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" *The role of micro-RNA 155 and 429 in diagnosis of thyroid tumors*"

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ABSTRACT:

The thyroid gland, located in the anterior neck, is essential for controlling metabolism, growth, and calcium homeostasis through the secretion of triiodothyronine (T3), thyroxine (T4), and calcitonin. Cancer of the thyroid represents the most prevalent endocrine malignancy, with papillary thyroid carcinoma accounting for over 80% of cases. Its incidence has significantly increased globally, particularly among women, due to factors including estrogen receptor involvement and improved diagnostic techniques. The recent WHO Classification of Endocrine and Neuroendocrine Tumors (5th edition) has refined the categorization of thyroid neoplasms based on molecular profiles and biological behavior, distinguishing benign, low-risk, and malignant follicular cell–derived tumors.

Diagnosis of thyroid nodules typically involves clinical examination, thyroid function tests, ultrasound, and fine-needle aspiration cytology (FNA), while molecular biomarkers have emerged as powerful tools to enhance diagnostic accuracy and guide treatment strategies. Among non-coding RNAs, microRNAs (miRNAs) have gained attention for their regulatory roles in tumorigenesis, acting as oncogenes (oncomiRs) or tumor suppressors. Dysregulated miRNA expression causes cancer initiation, progression, and therapeutic resistance. miR-155 functions as an oncomiR, promoting cell proliferation and metastasis in thyroid and other cancers, while miR-429, a member of the miR-200 family, exhibits tumor-suppressive properties by inhibiting proliferation, invasion, and epithelial–mesenchymal transition.

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Evidence suggests that circulating miRNAs, particularly miR-155 and miR-429, hold promise as less invasive biomarkers for early detection, therapeutic monitoring of thyroid cancer, and prognosis. Future clinical applications may incorporate these miRNAs alongside conventional diagnostic approaches to improve patient outcomes.

Keywords: Thyroid cancer, miRNA 155, miRNA 429, miRNA biogenesis

Introduction

Anatomy and function of thyroid gland

The thyroid gland is a midline structure situated in the anterior neck, including an isthmus that connects two lobes over the upper trachea at the level of the second and third tracheal rings (Allen & Fingeret, 2025). It has an essential role in regulating metabolism, growth, and overall development. The gland supports various physiological processes through the continuous release of thyroid hormones into the circulation. The primary hormones secreted by the thyroid are thyroxine (T4) and triiodothyronine (T3), which are classified as true thyroid hormones. Calcitonin, produced by the parafollicular C-cells, is involved in calcium and bone metabolism (Al-Suhaimi & Khan, 2022; Shahid et al., 2025).

Classification of thyroid tumors

According to the WHO Classification of Endocrine and Neuroendocrine Tumors (the 5th edition), thyroid tumors are categorized into newly defined groups that enhance the study of the pathologic characteristics, such as cytopathology and histopathology, and the cell of origin, molecular profiles, and biological behavior. Most thyroid neoplasms are derived from follicular cells. In the updated classification, these tumors are divided into benign, low-risk, and malignant neoplasms (Baloch et al., 2022).

Benign tumors include not only follicular adenomas but also clinically and diagnostically significant adenoma variants, such as those with papillary architecture, often hyperfunctional, and oncocytic adenomas. Low-risk neoplasms comprise hyalinizing trabecular tumor, thyroid tumors of uncertain malignant potential, and non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). Follicle cell-derived malignant tumors are categorized based on their molecular traits and biological activity. Papillary thyroid carcinomas (PTCs), encompassing multiple Particular types of morphology, are predominantly categorized as *BRAF*-like tumors. In contrast, follicular thyroid carcinoma and invasive encapsulated follicular variant PTC are typically classified as *RAS*-like malignancies (Baloch et al., 2022).

