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Mini-Review

From transcriptional noise to tumor regulators: The role of long non-coding RNAs in thyroid cancer

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Thyroid cancer incidence has been reported to increase eminently in India in recent years with a significant preponderance in the females, highlighting the urgent need for deeper insights into its molecular mechanisms to improve diagnosis and treatment. While conventional genetic alterations have been widely studied, increasing evidence points to the vital role of non-coding RNAs especially long non-coding RNAs (lncRNAs) in the pathogenesis and progression of thyroid malignancies. These lncRNAs influence various cellular processes, including proliferation, apoptosis, migration, and invasion, primarily through interactions with microRNAs, proteins, and DNA. This review focuses on specific lncRNAs SNHG3, LINC00152, LUCAT1, UCA1, FER1L4, FALEC, and LINC01315 that are dysregulated in thyroid cancer. These molecules are involved in critical signaling pathways such as the AKT/mTOR/ERK, TGF-β, and IL-6/JAK2/STAT3 pathways. Moreover, they function as competing endogenous RNAs (ceRNAs), binding to and sequestering tumor-suppressive microRNAs, leading to the upregulation of oncogenes. Understanding these mechanisms provides valuable insights into thyroid tumor biology. Targeting these lncRNAs may offer promising therapeutic approaches and enhance the development of molecular markers for prognosis and treatment response. This review aims to highlight the emerging importance of lncRNAs in thyroid cancer and their potential as novel molecular tools in clinical oncology.

Keywords: Cancer invasion, Cancer progression, LncRNA, miRNAs, Papillary thyroid carcinoma, Thyroid carcinoma

Introduction

According to the American Cancer Society (ACS) 2025 report, an estimated 2,041,910 new cancer cases and 618,120 cancer-related deaths are projected to occur in the United States in 2025. Cancer continues to be one of the leading causes of morbidity and mortality worldwide, reflecting an increasing global burden. Among various malignancies, thyroid cancer represents one of the most rapidly rising endocrine tumors, with approximately 586,000 new cases reported globally in 2020, making it the 10th most common cancer worldwide. The age-standardized incidence rate was about 10.1 per 100,000 women and 3.1 per 100,000 men, while mortality remained comparatively low at 0.5 and 0.3 per 100,000, respectively. Although thyroid cancer generally has a favourable prognosis, its increasing incidence highlights the need for continued research into its risk factors, molecular mechanisms, and early detection strategies[1]. Thyroid cancer progression is a multistep process driven by a combination of genetic, epigenetic, and signaling alterations that collectively increase tumor aggressiveness. The process is typically initiated by driver mutations in the MAPK pathway, notably BRAF V600E in papillary thyroid carcinoma (PTC) and RAS mutations in follicular thyroid carcinoma, which promote uncontrolled cellular proliferation and tumor initiation[2]. As the disease advances, differentiated thyroid cancers (DTC) gradually evolve into poorly differentiated (PDTC) and anaplastic thyroid carcinoma (ATC) through the accumulation of additional mutations, particularly TP53 loss-of-function and TERT promoter alterations, which enhance telomerase activity, genomic instability, and uncontrolled cell division. Concurrent epigenetic changes, including modifications in chromatin remodeling complexes such as SWI/SNF, further drive dedifferentiation and contribute to resistance to therapies like radioiodine. Progression is also facilitated by activation of the PI3K/AKT/mTOR pathway, which supports metabolic reprogramming, survival, and metastasis, while MAPK signaling promotes invasion through upregulation of matrix metalloproteinases (MMPs) that degrade extracellular barriers. In advanced stages, tumor cells acquire additional mechanisms of immune evasion, such as increased PD-L1 expression,

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allowing them to escape immune surveillance. Together, these molecular and cellular changes orchestrate tumor dedifferentiation, invasion, metastasis, and therapy resistance, ultimately leading to highly aggressive thyroid cancer phenotypes[3,4].

Cancer invasion is the process by which malignant cells spread from their site of origin into the surrounding normal tissues. During invasion, cancer cells lose their normal cell-to-cell adhesion, degrade the extracellular matrix using enzymes such as matrix metalloproteinases (MMPs), and acquire the ability to migrate through tissue barriers. This invasive behaviour allows tumor cells to penetrate blood and lymphatic vessels, facilitating metastasis to distant organs. Invasion is, therefore, a key hallmark of cancer progression and malignancy[5]. This contradiction highlights the need to investigate lncRNAs, which regulate gene expression and epigenetics, and show promise as biomarkers and therapeutic targets in cancer biology. The thyroid gland, the primary site of origin of malignancy, is a butterfly-shaped bi-lobed endocrine gland, located at the base of the neck just below the larynx. It is composed of right and left lobes, which are connected by an intervening anatomic structure known as the isthmus[6]. It is primarily responsible for synthesizing and secreting thyroid hormones, including triiodothyronine (T3), thyroxine (T4), and calcitonin. Thyroxine or Tetra-iodothyronine (T4) and Triiodothyronine (T3) are produced by follicular cells whereas para-follicular cells are responsible for the production of Calcitonin, a hormone that helps control the level of calcium and phosphates in the body. Hormones produced by thyroid gland aids in controlling body temperature, blood pressure, heart rate and metabolism[7,8]. The biosynthesis and metabolic processing of thyroid hormones is governed by at least three critical factors, encompassing stimulation by thyrotropin (TSH), the availability of iodine, and the enzymatic activity of deiodinases[9].

