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Micro RNA-Mediated Epigenetic Regulation in Hormonal Pathways: Insights into Thyroid Cancer Progression

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ABSTRACT

Thyroid cancer is the most prevalent endocrine malignancy, and its prevalence is continuously increasing globally. Thyroid cancer is a complicated disease that is impacted by environmental, genetic, and epigenetic factors. Among these, epigenetics, which are heritable variations in gene expression that do not include changes in the DNA sequence, has drawn much interest. The physiology and pathology of the thyroid gland depend heavily on hormonal pathways, especially those involving thyroid hormones. It has been demonstrated that their dysregulation promotes the development of tumors and the progression of cancer. MicroRNAs (miRNA or miRNAs) are key regulators of these epigenetic modifications. They modulate gene expression through chromatin remodeling, DNA methylation, and histone modifications, thereby influencing hormonal signaling pathways critical to thyroid physiology and pathology. Dysregulation of miRNA can disrupt thyroid hormone signaling, affect the expression of hormone-responsive genes and receptors, and contribute to tumor initiation, progression, and metastasis. Recent studies highlight the interplay between thyroid hormone signaling and miRNA-mediated epigenetic regulation in thyroid cancer. Understanding these molecular mechanisms is crucial for the development of novel diagnostic biomarkers and targeted therapeutic strategies.

INTRODUCTION

The thyroid is the largest endocrine gland in the human body and is essential for the development and differentiation of cells. Thyroid cancer is the abnormal proliferation of cells or tissues of the thyroid gland. It is the endocrine system's most prevalent malignant disorder, and the prevalence of thyroid cancer is continuously increasing globally. (Bible et al., 2021). Thyroid cancer is a complex disease that is influenced by hormone signals that regulate thyroid gland function, cellular proliferation, and survival. Hormone dysregulation contributes to the onset and development of several diseases, including thyroid cancer. (Cabanillas et al., 2016). The hypothalamic-pituitary-thyroid (HPT) axis is the primary regulator of the thyroid gland. The thyroid-stimulating hormone (TSH) is a key component of the HPT axis, which regulates the thyroid gland. (L. H. Chen et al., 2024). Elevated levels of TSH are closely associated with tumorigenesis and recurrence in well-differentiated thyroid tumors. (Goemann et al., 2017). Women are diagnosed with thyroid cancer about three times more frequently than men, pointing to a significant role for sex hormones, particularly estrogen. (Xu et al., 2024). Thyroid cancer aggressiveness and progression are influenced by receptors that mediate signaling pathways essential for cell proliferation and metastasis. These receptors include hormone receptors like thyroid hormone receptors (TR) and estrogen receptors (ER) (Brent, 2012). The Thyroid-Stimulating Hormone Receptor is essential in thyroid cancer development, particularly in well-differentiated types such as follicular thyroid carcinoma (FTC) and papillary carcinomas (PTC) (Hwang et al., 2023). Thyroid cancer cells overexpress estrogen receptors (ERα and ERβ), and it has been shown that estrogen signaling promotes tumor cell invasion and proliferation. (Gong et al., 2022).

Hormonal control of thyroid cancer is closely linked to epigenetic changes and miRNA functions. Epigenetic regulation means a change in the expression of a gene that can be passed down without altering the DNA sequence. These modifications influence the accessibility and structure of chromatin, which regulates gene activity (D. Li et al., 2021). DNA methylation, histone changes, and chromatin remodeling are critical epigenetic mechanisms that either activate or inhibit the hormonal response at the molecular level (Sarropoulou & Fernández, 2023). Epigenetic modifications stimulate tumorigenesis and alter tumor behavior by contributing to dysregulation of

