LncRNAs as Potential Therapeutic Targets in Thyroid Cancer

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Abstract

Thyroid cancer (TC) is the most common cancer of endocrine system. TC can be subdivided into 4 different entities, papillary, follicular, medullary and anaplastic thyroid cancer. Among them, anaplastic thyroid cancer has the poorest prognosis. Exploring new therapeutic approach may entail favorable prediction as well as increasing overall survival rate of patients. Long non-coding RNAs (lncRNAs), have vast implications in different cancer types. Although they are not transcribed into proteins, they can act as a harness in regulating a plethora of biological functions. They have been implicated in a decisive role in gene expression via modulation of both coding and non-coding RNAs. This article discuss the multi-facet role of lncRNA in thyroid cancer biology.

Keywords: LncRNA- treatment- genetic alterations- thyroid cancer

Introduction

Among malignant tumors, thyroid cancer (TC) has been the most common cancer of endocrine gland. It has been estimated that the overall incidence of the TC in the US alone has escalated from 2.4% per year to 6.6% per year (Solomon et al., 2019). The incidence of TC has been escalating for the past thirty years. In the US alone endocrine cancers prevalence is mounting with roughly 1-1.5% of all newly diagnosed cancers every year (Orosco et al., 2019). The annual percentage change of thyroid tumors is increasing in the globe except Africa at where detection is not popular (Kilfoy et al., 2009). Appertaining to these findings it has been perceived that TC is the fifth most prevalent type of anomaly in females and it severely affects women under the age 45 years (Guerra et al., 2014). Several factors have been investigated for this robust high variability of thyroid tumors. Genetic predispositions an environmental factors may account for the disease access to the medical facilities are the key for the diagnosis of TC. Among thyroid tumors, papillary thyroid cancer is more common in black females while male proportions were found to be highest in percentage in white males 6.3-7.1%. Similar percentage prevalence was observed in various male populations such as the Hispanic 6.7%, Asian 6.4% and 8.4% in African males (Pellegriti et al., 2013). TC account for 0.3% mortality incidence in the US and rates of mortalities are similar around the world. TC incidence is 10.5 per 100,000 in the US (Alok Pathak et al., 2013). Based on its cellular origin, TC is classified into 4 different entities, papillary (PTC), follicular (FTC), medullary (MTC) and anaplastic thyroid carcinoma (ATC) (Trimboli et al., 2006). Papillary carcinoma is the most common one, has an incidence rate ranging between 80-85%, with the highest prognostic rate in ten years with a survival ratio >90-95% with low metastatic potential. Follicular carcinoma is the second most prevalent tumor of thyroid followed by medullary and anaplastic cancers (Aboelnaga and Ahmed, 2015).

A surfeit of cellular as well as genetic processes such as genetic aberrations, epigenetics, and dysregulated cellular signaling have been reported to orchestrate the...
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LncRNAs are at least > 200 bp in these tiny molecules were once referred to as “junk DNA.” LncRNAs encompasses 80% of the human genome that remains untranslated. They are distinctly different from the coding regions in their biogenesis and functions (Hangauer et al., 2013; Starren et al., 2013). They also entail unique properties from the coding RNAs which confer them incomparable structural and functional superiority over the coding genome. Despite their exceptional physiology, they share some similarities with other RNA molecules such as microRNAs, small nuclear RNAs, etc. Yet, they have been shown to play a pivotal role in eukaryotic mammalian cells (Bierhoff et al., 2011). They are transcribed by RNA polymerase II and in some cases by RNA pol III. They have been reported as mediators and regulators of epigenetic activation of specific oncogenes (Guttman et al., 2009; Gutschner and Diederichs, 2012). Owing to these characteristics, LncRNAs are a hallmark in tumor biology of TC as they can promote cellular proliferation. The interplay between LncRNAs and oncogenes may lead to tumor progression (Zheng et al., 2016). Understanding this area is promising for impeding TC progress or fostering new strategies for TC treatment (Jalali et al., 2013; Liao et al., 2017). They also recruit proteins that differ from other RNA molecules such as microRNAs, small nuclear RNAs, etc. Yet, they have been shown to play a pivotal role in eukaryotic mammalian cells (Bierhoff et al., 2011). They are transcribed by RNA polymerase II and in some cases by RNA pol III. They have been reported as mediators and regulators of epigenetic activation of specific oncogenes (Guttman et al., 2009; Gutschner and Diederichs, 2012). Owing to these characteristics, LncRNAs are a hallmark in tumor biology of TC as they can promote cellular proliferation. The interplay between LncRNAs and oncogenes may lead to tumor progression (Zheng et al., 2016). Understanding this area is promising for impeding TC progress or fostering new strategies for TC treatment (Jalali et al., 2013; Liao et al., 2017). They have been linked to unabated cell growth, prolonged metastasis and upregulation of oncogenes, which are summarized in Figure 1. They act via either activation of promoters or recruitment by either NEAT1 (Nuclear enriched abundant transcript 1), BANCER (BRAF-activated LncRNA) or PVT1 (plasmacytoma variant translocation 1), MALAT1 (Metastasis-associated lung adenocarcinoma transcript 1) and HOTAIR (HOX transcript antisense RNA) results in the activation of thyroid stimulating hormone receptor (TSHR) which in turn promotes the expression of Cyclin D1 that triggers cellular proliferation in TC (Zheng et al., 2016).

