



# Long non-coding RNA signatures as predictors of prognosis in thyroid cancer: a narrative review

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**Abstract:** Thyroid cancer (TC) is the most common endocrine malignancy, with high incidence rates in recent decades. Most TC cases have good prognoses, but a high risk of recurrence and metastases poses challenges, especially for patients with high-risk factors. Currently used prognostic markers for TC involve a combination of genetic factors and overexpressed proteins. Long non-coding RNAs (lncRNAs) regulate several integral biologic processes by playing key roles in the transcription of several downstream targets maintaining cellular behavior. Prior studies have revealed that lncRNAs promote tumor cell proliferation, invasion, metastasis, and angiogenesis, making them important targets for therapeutic intervention in cancer. While the exact molecular mechanisms underlying the role of lncRNAs in modulating TC progression and recurrence is still unclear, it is important to note that some lncRNAs are upregulated in certain cancers, while others are downregulated. In the present study, we review several key lncRNAs, their association with cancer progression, and the important roles they may play as tumor suppressors or tumor promoters in tumorigenesis. We discuss the potential mechanisms of lncRNA-mediated pathogenesis that can be targeted for the treatment of TC, the existing and potential benefits of using lncRNAs as diagnostic and prognostic measures for cancer detection, and tumor burden in patients.

**Keywords:** Thyroid cancer (TC); long non-coding RNAs (lncRNAs); tumor promoters

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## Introduction

Thyroid cancer (TC) is the most common endocrine malignancy, with high incidence rates. According to the American Cancer Society's most recent statistics, it has

been estimated that there will be 52,890 new cases of TC (12,720 in men and 40,170 in women) and about 2,180 deaths (1,040 men and 1,140 women) in the USA by the end of 2020. TC can be classified into 2 main subtypes based on gross histological features: differentiated and

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undifferentiated. Differentiated TC includes papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC), which account for approximately 90% of all cases. Undifferentiated TC includes anaplastic thyroid carcinoma (ATC), which is the most aggressive form of TC and has poor clinical outcomes and limited treatment options. Medullary TC (MTC), which originates from parafollicular thyroid “C” cells are even less frequent, with incidence rates ranging from 3% to 5%. Conventionally, surgical resection is the main therapeutic strategy, along with adjuvant therapies that include radioactive iodine therapy and hormone-based therapy. Most TC cases have good prognoses, but a high risk of recurrence and metastases poses challenges, especially for patients with high-risk factors. Prior research has revealed that the molecular pathogenesis of TC is governed by underlying dysregulated genetic and epigenetic determinants. It is imperative to identify biomarkers that can be accurately used to predict diagnosis, prognosis, and treatment response with high specificity and sensitivity in patients with TC. Long non-coding RNAs (lncRNAs) are one of the most important regulatory factors implicated in TC carcinogenesis (1). These evolutionarily distinct non-coding transcripts exist in lengths longer than 200 nucleotides (2). While some studies have shown that lncRNAs can play opposing roles and behave like oncogenes or tumor-suppressor genes during tumorigenesis, there is still no consensus about the biologic implications of these non-coding transcripts in the clinical setting (3). Prior studies have demonstrated the significant roles that lncRNAs play in fundamental cellular functions, such as pre-transcription, post-transcription, cell proliferation, invasion, differentiation, apoptosis, and migration (4). Increasing evidence suggests that lncRNAs also play a role in regulating cellular functionality and pathogenesis in TC (5). In addition, the expression of lncRNAs plays a role in modulating recurrence and survival rates in TC patients (6). For example, the lncRNA HOXA transcript at the distal tip (HOTTIP) knockdown inhibits cellular proliferation, invasion, and migration *in vitro* and *in vivo* (7). A recent study explored the high expression of metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) and its correlation with tumor size, lymph node metastases, and World Health Organization (WHO) disease stage (8). These lncRNAs have received increasing attention as potential markers in the diagnosis and treatment evaluation of TC, especially for unclear cytological findings that cannot distinguish malignant from benign nodules. In the present study, we review some of the common lncRNAs

and their association with prognoses in different cancer types. We further discuss their relevance and significance if adopted as a clinical measure in TC, and the role that these lncRNAs may play as targets for genetic or therapeutic intervention for disease prevention and control.

We present the following article in accordance with the Narrative Review reporting checklist (available at <http://dx.doi.org/10.21037/atm-20-8191>).

