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LONG NON-CODING RNAS AT THE INTERFACE OF EPIGENETICS AND HORMONAL SIGNALING IN THYROID CANCER

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Abstract

Thyroid cancer has emerged as the most common endocrine malignancy and the fifth most frequent cancer among women globally. Rates have roughly doubled compared to previous decades. Hormonal signaling plays a major role in this rise, with receptors for thyroid hormone, estrogen, progesterone, and HER2 activating pathways such as MAPK and PI3K/AKT that drive tumor cells toward proliferation and invasion. Increasingly, research points to long non-coding RNAs (lncRNAs) as the link between these hormone-driven signals and the epigenetic changes occurring inside the cell. Acting as scaffolds, guides, or decoys, lncRNAs shape chromatin structure, DNA methylation, and histone modification in ways that switch tumor suppressor genes off or oncogenes on. Molecules such as HOTAIR, NEAT1, ANRIL, GAS5, CASC2, and MALAT1 have been associated with tumor aggressiveness. Because these RNAs are stable and can be picked up in tissue or body fluids, they're gaining attraction as diagnostic and prognostic markers, which matters given how often fine-needle aspiration biopsies come back inconclusive. The convergence of lncRNA-driven epigenetic regulation and hormonal signaling thus emerges as a central feature of thyroid cancer biology, one with meaningful implications for future biomarkers and treatment strategies.

INTRODUCTION:

The thyroid gland is a butterfly-shaped endocrine gland situated at the base. It is one of the largest endocrine glands in the human body that plays an important role in the development of organs, differentiation of cells, and metabolism [1]. Thyroid cancer is a common malignancy of the endocrine system and the fifth most common cancer among females worldwide. Thyroid cancer accounts for over 3.4% of all malignancies, and its prevalence is now growing at a pace that is twice that of the previous several decades.[2]. The development and progression of thyroid cancer are driven by a complex interplay of hormonal signaling pathways that regulate thyroid gland function and cellular proliferation [3].

Emerging evidence has established a close association between thyroid hormones and various malignancies, emphasizing the role of hormonal signaling in thyroid tumorigenesis [4]. The hypothalamic-pituitary axis regulates the release of thyroid hormones, and thyroid-stimulating hormone is the primary stimulus for thyroid hormone production by the thyroid gland [5]. The thyroid gland is composed of follicular cells that produce and store thyroid hormones, which are thyroxine (T4) and triiodothyronine (T3). These hormones play roles in the regulation of growth and metabolism [6]. Thyroid tumorigenesis is driven by a complex network of signaling pathways regulated by multiple receptors that influence cellular proliferation, survival, invasion, and metastasis [7]. Among these, thyroid hormone receptors, human epidermal growth factor receptor 2 (HER2), estrogen receptors (ER), and progesterone receptors (PR) have been recognized as key modulators of thyroid cancer progression and aggressiveness [8].

Hormonal regulation of thyroid cancer is strongly influenced by epigenetic alterations and long non-coding RNA (lncRNA). Epigenetic regulation refers to heritable changes in gene expression without altering the DNA sequence [9]. These changes regulate chromatin organization and gene accessibility, ultimately influencing transcriptional activities [10]. Dysregulation of epigenetic processes contributes to thyroid tumorigenesis by altering the expression of oncogenes and tumor suppressor genes [11]. In this context, lncRNAs act as key epigenetic regulators by modulating gene expression at transcriptional, post-transcriptional, and epigenetic levels, thereby contributing to thyroid cancer development and progression [12].

Long non-coding RNAs are key effectors that integrate the epigenetic processes underlying thyroid cancer with hormonal control. These lncRNAs, via their interactions with proteins, chromatin, and RNA, coordinate complex regulatory networks controlling tumor progression [13]. Long non-coding RNAs are key effectors that integrate the epigenetic processes underlying thyroid cancer with hormonal control. LncRNAs like HOTAIR and MALAT1 associate with

chromatin-modifying complexes and have been associated with either repression or transcriptional enhancement of hormone-responsive genes [14]. The interplay between hormonal signaling, epigenetic modifications, and long non-coding RNAs (lncRNAs) drives thyroid cancer progression and influences tumor aggressiveness and therapeutic response. Understanding these interactions may facilitate the development of novel biomarkers and targeted therapies for precision medicine.

HORMONAL RECEPTOR SIGNALING PATHWAYS IN THYROID CANCER PROGRESSION:

Hormone receptor signaling pathways regulate functions such as growth, differentiation, metabolism, and apoptosis. Dysregulation of these pathways is a characteristic of thyroid carcinoma and many other types of cancer [15]. Thyroid cancer progression is influenced by various receptors that include hormone receptors like thyroid hormone, HER2, estrogen, and progesterone receptors. Upon binding to their ligands, these receptors activate pathways such as RAS/RAF/MEK and PI3K/AKT to promote tumor progression and therapy resistance [16].