oncogenes and tumor suppressor genes (Kumar et al., 2020). These processes might be targets for therapy since they are reversible and strictly controlled (Frías-Lasserre & Villagra, 2017). MiRNAs considerably influence epigenetic regulation of thyroid cancer. MiRNAs have been linked to thyroid cancer biology and, via their interactions with proteins, chromatin, and RNA, they coordinate complex regulatory networks controlling tumor progression (H. Li & Wu, 2024). This dynamic interplay between hormonal regulation, epigenetic changes, and miRNA activity creates a complex regulatory network that promotes tumorigenesis and metastasis in thyroid cancer. This integration not only promotes tumorigenesis but also determines the aggressiveness and therapeutic response of thyroid cancer. By understanding these interconnections, we gain insights into the molecular mechanisms driving thyroid cancer, as well as offer new opportunities for specific therapies and precision treatment strategies. The interaction of miRNAs and epigenetic modifications in the regulation of hormonal pathways of thyroid cancer reveals novel miRNA targets for hormonal pathway intervention and potential biomarkers for prognosis and early detection.

Hormonal Regulation in Cancer Progression

Role of Thyroid and Estrogen Hormones in Thyroid Cancer

The thyroid gland is a bilobed structure, and thyrotroph cells in the anterior pituitary gland produce the peptide hormone TSH, which is a driving hormone that regulates thyroid hormone synthesis (Foster et al., 2021). The anterior pituitary secretes TSH, which promotes the development of thyroid follicular cells and secretes thyroxine (T4) and triiodothyronine (T3). T4 is the primary thyroid hormone released via the thyroid gland and acts as a precursor of T3 (Casula & Bianco, 2012). Thyroid hormones play significant roles as modulators of physiological processes, including normal development, metabolism, proliferation, and differentiation in all tissues. However, their dysregulation can contribute to thyroid cancer development and progression (Udelsman & Zhang, 2017). Several clinical investigations in recent decades have proposed that an altered TSH level may increase the chance of developing tumors. Epidemiological studies have shown a correlation between decreased TSH and a greater incidence of breast, prostate, and lung cancer, even suggesting a TSH dosage impact on cancer occurrence (Moeller & Führer, 2013). Variations in TSH levels triggered by thyroid dysfunction or thyroid receptor expression in tumor cells affect cell invasion, proliferation, and differentiation through a variety of mechanisms. Thyroid hormones can stimulate cell proliferation in both normal and cancerous thyroid tissues. The metabolic activity of thyroid cells is increased by elevated T3 and T4 levels, which promotes the growth of tumors (Petranović Ovčariček et al., 2024). Excessive metabolic stimulation can cause reactive oxygen species (ROS) to be produced more often, which can damage DNA and potentially promote oncogenic alterations. Furthermore, T3 and T4 have been demonstrated to assist tumorigenesis by promoting cell cycle progression through their effects on gene expression involved in DNA replication and repair (Kim et al., 2021).

Estrogens are steroid hormones that are essential for controlling the development, differentiation, and function of the reproductive organs as well as skeletal and circulatory systems in males and females. Human-effective estrogens include estrone, estriol, and E2, with E2 having the highest affinity for ER. (Hima & Sreeja, 2016). E2 influences the metastatic phenotype of thyroid cancer cells through increasing their migration, as well as by downregulating β-catenin and encouraging stem cell self-renewal. Therefore, they may have a role in the progression of tumors. (J. Liu et al., 2014). The effect of estrogen on its receptors is clinically significant for the development of thyroid adenomas and thyroid cancer in females. It is well documented that E2 promotes proliferation in both normal and thyroid cancer cells, and this effect is enhanced by upregulating ERα. (Faria et al., 2019). The progression of thyroid cancer is significantly influenced by estrogen, which also contributes to the gender difference in thyroid cancer incidence that has been observed. This hormone promotes apoptosis and increases cell proliferation, both of which are crucial for the growth of tumors. (Rahbari et al., 2010). Estrogen modulates signaling pathways, which have a direct impact on thyroid cell development and function. It lowers the possibility of programmed cell death in thyroid cells by fostering an environment that makes mutant cells less likely to die by adjusting the ratio of pro-apoptotic to anti-apoptotic molecules. (Denaro et al., 2023). Thyroid hormones and estrogen have intricate impacts on the development and progression of thyroid tumors. Their corresponding receptors and signaling pathways mediate their actions. These hormones can cooperate to promote cell division and create an environment that is favorable to tumor development and metastasis. (H. Wang et al., 2023). It may co-activate growth-promoting mechanisms to increase tumor development synergistically. Common signaling molecules interact with estrogen and thyroid hormone receptors to enhance their effects on tumor development and thyroid cell differentiation. (Vasudevan et al., 2002).