### Existing prognostic markers for TC

Currently used prognostic markers for TC involve a combination of genetic factors and overexpressed proteins. Well-differentiated thyroid carcinoma subtypes have good prognosis following the complete removal of the thyroid tumor, with a few cases of recurrence (9). Poorly differentiated thyroid carcinoma has a worst prognosis with ATC, with poor prognosis despite available treatment regimens (10). The overexpression of protein biomarkers has been studied, and galectin-3 (LGALS3) and FOXP3 have been identified as candidates for diagnosis and prognosis in differentiated thyroid carcinomas, with *LGALS3* found to be associated with lymph node metastasis (11,12). Genetic markers include mutations in oncogenes, such as *RAS* and *BRAF*, and the promoter regions of telomerase reverse transcriptase (*TERT*). *RET/PTC* (rearrangement of *RET* gene) and *PAX8/PPAR $\gamma$*  chromosomal rearrangements have also been reported as markers for individuals exposed to radiation, with emphasis on the development of a more aggressive form of PTC (13,14). Three variants of the mutation in *RAS*—*KRAS*, *HRAS*, and *NRAS*—have been reported in TC, with the *NRAS* codon 16 mutation found to be associated with distant metastasis in FTC (15). Mutations in the *TERT* promoter, which were found to be associated with malignancy in TC and in combination with *BRAFV600E*, were used to identify patients who could develop aggressive subtypes. *BRAFV600E* was found to be present in a majority of TC subtypes; however, it was not found to be associated with distant metastasis (16). Mutations in *BRAF* were also reported to be a biomarker for prognosis associated with recurrence (17), while another study concluded *BRAF* to be of minimal prognostic value in PTC (18). *LGALS3* has been found to be unreliable as an exclusive prognostic marker (19-21). Conflicting studies on these biomarkers highlight the need for consistent and reliable prognostic indicators that can efficiently differentiate between TC subtypes and determine treatment regimens.

**Table 1** LncRNAs upregulated in TC

LncRNAs	Tumor	Function	Molecular mechanisms	Source
H19	TC	Promotes proliferation, migration, and invasion	Binds miR-17-5p to regulate YES1 expression	(22)
HCP5	FTC	Promotes proliferation, migration, invasiveness, and angiogenic ability of FTC cells	Competitive endogenous RNA and acts as a sponge for miR-22-3p, miR-186-5p, and miR-216a-5p, which activates ST6GAL2	(23)
HOTTIP	PTC	Promotes papillary thyroid carcinoma cell proliferation, invasion, and migration	Regulates miR-637	(7)
MALAT1	MTC	Decreases cell proliferation and invasion	Regulates miR-21	(24)
SNHG15	PTC	Promotes cell growth and migration in papillary thyroid carcinoma	Regulates YAP1-Hippo signaling pathway by sponging miR-200a-3p	(25)
SPRY4-IT	PTC	Correlated with poor prognosis, and promotes proliferative and migratory abilities of TC cells	Targets TGF- $\beta$ 1/Smad signaling pathway	(26)
OIP5-AS1	TC	Promotes cell proliferation and migration	Via FXR1/YY1/CTNNB1 axis	(27)
Linc00210	TC	Augments proliferation, migration, and invasion of TC cells	Modulates miR-195-5p/IGF1R/Akt axis	(28)
UCA1	TC	Promotes cell proliferation and the EMT phenotype	Via the UCA1/miR-15a axis	(29)
CCAT1	TC	Promotes cell proliferation, migration, and invasion	Activate PI3K/Akt and MAPK signaling pathways via downregulation of miR-143	(30)
XIST	TC	Modulates cell proliferation and tumor growth	As a ceRNA for miR-34a through sponging miR-34a, competing with MET for miR-34a binding	(31)
NEAT1	TC	Accelerates thyroid cancer cell growth and metastasis	Regulates miRNA-214 expression	(32)
LINC00511	PTC	Influences cellular proliferation	Through cyclin-dependent kinases	(33)
NR2F1-AS1	PTC	Promotes proliferation and invasion	Regulates miR-423-5p/SOX12	(34)
LINC00152	PTC	Promotes cell growth and invasion	Regulates miR-497/BDNF axis	(35)
MCM3AP-AS1	PTC	Promotes papillary thyroid cancer proliferation, migration, and invasion	Regulates MCM3AP-AS1/miR-211-5p/SPARC axis	(36)

LncRNA, long non-coding RNA; TC, thyroid cancer; FTC, follicular thyroid carcinoma; PTC, papillary thyroid carcinoma; MTC, medullary TC.

## LncRNAs overexpressed in TC

While the exact molecular mechanisms underlying the role of lncRNAs in modulating TC progression and recurrence is still unclear, it is important to note that some lncRNAs are upregulated in certain cancers, while others are downregulated. To understand the distinct roles each of these lncRNAs play in TC progression, we discuss the lncRNAs that are upregulated and those that are downregulated in different cancer types (Tables 1 and 2), along with the molecular mechanisms governing their regulatory behaviors. This information will help identify key patterns and phenotypic behaviors associated with each

of these lncRNAs, therefore providing specific strategies for therapeutic intervention. A schematic describing the major mechanisms through which lncRNAs can regulate cell growth, metastasis, and cancer progression is shown in Figure 1.

## LncRNAs upregulated in TC

### Colon cancer-associated transcript-1 (CCAT1)

CCAT1 is a 2628-bp lncRNA that was initially identified in colon cancer. It is located at chromosome 8q24.21, and is in the vicinity of the proto-oncogene *c-MYC* (51). CCTA1 has