✓ **Thyroid Hormone Receptors (TRs):**

The main thyroid hormones are produced by the thyroid gland, which are triiodothyronine (T3) and thyroxine (T4). These hormone secretions are controlled by thyroid-stimulating hormone (TSH). The actions of thyroid hormone are classified into two main mechanisms, which are non-genomic and genomic. Thyroid hormone receptors (TRs) are factors that facilitate the actions of the thyroid hormone in development, growth, and differentiation [17]. The two human thyroid hormone receptor (TR) genes, **THRA** and **THRB**, are located on separate chromosomes and encode the T3-binding receptor isoforms TRα1, TRβ1, TRβ2, and TRβ3. Thyroid hormones (THs) interact with plasma membrane integrin αvβ3, activating different signaling pathways and promoting papillary and follicular thyroid cancer cell proliferation and anti-apoptosis [18].

The MAPK signaling pathway is activated in nearly 70% of thyroid carcinomas due to genetic alterations. Key driver mutations in thyroid cancer are BRAF and RAS point mutations, as well as RET/PTC rearrangements. This indicates that MAPK activation is a fundamental mechanism in thyroid malignancies [19]. In thyroid cancer, PI3K is the main driver of signaling pathways that include PTEN, PIK3CA, and RAS mutations. RAS mutation is the second most common mutation and mainly activates the PI3K/AKT pathway [20]. The PI3K/protein kinase B (AKT) pathway is involved in several genomic and nongenomic thyroid hormone activities in cancers [17]. Mutations and dysregulation of Wnt pathway expression can contribute to thyroid

cancer development. Increased β-catenin expression was noted in anaplastic thyroid cancer (ATC) compared to differentiated thyroid cancer (DTC). This suggests that the WNT–β-catenin pathway plays a significant function in the aggressiveness of thyroid tumors [21].

In the TGFβ Signaling Pathway, the effect of activated TGFβ signaling varies depending on conditions and may be categorized as either a tumor promoter or a tumor suppressor. Nevertheless, nothing is known about the mechanism behind this change in TGFβ function. TGFβ frequently functions as a tumor suppressor in early stages of thyroid cancers, but as a tumor promoter in the later stages [22]. TGFβ activation plays a significant role in BRAF-mutated papillary thyroid cancers. The TGFβ pathway inhibits the formation of thyroid follicular cells in the early stages of carcinogenesis. In subsequent stages, the TGFβ pathway works with BRAF to produce EMT, migration, and invasion [23].

✓ **Estrogen Receptors (ERs):**

Estrogen exerts its biological effects primarily by binding to intracellular estrogen receptors (ERs) in target tissues. Thyroid cancer cells overexpress estrogen receptors (ERα and ERβ), and it has been shown that estrogen signaling promotes tumor cell invasion and proliferation. Estrogen stimulates the spread and metastasis of tumor cells via triggering pathways such as PI3K/AKT and MAPK [24]. Estrogen enhances cell proliferation through classical genomic and non-genomic pathways mediated by membrane-bound estrogen receptors. In addition, it promotes tumor progression by modulating the tumor microenvironment. Estrogen receptors (ER) modulate PI3K/AKT/mTOR and RAS/RAF/MEK signaling pathways [25].

Estrogen promotes thyroid cancer progression by regulating several signaling pathways involved in cell proliferation, survival, and metastasis. Through ERα, it activates the PI3K/Akt/mTOR pathway, enhancing protein synthesis and cell survival, whereas ERβ suppresses this pathway by reducing Akt activation and promoting apoptosis [26]. Estrogen also stimulates the MAPK pathway through rapid, non-genomic ERα signaling, leading to ERK1/2 activation and increased cyclin D1 expression, which promotes thyroid cancer cell proliferation. In contrast, ERβ inhibits MAPK signaling and limits tumor growth [27]. Additionally, estrogen enhances Wnt/β-catenin signaling by stabilizing β-catenin and promoting its nuclear translocation, thereby increasing the expression of genes associated with proliferation and metastasis. Conversely, ERβ suppresses this pathway by facilitating β-catenin degradation, reducing tumor growth and invasion [28].

✓ **Progesterone Receptors (PRs):**

Progesterone's actions are mediated by nuclear hormone receptors called progesterone receptors (PRs). Few investigations on the expression of PR in thyroid tissues have been reported. Although they have not been as well investigated as estrogen receptors, there is emerging evidence that PRs have a function in the pathogenesis and development of thyroid cancer [29]. PRs influence tumor development, migration, and treatment responses by mediating the cellular effects of progesterone through a variety of signaling pathways. PR expression in thyroid cancer varies, with some research having found that papillary thyroid carcinoma (PTC) had greater PR levels than normal thyroid tissue[30].

There are two primary isoforms of PRs, PR-A and PR-B, which vary in structure and function. PR-A has anti-proliferative properties and functions as a transcriptional inhibitor. PR-B may stimulate cell proliferation by acting as a transcriptional activator. PRs interact with important signaling pathways to affect thyroid cancer development through both genomic (transcriptional regulation) and non-genomic processes, including cytoplasmic signaling [31]. In the genomic pathway, PRs enter the nucleus after binding progesterone, where they attach to progesterone response elements (PREs) to control gene expression. This modification impacts genes related to cell division, proliferation, and apoptosis. In non-genomic pathways, PRs can rapidly activate cytoplasmic signaling cascades through the MAPK Pathway and PI3K/Akt Pathway [32].

