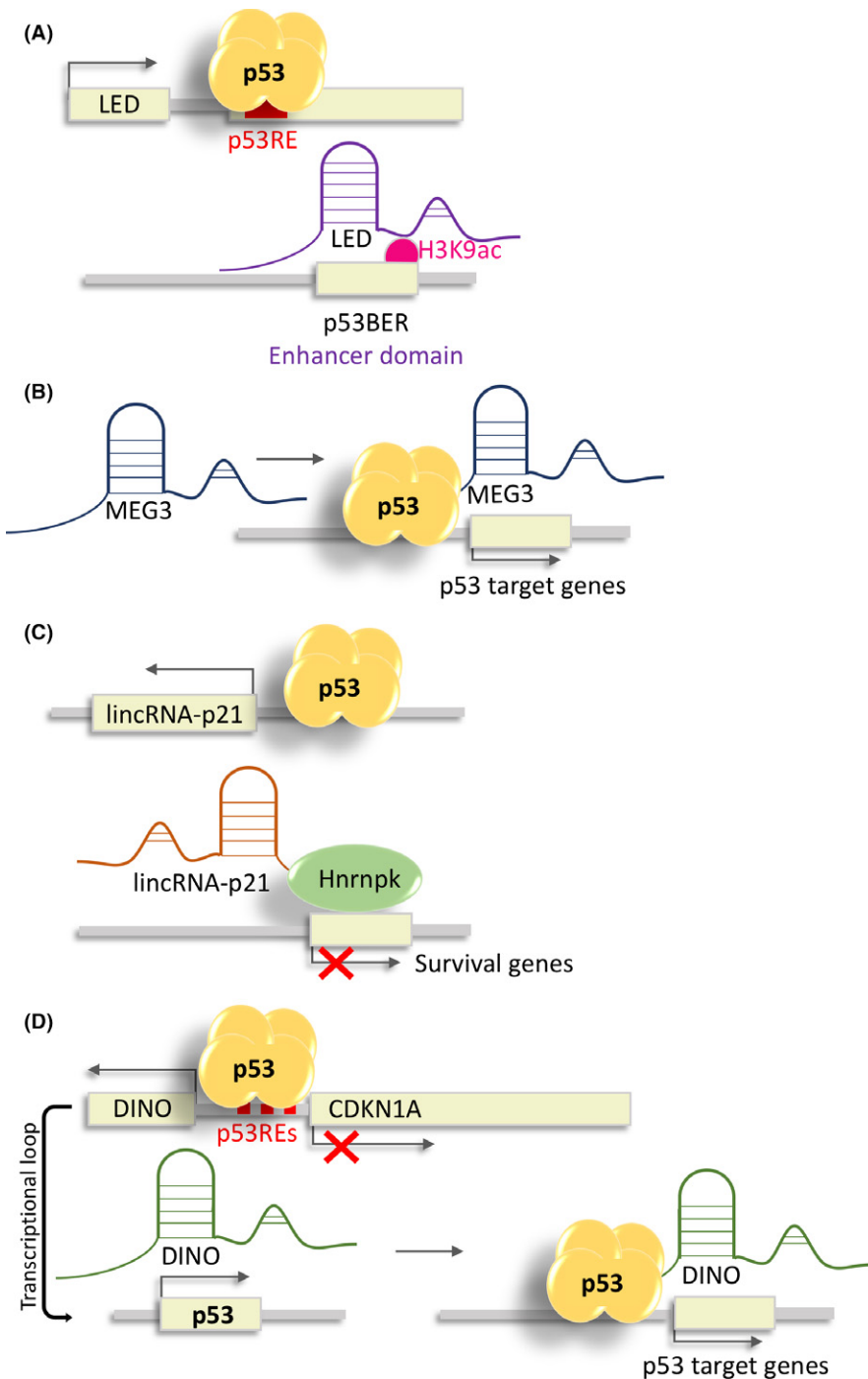


FIGURE 1 Long non-coding RNA (lncRNA) and the p53 network. A, LED is transcriptionally induced by p53 and epigenetically stimulates the production of eRNA (enhancer RNA) by the acetylation of histone H3K9 on the p53-bound enhancer regions (p53BER). B, Transactivation of p53-target genes is activated by means of direct binding between p53 and lncRNA MEG3. C, LincRNA-p21 is transcribed by p53. Next, LincRNA-p21 forms the repressive complex together with the ribonucleoprotein Hnrnpk to suppress survival-related genes. D, Transcriptional divergence of p53 resulting in the transcription of DINO, which, in turn, may activate p53 transcription. Physical interaction of DINO and p53 induces p53-target genes

development and normal tissue homeostasis.⁴² Depletion of MALAT1 in breast cancer ER-positive luminal cells showed a reduction in cell proliferation, demonstrating its involvement in tumor progression.⁴³ The chromatin-associated HuR/MALAT1 functional complex controls CD133 gene expression during the dedifferentiation process of breast cancer cells, both in vitro and in vivo.⁴⁴ In the most representative form of ovarian cancer, epithelial ovarian cancer (EOC), MALAT1 induces an epithelial-to-mesenchymal transition (EMT) switch via the PI3K/AKT pathway.⁴⁵ In CRC tumor tissues, MALAT1 expression has been reported to be a potential predictor of tumor metastasis and prognosis.^{46,47} Similarly, its implication has been reported in studies of glioma,

HCC and prostate cancer, among others.⁴⁸⁻⁵⁰ Overall, these findings suggest the possibility that the inhibition of MALAT1 might impair cancer-cell growth, metastasis, or both with minimal side effects, making it a promising candidate of drug-targeted therapeutics (Table 2).