**Table 2** LncRNAs downregulated in TC

LncRNAs	Tumor	Function	Molecular mechanism	Source
BANCR	PTC	Suppresses the proliferation and invasion of PTC cell lines	Via the MAPK and PI3K pathways	(37)
AB074169	PTC	Causes cell-cycle arrest and inhibits PTC cell growth	Via modulation of KHSRP-mediated CDKN1a expression	(38)
ASMTL-AS1	PTC	Inhibits PTC cell proliferation and glycolysis	Regulates miR-93-3p/miR-660/FOXO1 axis	(39)
BLACAT1	PTC	Acts as an independent risk factor for lymph node metastasis and sex	N/A	(40)
CASC2	PTC	Suppresses cell proliferation and promotes apoptosis in PTC cells	Inactivates the Akt/ERK1/2 signaling pathway	(41)
GAS8-AS1	PTC	Inhibits proliferation and activates autophagy	Through ATG5-mediated autophagy	(42)
MEG3	TC	Suppresses iodine-resistant cell viability, promotes apoptosis, and induces DNA damage	Via sponging miR-182	(43)
PAR5	ATC	Reduces proliferation and migration rates of ATC-derived cell lines	Impairs Enhancer of Zeste Homolog 2 (EZH2) oncogenic activity	(44)
SNHG3	PTC	Inhibits proliferation, migration, and invasion abilities of PTC cells	Regulates the Akt/mTOR/ERK pathway	(45)
LINC00982	TC	Suppresses cell proliferation and tumor growth	Through PI3K/ATK signaling pathway	(46)
HOTAIRM1	PTC	Inhibits PTC cell proliferation, invasion, and migration	Regulates the expression of TDG in an miR-107-mediated manner	(47)
SLC26A4-AS1	PTC	Decreases cell migration, proliferation, and invasion, and inhibits epithelial-mesenchymal transition	Via the MAPK pathway	(48)
PAPAS	PTC	Inhibits cell proliferation	Downregulation of lncRNA HOTTIP	(49)
LINC003121	TC	Inhibits proliferation and invasion	Attenuates the PI3K/Akt signaling pathway	(50)

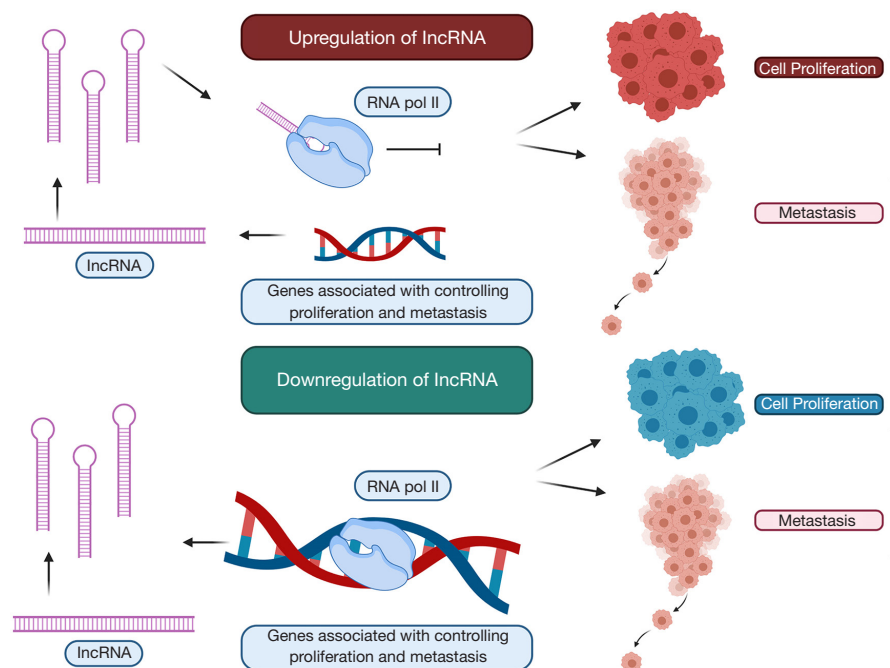
LncRNA, long non-coding RNA; TC, thyroid cancer; PTC, papillary thyroid carcinoma; ATC, anaplastic thyroid carcinoma.

been previously demonstrated to be significantly associated with tumor progression of different cancers, including PTC. Prior studies have reported CCAT1 to be highly expressed in the human TC cell line FTC-133, and CCAT1 suppression was found to reduce cell viability, proliferation, migration, invasion, and miR-143 expression (30). In addition, CCAT1 elevates apoptosis and vascular endothelial growth factor expression. Further studies have revealed that CCAT1 acts as a competitive endogenous RNA (ceRNA) to activate the phosphoinositide-3 kinase (PI3K)/Akt and mitogen-activated protein kinase (MAPK) signaling pathways via the inhibition of miR-143. In another recent study, CCAT1 was demonstrated to be one of the most significantly downregulated transcripts in ASH1L knockout cells. Further studies have shown that CCAT1 knockdown could suppress cell growth in ATC. ChIP-sequencing data analysis found that CCTA1 is likely involved in the

regulation of ASH1L histone methyltransferase (52). These prior experimental data strongly suggest that CCTA1 exhibits oncogenic behavior in TC.

### H19

H19, a 2.7-kb lncRNA, has been found to play a pivotal role in both embryonic development and tumorigenesis, and is located on chromosome 11p15.5 (53). H19 has been previously shown to be upregulated in tumor samples and in TC cell lines (22). The overexpression of H19 was observed to correlate significantly with proliferation, migration, and invasion, whereas the low expression of H19 reduced cell viability and invasion, inducing growth arrest *in vitro* and *in vivo*. Further studies found that H19 acts as ceRNA through competitively binding to miR-17-5p to upregulate its target YES1 to promote cell cycle progression in a TC



**Figure 1** Long non-coding RNA (lncRNA) can transcriptionally regulate several key transcription factors and cell growth and invasion to promote cancer.

model. A recent study showed that the overexpression of H19 contributed to higher tumor burden in PTC (54). In addition, H19 promotes the epithelial-mesenchymal transition (EMT), mediating the migration and invasion of PTC cells. Other studies have found that H19 expression is upregulated in TC (55). Moreover, silencing H19 leads to increased levels of phosphorylated PI3K and Akt, resulting in an inhibition of cell viability and higher levels of apoptosis. These studies indicate that H19 is another oncogenic regulator of TC.