Hormone Receptor Signaling Pathways

Hormone receptor signaling pathways regulate functions such as growth, differentiation, metabolism, and apoptosis. Dysregulation of these pathways is characteristic of thyroid carcinoma and many other types of cancer. Thyroid cancer progression is influenced by various receptors that include hormone receptors like thyroid hormone receptor (TR), and estrogen receptors (ER) (Bolf et al., 2020).

Thyroid Hormone Receptors (TR)

Vital capacity acquired by cancer cells is to sustain chronic proliferation through different pathways. Numerous cellular signaling pathways and the dysfunction of associated molecules are involved in the onset, progression, and metastasis of thyroid cancer. This work via both nongenomic and genomic mechanisms (Mousa et al., 2021). T3 primarily uses nuclear TR to mediate genomic processes. T3 binds to nuclear TRs that activate transcription of target genes. TR binds to TH response

elements (TRE) that are located in regulatory regions. However, thyroid hormones binding to the integrin αVβ3 receptor trigger the nongenomic effects by activating various signaling pathways, such as MAPK, PI3K/AKT, and Wnt-β-catenin (Jin et al., 2018).

Mutations that activate the MAPK pathway are responsible for around 70% of thyroid carcinomas, thus driving most of the cancers. Thyroid cancer is mainly caused by BRAF and RAS point mutations as well as RET/PTC rearrangements, which are regarded as driver mutations. This indicates that thyroid malignancies are dependent on MAPK activation. (Zaballos & Santisteban, 2017). The BRAF genetic mutation is the primary cause of the activation of the MAPK, which is important in the development of PTC. It has been shown that FTC and PTC are affected by activation of MAPK (ERK1/2) by functional levels of T4. Additionally, T3 nongenomically activates MAPK, but only at a supraphysiological level. (Lin et al., 2015).

In thyroid cancer, somatic mutations of PI3K/AKT are uncommon in PTC but relatively common in FTC, PDTC, and ATC. PI3K is the primary driver of the signaling pathway of thyroid cells that includes PTEN, PIK3CA, and RAS mutations. It increases the expression level and copy of AKT, PIK3CB, PDK1, and multiple kinase-related genes. RAS mutation mainly activates the PI3K/AKT pathway and is the second most common genetic mutation (Mousa et al., 2018). The PI3K/protein kinase B (AKT) is involved in several genomic and nongenomic TH activities in cancers. AKT is phosphorylated and activated when endothelial cells are incubated with T3, which boosts TRα1's interaction through non-transcriptional processes. Through TRβ1, T3 can also cause AKT phosphorylation. (Y. C. Liu et al., 2020).

The Wnt signaling system is essential for tissue regeneration and embryonic development. Cancer can be induced by mutations or dysregulation of the Wnt pathway expression. β-catenin expression was greater in ATC than in DTC; therefore, the WNT–β-catenin pathway seems to have a significant function in the aggressiveness of thyroid tumors (Xing, 2013). T3/TR signaling can suppress β-catenin/Tcf transactivation of the cyclin D1 promoter, therefore negatively regulating the Wnt pathway. T3 binding to TRβ increases the amount of β-catenin that could be degraded by weakening the β-catenin/TRβ connection. (Mullur et al., 2014). Similar to the β-catenin/TRβ connection, β-catenin also interacts with TRα1, although the results are different. The transcription of β-catenin is directly regulated by the T3-activated-TRα1 receptor, which promotes cell proliferation. (Davis et al., 2008).