PR activation promotes the Ras-Raf-MEK-ERK pathway in the MAPK pathway. Enhanced phosphorylation of ERK stimulates invasion, migration, and cell division.PR-B is particularly associated with activating MAPK signaling. PRs have the same ability to activate the PI3K/Akt pathway as estrogen receptors [33]. PRs cause Akt phosphorylation by interacting with PI3K via membrane-associated signaling complexes. This enhances resistance to apoptosis, proliferation, and cell survival in thyroid cancer cells. PR-A has been linked to mTOR inhibition, which in some situations may mediate anti-proliferative effects [34].

✓ **HER2:**

The oncogene ERBB2, also known as HER2, is found on chromosome17. This gene encodes a tyrosine kinase receptor called erbB-2 or human epidermal growth factor receptor 2 (HER2). Oncogenic pathways are triggered by HER2 activation, which promotes tumor angiogenesis, invasiveness, and cell proliferation. HER2 has the highest catalytic kinase activity and the most aggressive signaling among the four HER proteins [35]. Research on HER-2 in thyroid cancers has shown a correlation between aggressive behavior in differentiated thyroid carcinomas and overexpression of the gene. It's interesting to note that undifferentiated thyroid cancers have

been shown to have low or absent HER-2 expression, indicating that the tumors' biologic development may be influenced by its downregulation. [36].

HER2 overexpression was found in 44% of follicular thyroid cancers and in 18% of papillary thyroid cancers. HER2 is also amplified in certain ATCs. [37]. HER2 signaling involves homodimerization or heterodimerization with other EGFR family members, resulting in activation of MAPK and PI3K/Akt pathways [38]. HER2 triggers the Ras-Raf-MEK-ERK cascade in the MAPK Pathway by means of proteins such as Grb2 and SOS. It encourages proliferation and progression of tumors by promoting cell proliferation. In the PI3K/Akt Pathway, HER2 phosphorylates PI3K, which activates Akt. It improves epithelial-to-mesenchymal transition (EMT), anti-apoptotic signals, cell survival, and invasiveness of cancer cells. [39].

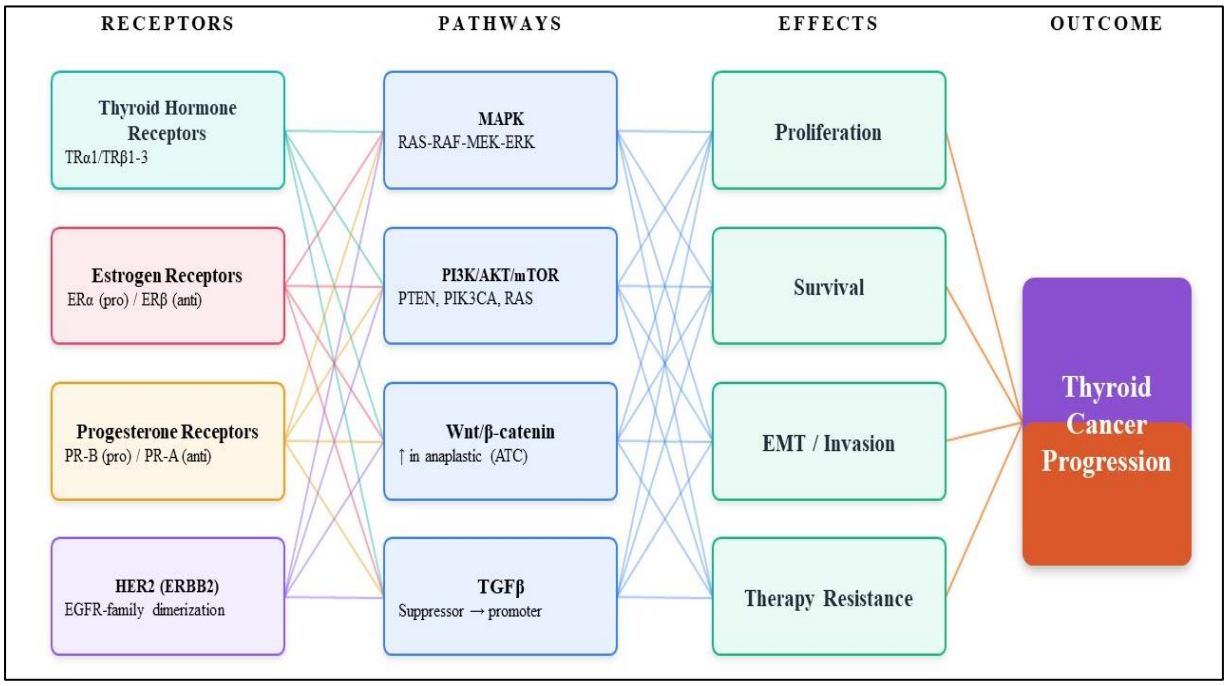


Fig 01: Illustration of the shared signaling landscape in thyroid cancer, wherein hormonal receptors (TR, ER, PR, HER2) converge on the MAPK, PI3K/AKT/mTOR, Wnt/β-catenin, and TGF-β cascades to promote tumor cell proliferation, survival, EMT/invasion, and resistance to treatment.