Thyroid disorders: An overview

Thyroid disorders are broadly classified into structural and functional categories. Structural disorders include benign and malignant neoplasms, as well as nodular and diffuse goiter, whereas functional disorders involve hypothyroidism, hyperthyroidism, and thyroiditis. Hypothyroidism results from decreased secretion of thyroid hormones, leading to reduced metabolism, fatigue, weight gain, and cold intolerance, with Hashimoto's thyroiditis being the most common cause. Hyperthyroidism, on the other hand, is characterized by excess thyroid hormone production, resulting in symptoms such as heat intolerance, weight loss, sweating, palpitations, and hypertension[8]. Graves' disease is the most frequent cause, followed by toxic multinodular goiter and solitary toxic nodule. Goiter refers to the enlargement of the thyroid gland, often caused by iodine deficiency, genetic predisposition, or environmental factors, and may occur with normal, low, or high thyroid function. Benign thyroid nodules include both neoplastic forms, such as follicular adenomas (the most common subtype), and non-neoplastic forms like colloid and hyperplastic nodules. Thyroid cancers arise from either follicular or parafollicular cells and are classified into papillary (PTC), follicular (FTC), medullary (MTC), and anaplastic (ATC)[10,11]. PTC is the most prevalent (>85%) and well-differentiated form, FTC accounts for 5–10% and shows capsular or vascular invasion, MTC originates from parafollicular C cells and exhibits amyloid deposits, while ATC is undifferentiated, rare (<3%), and highly aggressive. In India, thyroid cancer incidence is increasing, with a lifetime risk of 1 in 752 males and 1 in 285 females. Although the overall incidence remains low, urban areas report higher cases. Globally, thyroid cancer constitutes 1–2% of all malignancies, with a rising trend attributed to improved diagnostics, radiation exposure, and environmental factors, and it is more common in females than males[12,13].

Various risk factors of thyroid cancer

Varied etiological factors contributing to elevated thyroid cancer incidence rates include chromosomal and genetic aberrations, iodine consumption, thyroid-stimulating hormone levels, autoimmune thyroid pathology, gender, hormonal influences, obesity, lifestyle modifications, and environmental toxin exposure. While childhood ionizing radiation has been conclusively established as a risk factor, additional stated contributors await further validation[14]. Notably, some evidence suggests an inverse association with tobacco smoking, potentially mediated through modulation of hormone homeostasis and estrogen metabolism[15,16]. A significant risk factor is a prior history of benign thyroid pathology, such as goiter and thyroid nodules, with a particularly elevated risk observed for follicular thyroid carcinoma[12].

Unraveling the non-coding landscape of thyroid cancer

Subsequent to the conclusion of the human genome project, research revealed that mere 1.5% of the human genome comprises protein-coding genes, whilst the prevailing share (in excess of 90%) consists of non-coding RNAs they lack the capacity to encode proteins. A substantial body of evidence associates ncRNAs with various diseases and biological processes, including cancer, inflammation, and neurological disorders. Based on their nucleotide length, ncRNAs are categorized into two main subtypes; short non-coding RNAs (< 200 nt) and long non-coding RNAs (> 200 nt). Specific examples of the former include small interfering RNA, PIWI interacting RNAs, and microRNAs (MiRNAs)[17].

Transcription factors like FOXA1 are highly upregulated in thyroid carcinoma and have been related to poor survival. FOXA1 induces proliferation, invasion and apoptosis in TPC-1 cells in part via CYCLIN D1/E and p27^Kip1. Emerging data indicate that long non-coding RNAs (lncRNAs) could be involved in these oncogenic cascades, potentially making FOXA1 one of the downstream effectors of lncRNA-dependent signaling in thyroid cancer[18].

In SCLC, this non-coding miR-20a-5p/CCNG2 axis directly shows the impact of non-coding RNA networks in driving cell cycle progression through the targeting of established inhibitors of this pathway, such as CCNG2. Likewise, omega-3 and omega-6 fatty acids induced apoptosis in MCF7 breast cancer cells, by upregulating pro-apoptotic proteins including Bad, cleaved Caspase-3 and cleaved PARP irrespective of p53 activation. It has been noted that apoptotic process that proceeds through non-conventional pathways is involved in this role, several of which lncRNA mediated[19].

lncRNAs in Thyroid Cancer Might Also Affect Intrinsic Mitochondrial Apoptotic Pathways. Mitochondria are essential for various cellular processes, including the regulation of Ca^{2+} and redox balance, as well as the production of heme and iron–sulfur clusters. They play a crucial role in apoptosis through the intrinsic pathway, which is activated when cellular stress, such as oxidative stress, radiation, or cytotoxic drugs, surpasses the cell's defense mechanisms. This pathway is modulated by Bcl-2 family proteins; pro-apoptotic proteins Bax and Bak embed themselves in the mitochondrial outer membrane, leading to mitochondrial outer membrane permeabilization (MOMP) and the release of cytochrome c into the cytoplasm, while anti-apoptotic proteins like Bcl-2 and Bcl-xL prevent this occurrence. Once released, cytochrome c interacts with Apaf-1 and procaspase-9 to create the apoptosome, which activates caspase-9 and later initiator caspases such as caspase-3, ultimately resulting in apoptosis. Additional proteins like SMAC/DIABLO promote apoptosis by inhibiting the blockers of programmed cell death. The behavior of mitochondria also plays a role in apoptosis, where proteins such as Mfn1, Mfn2, and Drp1 interact with Bax/Bak; heightened mitochondrial fission speeds up the release of cytochrome c, whereas reduced fission delays apoptosis. Moreover, mitochondrial fission contributes to the migration and invasion of cancer cells, and mitochondrial dysfunction—characterized by a loss of membrane potential, high levels of ROS, and calcium imbalance—amplifies apoptotic signaling and presents a possible target for cancer therapies[20,21]. These findings, suggest that lncRNAs might be potential candidates in mediating intrinsic mitochondrial apoptotic pathways. Modulation of lncRNAs that govern Bad, Caspase-3, and PARP may imitate the tumor suppressive properties of the effect of the omega fatty acid and provide new targets for intervention[22].