Another metastasis-associated lncRNA is the HOX antisense intergenic RNA HOTAIR. Genome-wide analysis from CRC patient specimens supported that HOTAIR is involved in tumor promotion and that its decay enhances radio-sensitivity.^{51,52} In breast cancer, it works as a predictive marker for metastatic progression and overall survival in early-stage surgically resected tumors.⁵³ Of note, emerging studies on the susceptibility of breast cancer have indicated the

TABLE 2 Tumor promotion-associated lncRNA

lncRNA	Cancer type	Function	Aberrant phenotype
MALAT1 ³⁸⁻⁵⁰	Lung adenocarcinoma Breast cancer Ovarian cancer CRC Glioma HCC Prostate cancer	Nuclear speckles scaffold mRNA splicing	Tumor progression Metastatic-phenotype induction
HOTAIR ⁵¹⁻⁵⁶	CRC Breast cancer Prostate cancer	Repressive chromatin marks Recruitment of PRC	Tumor promotion Decreased radio-sensitivity
NORAD ⁵⁸⁻⁶²	CRC ESCC Bladder cancer	Negative regulator of RNA-binding proteins PUMILLO	Chromosomal instability
PVT1 ⁶³⁻⁶⁶	CRC Bladder cancer Cervical cancer	Epigenetic arrest of G1 checkpoint	Expression of c-MYC Uncontrolled cell proliferation

CRC, colorectal cancer; lncRNA, long non-coding RNA.

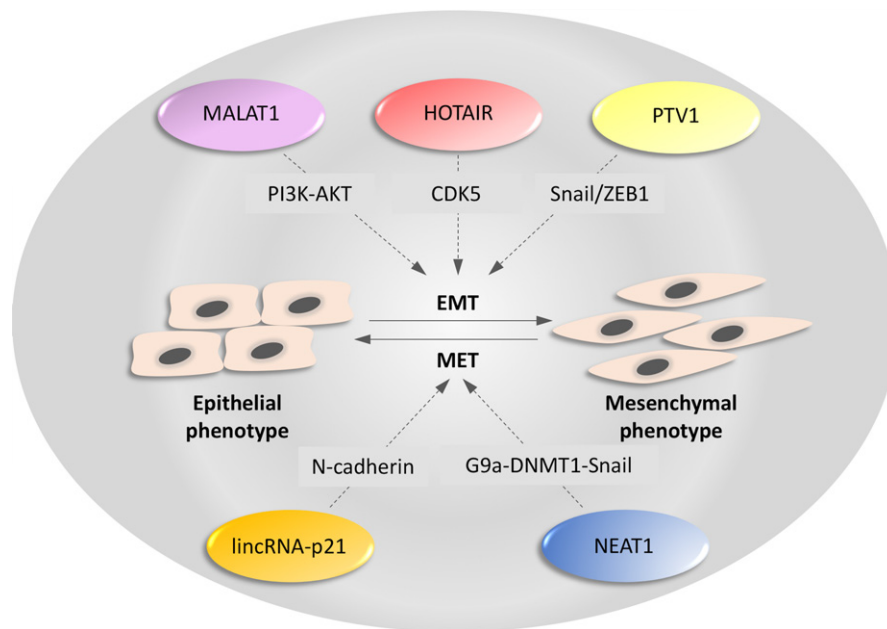


FIGURE 2 Long non-coding RNA (lncRNA) involved in tumor plasticity. Aberrantly expressed lncRNA may have an important impact in the EMT-MET processes by interacting with diverse signaling cascades

genetic polymorphisms of HOTAIR.^{54,55} HOTAIR acts as a scaffold in a chromatin-repressive mechanism. One of the chromatin-modifying complexes is the polycomb repressive complex 2 (PRC2), which catalyzes the repressive histone mark H3K27me3. Intriguingly, in breast cancer, HOTAIR repression is PRC2-independent and influences the expression of a limited number of target genes, suggesting a distinct function for PRC2-RNA binding other than chromatin targeting.⁵⁶