Estrogen Receptors (TR)

Estrogen primarily combines with the intracellular estrogen receptor (ER) to carry out its biological function in target areas. Estrogen receptor alpha (ER-α) and beta (ER-β) are the two isoforms of estrogen receptors. The two isoforms seem to have distinct impacts on tumor cells, showing that ER-β has proapoptotic and differentiative effects while ER-has anti-apoptotic and proliferative activity. (Tafani et al., 2014). Estrogens employ their activity through both genomic and non-genomic signaling. The classical or genomic mechanism of action of estrogen can control target gene expression. Estrogen binds to ER to create complexes that function as ligands to activate transcription factors. Another method is that estrogen binds to membrane-associated ER (mER) to cause fast signal transduction. This non-genomic activity is exceedingly fast in contrast to gene transcription. (Dong et al., 2013). In TC cells, both ERα and ERβ are expressed. Erα expression is elevated in thyroid cancer cells, but ERβ expression is lower or nonexistent in thyroid cancer cells. ERα agonists can promote cell proliferation in thyroid cancer, but increased ERβ expression or ERβ agonist use can inhibit cell growth. (Vannucchi et al., 2015). The proportion of ERα-positive cells, or the ERα marker index, was noticeably greater in thyroid cancer than in healthy thyroid glands. Several types of thyroid carcinoma cells showed an imbalance between elevated ERα and reduced ERβ, which may change cell activity. ERs modulate PI3K/AKT/mTOR and RAS/RAF/MEK signaling pathways. (Denaro et al., 2023).

Circulating estrogen is a direct source of PI3K pathway activation and can enhance a woman's vulnerability to thyroid disease. AKT is the core of complex signal cascades, and ERα activates Akt (protein kinase B) through interacting with PI3K. Activated Akt enhances protein synthesis and cell survival via promoting the phosphorylation of downstream targets, including mTOR (Fan et al., 2015). ERβ inhibits the development of tumors by antagonizing the PI3K/Akt pathway, which lowers Akt phosphorylation. Inhibiting mTOR signaling and promoting apoptotic pathways slows the progression of cancer. In thyroid cancer cells, aberrant estrogen-induced PI3K/AKT/mTOR pathway activation might result in several gene alterations (Rubio et al., 2018). Thyroid cancer frequently exhibits hyperactivation of the MAPK pathway, which is a regulator of cell proliferation and differentiation. Estrogen uses cytoplasmic signals from MAPK to promote the proliferation of thyroid tumors (J. Liu et al., 2021). Thyroid cancer cell growth factor primarily controls the activity of E2, which controls the production of MAP kinase. E2 can cause MAP kinase isozymes to become highly phosphorylated. The difference between elevated ERα and decreased ERβ in PTC and ATC cells increases ERK1/2 activation (N. Wang et al., 2019).

ERα stimulates the MAPK pathway by fast, non-genomic signaling. It phosphorylates and activates the Ras-Raf-MEK-ERK cascade by interacting with cytoplasmic proteins like Src kinase. In a non-genomic action, ERβ counteracts ERα signaling to reduce MAPK pathway activation, which can prevent proliferation and promote apoptosis. (Shinderman-Maman et al., 2016). Thyroid cancer frequently exhibits dysregulation of the Wnt/β-catenin pathway, which increases proliferation and metastasis. This pathway is essential for maintaining homeostasis of cellular functions. Thyroid cancerous cells enhance the WNT/β-catenin pathways by activating the PI3/AKT pathway and phosphorylating β-catenin. (Ely et al., 2018). Estrogen increases its stability and causes nuclear translocation by preventing β-catenin from degrading. Additionally, it has direct interactions with β-catenin, increasing its transcriptional activity. ERβ promotes β-catenin breakdown and decreases its nuclear

location, which in turn reduces Wnt/β-catenin signaling. This suppresses invasion and proliferation by suppressing the expression of β-catenin target genes. (A. Geng et al., 2020).