Involvement of Oncogenic LncRNAs in Thyroid Cancer

LncRNAs do not code for proteins and the best way to understand their function is through expression analysis (Derrien et al., 2012). Tumor diagnosed at an early stage could provide extended survival or characterize pathological features of the tumor as well. LncRNAs have the potency to be detected in blood as well as in tissue well, thus making them a diagnostic tool that can be easily detected (Schwarzenbach et al., 2011). In addition, LncRNAs could also aid in the diagnostic assessment of PTC via ultrasonography. An extracellular protein highly expressed on cell surface known as fibronectin 1 promotes transcription of the NONHSAT076754 a long non-coding RNA. NONHSAT076754 has been involved in cellular processes such as cell adhesion, migration and injury response. Xiang et al., (2017) studied the involvement of NONHSAT076754 in PTC. Their findings revealed that NONHSAT076754 promoted migration and invasiveness in PTC and addition of NONHSAT076754 along with ultrasonography led to an increased in the diagnostic credibility of PTC. Therefore, NONHSAT076754 could be used as a valuable auxiliary diagnostic biomarker with ultrasonography for the prediction of cervical lymph node metastasis in PTC. All these evidence suggest that LncRNAs have potential in diagnostic or prognostic. Moreover, they are engaged in the thyroid carcinogenesis as below:
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Another important lncRNA that has been reported to be overexpressed in a plethora of cancer types. However, limited data is available on the role of HOTAIR in TC. A recent study has indicated the oncogenic role of HOTAIR in PTC. SNP based analysis conducted by Zhu et al. demonstrated that SNP variation in HOTAIR (rs920778 SNP) has been importantly affiliated with down regulation of the Wnt-beta catenin pathway in PTC cell lines. This down regulation resulted in increased cell survival and proliferation indicating that HOTAIR could be implicated in oncogenesis (Zhu et al., 2016). Overexpression of HOTAIR promptly decreased the overall survival in PTC patients via modulation of Wnt signaling cascade (Murugan et al., 2018). Another study conducted by Di et al., (2017) demonstrated that HOTAIR plays a pivotal role in the development and differentiation of PTCs. Using functional assays and nude mice model they showed suppression of HOTAIR with antisense RNAs which resulted in growth arrest. Overexpression of HOTAIR increased the expression of CCND2 a tumor promoting protein under the influence of miR-1. This revealed that HOTAIR could be utilized as a diagnostic approach to understand tumor pathology in PTC. Furthermore, exploring the role miR-1/HOTAIR interaction can open new fields for the development of therapeutic strategies.

In a recent microarray-based study on the role of HOTAIR along with ROR and PVT1 in PTC has been evaluated. HOTAIR, PVT1 and ROR modulate protein expression of PTC and their upregulation increases the cell proliferation in PTC (Zhang et al., 2018c). These findings showed that HOTAIR as a useful diagnostic tool for the detection of disease progression in PTC.

MALAT1

MALAT1 (Metastasis-associated lung adenocarcinoma transcript 1) has been investigated extensively in TC. MALAT1 targets IQGAP1. Overexpression of MALAT1 resulted in increased cell growth and invasion in vitro. Huang et al., (2016) showed that MALAT1 expression

Figure 1. Functions and Mechanism of Action of lncRNAs in Different Biological Processes such as Transcription, Post-Transcription and Epigenetic Regulation.
aid in the induction of tumor growth in mice model, antagonistically acting on IQGAP1, indicating the crucial involvement of MALAT1 in TC. Furthermore, MALAT1 overexpression has been related to EMT transition in TPC1 cell lines under the influence of TGF beta action suggesting a role of MALAT1 in tumor metastasis (Zhang et al., 2017). In situ hybridization indicated that MALAT1 and miR-885 interplay one each other in follicular and Hurthle cell thyroid (HTC) neoplasms. Increased expression of both was observed in FTC as well HTC compared to normal tissue. Furthermore, phosphorylation of mammalian target of Rapamycin (mTOR) was also overexpressed by MALAT1 and miR-885 activity in FTC. These findings suggest that this pathway could be targeted for possible drug delivery system (Covach et al., 2017).