An interesting new report suggests that MALAT1 and HOTAIR are ER transcriptional targets and mediators in the ER-dependent or ER-independent transcriptional response in prostate cancer. MALAT1 and HOTAIR, which have been shown to be associated with ER α /ER β at the chromatin level, display different mechanisms to abrogate

the ER response, suggesting a new type of hormone action.⁵⁷ The lncRNA NORAD is regulated in the DDR and exerts a key role on chromosomal instability.^{58,59} Whereas NORAD^{-/-} cells develop genomic instability and aneuploidy, the overactivation of NORAD is significantly found in tissues of CRC, esophageal squamous cell carcinoma (ESCC) and bladder cancer, contributing to tumor progression.⁵⁹⁻⁶² In an attempt to determine whether a low-copy-number gain of the genes accompanying MYC in the 8q24.21 region generates neoplasia, chromosome engineering was used in mice. These results revealed that high levels of Myc protein are dependent upon lncRNA Pvt1 to promote tumor development and that Myc alone is insufficient otherwise.⁶³ Concomitantly, PVT1-null CRC cell lines

failed to generate xenograft tumors. Consistent data highlight the relevance of PVT1 in MYC-driven cancers, such as CRC, bladder cancer and cervical cancer.⁶⁴⁻⁶⁶

5 | LONG NON-CODING RNA AND TUMOR PLASTICITY

The tumor microenvironment is represented by the presence of non-tumoral cells and modified extracellular matrix. In this scenario, tumor cells meet stromal and immune cells, leveraging interactions and contributing to tumor progression. As a result of intercellular communication, subpopulations of cancer cells acquire new properties of plasticity, stem-like features and immune suppression and are prone to becoming resistant to therapy. Reprogramming into new phenotypes requires EMT. EMT may be induced through different biological stimuli, and it is regulated by transcriptional factors.^{67,68} Better pharmacological targeting of cancer-associated lncRNA is a *must* for understanding their participation at distinct cancer levels.

Tumor stroma cells from breast cancer were found to preferentially express MEG3.⁶⁹ Genome-wide mapping of MEG3 in ovarian cancer shows that it is significantly associated with EMT-linked canonical pathways. Genome-wide analysis highlighted the epigenetic regulation of EMT in lung adenocarcinoma.^{70,71} When lincRNA-p21 is overexpressed in HCC, N-cadherin and snail expression is decreased, inhibiting the EMT.⁷² Consistently, its depletion in gastric cancer promotes EMT phenotypic changes in cells, and these changes are also seen at the transcriptome level.⁷³ In nasopharyngeal carcinoma (NPC), NEAT1 regulates EMT via the miR-204/ZEB1 axis, and breast cancer cells show decreased β -catenin and N-cadherin and increased E-cadherin after NEAT1 suppression.^{74,75} Furthermore, NEAT1 can epigenetically suppress E-cadherin expression through the association of G9a-DNMT1-Snail complex.⁷⁶ MALAT1 intervenes in the endothelial-to-mesenchymal transition (EndMT) induced by TGF β 1, a key mediator between stromal and cancer cells. Its silencing hinders EMT via PI3K-AKT in ovarian cancer and can result in different phenotypes depending on breast cancer subtypes.^{44,45} Of note, triple negative breast cancer generally displays lower levels of MALAT1 per se than luminal phenotypes. Indeed, as we have noted, tissue/cell-specificity has major significance. HOTAIR acts as a scaffold by recruiting EZH2 to Snail, forming a repressive complex that suppresses E-cadherin and promotes mesenchymal phenotypes in non-tumorigenic hepatocytes. Consistently, in HCC, EZH2/HOTAIR/Snail are upregulated and correlate with tumor progression and aggressiveness.⁷⁷ In breast cancer, cancer-associated fibroblasts (CAF) transcriptionally activate HOTAIR through the direct binding of SMAD2/3/4 to the HOTAIR promoter region. Then, HOTAIR epigenetically represses CDK5RAP1, stimulating CDK5 signaling and inducing EMT.⁷⁸ PVT1 acts as competing endogenous RNA (ceRNA) for miR152, activating Hedgehog signaling and promoting EMT in hepatic stellate cells and thereby contributing to liver fibrosis.⁷⁹ Likewise, the overexpression of PVT1 resulted in an increase of Snail and ZEB1 expression in pancreatic cancer (Figure 2).⁸⁰

6 | CONCLUDING REMARKS

Collectively, these studies highlight the importance of lncRNA in the cancer landscape. lncRNA are capable of *tuning* gene expression and impacting cellular signaling cascades. Occasionally, this impact can be easily seen at the phenotypic level; however, in other cases, it may result in more subtle phenotypes that can solely be detected after comprehensive analysis. The latter must be considered carefully; based on their translational relevance, the pharmacological targeting of lncRNA that display minor phenotypes upon depletion may represent an opportunity for clinical application.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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How to cite this article: Sanchez Calle A, Kawamura Y, Yamamoto Y, Takeshita F, Ochiya T. Emerging roles of long non-coding RNA in cancer. *Cancer Sci*. 2018;109:2093-2100. <https://doi.org/10.1111/cas.13642>