MicroRNAs and Epigenetic Regulation

MicroRNAs, also known as miRNA or miRNAs, are small endogenous, single-stranded, and non-coding molecules with a length of 19 to 22 nucleotides. They control the expression of genes through complementary binding with miRNA at the post-transcriptional level. MiRNAs work by either degrading mRNA or by suppressing translation of mRNA (De La Chapelle & Jazdzewski, 2011). MiRNAs regulate various cell functions, such as effects on cell proliferation, development, apoptosis, and metastasis. However, their abnormal expression in several types of carcinomas has contributed to the development of tumors and progression (L. Zhu et al., 2018). MiRNAs are classified as oncogenic and tumor suppressor miRNAs. OncomiRNAs are upregulated, enhancing the progression of the cell cycle in tumor cells. Tumor suppressor miRNAs are downregulated and inhibit the cell proliferation and metastasis of tumor cells (Ghafouri-Fard et al., 2020).

Epigenetic regulation refers to alterations in gene expression that are reversible and heritable in response to outside stimuli without affecting DNA sequence. It is fundamental for understanding the pathogenesis of various diseases, including thyroid cancer. (H. Li & Wu, 2024). These processes are essential for understanding the complex mechanisms behind the development and progression of thyroid cancer. Epigenetic modifications can be mediated by three primary mechanisms, which include DNA methylation, histone modifications, and chromatin remodeling. (Golbabapour et al., 2011). The identification of epigenetic biomarkers has profound implications for the diagnosis and prognosis of thyroid cancer. Several studies, including aberrant expression of miRNAs, specific histone modification patterns, and methylation signatures, have suggested potential biomarkers. (Z. Chen et al., 2017). Recent studies have discovered a panel of DNA methylation patterns that may accurately differentiate between benign and cancerous thyroid nodules. Similarly, it has also been demonstrated that changes in histone modification patterns are markers for aggressive diseases. (Wu et al., 2023).

Epigenetic Regulation by MicroRNAs

The expression profile of miRNA is an important characteristic of epigenetic alteration. They play an important role in the pathophysiology of thyroid cancer by either downregulating tumor suppressor genes or upregulating oncogenes, which affects the onset and progression of thyroid cancer. Different miRNAs play a role in thyroid carcinogenesis and regulate the main signaling pathways linked to thyroid cancer. In thyroid cancer, miRNA expression profiles have also gained interest as diagnostic and prognostic tools. (W. Sun et al., 2024).

Chromatin Remodeling

Gene regulation and the maintenance of standard chromatin structure depend on the SWI/SNF chromatin remodeling complex. Dysregulation of its components, including BRM (SMARCA2) and BRG1 (SMARCA4), which aids in the progression of thyroid cancer (Wade et al., 2015). For instance, miRNA-155 targets ARID1A, a tumor suppressor component of the SWI/SNF complex, which is increased in PTC. When ARID1A is lost, chromatin remodeling is impaired, which results in uncontrolled cell invasion and proliferation (Singh et al., 2017). Overexpressed in PTC, miRNA-146b affects chromatin remodelers that regulate nucleosome dynamics, which promotes progression of thyroid cancer and oncogene transcription (Acuña-Ruiz et al., 2023).

DNA Methylation

Various miRNAs abnormally silenced are involved in DNA methylation, histone acetylation, and H3K4me3 modifications. Several studies have demonstrated that aberrant methylation of CPG islands next to their promoters can mute tumor suppressor miRNAs, including miRNA-203. In human malignancies, miRNA-203 can become inactive by both genetic and epigenetic pathways. DNMT expression is regulated by miRNAs, which in turn affect DNA methylation indirectly (Taufiqul Arif et al., 2020). MiRNAs directly target several key components of the epigenetic apparatus, such as DNA methyltransferases, histone deacetylases, and histone methyltransferases. For instance, miRNA-29b directly targets DNMT3A and DNMT3B and indirectly targets DNMT1 to cause global hypomethylation in thyroid carcinoma. Tumor growth is slowed as a result of the reactivation of tumor suppressor genes. (Yao et al., 2022).

Histone Modifications

The aggressiveness and development of thyroid cancer have been associated with abnormal production of histone methyltransferases and histone deacetylases (HDACs). For instance, aggressive tumor behavior is linked to elevated expression of HDAC in anaplastic thyroid cancer. (Morales et al., 2017). For example, miRNA-449a increases histone acetylation and promotes the tumor suppressor genes by downregulating HDAC1. This regulation impacts thyroid cancer cells' apoptosis and cell cycle regulation. (Han et al., 2020).