LINC00284 functions as a competing endogenous RNA (ceRNA) by interacting with miRNA-3127, which in turn targets E2F7. This interaction leads to an indirect enhancement of E2F7 expression, influencing various biological processes such as cell proliferation and suppressing E2F7-regulated apoptosis by acting as a sponge for miR-3127. In a similar manner, findings from another study indicated that miR-489-3p, which associates with EVA1A in thyroid cancer (TC) cells, is regulated by LINC00115, which is found to be over-expressed in both TC cell lines and tumor tissues. Additionally, Zou *et al.* found that the silencing of LINC00460 inhibited the proliferation of papillary thyroid carcinoma (PTC) cells and enhanced apoptosis by reducing MMP-9 levels through the sponging of miR-539. Recent studies indicate that LINC00887 acts as an oncogenic lncRNA, and its knockdown resulted in increased apoptosis, prolonged the cell cycle, and decreased levels of PD-L1, as well as diminished cell proliferation, colony formation, and migration. LncRNA DUXAP8 promotes cell survival in PTC cells by targeting miR-20b-5p and activating SOS1. The knockdown of DUXAP8 led to a reduction in the

expression of SOS1, cyclin D1, and c-Myc, along with decreased phosphorylation of MEK1/2 and ERK1/2[23] Fascinating findings showed that curcumin inhibited the expression of LINC00691, enhanced apoptosis, and decreased cell proliferation in PTC BCPAP cells. Administration of curcumin or transfection with si-LINC00691 caused a decrease in AKT levels, resulting in cell death, suggesting that the anticancer effects of curcumin are linked to the inhibition of LINC00691. Autophagy can both promote cell survival and induce cell death. Additionally, lncRNA is capable of activating specific enzymes, which in turn initiates autophagy. By targeting the miR-1343-3p/ATG7 and miR-187-3p/ATG5 pathways to promote autophagy in thyroid cancer (TC) cells, the lncRNA growth arrest-specific 8 (GAS8)-AS1, which is inducible by the transcription factor-2 (ATF2), enhances the growth of TC cells. Conversely, a reverse autophagy effect was observed in papillary thyroid cancer (PTC). The overexpression of lncRNA SLC26A4-AS1 led to a reduction in PTC cell proliferation and an increase in autophagy by engaging the transcription factor ETS1 and raising ITPR1 expression[24].

In thyroid cancer, lncRNAs can influence the intrinsic mitochondrial apoptotic pathway by regulating key pro-apoptotic molecules such as Bad, Caspase-3, and PARP. Dysregulation of these lncRNAs can disrupt normal apoptosis, allowing cancer cell survival. Conversely, modulating tumor-suppressive lncRNAs may enhance mitochondrial-mediated apoptosis, mimicking the effects of omega-3 fatty acids, which activate caspase signaling and PARP cleavage. Thus, targeting such lncRNAs offers a promising strategy to restore apoptosis and inhibit thyroid tumor growth[25]. More investigation of the lncRNA–protein interaction network may reveal new regulators of thyroid cancer cell destiny. Insights into these mechanisms could help develop more potent and specific RNA-based therapies[26].

MicroRNAs

(MiRNAs) are inherent, single stranded RNA sequences that do not encode for proteins and they generally comprise of 19 to 24 nucleotides in their structure. They are crucial in post-transcriptional processes, regulating numerous proteins that are vital for various cellular functions[27]. MicroRNAs 146a and 146b are highly upregulated in thyroid cancer. Elevated miR-146a hinders HIFα degradation via increased LSD1, leading to GABPA repression, promoting apoptosis and cancer cell malignancy[28]. MiR-146b targets MAPK/ERK and TGF-b pathways, influencing actin cytoskeleton formation and thus impacting cell migration and invasion in thyroid cancer[27,29,30].

CircRNAs

Mostly derived from gene exons, are non-coding RNAs involved in cancer and cellular physiology[31]. They function by (1) acting as miRNA sponges, (2) interacting with proteins, and (3) potentially translating into peptides. Notably, circRNAs can sequester miRNAs via numerous binding sites, modulating downstream target gene expression through the competitive endogenous RNA (ceRNA) mechanism, a strategy widely used in cancer research[17,32].

