



Review article

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MicroRNA-Tumour Microenvironment Crosstalk in Thyroid Cancer: Emerging as Diagnostic and Prognostic Biomarkers



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Abstract

Thyroid carcinoma (TC) is the most common endocrine malignancy, with a steadily increasing global incidence. While most cases are indolent, a subset, including poorly differentiated and anaplastic thyroid carcinomas, exhibits aggressive behavior, therapeutic resistance, and poor prognosis. Emerging evidence highlights the pivotal role of microRNAs (miRNAs) in regulating tumor initiation, progression, and the dynamic interactions within the tumor microenvironment (TME). miRNAs act as post-transcriptional regulators of key oncogenic pathways, immune checkpoints, stromal signaling, angiogenesis, and extracellular matrix remodeling. In thyroid cancer, dysregulated miRNAs promote immune evasion by modulating PD-1/PD-L1 signaling, macrophage polarization, and T-cell infiltration.

Beyond immune regulation, miRNAs influence stromal-tumor crosstalk, fibroblast activation, and VEGF-mediated angiogenesis, contributing to a pro-tumorigenic microenvironment. Circulating miRNAs have also emerged as promising non-invasive biomarkers for diagnosis, prognosis, and disease monitoring. Additionally, miRNA-based therapeutics, including mimics and inhibitors, offer novel strategies to restore tumor-suppressive pathways or inhibit oncogenic signaling. However, challenges such as delivery efficiency, specificity, and off-target effects limit their clinical application. This review highlights the multifaceted roles of miRNAs in thyroid cancer TME and underscores their potential in advancing precision-based therapeutic approaches.

Keywords: Thyroid Cancer; microRNAs; Tumor Microenvironment; Immune Modulations; Biomarkers; Therapeutic Targets

Abbreviations: TC: Thyroid carcinoma; PTC: Papillary Thyroid Carcinoma; DTC: Differentiated Thyroid Cancers; TME: Tumor Microenvironment; CAFs: Cancer-Associated Fibroblasts; TILs: Tumor-Infiltrating Lymphocytes; ECM: Extracellular Matrix; miRNAs: microRNAs; CAFs: Cancer-Associated Fibroblasts; APC: Antigen-Presenting Cells; PTC: Papillary Thyroid Carcinoma; TME: Tumor Microenvironment; CAFs: Cancer-Associated Fibroblasts; MDSCs: Myeloid-Derived Suppressor Cells; DCs: Dendritic Cells; CTL: Cytotoxic T Cell; ATC: Anaplastic Thyroid Carcinoma; ROS: Reactive Oxygen Species; EMT: Epithelial-Mesenchymal Transition; TAMs: Tumour-Associated Macrophages; TSP-1: Thrombospondin-1; VEGF: Vascular Endothelial Growth Factors; FTUMP: Follicular tumour of uncertain malignant potential; AUCs: Area Under the Curve; ATA: American Thyroid Association; LNA: Locked Nucleic Acid; TKIs: Tyrosine Kinase Inhibitors; IRAES: Immune-Related Adverse Events

Introduction

Thyroid Cancer (TC) is the most common among all the endocrine malignancies [1], and over the past few decades, the incidence of thyroid carcinoma cases has been globally rising. The differentiated thyroid cancers (DTC), especially papillary thyroid carcinoma (PTC) have a favorable prognosis, however, a subset of patients develops aggressive disease characterized by lymph node metastasis, recurrence, and therapeutic resistance [2]. Increasing evidence suggests that these variations in tumor behaviour

cannot be unfolded by tumor cell-intrinsic factors alone but are strongly influenced by the surrounding tumor microenvironment (TME) [3].

The TME comprises of diverse cellular, acellular and molecular components, including tumor-infiltrating lymphocytes (TILs), macrophages, cancer-associated fibroblasts (CAFs), endothelial cells, and extracellular matrix (ECM) elements [4-7]. Within this complex network, microRNAs (miRNAs) which are small non-

coding RNAs of about 18-25 nucleotide in length, that regulate gene expression at the post-transcription level. MicroRNAs have attracted great attention since last decade and emerged as a crucial regulator of gene expression as well as intercellular communication. The aberrant expression of various miRNAs has been documented in thyroid cancers, where they act as either oncogenes (oncomiRs) or tumor suppressors miRNAs [8]. Interestingly, miRNAs do not act in isolation within tumor cells; they actively mediate crosstalk between cancer cells and immune microenvironment [9].

The function of miRNAs as molecular messengers within the thyroid cancer ecosystem is highlighted by this reciprocal or two-way communication. They orchestrate pathways that govern immune modulation (e.g. PD-1/PDL-1 signaling, Treg expansion), angiogenesis, and ECM remodelling, ultimately determines tumor behaviour [4,10,11]. Furthermore, the stability of circulating

miRNAs in body fluids makes them attractive candidates as non-invasive biomarkers for risk stratification and prognosis in TC [12]. Thus, by understanding the interplay between miRNAs and the TME with dual role of microRNAs as regulators and messengers is essential for unravelling the mechanisms underlying thyroid cancer aggressiveness. This review focuses and discusses on the emerging evidence of miRNA-TME crosstalk in thyroid cancer, highlighting their role as potential biomarkers and therapeutic targets.