The most prevalent endocrine system cancer is thyroid cancer(F. Zhang et al., 2024). Its incidence in women is approximately threefold higher than in men, a disparity likely attributable to the role of estrogen receptor development and proliferation in the carcinogenic process. Between the 3rd and 4th decades of life, the largest prevalence is noted(Mahmoudian-Sani et al., 2017). Globally, the occurrence of thyroid cancer is rising; it is now the fifth most common malignancy to be diagnosed in the United States (Shank et al., 2022). In the United Kingdom, incidence rates have more than doubled since the 1970s and are projected to increase by 74% between 2014 and 2035 (Elbalka et al., 2021).

Most thyroid cancer cases (80%) originate from PTC and represent the most common subtype in regions with Diets that include too much or too little iodine. Its incidence is steadily increasing, predominantly presenting as a sporadic tumor. Although the underlying causes remain unclear, this may reflect the improvements in diagnostic techniques enabling earlier detection. PTC is most frequently diagnosed between the 3rd and 5th decades of life, with an average age of onset around 40 years. Women are affected more frequently than males, and the incidence increases with age; female-to-male ratios have been observed to range from 2:1 to 4:1(Abdullah et al., 2019)**.** Most patients experience favorable prognoses following surgical resection and radioactive iodine therapy; however, a subset develop recurrent or metastatic disease, which is associated with diminished survival rates (F. Zhang et al., 2024).

Diagnosis of Thyroid Nodules

Clinical History

A medical history that suggests a higher risk of thyroid cancer involves a thyroid nodule's rapid growth, previous External radiation beam therapy for the head and neck (especially during childhood), A family history of thyroid cancer, and exposure to whole-body radiation (for example, prior to bone marrow transplantation)(Giovanella et al., 2024).

Clinical Examination

Palpation of the thyroid gland is typically the initial clinical examination, but its sensitivity for detecting thyroid nodules is low, ranging from 2% to 6%. The majority of thyroid cancerous nodules don't cause any symptoms, though certain clinical features are linked to a higher risk of malignancy. These consist of firm and fixed nodules, nodules exceeding 4 cm in diameter, cervical lymphadenopathy, obstructive symptoms,

dysphonia, and vocal cord paralysis. Notably, the coexistence of a solitary nodule, cervical lymphadenopathy greater than 1 cm, and vocal cord paralysis confers an almost 100% positive predictive value (PPV) for thyroid cancer (Giovanella et al., 2024).

Laboratory Medicine

Thyroid function is reliably evaluated through the measurement of thyroid-stimulating hormone (TSH) and free thyroid hormones (i.e., free thyroxine (FT4) and free triiodothyronine (FT3). Among these, the most sensitive and precise diagnostic procedure for identifying thyroid disorders is TSH testing(Giovanella et al., 2024).

Thyroid Ultrasound

In the context of clinical care, US serves as the initial imaging modality for evaluating Nature and structure of the thyroid, owing to its absence of ionizing radiation, cost-effectiveness, simple to understand , and versatility in contrast to other imaging techniques(Schenke et al., 2023).

Fine-Needle Aspiration Cytology and Cytopathology

Neck ultrasound and fine-needle aspiration (FNA) are commonly used to diagnose thyroid nodules. FNA is a first-line diagnostic method for nodule assessment that is safe, easy, and somewhat accurate(Giovanella et al., 2024; Siegel et al., 2019). Cytological findings from FNA are classified based on the Bethesda criteria, which stratifies the risk of malignancy (Schneider & Chen, 2013).

Molecular Biomarkers

Molecular biomarker analysis represents a valuable adjunct to conventional pathological evaluation of carcinomas. Numerous molecular markers have been identified and applied in the development of precise diagnostic means and new therapeutic approaches. These biomarkers are derived from analyses of Sequences of genes for RNA-based tests, gene expression profiling, gene rearrangements, gene mutations, and immunohistochemistry (D. Wu et al., 2020). Roughly 75% of the human genome is made up of RNA, yet only around 3% encodes protein-coding mRNAs (Kimura 2020). Non-coding RNAs (ncRNAs) are categorized according to their length, structure, and placement into distinct categories, among which microRNAs (miRNAs), PIWI-interacting RNAs (piRNAs), long ncRNAs (lncRNAs), and circular RNAs (circRNAs) constitute the four principal types, each possessing unique functional roles in cancer biology (Vos et al., 2019).