LncRNAs in thyroid cancer

Recently emerging within the non-coding RNA category, a subfamily of transcripts designated as long non-coding RNAs (lncRNAs) exceeds 200 nucleotides in length, distinct from conventional protein-coding transcripts in their inability to serve as templates for protein synthesis[33]. LncRNAs are >200 nucleotide non-coding transcripts widely expressed and involved in key physiological processes like immunity, neuronal function, and cancer[34]. Their dysregulation is linked to human diseases[33]. LncRNAs regulate gene expression in *cis* and *trans*, and can act as competing endogenous RNAs (ceRNAs) by sponging miRNAs[17]. Based on function, they are classified as tumor-suppressive or oncogenic. For example, oncogenic TUG1 interacts with the miR-145/ZEB1 pathway, while LINC00313 and BISPR influence PTC progression by modulating specific miRNAs[35,36]. HOTAIR, deregulated in various cancers, acts as a miRNA sponge and epigenetically silences genes via PRC2 and LSD1, promoting PTC[10,37]. MALAT1 is upregulated in thyroid carcinoma, enhancing cell invasion and proliferation by controlling IQGAP1[33]. LncRNAs, including n384546 and MCM3AP-AS1, show promise as diagnostic and prognostic biomarkers in PTC[38]. The lncRNAs analyzed are distributed across various chromosomal regions, reflecting their diverse regulatory roles in cancer. SNHG3 (Chr.1p35.3), LINC00152 (Chr.2p11.2, LUCAT1 (Chr.5q14.3), and UCA1 (Chr.19p13.12) are generally linked to tumor promotion, while FER1L4 (Chr.20q11.22) often exhibits tumor-suppressive activity. FALEC

(Chr.1q21.2) and LINC01315 (Chr.22q13.2) also contribute to cancer-related pathways (Fig. 1). Their distribution across multiple chromosomes suggests that lncRNAs participate in diverse genomic regulatory mechanisms influencing thyroid cancer progression[39,40].

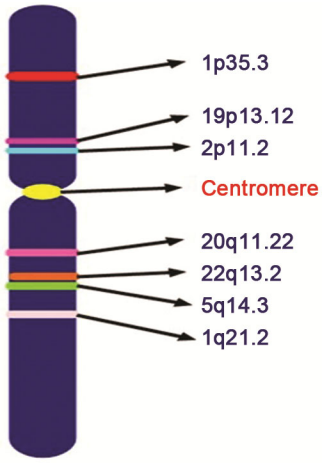

Fig. 1 — Distribution of LncRNAs across chromosomal locations. SNHG3- Chr.1p35.3[41] LINC00152- Chr.2p11.2[39] LUCAT1- Chr.5q14.3[46] UCA1- Chr.19p13.12[51] FER1L4- Chr. 20q11.22[59] FALEC- Chr. 1q21.2[60] LINC01315- Chr. 22q13.2[62]

SNHG3

The Small nucleolar RNA host gene 3 (SNHG3), located on chromosome 1p35.3, is a novel long non-coding RNA (lncRNA) that exhibits significant upregulation in various human cancers, including thyroid carcinoma, breast cancer, and lung adenocarcinoma. Recent evidence suggests a correlation between aberrant SNHG3 expression and oncogenic processes, such as tumour cell differentiation, proliferation, metastasis, and invasion. Through transcriptional regulation of p53, AKT/mTOR/ERK, and TGF-β signalling pathways, SNHG3 mediates carcinogenesis (Fig. 2). Furthermore, aberrantly expressed SNHG3 plays a pivotal role in the progression of multiple malignancies, and its elevated expression is a prognostic indicator for poor outcomes in patients with ovarian cancer, glioma, hepatocellular carcinoma, osteosarcoma, and colorectal cancer[41].