Tumor Microenvironment in Thyroid Cancer

There is a heterogeneous histological zone where cancerous cells interact with normal cells. Majorly there are three components which include: i) Cellular components, ii) Extracellular Matrix, iii) Soluble factors. Figure 1 shows representation of tumour microenvironment and their effect on tumour cells.

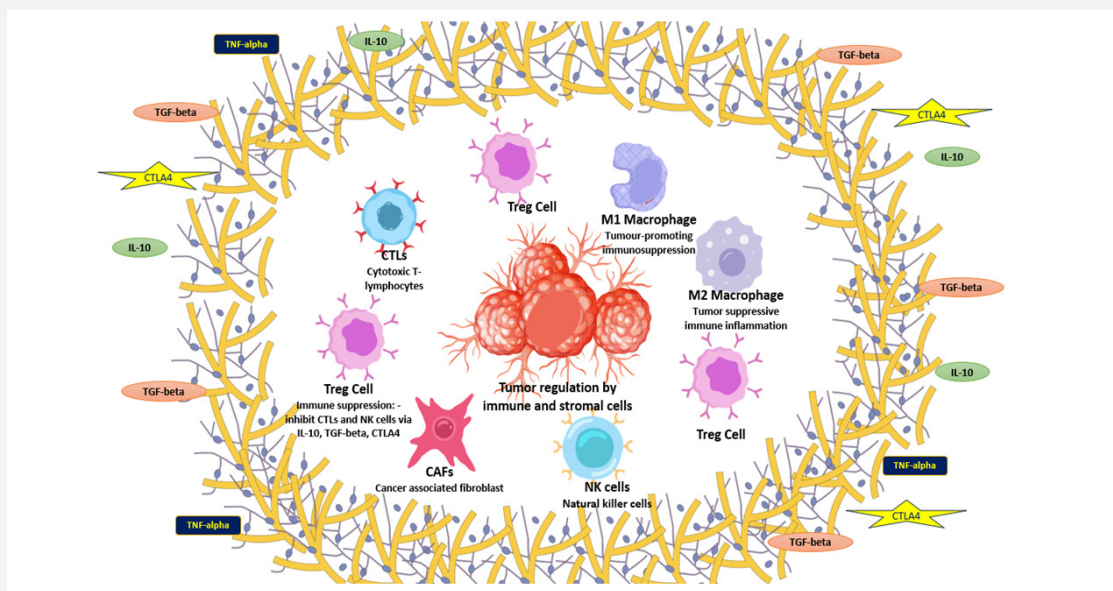


Figure 1: Pictorial depiction of Tumor immune microenvironment.

Cellular Components are Composed of Immune Cells, Fibroblasts, Myofibroblasts, Endothelial Cells, Adipocytes and CAFs.

- **Immune cells:** Thyroid cancer unable to grow in isolation; it evolves under constant immune surveillance, dynamic interaction, and escape. Immune cells shape the TME in TC. As there are two kinds of immune cells present in microenvironment: pro-tumorigenic and anti-tumorigenic, showing properties of cancer progression and elimination respectively. Pro-tumorigenic cells include Tregs, M2 macrophages, myeloid-derived suppressor cells (MDSCs), mast cells; which derive immune suppression and help cancer cells to escape immune environment. Anti-tumorigenic cells include primarily CD8+ T cells, NK cells, M1 macrophages and certain activated dendritic cells (DCs); which helps in tumour

killing and immune surveillance.

- **Cytotoxic T cell (CTL)s:** These are the key player in anti-tumour immunity by infiltrating tumour and initiating cell death. In PTC with LT, CD8+ cells dominantly present as compared to Tregs; correlating with anti-tumour responses [13]. The CTLs infiltrate in around 83% cases of PTC with LT; showing dominance in IHC and flowcytometry as compared to Tregs [14,15]. The CD8+ CTL in TME results into non-functional due to expression of its co-inhibitory receptor PD-1, which is also a receptor for PD-L1 expressed by the tumour cells. Significant expression of PDL-1 is associated with the aggressive behaviour of PTC. Thus, PD-1/PD-L1 can be useful immunotherapeutic approach in patients of PTC with LT [15]. Certain CD8+ subsets (PD-1+CD39+CD103+ and PD-1+CD39+CD103-) are elevated in recurrent PTC, confirmed

by multiplex IHC and TCGA analysis, associated with worse recurrence-free survival.

- **NK cells:** These play a key role in anti-tumour immune surveillance against thyroid cancer and is seen in the early-stage PTC compared to normal healthy thyroid and goitre [16]. However Anaplastic thyroid carcinoma (ATC), exhibit dysfunctional NK cell population with high CD56, high/low CD16 subsets, known to be significantly higher, but also shows PD-1 and Tim-3 exhaustion markers, which reduces cytotoxicity [16]. There is a downregulation of NKG2D receptors (triggers NK cell mediated cell cytotoxicity) on NK cells by TME factors e.g. suppressive cytokines and COX2 expression. The blocking of PD-1 and Tim-3 revitalize NK cells further results into enhancing cytotoxicity in ATC patients [16].

