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# Long non-coding RNAs in thyroid cancer: Biological functions and clinical significance

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ABSTRACT

Thyroid cancer is the most common endocrine malignant tumor with rapidly increasing incidence in recent decades. Although the majority of thyroid cancers are relatively indolent, some cases still have a risk of developing into more aggressive and lethal forms of thyroid cancers. Similar to other malignancies, thyroid tumorigenesis is a multistep process involving the accumulation of a large number of genetic and epigenetic alterations. Thus, determination of the mechanisms of tumorigenesis is an urgent need for thyroid cancer treatment. Long noncoding RNAs (LncRNAs) have recently been demonstrated to participate in cancer progression. However, their role and molecular mechanism in thyroid cancer remain largely unclear. In this review, we focus on the dysregulation of lncRNAs in thyroid cancer, summarize the latest findings regarding the functions and mechanism of lncRNAs in thyroid cancer, and discuss their potential clinical significance in diagnosis and prognosis of thyroid cancer.



**Contents**



## 1. Introduction

Epithelial follicular cell-derived thyroid cancer is the most common endocrine malignancy that has rapidly increased in global incidence over the past several decades (Siegel et al., 2017). It is histologically classified into papillary thyroid cancer (PTC), follicular thyroid cancer (FTC), poorly differentiated thyroid cancer (PDTC) and anaplastic thyroid cancer (ATC). PTC and FTC are collectively called well-differentiated thyroid cancer (WDTC), accounting for more than 90% of all cases. Usually, the patients with

*Abbreviations:* $^{131}$I-WBS, $^{131}$I whole-body scan; ETE, Extrathyroidal extension; GEO, Gene Expression Omnibus; GWAS, Genome-wide association studies; K1, K1 cell; LncRNAs, Long noncoding RNAs; miRNAs, microRNAs; NPL, Nonparametric linkage; NSCLC, Non-small cell lung cancer; PARP-1, Poly ADP-ribose polymerase 1; *PAX8*, Paired-box gene8; *PPARγ*, Proliferator-activated receptor-γ; ROC, Receiver operating characteristic curve; siRNAs, Small interfering RNA; SNP, Single nucleotide polymorphism; TSCC, Tongue squamous cell carcinoma; TSH, Thyroid stimulating hormone; *TERT*, Telomerase reverse transcriptase; WDTC, Well-differentiated thyroid cancer.

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WDTC have a good prognosis and can be cured by surgical and radioiodinated therapy; however, about 10% of cases can dedifferentiate into more aggressive and lethal thyroid cancers (Burns and Zeiger, 2010). Although a number of genetic and epigenetic alterations have been identified in thyroid cancers over the past few decades (Aschebrook-Kilfoy et al., 2011; Nikiforov and Nikiforova, 2011), the exact pathogenesis of this disease remains largely unclear. Thus, a better understanding of pathogenesis of thyroid cancer may help us to develop novel diagnostic, therapeutic and preventive strategies for this disease.

In thyroid cancer, most of genetic events are closely associated with aberrant signaling of phosphatidylinositol-3-kinase (PI3K)/Akt and RAS/RAF/MEK/ERK (MAPK/ERK) pathways such as *BRAF* and *RAS* point mutations, which play a crucial role in the regulation of cell growth and survival (Aschebrook-Kilfoy et al., 2011; Handkiewicz-Junak et al., 2010; Nikiforov and Nikiforova, 2011; Xing, 2013). Among them, $BRAF^{V600E}$ is the most common genetic alteration and associated with high-risk clinicopathologic features of thyroid cancer (Kim et al., 2012); however, a recent study has demonstrated that PTC variants (such as follicular variant PTC) are also involved in the differential clinicopathological risk of major PTC which has led to confusion about the role of BRAF mutation as a predictor of outcome (Shi et al., 2016). Genomic arrangements are other frequent genetic alterations in thyroid cancer such as *RET/PTC* and *PAX8* (Paired-box gene8)/*PPARγ* (proliferator-activated receptor-γ), which also play an important role in thyroid tumorigenesis (Aschebrook-Kilfoy et al., 2011; Handkiewicz-Junak et al., 2010; Nikiforov and Nikiforova, 2011; Xing, 2013). In addition, *TP53* mutations are highly prevalent in ATCs, while relatively rare in WDTCs and PDTCs, which are strongly related to poor clinical outcomes of the patients (Landa et al., 2016). Beyond these alterations in protein-coding genes, somatic mutations in regulatory DNA such as *TERT* (Telomerase reverse transcriptase) promoter mutations also contribute to loss of differentiation and disease progression of thyroid cancer (Landa et al., 2016; Cancer Genome Atlas Research Network, 2014). Importantly, these molecular alterations have been regarded as valuable diagnostic and prognostic markers for thyroid cancer and are beginning to be introduced into clinical practices (Handkiewicz-Junak et al., 2010).