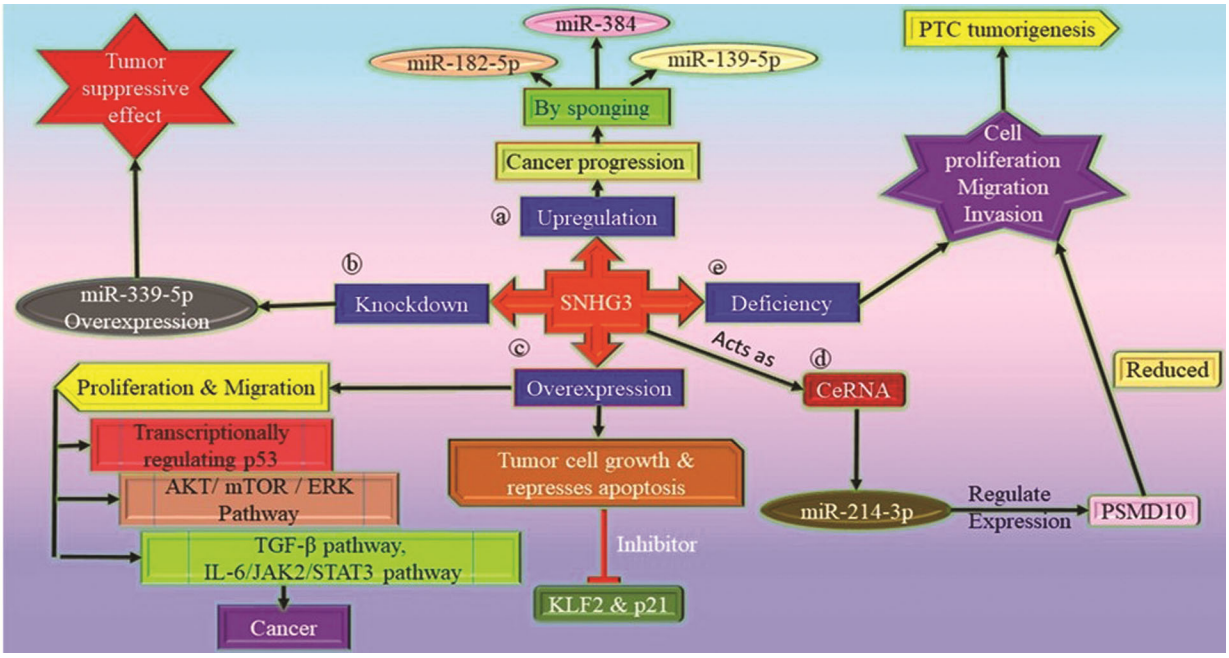

Fig. 2 — A schematic overview illustrating the role of Small nucleolar RNA host gene 3 (SNHG3) in cancer progression. The key elements include are-a) Upregulation of SNHG3 induces cancer progression by sponging microRNAs (miR-384, miR-182-5p, miR-189-5p)[41]. b) Knockdown of SNHG3 results in the overexpression of microRNA (miR-339-5p) which then exhibits tumor suppressive effects[43]. c) Its overexpression influences tumor cell proliferation & migration by transcriptionally activating p53 and activating pathways such as AKT/mTOR/ERK pathway (Phosphatidylinositol 3-K/Protein kinase B/ Mammalian Target of Rapamycin and Extracellular Signal-regulated kinase), TGF-β pathway (Transforming growth factor-β), IL-6 mediated JAK/STAT3 signaling pathway (Interleukin-6/ Janus kinase/ Signal transducer and activator of transcription 3) that leads to the development of cancer. It also induces Tumor cell growth & repression of apoptosis by inhibiting KLF2 & p21[40,42]. d) SNHG3 acts as endogenous competing RNA (ceRNA) by sponging microRNA (miR-214-3p), thus regulating expression of PSMD10 which results in reducing cell migration, invasion and proliferation. e) Deficiency of SNHG3 promotes cell proliferation, migration and invasion that eventually results in papillary thyroid cancer (PTC) tumorigenesis[40,41].

Table 1 — LncRNA-Mediated Regulatory Networks in Thyroid Cancer

S. No.	LncRNA	LncRNA Name	Mode of action	Expression	Molecules interacting	Ref.
1.	SNHG3	Small nucleolar RNA host gene 3	Enhance growth, migration & invasion of cancer cells	Upregulated	miR-339-5p/ GPR62	41,43
2.	LINC00152	Cytoskeletal regulatory RNA (CYTOR) or linc00152	Cell proliferation, migration, invasion, & colony formation	Upregulated	Sponge miR-497- ↓BDNF miR-873-5p	39
3.	LUCAT1	Lung cancer associated transcript 1	Regulates cell cycle progression, epigenetic modification, apoptosis, cell proliferation & metastasis	Upregulated	miR-493- ↑ADAM10 CDK1, EZH2, DNMT1, p57, p21, p53 & BAX	46,50
4.	UCA1	Urothelial carcinoma-associated 1	Cell proliferation, migration & invasion	Upregulated	miR-204 miR-135a miR-148a	54–57
5.	FER1L4	Fer-1 like family member 4	Promotes proliferation, migration, invasion, lymph node metastasis, extra-thyroidal extension & advanced tumor staging	Upregulated	miR-612	59
6.	FALEC	Focally amplified lncRNA regulator of ECM1	Promotes oncogenic processes, proliferation, migration & invasion by modulating Wnt/β-catenin pathway	Upregulated	- _	61,64
7.	LINC01315	Long intergenic non-protein coding RNA 1315	Promotes growth of cancer cells, colony formation & invasion	Upregulated	Sponge miR-497-5p	63

SNHG3, exhibiting extensive expression, exerts tumorigenesis, migration by stimulating the TGF- β pathway and activating the IL-6/JAK2/STAT3 cascade through a series of molecular interactions[42]. Notably, over expression of SNHG3 accelerates tumor cell growth by repressing KLF2 and p21, thereby mitigating apoptosis[40]. Moreover, empirical evidence suggests that SNHG3 upregulation fosters cancer progression by competitively inhibiting miR-384, miR-182-5p, and mir-139-5p[41]. An investigation revealed that silencing of SNHG3 substantially reduced the proliferation, migration, and invasion capabilities of CUTC5 and IHH-4 thyroid cancer cells. Furthermore, SNHG3 knockdown triggered apoptosis in these cells and markedly inhibited the growth of xenograft tumors *in vivo*. *In vitro* assays demonstrated a reciprocal interaction between SNHG3 and miR-339-5p in thyroid cancer cells. The expression of miR-339-5p was found to be significantly down regulated in thyroid cancer tissues and cell lines. Conversely, SNHG3 knockdown led to a notable up regulation of miR-339-5p. Moreover, the over expression of miR-339-5p exerted anti-tumorigenic effects in CUTC5 and IHH-4 cells via the post-transcriptional suppression of GPR62[43] (Table 1).

LINC00152

The long non-coding RNA, cytoskeletal regulatory RNA (CYTOR) or linc00152, localises to chromosomal region 2p11.2 and exhibits amplification in multiple carcinomas. Initially observed via variable DNA hypo-methylation during hepatocellular carcinoma progression[39].

Cytoskeletal regulators such as LINC00152 have been implicated in the regulation of gene expression through multifaceted mechanisms. This non-coding RNA can function as competing endogenous RNA (ceRNA) in the cytoplasm where it acts to sequester microRNAs, thereby regulating their suppressive effects on gene expression. Conversely, LINC00152 also facilitates epigenetic gene regulation through its interaction with the poly-comb repressive complex 2 (PRC2) in the nucleus[39,44].