miRNAs are non-coding short RNAs, typically having a nucleotide sequence of 19 – 24 bases in length that control gene expression by binding to specific mRNAs targets, most commonly at the 3′ untranslated region (3′-UTR) of the transcript. However, alternative, less conventional binding sites have been identified. One mRNA can be targeted by many miRNAs, and conversely, a single miRNA can target several mRNA targets. Beyond their role in post-transcriptional regulation, miRNAs participate in intercellular communication between the surrounding microenvironment of the tumor (TME) and the cancerous cells. This bidirectional interaction between tumor cells and TME components can directly influence various aspects of cancer biology (Vannini et al., 2018).

Various biological processes, including angiogenesis, migration, apoptosis, differentiation, cell division, and oncogenesis, are regulated by miRNAs. The genes encoding miRNAs are located within the introns or exons of protein-coding genes, as well as in intergenic regions, often situated in genomically unstable areas. As they do not encode proteins, miRNAs are classified as non-coding RNAs (Smolarz et al., 2022).

miRNAs' biogenesis and effector mechanisms

At first, RNA polymerase II transcribes miRNAs as pri-miRNAs. The Drosha complex processes these pri-miRNAs to create pre-miRNAs, which are then transported via exportin 5 (XPO5) to the cytoplasm. Dicer, an RNase III endonuclease, identifies the pre-miRNA in the cytoplasm when it binds to the HIV-1 TAR RNA binding protein (TRBP, also known as TARBP2). Dicer removes the pre-miRNA's terminal loop, generating a miRNA-miRNA* duplex, where the “miRNA*” denotes the passenger strand paired to the miRNA. The Ago N-terminal domain then loads this duplex into an Argonaute (Ago) family protein and unwinds it. The nucleotide composition of the duplex influences strand selection during loading into Ago complexes. Typically, the passenger strand (miRNA*) is degraded. In contrast, the guide strand is retained to form the mature miRNA, which assembles into the functional RNA-induced silencing complex (RISC), as illustrated in **Figure 1**(He et al., 2020; Yan & Bu, 2021).