### ***HLA complex P5 (HCP5)***

HCP5, an oncogenic lncRNA, has an important role in various types of cancers, including colon cancer (56,57), cervical cancer (58,59), and TC (60). HCP5 upregulation has been identified using next-generation sequencing technology in FTC (23). Moreover, the increased expression of HCP5 has been found to significantly promote cell proliferation, migration, invasiveness, and angiogenesis. Further studies have indicated that HCP5 acts as a ceRNA by competitively binding to miR-22-3p, miR-186-5p, and miR-216a-5p, promoting higher levels of ST6GAL2, resulting in increased cell proliferation and

invasion. Similarly, Chen *et al.* reported that the expression of HCP5 is upregulated in ATC (60). The decreased expression of HCP5 inhibits cell viability and promotes higher apoptotic rates and caspase-3/7 activity. Further studies have showed that HCP5 binds to miR-128-3p and regulates the expression of miR-128-3p using luciferase reporter and RNA immunoprecipitation assays. These studies demonstrate that HCP5 acts as an oncogene in tumorigenesis, and stimulates invasion and metastases in tumor progression.

### ***HOTTIP***

HOTTIP is a 3764-nucleotide lncRNA that is encoded from a genomic region in the 5' tip of the HOXA locus. Prior studies have shown that the expression of HOTTIP is upregulated in PTC tissues, as well as cell lines (7). HOTTIP knockdown has been shown to suppress cell proliferation, invasion, and migration *in vitro* and *in vivo*. HOTTIP knockdown inhibits Akt1 expression and regulates miR-637 to inhibit cell proliferation, invasion, and migration in PTC cells. HOTTIP may be a worthy therapeutic target for malignancies. Other recent studies have shown that HOTTIP plays an oncogenic role in PTC

via the negative regulation of miR-744-5p. This ultimately leads to elevated apoptosis. These studies suggest that HOTTIP is also a typical oncogenic lncRNA and may be an important therapeutic target in PTC (61).

#### ***HOXA cluster antisense RNA2 (HOXA-AS2)***

HOXA-AS2 is a novel cancer-related lncRNA that has been demonstrated to be aberrantly expressed in various cancer types (62-64). In TC, the expression of HOXA-AS2 is upregulated in PTC tissues (65). PTC cell growth was found to be inhibited through HOXA-AS2 knockdown *in vitro* and *in vivo*. PTC cell migration and invasion are promoted by HOXA-AS2 via the EMT phenotype. In addition, luciferase reporter assays have found that HOXA-AS2 could compete with miR-520c-3p at the 3'-untranslated region (UTR) with a complementary binding site and inhibit the expression of miR-520c-3p. S100 calcium-binding protein A4 (S100A4) was confirmed as a downstream target of the miR-520c-3p by luciferase reporter assays. The data suggest that the HOXA-AS2/miR-520c-3p/S100A4 axis may play a vital role in the regulation of PTC progression. A similar pattern was also observed in PTC cell lines. HOXA-AS2 overexpression was correlated with poor overall survival in patients with TC (66). This study had shown that HOXA-AS2 knockdown inhibits cellular proliferation, migration, and invasion, and accelerated apoptosis in PTC. The overexpression of HOXA-AS2 exhibited pro-oncogenic behavior. Moreover, the study found that HOXA-AS2 binds to miR-15a-5p and could upregulate HOXA3 expression. These studies demonstrate that HOXA-AS2 plays an important role in the progression of PTC, and could be a regulatory factor determining HOXA3 expression. Therefore, HOXA3 could also be a potential therapeutic target and biomarker for PTC diagnosis and prognosis.

#### ***MALAT1***

MALAT1 is an onco-lncRNA that has been found to be overexpressed in several cancers (67-69). A previously published study established that MALAT1 was upregulated specifically in PTC tissues relative to normal tissues. A high expression of MALAT1 was found to correlate with tumor size, lymph node metastases, and WHO disease stage (8). Chu *et al.* analyzed the expression of MALAT1 in MTC and found that a high expression of MALAT1 in 37 (95%) primary MTC and a strong expression of miR-21 in 17 (44%)

primary MTC *in situ* hybridization (70). Upregulated miR-21 and MALAT1 were found in MTC-derived cell lines compared with normal tissues. It was also shown that miR-21 and MALAT1 knockdown significantly increased cell proliferation and invasion. The data suggest that miR-21 and MALAT1 may regulate MTC progression. In a recent study, MALAT1 gene expression was significantly upregulated after dual MEK/Aurora kinase inhibitor "BI-847325" treatment in C643 and SW1736 cell lines. Further studies showed that Mcl1 and cyclin D1 expression were significantly reduced following BI-847325 treatment. Moreover, MALAT1 downregulated Mcl1 by competitively binding to and inhibiting miR-363-3p. These investigations show that MALAT1 plays a vital oncogenic function in TC (71).

