

Role of lncRNAs in Thyroid Cancer

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Abstract

Thyroid cancer is the most common endocrine cancer in the world and its incidence is on the rise. Though generally associated with a very good prognosis, few cases may demonstrate resistance to treatment such as radio-iodine therapy. lncRNAs have shown to be involved in several steps of thyroid carcinogenesis. It can act as a prognostic and diagnostic marker. Altered levels of specific lncRNAs have also shown to be associated with resistance to radioiodine treatment. Therapy with lncRNA has also shown to return radio-sensitivity in thyroid cancer cell lines.

Keywords: Thyroid; Papillary; lncRNA; I-131; Metastasis

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Thyroid cancer is the most common endocrine cancer in the world [1]. In United States, the incidence of thyroid cancer is on the rise due to several factors ranging from increased diagnosis to environmental exposure [2]. Broadly, thyroid cancer has been divided into well differentiated cancers and poorly differentiated cancers. Among the well differentiated cancers, papillary thyroid carcinoma (PTC) is the most common amounting to 80% of all thyroid cancers followed by follicular carcinoma. While PTC has more of localised metastasis, follicular carcinoma is known to have widespread systemic metastasis. Well differentiated thyroid carcinoma has a relatively good prognosis following surgery and radioiodine therapy with a 10 year survival rate of more than 90% [3]. Among the more aggressive tumours comes anaplastic thyroid carcinoma. These tumours are refractory to radioiodine therapy and usually have a poor prognosis. Other rare tumors of thyroid include lymphoma, squamous cell carcinoma and fibrosarcoma [4,5].

As in all malignancies genetic alterations are an integral part of thyroid cancer also. The specific pathways involved in thyroid carcinogenesis include genetic rearrangements in RET/PTC and PAX8/PPAR δ pathways, aberrant signalling in PI3K/Akt and MAPK/ERK pathways [6]. lncRNAs have also shown to play an important part thyroid carcinogenesis. lncRNAs are non coding RNAs with a nucleotide length more than 200 base pairs. What was earlier thought to be 'junk DNA', has shown to be involved in almost all facets of human physiology and pathology. lncRNAs have been seen as a key in understanding the exact pathogenesis of tumours. They also serve as a biomarker for tumours and could in the near future be used a therapeutical tool.

Studies have shown that almost 240 lncRNAs have an altered

expression in PTC. Few of the lncRNAs shown to be involved in thyroid tumour are given in table below (**Table 1**).

Specific genetic mutations have known to predispose patients to PTC. One such mutation is the single nucleotide polymorphism (SNP) rs965513 in 9q22 (28–30). This is associated with nearby FOXE1 gene. FOXE1 gene plays an essential part during embryonic development of thyroid and regulates several thyroid specific genes [7-32]. Further studies on the exact mechanism revealed the locus 9q22 to code for lncRNA PTCSC2 [33]. The role of this lncRNA is akin to a tumour suppressor and it was found to be absent or decreased in thyroid cancer cell lines. lncRNA PTCSC2 may be another missing link in understanding the exact pathogenesis of thyroid cancer.

Table 1 List of lncRNAs upregulated and downregulated in thyroid cancer.

Upregulated lncRNAs	Downregulated lncRNAs
ANRIL [7]	AK023948/PTCSC1 [8]
NEAT1 [9]	MEG3 [10]
LOC100507661 [11]	NAMA [12]
HOTAIR [13]	PTCSC2 [14]
H19 [15]	PTCSC3 [16]
ENST00000537266 [17]	BANCR [18]
ENST00000426615 [17]	NONHSAT037832 [19]
PVT1 [20]	LINC00271 [21]
HIT000218960 [22]	GAS8-AS1 [23]
NR_036575.1 [24]	NONHSAG051968 [25]
FAL1 [26]	NONHSAG018271 [25]
BANCR [27]	NONHSAG007951 [25]

Kim et al. conducted a study looking into the differential expression of lncRNAs [11]. It showed that LOC100507661 was over expressed in papillary and anaplastic thyroid cancers. Also patients with this specific over expression had increased lymph node metastasis and BRAF V600E mutation. They concluded that LOC100507661 played an important part in carcinogenesis of thyroid cancers and can act as a prognostic marker. Another similar study by Du et al. [33] used the RNA sequencing profile of PTC patients and compared it to a healthy cohort. It showed an altered expression of almost 240 lncRNAs. Further gene ontology analysis was used to investigate the related genes and a functional lncRNA-mRNA co expression network was used to investigate clinical relevance. The study validated differential expression of five lncRNAs namely CTD-3193O13.11, RP5-1024C24.1, AC007255.8, HOXD-AS1 and RP11-402L6.1. Also the varied expression of these lncRNAs were related to clinical stage, lymph node metastasis and tumour size [34].

Lungs are the most common site of distant metastasis in a case of Differentiated thyroid cancer (DTC) [35]. Radioiodine therapy with I-131 is the main treatment in these cases. However around one-third of such metastatic cases do not respond to I-131. At present to identify these non responders require a radioiodine scan. A study by Qiu et al. [36] has shown a differential expression of four lncRNAs in patients with non I-131 avid lung metastasis namely ENST00000462717, ENST00000415582, TCONS_00024700 and NR_028454. These lncRNAs can be detected in plasma and may predict responsiveness of metastasis to radioiodine without exposing patients to diagnostic isotope scan [37].

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