LONG NON-CODING RNAS (lncRNAs):

More than 98% of the human genome is made up of noncoding RNAs (ncRNAs), such as lncRNAs, which are transcribed but do not encode proteins. Less than 2% of the genome is made up of genes that code for proteins. Although the majority of ncRNAs' roles are still being studied, there is increasing evidence that they are highly regulated and functional [40]. Non-coding RNAs were often thought of as "junk genes," but they have recently been shown to have

important roles in various diseases, most notably cancer. They play a crucial part in the central dogma of molecular biology and control gene expression at transcriptional, post-transcriptional, and epigenetic levels. [41]. The two types of ncRNA were categorized based on their sizes, short ncRNAs and long ncRNAs (lncRNAs). The short noncoding RNAs (ncRNAs) include transcripts like microRNAs (miRNAs), transfer RNAs (tRNAs), small interfering RNAs (siRNAs), and certain ribosomal RNAs, of which lncRNAs have been most extensively studied in human malignancies [42].

LncRNAs are non-coding RNAs that intricately control gene expression across various levels of transcriptional, translational, and post-translational processes, despite lacking the ability to encode peptides or proteins. Dysregulation of lncRNA expression levels has been associated with various diseases, including malignancies [43]. The length of lncRNAs is between 1000 and 10,000 nucleotides. Because of their complex secondary and three-dimensional structures, lncRNAs can have both RNA and protein-like functions. RNA polymerase II transcribes lncRNAs and frequently undergoes splicing to produce mRNAs. They are mostly found in the nucleus and are expressed at a lower level than mRNAs [44].

Long noncoding RNAs (lncRNAs) perform a variety of tasks related to transcriptional control and are mostly found in the nucleus and chromatin. They also have roles in the cytoplasm, and some of these molecules are extracellular lncRNAs that are transferred by exosomes [45]. The versatility of lncRNAs in regulating gene expression at different levels is highlighted by their interactions with a wide range of molecular partners, such as transcription factors, chromatin-modifying complexes, RNA-binding proteins, microRNAs, and chromatin itself. Through precise binding to active proteins and establishment of precise positional relationships, lncRNAs exert significant regulatory control over gene expression processes [46]. The development and progression of thyroid cancer are significantly affected by dysregulation of long non-coding RNAs. These lncRNAs are actively involved in the regulation of genes in thyroid cancer [47].

EPIGENETIC REGULATION:

Epigenetic regulation involves heritable alterations in gene expression or cellular phenotype without altering the DNA sequence. Key epigenetic mechanisms include DNA methylation, chromatin remodeling, and the regulation of gene expression [48]. These mechanisms are fundamental to understanding the pathogenesis of various diseases, including thyroid cancer. They also provide insight into the complex molecular mechanisms underlying thyroid cancer development and progression [49].

The identification of epigenetic biomarkers has emerged as an important tool for improving the diagnosis and prognosis of thyroid cancer. Thyroid cancer's epigenetic regulation has highlighted the significance of long non-coding RNAs (lncRNAs) [50]. The epigenetic landscape of thyroid cancer is significantly influenced by these molecules, which can post-transcriptionally control gene expression [51]. These lncRNAs control tumor suppressors and oncogenes, promoting tumor metastasis through their interactions with epigenetic enzymes [52]. Understanding of lncRNA-mediated epigenetic processes provides important information on the development of thyroid cancer and possible treatment approaches [53].

EPIGENETIC REGULATION BY LONG NON-CODING RNAS:

Long noncoding RNA molecules are carriers of epigenetic information. They regulate epigenetic machinery by serving as scaffolds, guides, decoys, or signals. They epigenetically regulate the expression of several prominent genes that are involved in crucial cellular biological processes, such as cell differentiation, cellular autophagy, and cell cycle regulation [54]. They might be in direct interaction with PRC2 and guide the histone lysine methyltransferase EZH2 activity to certain genomic loci, which would cause chromatin condensation, promoter silencing, and trimethylation of histone H3 at lysine 27 (H3K27me3). LncRNAs also have interactions with other complexes involved in chromatin remodeling [55].

1.Chromatin Remodeling:

When lncRNAs interact with DNA, they may alter chromatin structure, which results in epigenetic changes and changes in target gene expression. LncRNAs can directly disrupt transcription through recruitment or tethering of chromatin-modifying complexes to either stimulate or suppress gene expression. Chromatin structure can be altered by lncRNAs by binding to certain chromatin regions and recruiting chromatin remodeling complexes [56]. Chromatin remodeling complexes like PRC1 and PRC2 are recruited by lncRNAs like ANRIL to regulate loci important in tumor suppression. Additionally, lncRNAs can interact with SWI/SNF complexes to bind with chromatin remodeling machinery to activate the Wnt signaling pathway in thyroid cancer [57].

HOTAIR is significantly upregulated in PTC. It binds with both PRC2 and the lysine- specific histone demethylase LSD1 to promote H3K27me3 and H3K4 demethylation to silence target genes. This leads to enhanced tumor invasion and metastasis in thyroid cancer [58]. In order to control gene expression, lncRNAs can either promote or prevent chromatin looping. It brings distal regulatory elements near to promoters. LncRNA CCAT1-L induces chromatin looping, which brings distant enhancers closer to gene promoters to enable gene activation in thyroid

cancer. Therefore, lncRNAs direct chromatin-modifying complexes to particular genomic loci and regulate promoter activity in thyroid cancer [59].