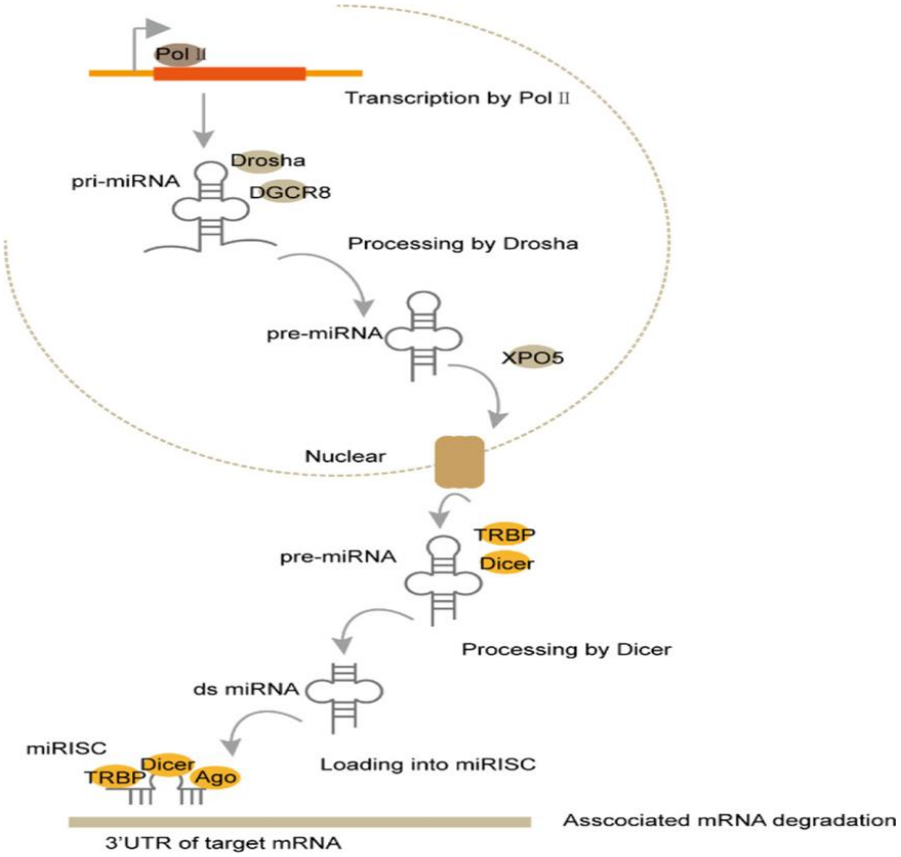

Figure1. The biogenesis and effector machineries of miRNAs (Yan & Bu, 2021)

Extensive research has demonstrated the crucial role of miRNAs in the pathogenesis of cancer. Based on their functional impact, miRNAs can be categorized into **oncomiRs** and **tumor-suppressor miRNAs.** OncomiRs inhibit the translation of tumor-suppressor genes and promote uncontrolled tumor cell proliferation through constitutive overexpression. In contrast, tumor-suppressor miRNAs inhibit tumorigenesis and progression by suppressing the translation of mRNAs encoding oncogenes, as shown in **Figure 2** (Chakrabortty et al., 2023). Furthermore, Depending on the kind of tumor cell, many miRNAs have two distinct roles: they can either function as oncomiRs or as tumor suppressors(Otmani et al., 2022).

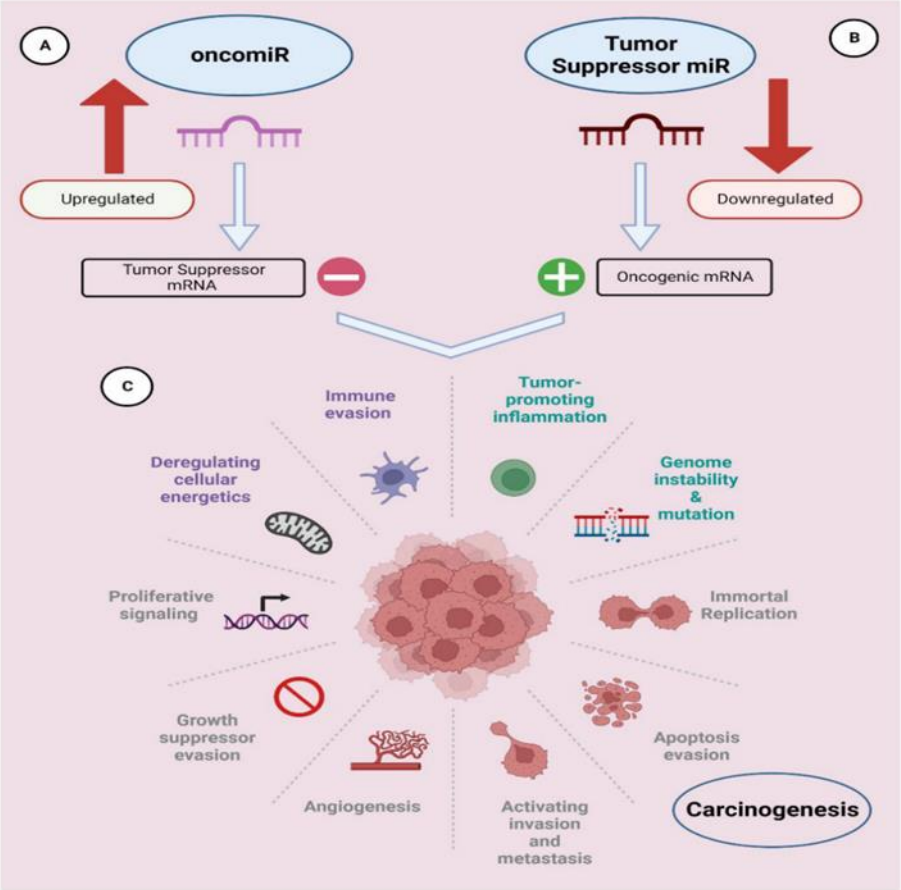

Figure 2miRNAs are categorized as tumor suppressors and oncomiRs (Chakrabortty et al., 2023).