#### ***SNHG15***

LncRNA SNHG15 has been identified as a tumor facilitator in several types of cancers, including TC (25,27,72-74). Wu *et al.* (25) reported that SNHG15 expression is significantly upregulated in PTC tissues and cell lines. In addition, SNHG15 expression was shown to be associated with the overall survival of PTC patients, and SNHG15 silencing led to the inhibition of cell growth and migration in PTC models. These studies indicate that SNHG15 upregulation can lead to the inactivation of the Hippo signaling pathway. Therefore, SNHG15 also acts as an oncogene in tumorigenesis and stimulates invasion and metastases in tumor progression.

#### ***SPRY4-IT***

SPRY4-IT is an lncRNA that has been demonstrated to be a vital role in tumorigenesis associated with various cancer types (26,75). In a study by Zhou *et al.* (26), SPRY4-IT expression was found to be upregulated in TC tissues and cells. This elevated expression was found to be associated with poor prognosis. Studies have revealed that SPRY4-IT silencing could suppress TC cell proliferation and migration, and other studies have shown that silenced SPRY4-IT promotes a higher expression of transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1) and p-SMAD2/3, which are known regulators of cell invasion and migration. Conversely, TGF- $\beta$ 1 could restore growth inhibition that had been induced by silencing SPRY4-IT1. These data suggest that SPRY4-IT contributes to the progression of tumor cell growth and acts via the TGF- $\beta$ 1/SMAD signaling pathway.

### *Urothelial carcinoma associated 1 (UCA1)*

UCA1, a 1.4-kb long transcription lncRNA, was first found in bladder cancer and is highly expressed in various carcinomas (76,77). UCA1 expression is upregulated in PTC tissues and cells, and has been observed to be positively correlated with tumor size, tumor stage, and metastasis of PTC (31). UCA1 overexpression promotes cell proliferation and invasion, and suppresses apoptosis in TC cells via the Wnt pathway. UCA1 acts as an oncogene in tumorigenesis, and stimulates invasion in tumor progression. Many studies have revealed that UCA1 elevates tumorigenesis mainly through binding to miRNAs, activating several vital signaling pathways and altering epigenetic and transcriptional regulation (78,79). In TC, the expression of UCA1 is significantly upregulated in PTC tissue compared with normal tissue (80). Through loss-of-function analysis, UCA1 knockdown was found to significantly inhibit PTC cell viability and promote the expression of BRD4. UCA1 was also found to promote the progression of PTC through sponging miRNA-204 and enhancing BRD4 expression. Li *et al.* found that the UCA1/miR-15a axis is involved in mediating EMT in PTC (29). In ATC, UCA1 promotes cancer progression through miR-135a-mediated *c-MYC* activation (81). Another study revealed that UCA1 knockdown inhibits cell proliferation and invasion by modulating the miR-204/IGFBP5 axis in PTC (82). These studies demonstrate that UCA1 plays a vital role in the progression of TC, and may be a potential target for TC treatment.

### **Mechanisms underlying lncRNA-mediated metastasis in PTC tumors**

EMT is implicated in the progression of FTC and PTC converting to PDTC and ATC by conferring stem-like properties to cancer stem cells (83). To enter the blood circulation, during EMT epithelial cancer cells undergo a decrease in cell-cell adhesion and cell polarity and an increase in mesenchymal features, and migrate to secondary areas; upon arrival in the secondary site, they invade the tissue through the MET, which is the reverse process of EMT (84). In cancer cells, changes in gene expression accompanying the EMT-MET process is controlled by multiple transcription factors, such as SNAIL, SLUG, and ZEB1 (85); growth factors and their associated signaling proteins (86); epigenetic regulators; and the tumor microenvironment. LncRNAs interacting with target genes

involved in the EMT-MET process have also been recently reported in the literature (87). LncRNAs regulate gene expression by functioning as signaling molecules inducing gene expression, decoys that sequester transcription factors, guides that recruit RNA binding proteins, and scaffolds that form protein complexes (88). In PTC, lncRNAs have been reported to regulate gene expression networks by a variety of methods, such as directly binding to miRNAs and preventing their interaction with target genes or proteins, directly binding to target genes, post-transcriptional epigenetic modification by recruiting histone modifiers [e.g., enhancer of zeste homolog 2 (EZH2)], and regulating proteins involved in signaling pathways (e.g., TGF- $\beta$ 1, PI3K/Akt, Wnt/ $\beta$ -catenin) (89). Given this range of mechanisms of lncRNAs in PTC, identification and further characterization of these molecules can pave the way for potential diagnostic, prognostic, and therapeutic targets.

### **LncRNAs downregulated in TC**

Understanding the molecular underpinnings of how these regulatory lncRNAs are downregulated in TC is of importance to develop novel diagnostic and prognostic markers that can serve to alter tumor functionality.