2.DNA Methylation:

Aberrant DNA methylation of tumour suppressor genes and proto-oncogenes is found in thyroid cancer and other human cancers. The thyroid has several distinct tumor suppressor genes, including PTEN, RASSF1A, TIMP3, SLC5A8, DAPK, RAPβ2, and RAP1GAP. Another epigenetic component, long non-coding RNAs (lncRNAs), mediates the processing of DNA methylation by DNMTs and demethylation by TETs [60]. These enzymes can be bound by lncRNAs, which then bind to their target areas to control gene transcription. For instance, thyroid cancer is associated with downregulated LncRNA PTCSC3. Oncogenesis is aided by its depletion, which alters the control of DNA Methyltransferases (DNMTs) and causes hypermethylation of tumor suppressor gene promoters [61]

DNA methyltransferases (DNMTs) can be directed to certain genomic loci by lncRNAs. For example, Kcnq1ot1 interacts with DNMT1 to preserve methylation at imprinted loci to ensure monoallelic expression [62]. Certain lncRNAs stop DNA methylation by preventing TET enzymes from catalyzing DNA demethylation. As an illustration, GADD7 maintains hypermethylated states by interfering with TET1 activity. These interactions alter the expression of many genes involved in cell proliferation, invasion, and stemness, which play crucial roles in thyroid cancer [63].

3.Histone Modifications:

Histone modifications such as acetylation, methylation, and phosphorylation can either relax or compact chromatin structure, thereby regulating gene expression. LncRNAs interact with histone-modifying enzymes such as histone methyltransferases and histone deacetylases to control gene expression. Histone methyltransferase EZH2 is part of PRC2, which HOTAIR binds and directs to target genes for H3K27 trimethylation, which silences transcription [64].

Similar to histone methylation, lncRNAs regulate histone acetylation/deacetylation. LncRNAs mobilize histone acetyltransferases or deacetylases to specific loci, which alters gene transcription. To alter histones and control a large number of genes in cis-regulation, ANRIL directly enlists PRC1 and PRC2 at tumor suppressor gene loci, facilitating thyroid cancer cell proliferation [65].

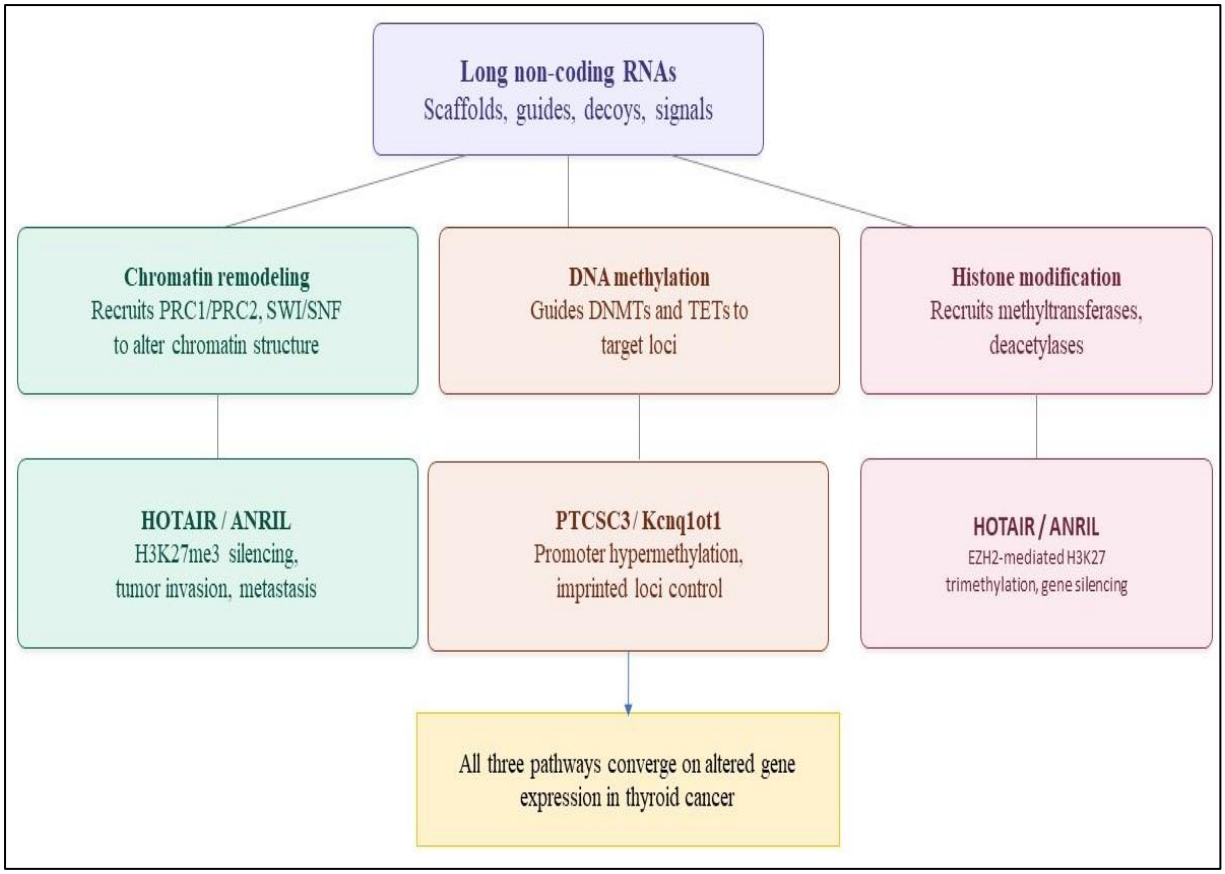


Fig 02: Overview of the epigenetic mechanisms by which long non-coding RNAs (lncRNAs) regulate gene expression in thyroid cancer, encompassing chromatin remodeling, DNA methylation, and histone modification.