- **Macrophages:** There is an intricacy of macrophages' behaviour in TME, as it can either show pro-tumour immunity or anti-tumour immunity. Therefore, two different populations are formed, i.e., M1 & M2 macrophages, showing anti- & pro-tumour immunity respectively. M1 macrophages produce pro-inflammatory cytokines e.g. IL-1 β , IL-6, TNF-alpha and reactive oxygen species (ROS) to kill tumour cells; and have anti-tumour effects in thyroid cancer [17]. Higher densities of M1 macrophages with high CD8+ cells show good prognosis in early stages of PTC [14]. CIBERSORT analysis of TCGA data identifies M1-related genes (SPP1, DHR3, SLC11A1, CFB) form risk model of four gene predicting overall survival [18].

In-vivo study in Follicular thyroid carcinoma (FTC) shows that with higher M1 macrophages infiltration and tumour suppressor genes e.g. GLIPR1, further activates CD8+T cells [17]. On the other hand, M2 macrophages are tumour-associated macrophages (TAMs) exhibiting alternative polarisation, enhancing tumour progression in thyroid cancer by promoting stemness, epithelial-mesenchymal transition (EMT), invasion and metastasis [19]. The ATC patients exhibit high expression of CD68+CD206+, which further correlates with poor prognosis [17].

Whereas M2 macrophages cluster around lymphatic vessels in PTC and lymphatic invasion alongside tumor cells is enhanced by MMP-2 (Matrix metalloproteinase-2) [20]. Increase in M2 macrophages density further correlates with poor prognosis, aggressiveness, lymph node metastasis and reduced survival in thyroid carcinoma [21]. Also, M2 macrophages act as biomarkers; e.g. upregulation of CD206+ predicts worse outcomes and linked to BRAFV600E mutations. Reprogramming of M2 to M1 via Zoledronic acid, low dose of bleomycin or CSF-1R inhibitors reduces tumour growth, angiogenesis, and metastasis in preclinical PTC/ATC research studies [17].

- **CAFs:** These are important non-parenchymatic supportive cells in thyroid cancer which correlate with disease aggressiveness and progression. The CAFs expresses alpha-SMA, FAP, PDGFR-alpha, showing extrathyroidal invasion, BRAF mutation, multifocality and metastasis in PTC [22]. Substantially

higher CAFs score predicts conversion of PTC into ATC, which also includes increased expression of alpha-SMA+ cells, lymph node involvement, extrathyroidal extension, and reduced survival [23]. The CAFs show upregulation of EMT, TNF- α /NF- κ B, IL6/JAK/STAT3, and immune checkpoints pathways; resulting immune suppression [24]. Hence, CAFs can be used as therapeutic marker by targeting ECM remodelling, TGF-beta inhibitors, antagonist of invasion, metastasis and therapy resistance help in lowering tumour burden [23].

- **Tregs:** Regulatory T cells, suppress anti-tumour immunity in thyroid cancer, especially PTC, by inhibiting effector T cells and promoting immune escape [25]. A high Treg density correlates with tumour size and lymph node metastasis via mechanism through cytokine secretion (IL-10, TGF-Beta), cyclin-AMP-mediated suppression and vesicle exosome pathways [21]. The Tregs inhibit dendritic cell and CD8+ function, fostering an immunosuppressive milieu in PTC microenvironment [26].

The Foxp3+ Tregs upregulation in DTCs tumours creates local immunosuppressive environment and interaction with BRAFV600E-mutated cells further increasing this effect [27]. The CD8+/Treg ratio correlates inversely with size of tumour and lower ratio predicts worse outcomes, importantly in BRAF-mutated cases [21]. The Treg depletion or inhibition enhances immunotherapy- anti-CTLA4 or PD-1/PD-L1 blockers such as Ipilimumab, Pembrolizumab, reduces Treg suppression and improving T cell infiltration. Combining with BRAF inhibitors synergizes in BRAFV600E+ tumour by decreasing Tregs [28].

- **Extracellular Matrix:** The extracellular matrix (ECM) in TC shows extensive remodelling, and facilitate progression of cancer, especially in aggressive ATCs. The major players in this process include collagen, fibronectin, and hyaluronic acid, which interact with CAFs and immune cells in the TME. The ECM signalling is upregulated in ATC compared to normal thyroid, with increased collagen synthesis, deposition, and organization pathways evident in GEO datasets (GSE29265, GSE33630, etc.). Cancer cells and CAFs promote covalent cross-linking and massive fibrillar collagen accumulation, which increases invasion by MMPs such as MMP-2 and MMP-9 [29].

- The stromal interactions densify ECM, promoting ATC proliferation and metastasis. Abnormal ECM activation is known to be associated with a poor prognosis of ATC, increased metastasis recurrence, and resistance to treatment, while collagen isoforms and MMPs are used as biomarkers for progression of thyroid cancer. The presence of ECM in TME promotes immunosuppression by increasing the levels of Tregs, M2 macrophages, and PD-L1, indicating a poor prognosis [29]. The modulation of ECM has shown potential as a therapeutic strategy, including the use of inhibitors of collagen cross-linking (e.g., LOX inhibitors), synthesis (halofuginone), or receptors (ibrutinib for integrin), which decrease stiffness and metastasis in preclinical models of ATC [29].