Hormonal Regulation by MicroRNAs

MiRNAs regulate gene expression and bind to miRNA response sites on target protein-coding and non-coding transcripts to control their expression. Numerous studies have demonstrated the link between the progression of thyroid cancer and loss of thyroid cell differentiation and the dysregulation of miRNA expression (Zembska et al., 2019). It has been shown that miRNAs can directly control genes that code for hormones or other enzymes. It indirectly alters transmission of hormone-mediated cell signals by targeting hormone antagonists or receptors, or could be regulated by hormones (Aranda, 2021). Different miRNAs play a role in thyroid carcinogenesis, which regulate the main signaling pathways linked to thyroid cancer. A strong relationship between dysregulation of miRNAs and thyroid cancer has been reported in PTC (Armos et al., 2024). Some of these miRNAs, which play an important role in thyroid cancer, are given below.

miRNA-221-222 Cluster

The highly homologous miRNAs miRNA-221 and miRNA-

222 are among the most extensively researched miRNAs. In humans, they are encoded together on the X chromosome. They belong to the first class of miRNAs known to be dysregulated in thyroid carcinoma. They are widely recognized for targeting and suppressing tumor suppressor genes through dysregulation in a variety of cancers. All thyroid cancers arising from follicular cells have been shown to have them upregulated. (Liang et al., 2018). It has been demonstrated that the miRNA-221-222 cluster interacts with p27, RECK, and PTEN in ATC and that it adversely regulates p27 in PTC. They control cell cycle and apoptosis and are downstream of the MAPK pathway. PTC cell lines' cell proliferation is inhibited when specific miRNAs are blocked, while their overexpression increases the capacity to form colonies (Acibucu et al., 2014). In thyroid cancer, upregulation of the miRNA-221-222 cluster is linked to a poor prognosis, a more aggressive course of the illness, and an increased incidence of therapy resistance and recurrence. (Kondrotienė et al., 2020).

miRNA-146

The miRNA-146 family comprises miRNA-146a and miRNA-146b. In thyroid cancers, miRNA-146 was shown to be upregulated in PTC, FTC, and ATC, but interestingly not in poorly differentiated thyroid carcinoma (N. Li et al., 2019). The PTEN/PI3K/AKT oncogenic pathway is modulated by miRNA-146b, which in turn affects the aggressiveness of thyroid tumors. The PI3K pathway's negative regulator, phosphatase and tensin homolog (PTEN), is a direct target of miRNA-146b, which stops PTEN from inhibiting PI3K pathway activity. Furthermore, NIS and PAX8 are two genes necessary for thyroid differentiation and iodide absorption, which are suppressed by miRNA-146b (Ramírez-Moya et al., 2018). The BRAF mutation has a strong correlation with miRNA-146b. Elevated expression of this miRNA causes thyroid cancer to often invade adjacent tissues in tumors with the BRAFT1799A mutation (Gómez-Pérez et al., 2019).

miRNA-200 Family

The genes miRNA-200a, miRNA-200b, and miRNA-200c make up the miRNA-200 family and are transcriptionally regulated by TP53. This family controls tumor growth and metastasis, in addition to preserving epithelial characteristics in cells or tissues. It was suggested that their downregulation in ATC might enhance the EMT brought on by the TGFβ and EGFR pathways (Z. Zhang et al., 2012). MiRNA-200 is persistently increased in well-differentiated thyroid cancers. The distinct downregulation of miRNA-200 in ATC in comparison with benign and well-differentiated thyroid tumors may serve as a prognostic and diagnostic marker (Pishkari et al., 2018). Overexpression of miRNA-200c stimulates PTC cell migration and proliferation in vitro, whereas downregulation of miRNA-200c has the opposite inhibitory impact. Bioinformatics investigation revealed that miRNA-200c bound to the 3-UTRs to reduce PTEN expression. So, miRNA-200c has an oncogenic function by negatively regulating PTEN (Guo et al., 2021).