Numerous research studies have substantiated the overexpression of LINC00152 in various types of human malignancies, including lung, liver, pancreatic, and breast cancer. Furthermore, evidence indicates that LINC00152 plays a role in modulating oncogenic processes, such as cancer cell proliferation, cell cycle progression, epithelial mesenchymal transition (EMT), and the development of resistance to chemotherapy and

radiotherapy[39]. Fibronectin 1 expression demonstrated a statistically significant augmentation in patients with papillary thyroid carcinoma harboring lymph node metastasis as opposed to patients without lymph node metastasis[45]. In thyroid cancer cells, TRIM29 decreases miR-873-5p expression by regulating LINC00152 levels, which in turn facilitates the upregulation of fibronectin 1. This in turn, leads to the enhancement of PTC cell motility, adhesion and invasivenes[39,44].

LUCAT1

The Lung cancer associated transcript 1 (LUCAT1) is located on chromosome 5q14.3, its expression levels were correlated with tumor aggressiveness, lymph node metastasis, and TNM staging[46]. LUCAT1 localisation in the cell nucleus of tumoral regions implies its role in regulating gene transcription, similar to that observed in renal carcinoma[47]. Recent research elucidated the function of the long non-coding RNA, LUCAT1, as a prognostic factor in papillary thyroid carcinoma (PTC) patients. An analysis of gene expression data from 61 PTC tissues compared to adjacent non-tumor tissues revealed LUCAT1 as the transcript exhibiting the most significant upregulation, displaying a correlation with advanced tumor prognostication. Furthermore, *in vitro* studies of LUCAT1 demonstrated its involvement in the regulation of cell cycle progression and its significant contribution to enhanced cell proliferation and metastatic potential in PTC cells[47,48]. Cell cycle progression is typically deregulated in cancer, often resulting from aberrant cyclin-dependent kinase (CDK) activity. The CDK1 protein, crucial for entry into S-phase and mitosis, is impeded by knockdown, thereby hindering G1/S progression. Downregulation of CDK1 in examined cell lines is consistent with the proposed role of LUCAT1 in cell cycle regulation, complementing previous evidence in various carcinomas[47,49]. The mechanism underlying this involvement is proposed to occur via the modulation of the p53 and p21 cellular pathway, proteins pivotal for inducing cell cycle arrest. Additionally, the inverse correlation observed between the expression levels of LUCAT1 and p53/p21 in both Wild-type and LUCAT1-knockdown models highlights the interconnectedness of these molecules in facilitating the ability of LUCAT1 to initiate cell cycle arrest in PTC cells[48]. The suppression of LUCAT1 expression leads to reduced levels of CDK1, EZH2, DNMT1, and HDAC1, while concurrently elevating the expression of p21, p57, p53, and BAX. Notably, CDK1 impairs cell cycle progression at the G1/S phase, whereas p21 and p57 are recognized tumor suppressor genes. EZH2 and DNMT1 repress the expression of p21 and p57 through mechanisms of DNA methylation, while HDAC1 suppresses the expression of these genes via histone de-acetylation. Conversely, p53 serves a pivotal role in promoting cell apoptosis through the actions of BAX, while NRF2 participates in cell survival by modulating reactive oxygen species. Consequently, LUCAT1 has been implicated in the regulation of cellular processes including cell cycle proliferation, epigenetic modification, and apoptosis via interactions with CDK1, EZH2, DNMT1, P57, P21, P53, and BAX[46].

Research revealed that LUCAT1 elevates ADAM10 expression by binding to miR-493, thereby initiating the JAK-STAT pathway and facilitating the proliferation and dissemination of thyroid cancer (TC) cells[50].

UCA1

Urothelial carcinoma-associated1, a long non-coding RNA (lncRNA) situated on chromosome 19p13.12, has been characterised as an oncogene in diverse malignancies[51]. Its sequence comprises three exons encompassing 1.4 kilobases, initially isolated in bladder transitional cell carcinoma and has been implicated in facilitating tumor progression in select carcinomas[52]. UCA1, a previously identified long non-coding RNA as a promoter of tumor progression across various tumor types, encompassing bladder carcinoma, breast carcinoma, hepatocellular carcinoma, colorectal carcinoma, and gastric carcinoma[53]. The long non-coding RNA urothelial carcinoma-associated 1 (UCA1) has been implicated in the development and progression of various cancer types, including its elevated expression in papillary thyroid carcinoma (PTC) cell lines and tissues compared to normal immortal human thyroid follicular cell lines and adjacent tissues[53]. Studies have demonstrated that silencing UCA1 expression resulted in a reduction in BRD4 protein levels, indicating BRD4's role in modulating UCA1's effects on cell proliferation and invasion. Moreover, a significant association was identified between UCA1 and miR-204 through the regulation of common downstream targets[54,55]. Interestingly, a reciprocal negative regulatory loop was discovered, where UCA1 downregulates miR-204, leading to increased