• **Soluble Factors:** The soluble components of thyroid cancer microenvironment include cytokines, chemokines, growth factors, and other mediators that are secreted by the tumor cells, immune cells such as M2 macrophages and Tregs, CAFs, and endothelial cells [30]. Major soluble factors such as IL-6, IL-10, TGF- β , VEGF, PDGF, CXCL8/IL-8, CXCL10/IP-10, and thrombospondin-1 (TSP-1), are often overexpressed in PTC and ATC. The tumor with BRAF V600E-mutation, have IL-6 and PDGF secretion by CAFs and induce fibroblast reprogramming into tumor-supporting CAFs, which induce EMT by activating Src/Akt and Vimentin, and reducing E-cadherin [30].

M2 macrophages secrete IGF-1/IGF-2 to activate PI3K/AKT/mTOR pathways for stemness; Tregs secrete IL-10/TGF- β for immune suppression; mast cells secrete histamine, TNF- α , and CXCL1 for proliferation [21]. These factors contribute to CAF recruitment/activation, immune evasion (e.g., Treg cell expansion, M1 to M2 transition), lymphatic invasion (MMP induction), and drug resistance (e.g., TSP-1 secretion from pericytes confers resistance to TKIs through AKT/ERK) [5]. In ATC/PTC, they increase ECM stiffness (VEGF/collagen crosstalk) and enhance metastasis/hypoxia [29]. High expression (e.g., IL-6, TSP-1) is associated with poor prognosis, metastasis, and recurrence, consistent with M2/Treg expression. CSF-1R/CCR2 inhibitors prevent recruitment and anti-VEGF/TKI combination therapies (e.g., lenvatinib) are known to be the therapeutic targets [5,21].

Biological Functions of miRNAs in Thyroid Cancer

The miRNAs are small non-coding RNAs of about 18-25 nucleotide in length, that regulate gene expression at post-transcription level [31]. The regulation is initiated via binding of miRNAs with the complementary sequence in the 3' untranslated regions (3' UTRs) of the target mRNAs [32]. This interaction usually results in either translational repression or mRNA degradation. Through this mechanism, miRNAs play a pivotal role in diverse biological processes such as cell proliferation, differentiation, apoptosis, immune regulation, and tissue homeostasis.

Dysregulation of miRNAs in Thyroid Cancer

The expression profile of distinct miRNAs is consistently found to be dysregulated in various forms of thyroid cancer i.e., PTC, FTC, ATC and MTC. These aberrations often correlate with aggressive clinical features, including lymph node metastasis, extrathyroidal extension, and resistance to therapy [33]. In thyroid carcinoma, certain sets of miRNAs (e.g., miR-146b, miR-221, and miR-222) are oncomiRs in nature and promote tumorigenesis when overexpressed [33-35], while some miRNAs (e.g., let-7, miR-9, and miR-199a) are classified as tumor suppressors [36-38], with enhanced oncogenic signalling. Such dysregulation alters oncogenic signaling pathways, including MAPK, PI3K/AKT, TGF- β , and immune checkpoints pathways, thereby shaping the immune microenvironment.

miRNAs and Immune Modulation in Thyroid TME

The miRNAs are known to be crucial modulators of anti-tumor immunity [39] as they can directly regulate immune checkpoint molecules, shaping myeloid cell phenotype (M1/M2 polarization), and influence T-cell recruitment and effector function.

miRNAs Regulate Immune Checkpoint Molecules (PD-1/PD-L1, CTLA-4)

There are several miRNAs that have been reported to bind the 3'-UTR of immune-checkpoint mRNAs or modulate upstream signaling pathways that control checkpoint expression [40]. For example, miR-34a has been shown to directly target PDL-1 mRNA and reduce PDL-1 expression on tumor cells [41]. Reduced miR-34a is frequently associated with elevated PDL-1 and immune evasion in multiple cancers [42]. Various reviews and mechanistic studies highlight a network of miRNAs (including members of miR-200 family, miR-33a, miR-424) that regulate PDL-1 and other immune checkpoints (CTLA-4) directly or via pathways such as p53, EMT and P13K/AKT [43-45].

Similarly, Lin et. al. [31] reported a functional miR-199a-5p/PDL-1 axis in FTC, where restoring miR-199a-5p resulted in decreased PDL-1 expression and reduced proliferation and metastatic behaviours in-vitro, supporting a direct role for miRNA control of PDL-1 in FTC [46]. Additionally, profiling studies in PTC show dysregulation of miRNAs with variable PDL-1 expression, suggesting miRNA-mediated immune escape mechanism may operate in PTC as well [47]. For ATC, immunotherapy literature stresses PDL-1 as an actionable target and upstream regulators including as potential modulators of responses [48].

Since miRNAs can down-regulate PDL-1, therapeutic restoration of such miRNAs (and mimics) or blockade of miRNAs that up-regulate these immune checkpoints could sensitize tumors to checkpoint inhibitors. However, clinical translation of miRNAs requires careful delivery and safety testing [10]. The miRNA regulation of CTLA-4 in thyroid cancer is mechanistically plausible as some miRNAs influence pathways that in turn regulate CTLA-4 expression on T cells or antigen-presenting cells (APC). However, specific miRNAs directly targeting CTLA-4 mRNA in thyroid cancer remain to be validated experimentally.

miRNAs Affecting Macrophage Polarization (M1 vs M2)

The TAMs in thyroid cancer commonly display a M2-like, pro-tumor phenotype that supports angiogenesis, matrix remodeling, and immunosuppression. Published literature demonstrated that tumor-derived miRNAs, either intracellularly dysregulated or packaged into exosomes, can reprogram macrophages toward M2 polarization. For instance, tumor cell release of miR-21 rich exosomes induces M2 features in macrophages in other solid cancers [49-51] and similar mechanisms have been invoked for thyroid tumors given the frequent upregulation of miR-21 in Differentiated Thyroid Cancer [52,53].