LONG NON-CODING RNA IN HORMONAL REGULATION OF THYROID CANCER:

LncRNAs are longer than 200 nucleotides in length. LncRNAs are not translated into proteins due to their lack of open reading frames and do not play a role in the transcription of proteins. However, they are linked to carcinogenesis and have the ability to control gene expression on several levels. Long noncoding RNAs (LncRNAs) have a role in nearly every stage of tumor development, including metastasis, cell proliferation, and survival [66]. Evidence highlights that numerous physiological and biological cell processes are influenced by lncRNAs. Long non-coding RNAs are emerging molecules with diverse abilities in promoting thyroid cancer upon dysregulation [67]. Dysregulated lncRNAs may promote carcinogenesis by controlling a variety of physiological and cellular processes that result in proliferation or suppression of cell death in thyroid cancer because of their tumor-suppressive or oncogenic effect [68].

Several lncRNAs linked to cancer have been found and shown to be essential for the development of tumors. In order to control gene expression and protein function, lncRNAs can

work mechanistically as miRNA sponges and reservoirs of short noncoding RNAs. Functionally, a variety of lncRNAs use different molecular processes to play crucial roles in epigenetic control [69]. LncRNAs play important roles in the intricate carcinogenesis process of thyroid cancer. Numerous lncRNAs that contribute to thyroid carcinogenesis are either up- or down-regulated in thyroid cancer tissues [70]. Many lncRNAs closely associated with the progression of thyroid cancer include NEAT1, HOTAIR, ANRIL, SPRY4-IT1, CASC2, and MALAT1[71]. Some of these lncRNAs, which play an important role in thyroid cancer, are given below.

1.HOTAIR:

HOTAIR is an RNA molecule expressed from the HOXC cluster. It is one of the best-studied lncRNAs in cancer and is up-regulated in several cancer types [72]. Overexpression of HOTAIR has been linked with increased invasiveness and poor prognosis in cancer. It was shown to be a poor prognostic factor for pancreatic, liver, and breast cancers [73]. Similarly, the level of HOTAIR is significantly elevated in thyroid cancer in contrast to healthy thyroid tissues. A significant increase in HOTAIR expression promotes cell proliferation in thyroid cancer cells. On the other hand, thyroid cancer cell growth was inhibited when its expression was reduced [74].

HOTAIR overexpression in PTC is associated with tumor growth and poor prognosis. HOTAIR uses the Wnt pathway to play an oncogenic function. It may cause activation of the Wnt/β-catenin pathway by inhibiting WIF1, which is a protein that antagonizes Wnt activity, resulting in PTC cell proliferation and metastasis [75]. CCND2 is a member of the cyclin family, which regulates the cell cycle. Overexpression of HOTAIR prevents activation of cyclin D2 (CCND2) and miR-1 proteins. By downregulating the expression of the tumor-suppressor gene miR-1, HOTAIR overexpression can accelerate the development of thyroid malignancies via the HOTAIR/miR-1/CCND2 pathway [76].

2.NEAT1:

The lncRNA NEAT1 is found on chromosome 11q13.1. LncRNAs function as molecular sponges in a variety of cancers. Tumor development of many malignancies, including PTC, is closely associated with it [77]. According to a previous study, NEAT1 was shown to be up-regulated in thyroid cancer cells, and its overexpression facilitated the proliferation of thyroid cancer cells. However, NEAT1 knockdown prevented cell invasion, survival, and the ability to develop tumors [78]. Thyroid cancer tissues and cells have higher levels of NEAT1 expression than normal thyroid tissues. Additionally, NEAT1 acts as a ceRNA by competitively binding

miRNA-214. NEAT1 prevents the activity of miR-214, which accelerates the growth of thyroid cancer cells [79].

Thyroid cancer is associated with an overexpression of NEAT1, which can also increase the expression of KLK7 and inhibit the effects of miRNA-129-5p. KLK, the seventh serine protease family member, is progressively overexpressed in human malignancies and promotes cancer progression by breaking down cell junction proteins. In thyroid carcinoma, overexpression of KLK7 is also strongly associated with a bad prognosis [80]. NEAT1 was found to upregulate fibronectin 1 (FN1) by suppressing the expression of miR-101-3p, hence neutralizing the effect of radioactive iodine therapy. RAI resistance in PTC is also caused by FN1 overexpression, which encourages the PI3K/AKT signaling pathway to become activated[81].