BRD4 expression, which in turn promotes thyroid cancer cell proliferation, migration, and invasion. Conversely, miR-204 suppresses UCA1 expression, leading to decreased BRD4 expression, thereby inhibiting tumor growth and metastasis. Collectively, these findings suggest that the UCA1/miR-204/BRD4 axis plays a pivotal role in PTC cell proliferation and invasion, indicating its potential as a therapeutic target for the treatment of thyroid cancer[53]. Research revealed the complex regulatory relationship between UCA1 and miR-135a in anaplastic thyroid carcinoma (ATC) cells. The investigation revealed that the UCA1/miR-135a/c-myc axis plays a pivotal role in regulating ATC cell proliferation and invasion. Additionally, a dual regulatory interaction was observed between UCA1 and microRNA-135a, which is potentially involved in a negative feedback loop. The UCA1/microRNA-135a/c-myc axis likely plays a crucial role in the proliferation and invasive capabilities of ATC cells, suggesting a potential therapeutic application in ATC patients. Furthermore, the suppression of UCA1 expression has been shown to impede cell proliferation, migration, and invasion. Importantly, UCA1 has been identified as a key target for numerous microRNAs, including microRNA-204, which interacts with IGFBP5 to modulate the proliferation and invasion of papillary thyroid carcinoma (PTC) cells, indicating a potential involvement in thyroid carcinoma progression[51,52]. Perturbations in UCA1 expression levels demonstrated a significant positive correlation with IGFBP5 expression in papillary thyroid carcinoma (PTC) lesions, thereby implicating the UCA1/miR-204/IGFBP5 axis in the pathological progression of PTC cells[51]. Research has elucidated the oncogenic function of UCA1 in anaplastic thyroid carcinoma (ATC) tissues and cells. Specifically, UCA1 upregulation was found to be significantly correlated with increased tumor volume, underscoring its status as an oncogene in this context. Further investigation revealed that UCA1's expression plays a pivotal role in moderating the cytotoxic capacity of CD8 + T cells towards ATC cells, with implications for the treatment of this disease. The specific mechanism underlying this phenomenon was found to involve the upregulation of UCA1, which in turn targets miR-148a and modulates cytokine secretion via the miR-148a/PD-L1 pathway. Conversely, the silencing of UCA1 or PD-L1 was observed to restore the suppressive effect of cytotoxic CD8 + T cells in vivo[56,57].

Notably, elevated UCA1 expression has been observed in various cancers, including papillary thyroid carcinoma (PTC), with such levels being inversely correlated with patient survival rates[58].

FER1L4

Fer-1 like family member 4, a long non-coding RNA, comprises a transcript of 6.7 Kb in length. Its genomic localisation is situated on the long arm of chromosome 20q11.22.

Recent research revealed a novel role of FER1L4 in promoting the proliferation, migration, and invasion of papillary thyroid carcinoma (PTC) cells. Concurrently, elevated FER1L4 expression in PTC tissues correlated with severe clinic-pathological features, including lymph node metastasis, extra-thyroidal extension, and advanced tumor staging, thereby substantiating FER1L4 as an oncogene in PTC. The present investigation further elucidated the tumor suppressor properties of miR-612, which restrains the proliferation, migration, and invasion of PTC cells. Furthermore, functional studies indicated that FER1L4-induced enhancement of PTC cell behavior was mediated by the inhibition of miR-612 expression[59].

FALEC

Focally amplified lncRNA regulator of ECM1, a long intergenic non-coding RNA, located on chromosome 1q21.2. It has been found to harbored oncogenic properties across a wide range of human malignancies. Upregulation of the FALEC gene has been observed in various malignancies, including ovarian carcinoma, prostate adenocarcinoma, colorectal adenocarcinoma, gastric adenocarcinoma, esophageal adenocarcinoma, non-small cell lung carcinoma, hepatocellular carcinoma, osteosarcoma, thyroid carcinoma, and melanoma[60]. There is growing evidence to suggest that FALEC is implicated in various pathophysiological processes, including embryonic development, diabetic arteriosclerosis, and Hirsch sprung's disease[60]. Studies have discovered a correlation between elevated levels of FALEC expression and a heightened risk of unfavorable clinical outcomes in patients afflicted with prostate cancer. Expression of FALEC is significantly increased in melanotic tumors[61]. In thyroid carcinoma, specifically papillary thyroid carcinoma (PTC), FALEC exhibited pronounced expression in afflicted tissues and derived cell lines. Elevated FALEC expression was found to promote oncogenic processes,

including proliferation, migration, and invasion, by modulating the Wnt/β-catenin signalling pathway[61].

LINC01315

Long-intergenic non protein coding RNA 1315, a long non-coding RNA located on chromosome 22q13.2. Recent investigations have elucidated the perturbation of the long intergenic non-coding RNA01315 (LINC01315) in carcinomatous conditions, notably in thyroid carcinoma. Elevated LINC01315 expression was observed in malignant tissues and relevant cell lines in comparison with non-cancerous and normal counterparts[62]. The results of loss-of-function assays in a study by Ren *et al*. demonstrated that LINC01315 silencing suppresses the proliferative capacity and colony formation of papillary thyroid carcinoma (PTC) cells. Conversely, LINC01315 upregulation enhances cell proliferation and colony formation, suggesting that it mediates a growth-modulating function analogous to other long non-coding RNAs[62]. LINC01315 promotes the malignant dissemination of papillary thyroid cancer cells by functioning as a microRNA sponge for miR-497-5p[63].

Discussion

Thyroid carcinoma, a malignancy with escalating global incidence, is attributable to enhanced detection rates, suspected environmental etiologies, and lifestyle factors. This disease presents histologically distinct variants, classified as papillary, follicular, medullary, and anaplastic carcinomas, with papillary thyroid carcinoma accounting for the predominant subtype. Recent studies indicate that non-coding RNAs, comprising microRNAs, circRNAs, and long non-coding RNAs (lncRNAs), emerge as a key element in the development, inflammation, cancer, cardiovascular diseases and neurological disorders. They have also emerged as crucial regulators in thyroid cancer. Aberrant LncRNA expression has been consistently associated with the initial stages and progression of various human pathologies, consequently necessitating consideration in the study of thyroid cancer. Herein, we have examined the functional contributions of several relatively underexplored long non-coding RNAs—specifically SNHG3, LINC00152, LUCAT1, UCA1, FER1L4, FALEC, and LINC01312—across the spectrum of thyroid cancer histotypes.