While miR-155 is another key regulator, it classically promotes M1 polarization by dysregulation in the tumor microenvironment and expression of its host gene MIR155HG has been associated with altered macrophage phenotypes and tumor-promoting inflammation [54]. Recent experimental studies show that manipulating miR-21, miR-155 and related miRNAs can shift macrophage phenotype and modulate tumor progression observations that are mechanistically and translationally relevant to thyroid cancer TAM biology [55,56].

Influence on T Cell Infiltration and Activity

The miRNAs can indirectly influence T-cell infiltration and function through several mechanisms-i.e. (i) by regulating chemokines and adhesion molecules that control immune cell recruitment,

(ii) by modulating PDL-1/PD-1 axis (thereby affecting T-cell exhaustion), and

(iii) by shaping antigen presentation via effects on tumor or stromal cells [46].

Altered miRNA expression that elevates PDL-1 levels or promotes M2 macrophage and Tregs can suppress CD8+ T-cell infiltration and diminish their cytotoxic and cytokine producing activity [40]. Integrative transcriptomics analysis of thyroid tumors shows correlations between specific miRNA signatures and immune-cell infiltration patterns, suggesting that miRNA dysregulation contributes to the “immune contexture” of PTC and other thyroid cancers. Functional studies linking single miRNAs to alterations in cytotoxic T-cell activity are more limited in thyroid-specific models. However, converging evidence from profiling and mechanistic papers supports a role for miRNAs in determining whether a thyroid tumor microenvironment is T-cell inflamed (immune-hot) or immune-excluded (immune-cold) [57,58].

Evidence from PTC, FTC, ATC

Papillary thyroid carcinoma shows consistent dysregulation of miRNA implicated in immune modulation, including upregulation of miR-146b, miR-221/222 and miR-21. These miRNAs correlate with clinically aggressive features (lymph node and distant metastasis, higher TNM stage) [59]. Various profiling studies with immune-related pathways and PDL-1 expression patterns in tumor tissue and Fine needle aspiration (FNA) samples have established this correlation [60]. In addition, recent reviews and profiling studies integrate miRNA changes with immune cell infiltration signatures in PTC [47,58]. Follicular thyroid carcinoma exhibits a partly distinct miRNA profile, e.g., differences in miR-21, miR-181a expression. The data suggest that these miRNAs influence angiogenesis, survival and possibly immune cell behaviour [53,61].

While fewer studies specifically tie FTC-miRNAs to immune modulation compared to PTC, cross-tumor mechanistic data

and differential expression analysis indicate that FTC miRNA dysregulation can also influence TME immune features [62]. Anaplastic thyroid carcinoma is an aggressive and immune-evasive thyroid cancer, and demonstrates miRNA alterations (e.g., miR-146b) that affect proliferation, apoptosis and possibly immune interactions [63]. Functional work in ATC cell lines shows miRNA effect on cell cycle regulators and survival pathways, though immune-specific mechanistic studies in ATC are fewer. Thus, an aggressive phenotype and altered miRNA landscape imply strong TME-related immune dysregulation [8]. Several groups are exploring circulating miRNAs as minimally or non-invasive biomarkers reflecting both tumor biology and immune milieu. These markers may help stratify patients for immunotherapy or for combined miRNA+checkpoint inhibitors approaches in the future.

miRNAs and Non-Immune Components of TME

Beyond miRNA's roles in immune modulation, they significantly influence the non-immune compartments of TME, including stromal-cancer cell interactions, angiogenesis, fibroblast activation, and ECM remodeling. These processes are critical in thyroid cancer progression, metastasis, and resistance to therapy in various tumors.

miRNAs in Stromal-Cancer Cell Interactions

The crosstalk between thyroid cancer cells and surrounding stromal cells is largely mediated by soluble factors, extracellular vesicles, and direct cell-cell communication. In this network, miRNAs are the crucial molecular messengers [64]. Tumor-derived exosomal miRNAs can reprogram stromal cells to acquire a pro-tumorigenic phenotype. For instance, studies in PTC have demonstrated that exosomal miR-21 and miR-146b-frequently upregulated in PTC, facilitate a microenvironment supportive of tumor proliferation and invasion. Similarly, miR-221/222 overexpression in thyroid cancer cells has been linked with enhanced communication with stromal compartments, influencing pathways related to migration and adhesion [65].

miRNAs in Angiogenesis

Angiogenesis is necessary for thyroid tumor growth and metastatic dissemination. Several miRNAs regulate angiogenic pathways, often by targeting vascular endothelial growth factors (VEGF) and related signalling molecules [66]. In thyroid cancer, miR-126 has been identified as a critical regulator of endothelial cell function; its downregulation is associated with increased VEGF expression and enhanced angiogenesis [67,68]. Conversely, the exosomal miR-181a promotes tumor angiogenesis through downregulation of MLL3 and DACT2 and overexpression of VEGF, like PTC cells under hypoxic conditions [69]. Another study where overexpression of miR-205 suppresses angiogenesis and EMT via targeting VEGF in ATC cells [70].