3.ANRIL:

ANRIL is a 3.8 kb lncRNA and is located on chromosome 9p21. It reverses from the INK4b-ARF-INK4a gene cluster, which codes for the three tumor suppressors p15 (INK4b), p14 (ARF), and p16 (INK4a) [82]. ANRIL was believed to cluster with other genes, including p14, and control nearby tumor suppressor genes. Prior research has demonstrated that elevated ANRIL is a risk factor for various malignancies. It has been shown that thyroid cancer cell lines and tissues have significant levels of ANRIL expression [83].

TGF-b/Smad signaling pathway activity is inhibited by ectopic production of ANRIL, which further reduces p15INK4B expression and encourages thyroid cancer cell metastasis. ANRIL silencing prevents TPC-1 cells from invading and spreading [84]. NF-κB and Wnt/β-catenin pathway activation were inhibited by ANRIL. PTC instances were associated with NF-κB activation, which may encourage PTC dedifferentiation and accelerate PTC invasion and development. By binding to miR-320a and competing with HMGB1 to prevent the activation of Wnt/β-Catenin and NF-κB pathways, ANRIL downregulation prevented the malignant tendencies of PTC cells [85].

4.GAS5:

The gene coding for lncRNA GAS5 is present on chromosome 1q25, and GAS5 expression decreases in thyroid carcinoma [86]. A tumor suppressor lncRNA, GAS5, is thought to have downregulated expression in several malignancies. It works on several levels to control genes involved in metastasis, apoptosis, and proliferation [87]. GAS5 expression was reported to decrease in cancerous tissues in comparison with the benign tumor tissues of the thyroid. In

individuals with thyroid cancer, low GAS5 expression levels are linked to numerous cancers and poor prognosis [88].

GAS5 regulates important signaling pathways that are essential to the development of cancer, such as PI3K/AKT/mTOR. GAS5 was discovered to be downregulated in thyroid carcinoma cell lines and tissues. GAS5, which is a ceRNA, activates the PTEN/AKT pathway. It has an anti-cancer impact through acting on miR-222-3p in thyroid cancer. PTEN is a key inhibitory gene for tumor cell growth that inhibits AKT phosphorylation, and its downregulation is related to tumorigenesis [85].

5.CASC2:

LncRNA CASC2 is located on chromosome 10q26 and is downregulated in thyroid cancer tissues. Overexpression of CASC2 may inhibit thyroid cancer cells from proliferating by disrupting the cell cycle [89]. Significant correlations were seen between downregulated CASC2 expression and tumor multifocality. In thyroid carcinoma, CASC2 downregulation is indicative of a bad prognosis [90]. The expression level of CASC2 in patients with PTC is much lower levels of CASC2 than do individuals with nodular goiter. CASC2 controls the EMT pathway, which in turn influences the metastasis of thyroid cancer cells [91].

Expression of CASC2 in PTC tumors was considerably lower in comparison with normal tissues. The occurrence of multifocal lesions, advanced clinical stage, and tumor size were substantially correlated with downregulation of CASC2. The inactivation of AKT and ERK1/2 caused by overexpression of CASC2 can dramatically reduce the proliferation of thyroid cancer cells [92].

6. MALAT1:

MALAT1 is involved in the regulation of cancer progression and is known to be deregulated in multiple cancers. Thyroid cancer cells may proliferate and multiply more readily when MALAT1 is present. Thyroid cancer tissues have elevated MALAT1 expression [93]. In thyroid cancer, MALAT1 stimulates the development of blood vessels, which stimulates biological processes including cell division and metastasis. When compared to normal thyroid tissue, the expression level of MALAT1 was markedly elevated in medullary thyroid cancer [94]. Anaplastic thyroid carcinomas (ATCs) have the lowest levels of MALAT1 expression, which is substantially lower than that of poorly differentiated thyroid carcinomas. Additionally, blocking MALAT1 prevents cell invasion and proliferation and has an anti-tumor impact [95].