Small nucleolar RNA host gene 3 (SNHG3) was found to be elevated in thyroid carcinoma, and is persistently linked to neoplastic processes, including cellular proliferation, differentiation, and the extrinsic migration of malignant cells. Mechanistically, the oncogenic potential of SNHG3 lies in its capacity to transcriptionally modulate critical signaling pathways, including those mediated by the p53, AKT/mTOR/ERK, and TGF-β molecules. Studies reveal that the upregulation of SNHG3 cultivates oncogenesis by sequestering specific microRNAs, namely miR-384, miR-182-5p, and miR-139-5p. CYTOR (linc00152), has been shown to exhibit elevated expression in carcinomas. Notably, in thyroid cancer cells, an alteration in LINC00152 levels mediates by TRIM29, leads to increased expression of microRNA-873-5p, resulting in increased expression of fibronectin 1. This phenolmenon enhances cellular motility, adhesion, and invasiveness in papillary thyroid carcinoma cells, underscoring the critical role of CYTOR in oncogenesis. The overexpression of LUCAT1 in thyroid malignancies is linked to enhanced cell proliferation and metastatic efficacy, and mechanistically mediates cell cycle progression and apoptosis through interactions with pivotal regulatory proteins. Notably, LUCAT1 upregulation elevates ADAM10 expression through a reciprocal interaction with microRNA-493, thereby activating the JAK-STAT signaling pathway and facilitating the proliferation and dissemination of tumor cells in thyroid cancer. UCA1 upregulation is implicated in the pathogenesis and progression of thyroid cancer, notably promoting cell proliferation and invasion. Previous studies highlight the UCA1/miR-204/BRD4 and UCA1/miR-135a/c-myc axes as pivotal regulatory mechanisms in papillary thyroid carcinoma (PTC) and anaplastic thyroid carcinoma (ATC), suggesting these axes as potential therapeutic targets. In thyroid cancer, the gene FER1L4 exhibits enhanced expression. This upregulation is connected with unfavorable clinic-pathological attributes in papillary thyroid carcinoma, encompassing lymph node metastasis, extra-thyroidal extension, and advanced tumor staging. Investigation into the biological functions of FER1L4 demonstrates that the induction of its upregulation is mediated by the suppression of microRNA-612 expression. FALEC exhibits upregulation in thyroid cancer and promotes oncogenic processes. This heightened expression modulates the Wnt/β-catenin signaling cascade, thereby facilitating oncogenic transformations, such as cell proliferation, migration, and invasiveness. Elevated expression of Long-intergenic non protein coding RNA

1315, results in enhanced cellular proliferation and colony morphology in papillary thyroid carcinoma cells, primarily contributed to by an oncogenic role. Mechanistically, this enhancement is mediated by the cells' ability to sequester the anti-proliferative microRNA-miR-497-5p. Although there is growing evidence that lncRNAs such as SNHG3, CYTOR, LUCAT1, UCA1, FER1L4, FALEC, and LINC01315 contribute to the advancement of thyroid cancer, several gaps remain.

Majority of the studies concentrate on specific lncRNA–miRNA–mRNA interactions, which leaves the broader regulatory framework and the potential connections between these lncRNAs ambiguous. Future research using integrative multi-omics strategies will be essential to clarify hierarchical and cooperative relationships among these noncoding transcripts. Clinical validation is still limited, with insufficient assessment of different thyroid cancer subtypes and inadequate evaluation of their prognostic or diagnostic potential. The upstream elements that cause lncRNA dysregulation, including both transcriptional and epigenetic factors, are poorly understood. In addition, the impact of lncRNAs on patient responses to radioactive iodine therapy, tyrosine kinase inhibitors, or immunomodulatory treatments remains largely unexplored. Given that many lncRNAs influence essential survival and growth pathways, comprehending their roles in treatment response could reveal new biomarkers for patient classification or identify possible targets for combination therapies. Future investigations should focus on thorough network analyses, rigorous clinical validation, clarification of upstream regulatory mechanisms, evaluation of implications for therapy, and the development of combined lncRNA biomarker profiles to enhance clinical application.

Conclusion

Thyroid cancer, a relatively uncommon yet clinically significant endocrine malignancy, is seeing increased interest in the role of long non-coding RNAs (lncRNAs) in its tumorigenesis. This review explores the functional roles of select lncRNAs in the development, progression, and metastasis of thyroid cancer. Specifically, it examines SNHG3, LINC00152, LUCAT1, UCA1, FER1L4, FALEC, and LINC01315, which are consistently upregulated in thyroid tumors. These lncRNAs exert oncogenic effects by modulating key signaling pathways (e.g., AKT/mTOR/ERK, TGF-β, IL-6/JAK2/STAT3), regulating the cell cycle, and promoting invasion and resistance to apoptosis. Functioning as competing endogenous RNAs (ceRNAs), they sequester tumor-suppressive microRNAs to upregulate oncogenes. Their expression also correlates with aggressive features of papillary thyroid cancer, including lymph node metastasis, extra-thyroidal extension, and advanced tumor stage. This review underscores that dysregulated lncRNA expression is emerging as a hallmark of thyroid cancer. Despite limited existing research, these molecules show promise as diagnostic and prognostic biomarkers and as targets for RNA-based therapies (Samimi *et al*. 2020). Further studies are essential to clarify their roles across different thyroid cancer subtypes and to realize their potential in clinical applications.

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Disclaimer

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