Fibroblast Activation and Extracellular Matrix Remodelling

The CAFs and ECM dynamics play major role in thyroid tumor progression. The miRNA influences CAF activation and ECM remodelling by regulating key genes involved in matrix deposition, degradation, and fibroblast signaling [71,72]. For example, miR-214 and miR-199a has been implicated in fibroblast activation and matrix modulation across multiple cancers [73,74], with emerging evidence suggesting similar functions in thyroid tumors. In PTC, aberrant expression of miR-29 family members (notably miR-29b) has been associated with regulation of ECM proteins such as collagens, influencing tumor invasion and stromal remodelling [75]. Moreover, exosomal miRNAs from thyroid cancer cells can activate fibroblasts to produce pro-invasive ECM molecules, creating a permissive environment for tumor spread.

Clinical Applications

Clinical targeting of the TME in thyroid cancer includes immune checkpoint blockade and anti-angiogenic therapy. The PD-1 inhibitor pembrolizumab enhances T-cell mediated anti-tumor immunity, while multi-kinase inhibitor Lenvatinib

modulates the TME by inhibiting VEGF signalling and reducing TAMs, thereby improving immune infiltration. This drug is also known to enhance NK cells numbers in advanced thyroid cancer that further helps in efficacy [76]. Lenvatinib is already FDA-approved for radioactive iodine-refractory DTC, and newer approvals such as Selpercatinib target RET-mutant thyroid cancer. Emerging combination strategies (e.g., Lenvatinib + pembrolizumab) further exploit TME-immune interactions and show promising responses in advanced TC [77].

Diagnostic and Prognostic Biomarkers

The miRNAs such as miR-21, miR-136, and miR-127 are used as diagnostic markers to differentiate thyroid cancers from benign or low malignant potential tumours such as Encapsulated Non-invasive Papillary thyroid carcinoma or Follicular tumour of uncertain malignant potential (FTUMP) [78]. The components of TME indicate patterns of immune infiltration and their association with prognosis. Overexpression of these miR-21, miR-136, and miR-127 is associated with aggressive PTCs [79]. Figure 2 highlights diagnostic and prognostic miRNAs in TC with their therapeutic targets.