Tumor-associated macrophages (TAM), could be elevated in PTC as well as other TC cells, inducing thyroid cells proliferation and angiogenesis. Huang et al demonstrated that MALAT1 directly promoted angiogenesis in TAM by interacting with FGF2. Using CCK8 assay and transwell assay they reported that MALAT1 and FGF2 expression was quite high in thyroid tissue as compared to normal control. Moreover, when the expression of MALAT1 and FGF2 was decreased in the FTC133 cells, proliferation, migration and invasiveness were increased explicitly. The interplay between MALAT1 and FGF2 resulted in the decreased inflammation and increased vascularization of TC in vitro (Huang et al., 2017). A qRT-PCR study conducted by Liu et al demonstrated the involvement of MALAT1 in PTC. Expression of MALAT1 confirmed that it played a diverse role in tumor prevalence and carcinogenesis of PTC in vivo. Correlation between tumor size, morphology and other characteristics compared to MALAT1 expression indicated that MALAT1 could be used as a diagnostic tool for the detection of PTC (Liu et al., 2018a).

**ANRIL**

ANRIL (Antisense non-coding RNA in INK4 locus) has been recently established as an oncogenic lncRNA. A study conducted by Zhao et al., (2016) demonstrated that ANRIL was highly overexpressed in TC. ANRIL modulates key signaling cascade such as the TGF beta which in turn inhibits apoptosis by hindering the activity of Smads. Cell line experiments further revealed inhibition of ANRIL in TPC-1 cell lines using siRNA approach which resulted in growth arrest and increased activity of Smads.

**BANCR**

BANCR (BRAF-activated lncRNA) has been documented to play a crucial role in the differentiation of thyroid tumor cells either by promoting cellular proliferation or growth arrest. BANCR overexpression is a benchmark in TC. BANCR upregulates TSHR which in turn promotes expression of Cyclin D1 that can lead to tumorigenesis (Zheng et al., 2016). A recent study conducted by Liao et al., (2016) demonstrated the double side role of BANCR in PTC cell lines and mice models. There was a reduction in PTC cell growth and increased apoptosis via overexpression of BANCR, also in xenograft mouse models. These results suggested that BANCR could inhibit tumorigenesis in PTC and that BANCR levels could be used as a novel prognostic marker. Moreover, BANCR promotes cellular growth and differentiation in thyroid cells by directly modulating the

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**Figure 2. Functions of lncRNAs in the Pathogenesis and Their Potential Clinical Applications or Therapeutic Strategies in TC.** LncRNAs play a vital role in Cell Migration, Metastasis, Cell Proliferation, Apoptosis, Cell cycle process and Invasion. Arrows indicate the inhibition and activation of these mechanisms by lncRNAs and how these lncRNAs can be exploited for the therapeutic effects.

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**Table 2. Functions of lncRNAs in the Pathogenesis and Their Potential Clinical Applications or Therapeutic Strategies in TC.**
expression of E-cadherin. This modulation results in the expression of EMT machinery that in turn promotes tumor metastasis and invasion in PTC (Su et al., 2015). Recently it has been brought to light that BANCR can modulate RAF/MEK/ERK signaling pathway (Wang et al., 2018b).

H19

A study investigated the role of H19 in PTC, whose overexpression leads to the poor prognosis of PTC. Moreover, interplay between estrogen receptor (ER) and estradiol E2 resulted in overexpression of H19 in PTC stem cells. However, H19 silencing decreased ER-beta expression and reduced tumor progression in PTC stem cells indicating the fact that ER-beta and H19 down regulation via E2 could be used as a therapeutic approach to reduce tumor progression in PTC (Chu et al., 2014). In addition, H19 has been shown to interact with insulin receptor substrate 1: this interaction promptly reduced cell growth and migration in various thyroid cell lines. H19 mediated negative down regulation of insulin receptor by inactivation of PI3 kinase/Akt and nuclear factor Kappa B pathway. Owing to these characteristics, H19 may be potentially used as a therapeutic target for TC (Wang et al., 2017). Using qPCR, it was they demonstrated that down-regulation of H19 was responsible of reduced metastatic potential in PTC and thus H19 expression could be utilized as diagnostic marker for PTC (Jiao et al., 2019).

XLOC_051122 and XLOC_006074

XLOC_051122 and XLOC_006074 are two recently identified lncRNAs that have been reported to be overexpressed PTC in correlation to BRAF mutations. Overexpression of either XLOC_051122 or XLOC_006074 greatly increased TC widespread to lymph nodes irrespective of BRAF mutations in PTC (Liyanarachchi et al., 2016).

HIT000218960, LOC100507661, ENST00000537266 and ENST00000426615

Other lncRNAs, the HIT000218960, LOC100507661, ENST00000537266 and ENST00000426615, have also been investigated in TC. They showed to play a role in tumor biology, even if only preliminary results are available (Kim et al., 2016; Xu et al., 2016; Li et al., 2017). Targeting these lncRNAs may have promising benefits for tumor eradication.