Mechanisms behind aberrant miRNA expression in tumors

Over recent years, expression abnormalities of miRNAs have been demonstrated in a wide range of neoplasms. The underlying mechanisms of miRNA dysregulation mainly include chromosomal abnormalities, such as defects in the miRNA biogenesis pathway, epigenetic dysregulation, altered activity of transcription factors, and amplification or deletion of miRNA genes. Additionally, competitive endogenous RNAs (ceRNAs) can decrease intracellular miRNA levels (Hussen et al., 2021).

miRNA in thyroid cancer

In the past years, great focus has been placed on assessing the potential of miRNAs as diagnostic biomarkers for thyroid cancer. Emerging evidence indicates that dysregulated miRNA expression plays a crucial role in the development, progression, and overall pathogenesis of the disease. Previous investigations analyzing miRNAs in

FNA samples have identified specific miRNAs implicated in thyroid cancer development (Mahmoudian-Sani et al., 2017). Depending on their target genes and their influence on critical oncogenic signaling pathways, miRNAs may function either as oncomiRs or tumor suppressor miRNAs (Klicka et al., 2022).

Given that tumors abnormally express miRNAs, analyzing patterns of miRNA expression and detecting their proportional expression in cancer patients' plasma holds promise for predicting prognosis of cancer in a diagnostic way. Advances in biotechnology have significantly enhanced detection sensitivity and expanded the range of kinds of identifiable samples, from fresh frozen tissue and formalin-fixed paraffin tissue to miRNA present in body fluid, thereby greatly facilitating the clinical application of miRNA-based diagnostics (Shi et al., 2021).

1.OncomiRs in thyroid cancer

Many studies have illustrated the involvement of several miRNAs in the pathogenesis of thyroid cancer. OncomiRs contribute to tumor development by downregulating the expression of multiple tumor-suppressor genes, thereby promoting cell proliferation and the progression of the cell cycle (Ghafouri-Fard et al., 2020). OncomiRs' overexpression in malignant cells has been correlated with the development of cancer of several types. It holds potential as a biomarker for detecting tumor initiation and monitoring cancer progression (Otmani et al., 2022).

miRNAs such as 146a, 146b, 221, 222, and miR-595 have been commonly found to be elevated in samples of PTC **tissue** (Chou et al., 2017; Mardente et al., 2015; Mei et al., 2016).

Inflammation-driven signaling molecules can elevate miR-155 expression in cancerous cells. miR-155 has been recognized as an oncogenic microRNA (oncomiR), meaning it promotes cancer development by enhancing cell proliferation, survival, and metastasis in T-cell lymphoma and various solid tumors. Its role in promoting malignant transformation appears to be context-dependent, impacted by the target genes' expression levels and the particular cellular environment (Mahesh & Biswas, 2019).

Zhang et al. reveal that miR-155's activity is correlated with extrathyroidal invasion and cervical metastases. The suppression of miR-155 was linked to considerable SOCS1 overexpression. Furthermore, according to luciferase reporter tests, miR-155 may

attach to SOCS1 3′-UTR, impairing its stability and ultimately reducing SOCS1 levels(W. Zhang et al., 2019).

Geng et al. indicate that an increase in miR-155-5p influences the development and progression of thyroid follicular carcinoma. The aberrant expression of MiR-155-5p could control cell apoptosis (Geng et al., 2020).

2. Tumor suppressor miRNAs in thyroid cancer

Tumor suppressor miRNAs avoid the initiation of cancer by modulating the expression of oncoproteins coding genes. Various studies have shown that the downregulation of some miRNAs is associated with the progression of cancer. Their abnormal underexpression could lead to cellular processes abnormalities, including enhanced cell growth, increased apoptosis, invasion, and metastasis, and decreased sensitivity to treatment through harmful suppression of oncogene function (Otmani & Lewalle, 2021).

miR-7, miR-335, miR-144, and miR-126 are examples of tumor-suppressive miRNAs that are discovered to be suppressed in PTC tissue samples (Hua et al., 2016; Kan et al., 2017; Salajegheh et al., 2016; Sun et al., 2018).