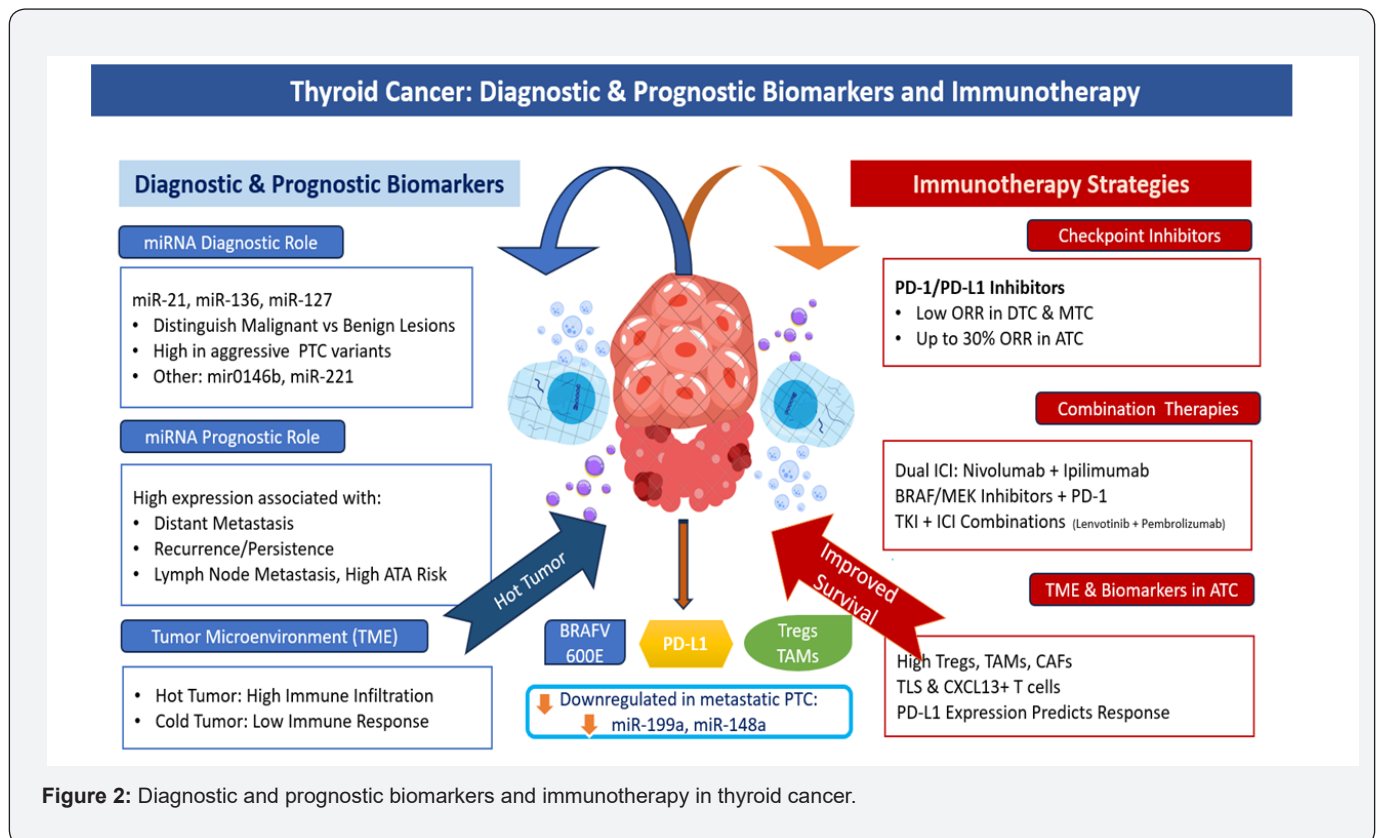


Figure 2: Diagnostic and prognostic biomarkers and immunotherapy in thyroid cancer.

• **miRNA Diagnostic Potential:** High expression of miR-21, miR-136, and miR-127 helps distinguish malignant thyroid lesions (such as PTC, FTC) from non-malignant lesions (such as Follicular adenoma, NIFTP) with high area under the curve (AUCs)

of 0.76-0.83 by qRT-PCR analysis on FFPE samples [79]. These miRNAs are also found to be highly expressed in PTC variants such as tall cell PTC compared to follicular variants. Other potential candidates include miR-146b-5p and miR-221-3p [80].

- **miRNA Prognostic Role:** In DTCs, high expression of miR-21, miR-136, and miR-127 is an independent predictor of distant metastasis (OR 4.52) and recurrence/persistence (OR 3.56) [78]. High expression is also linked to extrathyroidal extension, aggressive variants of PTC, lymph node metastasis, and high ATA (American thyroid association) recurrence risk [79]. Recent expression profiles have identified miR-199a-3p/5p and miR-148a-p in metastatic PTC [81].

- **TME Prognostic Insights:** The TME analysis by TCGA separates thyroid cancers into “hot” (high immune/stromal scores, clusters 3-4) and “cold” cancers. The “hot” cancers having lower stages and activated leukocyte activation pathways. The hub miRNAs in TME-ceRNA networks (hsa-miR-204, -128, -214, -150, -338) modulate immune infiltration, targeting mRNAs such as BCL2 and CDH2 [82]. However, the presence of TME characteristics in the primary tumor (fibrosis, lymphocytosis) does not predict metastatic prognosis, and PET parameters such as SUVmax [83].

Circulating miRNAs as Non-Invasive Markers

Circulating miRNAs have emerged as promising non-invasive biomarkers in thyroid cancer, particularly PTC, FTC and ATC. As miRNAs are stable in serum and plasma, and protected within exosomes or protein complexes, they can be reliably detected using quantitative PCR-based assays. Several studies demonstrated elevated circulating levels of oncogenic miRNAs such as miR-146b, miR-221, and miR-21 in patients with PTC compared with benign thyroid nodules and healthy controls [84-86].

Notably, circulating miR-146b and miR-222 levels have been associated with lymph node metastasis and extrathyroidal extension, suggesting potential markers for risk stratification on follow up [87,88]. In ATC, aberrant serum profiles of tumor-suppressive miRNAs, including miR-125b and miR-30 family members, correlate with aggressive clinical behaviour [89]. Thus, circulating miRNAs represents a minimally invasive tool for diagnosis, prognosis, and surveillance in thyroid malignancies.

miRNAs as Therapeutic Targets

Given the central role in tumorigenesis and TME modulation, miRNAs represent attractive therapeutic targets in thyroid cancer. Majorly, two principal strategies have been explored: i) restoration of tumor-suppressor miRNAs using synthetic miRNA mimics, and ii) inhibition of oncogenic miRNAs (oncomiRs) using antagomiRs or locked nucleic acid (LNA) inhibitors.

- **miRNA Mimic Therapy:** Restoration of downregulated tumor-suppressive miRNAs has shown encouraging pre-clinical results. The re-expression of miR-34, a p53-regulated tumor suppressor, suppresses proliferation and induces apoptosis in various cancers by targeting BCL-2, NOTCH and MYC [90]. Similarly, restoration of miR-199a-5p inhibits cell migration,

invasion and EMT through the suppression of SNAI1 in PTC [91]. miR-126 replacement has also been shown to inhibit angiogenesis and reduce metastatic potential in thyroid cancer by targeting VEGF signalling [68]. All these findings suggest that miRNA mimics not only inhibit tumor cell proliferation but also modulates tumor microenvironment by suppressing angiogenesis and stromal activation.

- **OncomiRs Inhibition:** The inhibition of overexpressed oncogenic miRNAs is another promising strategy with miR-21, frequently upregulated in PTC and FTC, and promotes tumor growth through PTEN/PI3K/AKT signaling. AntagomiR-mediated suppression of miR-21 reduces proliferation and invasion in thyroid cancer cells [92]. Likewise, targeting miR-146b, one of the most upregulated miRNAs in PTC, reduces migration and invasion by restoring SMAD4 expression and modulating TGF- β signalling [33]. In ATC, inhibition of miR-221/222 has been shown to restore cell cycle regulators such as p27kip1, thereby suppressing aggressive tumor behaviour [93].