miRNA-181

In thyroid cancer, miRNA-181a has an oncogenic function. It suppresses apoptosis and stimulates cell cycle progression by targeting RB1. Thyroid cancer tissues exhibited a markedly elevated expression level of miRNA-181a in contrast to the surrounding tissues. (Samsonov et al., 2016). Reduction of miRNA-181b expression results in increased apoptosis and suppression of cell growth in thyroid cancer cells. Its target gene is cyclin D1 (CYLD1), and thyroid cancer can be diagnosed and treated by reducing the expression of this miRNA (X. Geng et al., 2024). The miRNA-181a stimulates angiogenesis by blocking SRCIN1 through the SRC/VEGF signaling pathway. According to a study, miRNA-181a promoted NF-κB signaling, which triggered the pathogenesis of diffuse large B-cell lymphoma. (C. X. Sun et al., 2022).

Let-7

Let-7 family (let-7a, let-7b, let-7c, let-7d, let-7e, let-7f, let-7g, and let-7i) is an important tumor suppressor in various cancers. Let-7 family genes are among the most expressed miRNAs in normal thyroid glands. Let-7 family expression is downregulated in all thyroid cancers that start from follicular cells. (Perdas et al., 2016). Thyroid cancer cells have also been shown to exhibit this pathway, with RAS activation and downregulation of some let-7 family members. Expression of Let-7 serum levels in thyroid cancer was significantly different when compared with benign tissues. (Zabegina et al., 2020). Let-7d has a tumor-suppressive effect on the disease by dramatically reducing thyroid carcinoma cells' survival, invasion, and migration. DIO3OS directly targeted let-7d, and let-7d specifically targeted NF-κb2. Let-7d expression was significantly elevated in thyroid cancer cells upon DIO3OS knockdown. (M. Wang et al., 2021).

Therapeutic Implications of MicroRNAs

Standard treatment approaches for thyroid cancer include thyroid hormone suppression medication, radioactive iodine therapy, and surgical resection. However, there are fewer therapeutic choices available when the cancer progresses or develops resistance to these conventional therapies. (Davalos et al., 2012). Studies have revealed that these therapies greatly slow the progression of disease, but they do not eliminate the malignancy. This restriction highlights the need for new therapeutic strategies to control and overcome difficulties posed by advanced thyroid malignancies. (Bhattacharya et al., 2023). Targeting miRNAs to modulate hormonal pathways has emerged as a promising therapeutic strategy due to their regulatory role in tumor progression and resistance to treatment. MiRNAs contribute to regulating hormonal pathways through a variety of mechanisms. (Toden et al., 2021). Specific miRNAs function as tumor suppressors by inhibiting the proliferation of cancer cells and modulating hormone signaling. In thyroid cancer, their expression is frequently downregulated. In cancer patients with low expression of tumor suppressor-miRNAs, replacing downregulated miRNAs with several gene targets in oncogenesis may be an appealing therapeutic approach. (Reid et al., 2016).

miRNA Mimics

Recently, oligonucleotide-based mimics are now the most popular method for synthetically overexpressing target miRNAs and inhibiting miRNA expression. The synthetic

double-stranded RNA that makes up miRNA mimics miRNAs to bind to target genes and re-expresses silenced tumor-suppressive miRNAs or tumor suppressor genes, which prevents the growth and progression of cancer cells and restores regular expression. (Sousa & Conde, 2022). Several well-characterized miRNAs are now in early-phase clinical testing. One such example is miRNA-7, which inhibits the development of thyroid cancer by focusing on IRS2, an upstream PI3K/AKT pathway. Preclinical studies have revealed a considerable inhibition of tumor development when miRNA-7 mimics are delivered. (Gu et al., 2023). The miRNA-34a is a tumor suppressor miRNA that targets key oncogenes, including NOTCH and SIRT1. Mimics of miRNA-34a was demonstrated to decrease tumor growth, which in turn decreased tumor growth. (Kalfert et al., 2020).