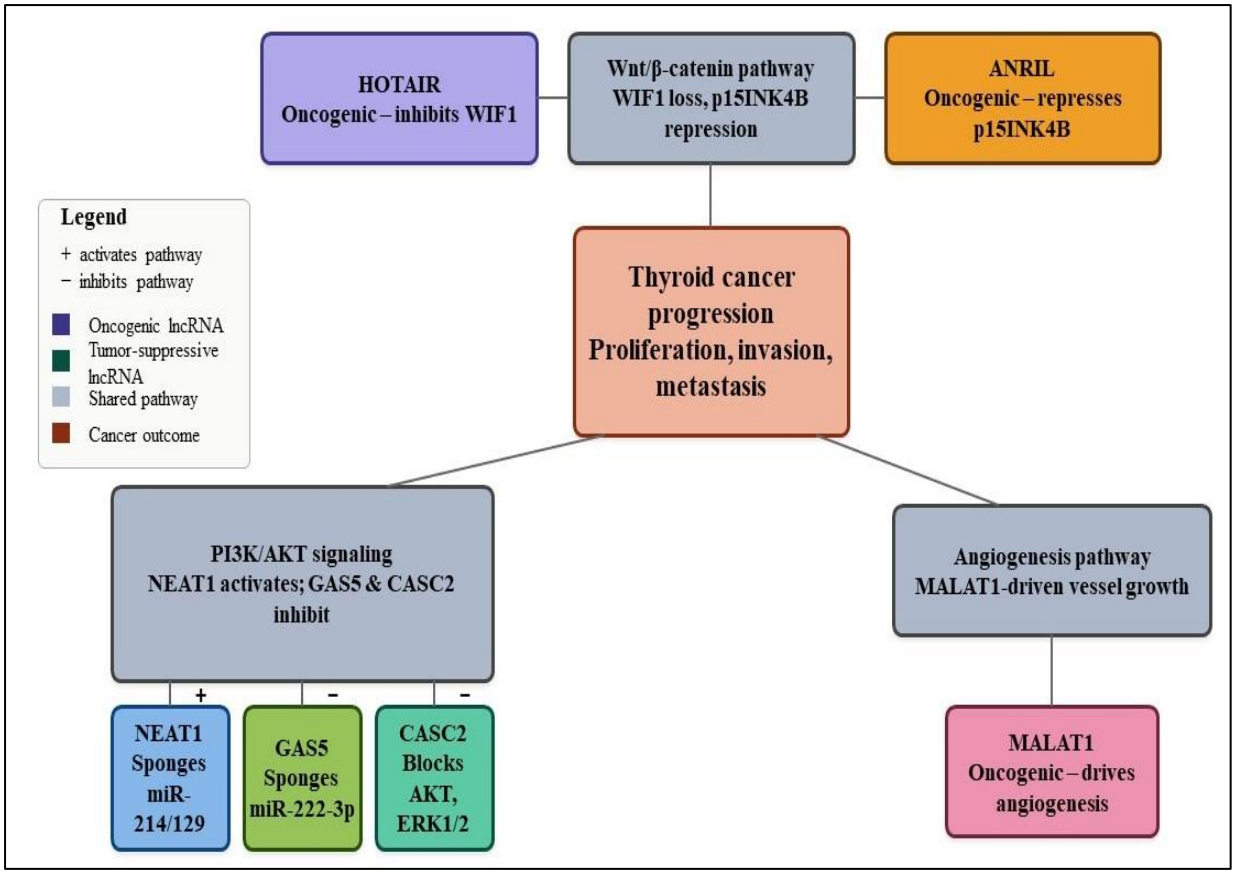


Fig 03: Schematic overview of lncRNA crosstalk in thyroid cancer pathogenesis, highlighting shared convergence of multiple lncRNAs on the Wnt/β-catenin and PI3K/AKT pathways, in addition to MALAT1-driven angiogenesis, ultimately promoting malignant progression.

DIAGNOSTIC POTENTIAL OF LONG NON-CODING RNAs:

The prognosis for thyroid cancer patients is thought to be generally good. However, aggressive behaviours in certain thyroid cancer patients have been linked to a poor prognosis and low resection rates [96]. Fine-needle aspiration (FNA) biopsy is widely used as the primary diagnostic approach for thyroid cancer. However, 10–40% of thyroid nodule cytology results are indeterminate or non-diagnostic, frequently requiring repeat FNA and resulting in delays in definitive diagnosis and treatment [97]. Understanding the underlying processes of thyroid cancer development to uncover new targets is a critical issue for the advancement of thyroid cancer therapies, since the majority of thyroid cancer patient fatalities are often brought on by inadequate therapeutic tactics and particular diagnostic biomarkers [98].

Long non-coding RNAs have immense potential as diagnostic biomarkers due to their stability and detectability in bodily fluids. The diagnostic value of miRNAs in blood has been extensively researched, while the diagnostic value of lncRNAs is mostly investigated in tissues.

The expressional alterations of lncRNAs in thyroid carcinogenesis have been identified by a number of investigations. Thyroid cancer is influenced by the lncRNAs MALAT1, HOTAIR, and BANCR, which are also suggested as biomarkers for early diagnosis and detection [99]. Other lncRNAs, such as H19, NEAT1, MEG3a, TUG1, UNC5B-AS1, LOC100129940-N, LINC00313, and HOXA-AS2, have also been shown to have altered expression linked to invasion and metastasis of thyroid cancer cells. These various studies on the clinical significance of ncRNAs have resulted in the advent of a commercial diagnostic product in thyroid cancer [100].

CONCLUSION:

In thyroid cancer, epigenetics and hormonal signaling don't operate independently; this review traces where the two actually converge, and that point turns out to be long non-coding RNAs (lncRNAs). Hormone receptors trigger the process, but lncRNAs like HOTAIR, NEAT1, ANRIL, and MALAT1 do the real work at the chromatin level, shutting down tumor suppressors or switching on genes that drive growth. When these lncRNAs are dysregulated, tumors tend to become more aggressive and respond worse to treatment. HOTAIR and MALAT1 are considered strong candidates for both diagnosis and treatment, given how often standard biopsies leave things unclear. Combining lncRNA-based approaches with existing therapies could offer a more direct way to target the hormonal drivers of this disease, and tracking lncRNA levels in tissue may turn up further leads worth pursuing. Tools like CRISPR/Cas9 and high-throughput sequencing are helping uncover lncRNAs whose roles weren't obvious before. Sustained progress here could bring us closer to treatments that restore hormonal sensitivity in tumors that stopped responding to standard therapy. Either way, lncRNAs may act as both diagnostic tools and treatment targets in thyroid cancer.

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