Combination with Immunotherapy (Checkpoint Blockade)

Immunotherapy/Checkpoint Inhibitors, particularly PD-1/PD-L1 inhibitors, hold promise in the treatment of advanced thyroid cancers, especially ATC, although responses are variable according to the histological type and can be optimized by combination therapies [94]. Reviews emphasize the use of combinations with Tyrosine kinase inhibitors (TKIs) or BRAF/MEK inhibitors based on TME biomarkers such as TLS and PD-L1.

- **Checkpoint Monotherapy:** The PD-1 inhibitors such as Pembrolizumab or Nivolumab have a low objective response rate (ORR), i.e., 9-16% in radioiodine-refractory DTC and MTC, though up to 30% in ATC with high PD-L1 expression [95]. Tolerability includes fatigue and lipase elevation, but immune-related adverse events (irAEs) such as thyroiditis [94].

- **Key Combinations:** Dual ICI (Nivolumab + Ipilimumab) shows 30% ORR in ATC exploratory studies. BRAF/MEK inhibitors (Dabrafenib+Trametinib) Pembrolizumab improves median overall survival (OS) to 17 months (vs. 9 months for dual therapy) in BRAF V600E-mutant ATC patients, with 63 months in neoadjuvant settings. TKI + ICI (immune checkpoint inhibitor), such as Lenvatinib + Pembrolizumab, achieves 66% complete responses in non-BRAF cancers; PD-L1 inhibition + targeted therapy reaches 14.7 months median OS in ATC [95].

- **TME and Biomarkers:** In ATC the TME is immunosuppressive (high Tregs, TAMs, CAFs), though surprisingly “hot” in responders with TLS and CXCL13+T cells predicting ICI responsiveness [94]. Hence the PD-L1 expression is prognostic and could improve objective classification in doubtful cases [96]. Thus, the biomarker-stratified combinations maximize efficacy in ATC compared to DTC [97].

Challenges and Future Perspectives

Despite significant advances in elucidating the role of miRNAs and tumour microenvironment TME in thyroid cancer there are several limitations in their clinical translation. One major challenge is methodological variability in miRNA detection, including differences in sample processing, RNA extraction protocols, and normalization strategies for circulating miRNAs, which affect reproducibility and inter-study comparability [98,99]. Additionally, most studies in PTC and ATC involve small cohorts, underscoring the need for large, multi centre validation trails to establish robust diagnostic and prognostic signatures.

In addition, efficient and tumour-specific delivery of miRNA mimics or inhibitors remains a critical hurdle. Therapeutically. The systemic administration may result in rapid degradation, poor cellular uptake, or unintended targeting of non-malignant tissues [100]. Furthermore, clinical experiences with miRNA-based therapeutics, such as MRX34 (a liposomal miR-34a mimics) revealed immune-related toxicities, highlighting safety concerns is quite limited [101].

Also, many studies focus on descriptive IHC or transcriptomic profiling without functional validation. This includes CRISPR-based knockdowns or co-culture assays that could confirm the immunomodulatory roles of TILs. Thus, there is a need for future guidelines to support IHC, for CD8+ T-cell infiltration, along with molecular panels like ThyroSeq to elucidate and overcome the challenges in aggressive TC's. This would enable early immunotherapy for high-risk immunogenic subsets. Future directions should emphasize the development of advanced delivery systems, including lipid nanoparticles and engineered exosomes, to enhance stability and tumor specificity [102].

Integrating miRNA profiling with genomic alterations (e.g. BRAF and RAS mutations) and immune signatures may refine risk stratification and guide precision therapy in thyroid cancer. Systems biology and network-based analyses will be instrumental in identifying clinically actionable miRNA regulatory circuits within the TME. Although preclinical data are encouraging, challenges related to delivery, specificity, and clinical validation remain a cornerstone in therapy of aggressive TC. Addressing these aspects through large multi centre collaborations, like TCGA expansions, will enhance the knowledge and understanding of immune-based strategies. This will improve survival rates in TC patients with advanced thyroid and other endocrine cancers.

Conclusion

The current review highlights various literature to better understand the complexity of thyroid cancer and its TME. Various microRNAs have emerged as key regulators of tumor progression by modulating immune checkpoints, macrophage polarization, stromal interactions, angiogenesis, and extracellular matrix remodelling. Circulating miRNAs proves to be a promising non-invasive biomarker/s for diagnosis and prognosis in TCs, while

miRNA-based therapeutics, including mimics and inhibitors, represent an evolving targeted strategy. A multicenter study in a larger cohort, integrating molecular and clinical insights is required essential to translate miRNA-based approaches into personalized therapy and precision management of thyroid cancer.

Conflict of Interest

The authors declare no conflict of interest.

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Chandni Kashyap and Ankita Chouhan contributed equally and should be considered as first co-authors.

Authors' Contribution

CK and AC contributed to conceptualization, investigation, data curation, visualization, and writing of the manuscript, SB in conceptualization, assistance and manuscript review, and U.N.S. in Conceptualization, supervision, validation, guidance, and critical review.

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