Epigenetic Reactivation

Epigenetic modifications of thyroid carcinoma have wide-ranging and intricate therapeutic consequences. Patients with thyroid cancer may see significant improvements in their prognosis if these epigenetic drugs are incorporated into individualized therapy plans. The expression of suppressed tumor-suppressive miRNAs can be restored by epigenetic drugs such as histone deacetylase inhibitors (HDACis) and DNA methyltransferase inhibitors (DNMTis) (X. Zhu & Cheng, 2017). DNMTi drugs are used to degrade DNMT and permanently inhibit its enzymatic activity. The use of this application as an epigenetic regulatory agent to suppress oncogene expression and epigenetic mutations is well known. HDACi changes histone lysine acetylation and deacetylation, and deacetylation is known to contribute to the aberrant expression of genes in cancer. Therefore, HDACis can be used to reverse the genesis and development of cancer by promoting differentiation, inhibiting cell proliferation, and inducing death (K. Zhang et al., 2023). For example, epigenetic reactivation with DNA methyltransferase inhibitors (DNMTis) of miRNA-200 family suppresses EMT and metastasis, has been explored as a therapeutic approach in thyroid cancer (H. Zhang et al., 2022).

MicroRNAs as Diagnostic Biomarker

In poorly differentiated, medullary, and anaplastic thyroid carcinomas, early cancer identification is essential to increasing the chance of a successful course of therapy and prolonging patient survival. Fine needle aspiration biopsy is the gold standard for thyroid cancer initial diagnosis, but it still has a high incidence of non-diagnostic findings. 10-40% of thyroid nodule FNA cytology results are ambiguous, resulting in a follow-up FNA a few months later (Ferraz, 2018). Delays in final therapy and care are caused by the difficulties in making a precise diagnosis for cytologically indeterminate FNA. MiRNAs have attracted attention as a novel research target for possible diagnostic biomarkers of thyroid cancer. (Macvanin et al., 2023). MiRNAs have immense potential as diagnostic biomarkers due to their stability and detectability in bodily fluids. The miRNA-146a-5p, miRNA-21, miRNA-199b-3p, miRNA-579, miRNA-95, miRNA-29b, miRNA-190, miRNA-25-3p, and miRNA-451a have diagnostic importance that has been shown by different studies (Park et al., 2021). A research study compared the serum expression levels of miRNAs in PTC samples with those in the benign nodule group. PTC tumors were shown to have higher blood levels of miRNA-222, miRNA-221, miRNA-199b-3p, and miRNA-21 than benign nodules, while let7b-5p and miRNA-10a-5p were down-regulated (Bielak et al., 2023). Another study found that the MTC group had higher blood levels of miRNA-222-3p and miRNA-17-5p, which were able to distinguish MTC from the benign nodule group and healthy controls. (Ricci et al., 2023).

CONCLUSION

In this review, the relationship of miRNA-mediated epigenetic regulation in hormonal pathways to the progression of thyroid cancer has been elaborated. Hormonal pathways driving thyroid cancer growth are critically regulated by miRNA. MiRNAs contribute to the regulation of tumor cell growth and differentiation, and are persistently involved in drug resistance. The patterning of miRNA-based treatments/modifiers for targeting classic systemic treatments could represent an effective means to modulate hormonal pathways related to thyroid cancer progression. Alterations of miRNA expression level may also provide the basis for identifying new miRNA targets, which influence hormonal pathways, and could be a novel therapeutic target for advanced thyroid cancer. With the help of advanced tools such as CRISPR/Cas9 genome editing, researchers can seek out previously unknown miRNAs with functional importance that contribute more to epigenetic regulation. These findings may lead to the possibility of accurate miRNA-based therapies for the recovery of hormonal sensitivity and ultimately better clinical outcomes for thyroid cancer patients. Targeting the miRNAs involved in the regulation of hormonal pathways, we may come closer to more efficient therapies and the understanding of the molecular drivers in the progression of thyroid cancer. Shortly, we anticipate that miRNA will be used as therapeutic targets and diagnostic indicators in thyroid cancer.

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