In addition to genetic alterations, other mechanisms such as long noncoding RNAs (LncRNAs) have received increasing attention to be implicated in almost all steps of tumor progression including cell growth, survival and metastasis (Prensner and Chinnaiyan, 2011). LncRNAs are a class of RNAs containing over 200 nucleotides which do not code for proteins (Djebali et al., 2012; Kapranov et al., 2007). Compared to protein-coding mRNAs, lncRNAs on average are present in lower abundance, frequently reside in the nucleus, are more tissue-specific and not conserved among different species (Khorkova et al., 2015). According to their genomic location relative to nearby protein-coding genes, lncRNAs can be grouped into intergenic lncRNAs, intronic lncRNAs, bidirectional lncRNAs, sense lncRNAs and antisense lncRNAs (Bouckenheimer et al., 2016; Min et al., 2017; Rinn and Chang, 2012). To date, a large number of cancer-related lncRNAs have been identified and demonstrated to play a critical role in tumorigenesis (Ergun and Oztuzcu, 2015). Mechanistically, lncRNAs can serve as molecular scaffolds, miRNA sponges, protein decoys and reservoirs of small noncoding RNAs to regulate gene expression and protein function (Fig. 1) (Khorkova et al., 2015; Li et al., 2013; Shi et al., 2013; Wahlestedt, 2013; Xiong et al., 2016). Although there is increasing evidence showing the importance of lncRNAs in human cancers, their role and mechanism in thyroid cancer remain largely unclear.

In this review, we summarize the most recent findings of lncRNAs in thyroid cancer and discuss their value as potential diagnostic and prognostic biomarkers and therapeutic targets for thyroid cancer.

## 2. Aberrant expression of lncRNAs in thyroid cancer

A large number of lncRNAs have been identified to be up-regulated or down-regulated in thyroid cancer tissues or cancer cell lines, which contribute to thyroid tumorigenesis, and their biological functions and possible mechanism in thyroid cancer are summarize in Tables 1 and 2, and Fig. 2.

### 2.1. Up-regulated lncRNAs in thyroid cancer

*ANRIL* (antisense noncoding RNA in the INK4 locus), also known as CDKN2B-AS, is a 3.8 kb lncRNA which was initially identified from melanoma patients (Pasmant et al., 2007). It is located at chromosome 9p21, reversing from INK4b-ARF-INK4a gene cluster encoding three tumor suppressors p15(INK4b), p14(ARF), and p16(INK4a) (Burd et al., 2010). The previous studies have showed that up-regulation of *ANRIL* is a risk factor in several cancers including gastric, lung, breast, bladder and ovarian cancer (Iranpour et al., 2016; Naemura et al., 2015; Zhang et al., 2014; Zhu et al., 2015). *ANRIL* has been reported to be highly expressed in thyroid cancer tissues and cell lines, and ectopic expression of *ANRIL* inhibits the activity of TGF-β/Smad signaling pathway, further decreasing $p15^{INK4B}$ expression and promoting thyroid cancer cell invasion and metastasis (Fig. 2) (Zhao et al., 2016). In addition, oncogenic function of *ANRIL in vitro* is also verified by metastasis of human cancer xenografts in nude mice (Zhao et al., 2016).

Nuclear enriched abundant transcript 1 (*NEAT1*), as a lncRNA, has been found to be tightly linked to tumor progression of different malignancies including PTC (Chakravarty et al., 2014; Guo et al., 2015; Kim et al., 2010; Zeng et al., 2014). A previous study indicated that *NEAT1* was up-regulated in thyroid cancer cells and *NEAT1* overexpression promoted thyroid cancer cell growth and invasion (Li et al., 2017b). On the other hand, *NEAT1* knockdown inhibited cell survival, invasion, and tumorigenic potential in nude mice (Li et al., 2017b). A number of previous studies have demonstrated that lncRNAs act as competing endogenous RNAs (ceRNAs) to sponge miRNAs (MicroRNAs), thereby regulating the derepression of miRNA targets and imposing an additional level of post-transcriptional regulation (Ebert et al., 2007; Jeyapalan et al., 2011; Poliseno et al., 2010; Salmena et al., 2011; Tay et al., 2014). Similarly, *NEAT1* also functions as a ceRNA by competitively binding miRNA-214 to inhibit its function, further promoting malignant progression of thyroid cancer cells (Fig. 2) (Li et al., 2017b).

*LOC100507661* is a 745 bp transcript consisting of 5 exons, which is located at 3q26.2 (Kim et al., 2016). Datasets of Gene Expression Omnibus (GEO) showed that *LOC100507661* was up-regulated in multiple cancers including thyroid cancer (Kim et al., 2016), suggesting that it may exert an oncogenic function in PTC (Kim et al., 2016). Gain of function assays demonstrated that elevated *LOC100507661* promoted thyroid cancer cell proliferation, migration and invasion (Kim et al., 2016). Moreover, increased expression of *LOC100507661* was associated with lymph node metastasis, $BRAF^{V600E}$ mutation and low thyroid differentiation score (TDS) in the patients with thyroid cancer (Kim et al., 2016).

*HOTAIR* (HOX antisense intergenic RNA), a 2158 bp lncRNA, has been found to be up-regulated in different types of cancer (Ozes et al., 2016; Zhu et al., 2016). It was originally identified in 2007 as a lncRNA located in the HOXC gene cluster on chromosome 12 (Kim et al., 2013), and was demonstrated to be a negative prognostic factor in breast, lung, esophagus, colon, bladder, prostate, glioblastoma, pancreas, and liver cancers (Gupta et al., 2010; Kogo et al., 2011; Pastori et al., 2015; Stratford et al., 2010; Xue et al., 2016; Yan et al., 2014b; Yang et al., 2011; Zhang et al., 2015).