While data on serum miR-429 in thyroid malignancies is minimal, a single study has been done to discover the effect of miRNA-429 on the thyroid. Fifty-nine cases of thyroid cancer specimens and their corresponding healthy tissues were collected. The study noticed that miR-429 expression was considerably downregulated in tissues of thyroid cancer, and it has been demonstrated to increase apoptosis while inhibiting cell invasion and proliferation(G. Wu et al., 2019).

miR-429 is a member of the miR-200 family. Their amount is changed in cancer patients' body fluids, and their expression is dysregulated in cancerous tissue. Furthermore, the levels of members of the miR-200 family are linked to clinical characteristics, including the survival of cancer patients, suggesting that they could be helpful as prognostic and diagnostics biomarkers (Klicka et al., 2022)

This is previous evidence suggesting a tumor-suppressive role for miR-429 in various types of cancer. As an example, according to recent research, miR-429 may decrease the number of malignancies, including those of the liver, lungs, and breast. MiR-429 may be essential for both tumor invasion and vascularization via targeting its target gene, according to in-vitro and in vivo research. One of the targets of miR-429 has been

identified as zinc finger E-box-binding homeobox 1 (ZEB1), which has been implicated in the carcinogenesis of several cancers. According to a study, miR-429 may prevent ZEB1 expression, hence preventing breast cancer from developing(G. Wu et al., 2019). Wu et al. found that tumor tissue expressing higher miR-429 correlates with better survival. Mechanistically, miR-429 suppresses EMT by reducing ZEB1/2 and β-catenin and restoring E-cadherin. Higher miR-429 predicts improved overall and recurrence-free survival. Based on these findings, miR-429 is suggested as a potential adjunctive prognostic marker in bladder cancer, complementing existing markers like tumor grade and stage (C.-L. Wu et al., 2018).

Research has demonstrated that miRNAs are compromised in cancer and crucial to the initiation and spread of the disease. Thus, looking for miRNA as a target for thyroid cancer detection or prognosis may be an effective strategy. In the near future, miRNA 155 and 429 can be measured in blood samples to act as molecular indicators for the Identification and prognosis of thyroid cancer. They can also be employed as biomarkers for prognosis and diagnosis in conjunction with other diagnostic-clinical techniques.

Conclusion and Recommendations:

Among endocrine cancers, thyroid carcinoma is the most common cancer. Early detection is crucial for improving prognosis, but it can be challenging due to its asymptomatic nature in the initial stages. Diagnosis typically involves a combination of clinical examination, ultrasonography, fine-needle aspiration biopsy, and molecular testing, including the assessment of specific biomarkers such as microRNAs. These diagnostic approaches enable accurate tumor characterization and guide treatment strategies.

Based on current evidence, miRNA-155 and miRNA-429 show promising potential as molecular biomarkers for improving Thyroid cancer diagnosis and prognosis. miRNA-155 is frequently upregulated in thyroid malignancies and has been linked to enhanced tumor growth, invasion, and metastasis, indicating its role as an oncogenic marker. Its elevated levels may aid in identifying aggressive tumor behavior and predicting poor clinical outcomes. Conversely, miRNA-429, typically downregulated in thyroid cancer, functions as a tumor suppressor by inhibiting proliferation. Incorporating these miRNAs into diagnostic workflows could complement traditional tools such as FNA

cytology and imaging, particularly in indeterminate or borderline cases. Measuring circulating levels of miRNA-155 and miRNA-429 in blood or other body fluids offers a less invasive approach for early detection, risk stratification, and post-treatment monitoring. Future clinical applications should focus on developing standardized, sensitive essays for their quantification and validating their combined use in large-scale prospective studies to establish their diagnostic specificity and prognostic value. Integrating miRNA profiling with conventional diagnostic modalities has the potential to enhance early detection, guide treatment decisions, and improve overall management of thyroid cancer patients.

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