Potential applications of lncRNAs in TC

A number of lncRNAs have been reported to be overexpressed in tissue and cancer specific manner. Certain lncRNAs show high expression in a specific tissue while others have fairly low expression in malignant tissue. Such apparently contrasting expression entails lncRNAs as an excellent diagnostic marker for evaluating disease progression. Oncogenic lncRNAs overexpression is a clear signature for several tumors. The susceptibility of lncRNAs as a diagnostic marker for various human pathologies has been well established given their existence in body fluids.

For example, in human cancer, lncRNAs have been showed to be useful potential diagnostic markers: lncRNA XLOC_009167 was screened as a candidate biomarker for lung cancer by Jiang et al., (2018). Their findings showed that lncRNA XLOC_009167 was hugely overexpressed in human blood and gave a better idea of disease progression compared to other current available diagnostic tools suggesting that lncRNAs could be utilized as an essential tool for detection as well as monitoring lung cancer (Jiang et al., 2018). In hepatocellular carcinoma (HCC), another oncogenic lncRNA, uc007biz.1 (LRB1) has been reported to act as a marker for the determining disease pathogenicity (Wang et al., 2018d). Elevated serum levels of LRB1 was found to be associated with the disease progression in the 326 patients with HCC compared to 73 control patients. Furthermore, LRB1 expression was tightly linked with alpha-fetoprotein. A combination of LRB1, AFP and des-y-carboxyprothrombin (DCP) could be used as a diagnostic marker for the detection of cell damage in HCC (Wang et al., 2018c). DUXAP8 and LINC00460 are the two lncRNAs that can have a potential diagnostic role for the detection of esophageal cancer (Liu et al., 2018c). Furthermore, PCA3 has been overexpressed in prostate cancer. This overexpression compared to normal cells has proven to be an excellent diagnostic marker in prostate tumors (Lee et al., 2011). lncRNA HOTTIP (HOXA distal transcript antisense RNA) an active oncogenic lncRNA whose expression is strictly related to the metabolotropic glutamate receptor 1 (mGluR1) has been demonstrated to be used as an effective diagnostic marker for pancreatic cancer (Wang et al., 2018a). In addition lncRNA, UCA1 has been involved in bladder cancer, while HULC in liver pathologies and AA174084 in oral cancers (Murugan et al., 2017).

Indeed CCND2-AS1 lncRNA is highly expressed in PTC and gain or loss of function mutation of CCND2-AS1 resulted in deregulated cellular growth, migration and invasion of PTC. Owing to these peculiarities CCND2-AS1 can be used as diagnostic as well as a prognostic marker for the PTC (Xia et al., 2018). LncRNAs cancer susceptibility candidate 2 (CASC2) has been demonstrated to be correlated to tumorigenesis of a large number of tumors. Overexpression of CASC2 has been showed to trigger growth arrest in TC indicating the fact that CASC2 could be used as diagnostic as well as a prognostic marker (Xiong et al., 2017). NONSHAT037832 down regulation is indispensable for understanding tumor physiology and TNM staging of PTC. Lower levels of expression of NONSHAT037832 in PTC cell line such as the IHH-4 suggested its importance as a prognostic marker (Murugan et al., 2018). rs2439302 is another lncRNA whose down-regulation has been affiliated with a greater survival rate in PTC patients (Murugan et al., 2018). In addition, lncRNA-DR_036575.1 overexpression in extrathyroidal extension (ETE) and tumor size maintenance has managed it as an essential prognostic marker for both PTC as well as ATC (Sun et al., 2016). XLOC_051122 and XLOC_006074, two lncRNAs have been reported to be overexpressed in PTC and other TC such as the FTC and MTC. Recent evidence showed the correlation between these lncRNAs and BRAF mutations. XLOC_051122 and XLOC_006074 positively regulate BRAF axis resulting in cell growth

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and differentiation of tumor cells. This lead to adverse prognosis and dis-oriented TNM grading (Liyanarachchi et al., 2016). Lately SLC6A9-5:2 expression has been related to iodine resistant TC. Lower expression of SLC6A9-5:2 increased the levels of PARP-1 that could result in triggering tumor growth and proliferation with a consequently poor prognosis. Owing to these characteristics SLC6A9-5:2 could be used as prognosis biomarker in iodine resistant TC (Xiang et al., 2017). Altogether these findings stress on the use of IncRNAs for development of diagnostic and prognostic tools in TC.

In conclusion, IncRNAs can be considered the regulator of TC. Aberrant expression of IncRNAs in TC may lead to altered physiology and have provided significant clues on the mechanism of tumorigenesis.

Conflict of Interest
There is no conflict of interest.

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