### ***BRAF-activated non-coding RNA (BANCR)***

BANCR is a 693-bp lncRNA that was first identified by Flockhart in 2012 (90). BANCR expression is detected in many tumors, including melanoma (91,92), gastric cancer (93), lung cancer (94), and endometrial cancer (95). Liao *et al.* (96) analyzed BANCR expression in 92 patients with PTC and normal thyroid epithelial tissues using quantitative reverse transcription polymerase chain reaction. BANCR was found to be downregulated in PTC tissue compared with control tissue. Decreased BANCR expression is associated with tumor size, multifocal lesions, and tumor stages. Furthermore, increased BANCR expression was also found to decrease PTC cell proliferation and increase apoptosis. BANCR expression also inactivates ERK1/2 and P38 inhibiting tumorigenesis in PTC. A previous study reported BANCR to be significantly downregulated in PTC tissues compared with matched normal thyroid tissues, and it was found to be strongly correlated with lymph node metastasis. Functional studies have indicated that the overexpression of BANCR leads to G2/M cell-cycle arrest and increased apoptosis (37). In addition, the MAPK and PI3K/Akt pathways are aberrantly activated by western blotting,

resulting in decreased cancer cell proliferation and invasion. These studies demonstrate that BANCR could play an integral role as a tumor suppressor in TC.

#### ***AB074169***

AB074169 is a novel lncRNA. AB074169 expression has been previously shown to be significantly downregulated in PTC (38). The decreased expression of AB074169 was found to be related to CpG hypermethylation within its gene promoter. Through loss- and gain-of-function analyses, AB074169 overexpression was found to cause cell-cycle arrest and inhibit the growth of PTC cells. However, AB074169 knockdown promoted cell proliferation. Further studies demonstrated that AB074169 binds to the splicing regulatory protein (KHSRP) and inhibits the expression of KHSRP, therefore increasing CDKN1a (p21) expression and decreasing CDK2 expression to inhibit cell proliferation. These data suggest that AB074169 acts as a tumor suppressor during PTC tumorigenesis.

#### ***ASMTL antisense RNA1 (ASMTL-AS1)***

ASMTL-AS1 is a novel lncRNA that is significantly downregulated in PTC. A low expression of ASMTL-AS1 has been found to be positively associated with larger tumor size, advanced clinical stages, and an unfavorable outcome (39). Gain-of-function assays have demonstrated that elevated ASMTL-AS1 promotes PTC cell proliferation and glycolysis. Loss-of-function analysis have found that ASMTL-AS1 knockdown has the opposite effect. Luciferase reporter gene demonstrated that ASMTL-AS1 also promotes the expression of FOXO1 via sponging miR-93-3p and miR-660, and inhibits glycolysis and tumorigenesis. In addition, FOXO1 is capable of binding to the ASMTL-AS1 promoter to elevate ASMTL-AS1 expression, which leads to a feedback regulation loop. The regulatory axis of ASMTL-AS1/miR-93-3p/miR-660/FOXO1 was identified in the animal study. This study concluded that ASMTL-AS1 is likely to play a role as a tumor suppressor gene and could be used as a potential predictor in PTC patients.

#### ***Bladder cancer-associated transcript 1 (BLACAT1)***

The BLACAT1 lncRNA was first found in bladder cancer and is also expressed in several other of human cancers. In

PTC, BLACAT1 expression was found to be significantly downregulated in the plasma of 87 PTC patients (case group) compared with 36 patients with nodular goiter (control group) (40). Low plasma BLACAT1 expression is correlated with lymph node metastasis. A multivariate analysis demonstrated that BLACAT1 is an independent risk factor for lymph node metastasis and sex. Collectively, these data indicate that BLACAT1 acts as a vital tumor suppressor gene, and a potential biomarker for the prediction of prognosis in PTC.

#### ***Cancer susceptibility candidate 2 (CASC2)***

CASC2 is a lncRNA that been identified as a tumor suppressor gene in several types of cancers, including colorectal, lung, and renal (97-99). A recent study showed that expression was significantly downregulated in PTC tissues compared with adjacent normal tissues (41). Gain-of-function assays have demonstrated that elevated CASC2 expression inhibits cell proliferation and increases apoptosis in PTC cells. CASC2 overexpression leads to the inactivation of protein kinase B/Akt and extracellular signal-regulated kinase 1/2. Other studies have found that MAPK (MEK) inhibitor U0126 or Akt1/2/3 inhibitor MK-2206 2HCl enhances the regulatory effects of CASC2 on the biologic behavior of PTC. Similarly, CASC2 overexpression inhibits tumor growth in PTC cells *in vivo*. These observations suggest that CASC2 significantly inhibits tumorigenesis in PTC. Therefore, CASC2 shows promise as a potential prognostic marker and therapeutic target.

#### ***HOX antisense intergenic RNA myeloid 1 (HOTAIRM1)***

HOTAIRM1 is a lncRNA that is associated with various cancers (100-102). HOTAIRM1 expression is significantly downregulated in PTC tissues and the low expression of HOTAIRM1 is associated with lymph node metastasis and advanced TNM stage. Moreover, gain-of-function assays have demonstrated that elevated HOTAIRM1 inhibits PTC cell proliferation, invasion, and migration *in vitro*. Subsequent studies have also confirmed that HOTAIRM1 competes with endogenous miR-107. In addition, these studies also demonstrated that HOTAIRM1 regulates the expression of TDG in a miR-107-mediated manner (47). These data indicate that HOTAIRM1 acts as a tumor suppressor gene in PTC, and may serve as a therapeutic



target for PTC patients.

### ***Growth arrest-specific 5 (GAS5)***

GAS5 is a non-coding gene that hosts several small nucleolar RNAs. It was originally isolated from mouse NIH 3T3 cells using subtraction hybridization. GAS5 is induced by cellular stressors, such as serum starvation and cell–cell contact inhibition (103). Guo *et al.* analyzed the expression of GAS5 in 212 TC patients and 61 benign thyroid tumor patients (104). The patients were divided into high-risk and low-risk groups according to the MACIS, AGES, and AMES prognostic scoring systems. It was found that the expression of GAS5 was downregulated in TC tissues compared with benign tissues. This GAS5 downregulation was significantly associated with TNM staging, lymph node metastasis, and multiple cancer foci of TC. GAS5 expression decreased in the MACIS high-risk cohort compared with the AMES low-risk patients. Similarly, TC patients with high GAS5 expression had a better disease outcome compared with TC patients with low GAS expression. These data suggest that GAS5 can function as a biomarker for the diagnosis and prognosis of TC.

### ***LncRNA Prader Willi/Angelman region RNAs (PAR5)***

PAR5, also known as PWAR5, plays an important role in various types of cancers, including glioma and ATC (44,105). Pellicchia *et al.* (105) investigated the lncRNA expression profiles of 9 ATC samples compared with 5 normal thyroid tissues and identified 19 upregulated and 28 downregulated lncRNAs with a fold change >1.1 or <-1.1. Other studies found that the expression of PAR5 was significantly downregulated in ATC samples, and that the downregulation of PAR5 contributes to the restoration of reduced proliferation and migration (105). Studies also have found that PAR5 impacts EZH2 oncogenic activity by impacting its transactivation potential on E-cadherin. These results suggest that PAR5 has typical tumor suppressive behavior in TC.

### ***SNHG3***

SNHG3 is a novel lncRNA expressed in various types of cancers, including PTC (45,106,107). The expression of SNHG3 has been reported to be significantly downregulated in PTC tissues and cell lines (45), and was observed to be significantly correlated with TNM stage

and poor prognosis of PTC patients. SNHG3 depletion promotes proliferation, migration, and invasion in PTC cells. Similarly, silenced SNHG3 was found to promote malignant progression in tumor xenograft models. Further analyses demonstrated that SNHG3 knockout activates the Akt/mTOR/ERK pathway in PTC cell lines. These effects could then be rescued using the mTOR inhibitor AZD8055. These findings indicate that SNHG3 can act as a tumor suppressor gene in PTC, and might serve as a promising candidate for target therapy of PTC.

### ***GAS8-AS1***

*GAS8-AS1* is the second most frequently altered gene, after the *BRAF* gene in PTC. Previous studies have indicated that *GAS8-AS1* functions as a tumor suppressor in PTC. In a recent study (42), *GAS8-AS1* expression was found to be downregulated in PTC cells compared with a normal thyroid cell line. Gain-of-function studies have demonstrated that *GAS8-AS1* overexpression suppresses cell proliferation, increases the ratio of LC3-II/LC3-I, and reduces p62 expression, whereas *GAS8-AS1* the knockdown is pro-oncogenic. *GAS8-AS1* overexpression produces higher levels of LC3 staining and increases the expression of autophagosomes. Autophagy-related gene 5 was found to be significantly upregulated by *GAS8-AS1* overexpression and downregulated by *GAS8-AS1* knockdown. These data indicate that *GAS8-AS1* can modulate cell death in PTC via the autophagy pathway. Chen *et al.* found that the *GAS8-AS1* was downregulated in PTC cell lines and suppressed the cell proliferation and cycle of PTC cells. Further studies showed that *GAS8-AS1* regulates a downstream target of miR-135b-5p, cyclin G2, whereas overexpressed *GAS8-AS1* inhibits tumor formation and suppresses PTC cell growth (108). These studies demonstrate that *GAS8-AS1* inhibits PTC cell growth via the miR-135b-5p/CCND2 axis, and acts as a tumor suppressor gene in PTC.

### ***Maternally expressed gene 3 (MEG3)***

MEG3 is an imprinted gene belonging to the imprinted DLK1-MEG3 locus located at chromosome 14q32.3 in humans. Its mouse ortholog, MEG3, also known as gene trap locus 2 (Gtl2), is located at distal chromosome 12 (109). A recent study showed that a low expression of MEG3 was found in TC tissues, and low MEG3 expression was positively correlated with the low cumulative survival rate in PTC patients under iodine treatment. Further studies

found that MEG3 overexpression inhibits iodine-resistant cell viability, elevates the level of apoptosis, and induces DNA damage. In addition, MEG3 leads to the sponging of miR-182, and MEG3 knockdown substantially inhibits the anti-cancer functions of anti-miR-182. These experiments indicate that MEG3 could be a suitable target for TC patients with iodine resistance (43). MEG3 expression was found to be significantly downregulated in PTC tissues with lymph node metastasis compared with primary TC. Moreover, the low expression of MEG3 is associated with relative lymph node metastasis. MEG3 inhibits the migration and invasion of PTC cells. Further studies have demonstrated that MEG3 negatively regulates post-transcriptional processing through a specific target site within the 3'UTR.

### LncRNAs as diagnostic and prognostic markers in TC

We previously discussed the role of current genetic markers as prognostic and diagnostic markers for TC patients. It is also important to focus on lncRNAs as novel targets that show promise for their benefits as prognostic or diagnostic markers in TC progression and recurrence. Currently, the cytological evaluation of fine-needle aspiration (FNA) of thyroid nodules is the standard procedure to determine the need for surgical resection in TC patients. However, there are significant drawbacks in the use of FNA, and studies have reported the use of microarray analysis for FNA (110). Several lncRNAs have been described as significantly specific for TC. The differential expressions of those lncRNAs have also been found to be cells, tissue, and plasma in the TC.

As discussed earlier, some lncRNAs, such as CCAT1, H19, HCP5, HOTTIP, MALAT1, HOXA-AS2, SNHG15, SPRY4-IT, and UCA1, have been found to be upregulated in TC (7,23,25,26,30,42,70,111,112), whereas others, such as BANCR, AB074169, ASMTL-AS1, BLACAT1, CASC2, HOTAIRM1, GAS5, PAR5, SNHG3, GAS8-AS1, and MEG3 are downregulated (38-40,43-45,47,104,108,112,113). This unique biologic behavior exhibited by different groups of lncRNAs shows value for the prognostic and diagnostic determination in TC patients. However, further research is required to elucidate the mechanisms of action through which each of these lncRNAs exerts their effects. Further development, characterization, and standardization are essential if lncRNAs are to be used as prognostic markers in the clinical setting.

Most patients with TC are treated with surgical resection, thyroid hormone therapy, chemotherapy, and radiotherapy. However, recurrence due to metastasis can still occur despite treatment. This recurrence is often linked to EMT, and therefore, identifying lncRNAs specific for EMT may help diagnose the disease earlier. As metastasis is reported to occur due to genetic changes during the development of primary tumors, identifying metastatic-specific biomarkers can assist in the early detection of metastatic cancers (114). LncRNAs H19, HOXA-AS2, and UCA1 have been reported to affect the invasive nature of TC cells. The clinical significance of some lncRNAs as prognostic determinants in clinical studies are described in *Table 3*.

### Discussion

LncRNAs regulate various mechanisms involved in tumor initiation, progression, and metastasis (87). Due to spatiotemporal expression and plasma stability, the detection of circulating lncRNAs as prognostic and diagnostic biomarkers for TC is developing as a viable field of research. Moreover, lncRNAs detection in circulating fluids provides a non-invasive approach, avoiding the need for invasive biopsies (118). Despite these advantages, there are still challenges that affect the use of lncRNAs as biomarkers, including factors affecting the stability and bioavailability of lncRNAs in fluids and lncRNA extraction (89).

The targeting of lncRNAs through RNAi technology, anti-sense oligonucleotides (ASO) and small molecule inhibitors has also been investigated as a therapeutic approach in other cancers (119,120). For instance, the subcutaneous injection of ASO targeting MALAT1 has been shown to block lung metastasis in mouse xenograft models. HOTAIR targeting small molecule inhibitor AC1NOD4Q has been shown to inhibit the binding of HOTAIR with EZH2, and reduces cancer metastasis *in vitro* and in orthotopic breast cancer models (120). At the same time, bioinformatics and database are used as important tools to predict co-genes and ce-RNA in the researches of lncRNA. In particular, there has been significant research demonstrating the presence of specific lncRNAs associated with various tumor mechanisms and disease stage (121). Currently, the mechanisms involved in lncRNA production, transportation, binding partners, and targets are not well understood, and further research is required to enable the clinical use of lncRNAs as biomarkers and potential therapeutic targets.

In the present study, we provided a comprehensive

**Table 3** Clinical significance of lncRNAs as prognostic markers in TC patients

lncRNA	Tumor	Samples	Clinical significance	Source
BLACAT1	PTC	87 PTC patients	Correlates with lymph node metastasis (P<0.001)	(40)
CASC2	TC	172 thyroid carcinoma tissues	Correlates with multifocality and advanced TNM stage	(41)
LINC02454	PTC	104 PTC tissues	Closely related to tumor size, T stage, lymph node metastasis and disease-free survival.	(115)
GAS5	TC	212 TC patients	TNM staging, lymph node metastasis, and multiple cancer foci were independent risk factors for poor prognosis in TC patients	(104)
H19	PTC	410 PTC patients	Associated with patient age, tumor size, extrathyroidal extension, pathological lateral node metastasis (pN1b), histological aggressive type, and poorer disease-free survival (P<0.0001).	(116)
MIR22HG	ATC	9 ATC patients and 20 PTC	Significantly related to higher age, lymph node metastasis status, residual tumor status, N stage, grade, and T stage in TC	(91)
SNHG22	PTC	65 PTC tissues	Closely associated with unfavorable clinicopathological characteristics and worse overall survival in patients with PT	(117)
SPRY4-IT	TC	80 TC tissues	Correlated with poor prognosis	(26)

lncRNA, long non-coding RNA; TC, thyroid cancer; PTC, papillary thyroid carcinoma; ATC, anaplastic thyroid carcinoma.

description of the lncRNAs involved in TC and their respective mechanisms of action during cancer growth and development. We also discussed their use as prognostic and diagnostic markers and the challenges in enabling lncRNAs to be used as prognostic markers in the clinical setting, as well as strategies to overcome these challenges. Further studies are warranted to better understand the role of lncRNAs in EMT, prevent the recurrence of TC and design effective treatment strategies.

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