Thyroid cancer: From molecular insights to therapy (Review)

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Abstract. Thyroid cancer, a prevalent endocrine malignancy with rising global incidence, encompasses four primary subtypes: Papillary (PTC), follicular (FTC), medullary (MTC) and anaplastic thyroid carcinoma (ATC). PTC, accounting for 85-90% of cases, is primarily driven by BRAF V600E mutations alongside dysregulated non-coding RNAs, such as long non-coding RNA metastasis-associated lung adenocarcinoma transcript 1 and microRNA (miR)-1270. These alterations collectively activate MAPK signaling, promoting tumorigenesis. Furthermore, PTC exhibits metabolic reprogramming characterized by dysregulated glucose and lipid metabolism, where tumor suppressors, including family with sequence similarity 111 member B and fat mass and obesity-associated genes, constrain glycolytic flux. FTC, characterized by Ras mutations, exhibits enhanced lipid metabolism and PI3K/AKT pathway activation. Methyltransferase-like protein 16 and sclerostin domain-containing protein 1 have been highlighted as regulators of FTC progression. MTC, associated with rearranged during transfection (RET) proto-oncogene mutations, demonstrates programmed cell death protein-1/programmed death ligand-1 pathway involvement, which offers potential immunotherapy targets. ATC, the most aggressive subtype, is characterized by recurrent genetic alterations such as telomerase reverse transcriptase promoter and tumor protein p53 mutations, cAMP-responsive element-binding protein 3-like 1-driven activation of cancer-associated fibroblasts and hematological and neurological expressed 1-stathmin 1 signaling-mediated invasiveness. Recent diagnostic innovations encompass serum biomarkers, such as stanniocalcin-1, microRNA signatures (including miR-26b-5p) for PTC and MTC detection, radiomics-based differentiation of ATC from other subtypes and optical imaging techniques for precision diagnosis. Molecularly targeted therapies constitute the cornerstone of current strategies, with vemurafenib inhibiting BRAF/MEK in PTC, sorafenib acting as a multikinase suppressor in FTC, vandetanib blocking RET in MTC and berberine-doxorubicin combinations overcoming chemoresistance in ATC. Metabolic interventions, including metformin for glucose modulation in PTC and novel delivery systems such as micelle-encapsulated AB3 for MTC, demonstrate translational potential. The present review summarizes molecular mechanisms, diagnostic tools and emerging therapies while emphasizing the necessity of subtype-specific approaches to improve clinical outcomes in thyroid oncology.

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Contents

1. Introduction

Thyroid cancer, a leading concern among endocrine system tumors, has demonstrated a consistent rise in global incidence.

Thyroid cancer ranked as the seventh most common malignancy globally in 2022, with >821,000 reported cases (1). The diverse pathological types and clinical manifestations of thyroid cancer pose notable challenges for both medical research and clinical management. As it occurs within a vital organ within the human endocrine system, thyroid gland dysfunction not only disrupts metabolic homeostasis but also endangers overall health when compromised by cancer progression (2).

Thyroid cancer arises from follicular or parafollicular epithelial cells, representing the most common head and neck malignancy. Thyroid cancer can be histologically classified into several types, including papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), medullary thyroid carcinoma (MTC) and anaplastic thyroid carcinoma (ATC), with PTC being the most prevalent. The global incidence of thyroid cancer continues to rise, particularly among high-risk groups, such as women, individuals with genetic predispositions or those with a family history of the disease (3).

PTC, accounting for 85-90% of thyroid malignancies, is characterized by papillary structures and a favorable prognosis, yet recurrence and lymph node metastasis remain clinical challenges (4). FTC, comprising ~10% of cases, exhibits greater invasiveness and a higher probability of distant metastasis to the lungs and bones compared with PTC, which necessitates precise and individualized treatment strategies (5). MTC, a neuroendocrine malignancy originating from calcitonin-secreting parafollicular C cells, constitutes 1-5% of thyroid malignancies. The pathogenesis of MTC has been significantly associated with rearranged during transfection (RET) proto-oncogene mutations and exhibits notable hereditary predisposition, notably mediated by gain-of-function mutations, which necessitates comprehensive genetic counseling and multidisciplinary approaches for optimal management (6). ATC, although accounting for only 1-2% of all thyroid malignancies, is the most aggressive form. It is characterized by poor differentiation, rapid progression, a poor prognosis and limited responsiveness to current treatments (7).

The present comprehensive review systematically evaluates recent progress in understanding the four principal histological subtypes of thyroid carcinoma. While PTC remains the most extensively characterized subtype, notable knowledge gaps persist regarding the signaling cascades and metabolic reprogramming in FTC, MTC and ATC, as schematically illustrated in Fig. 1. The present review summarizes notable findings spanning molecular pathogenesis, diagnostic biomarker development and emerging therapeutic modalities specific to these understudied thyroid cancers. Particular emphasis has been placed on delineating subtype-specific molecular signatures that may inform precision diagnostics and targeted intervention strategies. The present review aims to establish a comprehensive framework to guide subsequent mechanistic investigations and clinical translation in thyroid oncology.

2. PTC

PTC is the most prevalent form of thyroid cancer and its incidence is rising globally. The pathogenesis of PTC is intricate, involving a range of genetic and epigenetic alterations. Among these, the BRAF V600E gene mutation is one of the most frequently observed molecular events in PTC, the pooled sensitivity of IHC for detecting BRAF V600E mutation was 96.8% [95% confidence interval (CI): 94.1-98.3%] (8). This mutation primarily impacts the MAPK signaling pathway, resulting in the persistent activation of the downstream MEK protein, which in turn promotes cell proliferation, differentiation and tumorigenesis (9). A thorough understanding of these molecular mechanisms not only elucidates the pathogenesis of PTC but also identifies key molecular markers for its diagnosis, treatment and prognostic evaluation in the future.

Molecular mechanisms. PTC accounts for 85-90% of all thyroid cancer cases, with its molecular mechanisms being both complex and diverse (4). These mechanisms involve various genetic mutations (such as BRAF, RAS, RET/PTC) and the dysregulated expression of non-coding RNAs (10). Recent studies have highlighted genes, like methyltransferase-like 3 (METTL3), METTL16, METTL7B and transducin-like enhancer of split 4, closely associated with the onset progression invasiveness and prognosis of PTC. Emerging evidence identifies long non-coding RNAs (lncRNAs) among key non-coding RNA regulators driving PTC pathogenesis (11-14). Deciphering these molecular pathways enhances mechanistic insights into PTC pathogenesis, while establishing essential frameworks for early detection, therapeutic development and outcome prediction (Fig. 2).

The molecular landscape of PTC is notably shaped by mutations in various coding genes, with the BRAF gene mutation being one of the most prevalent. Located on chromosome 7q34, BRAF serves a key role in the Ras/Raf/MEK/ERK signaling pathway. The BRAF V600E mutation is present in up to 90% of PTC cases and leads to the continuous activation of the MEK protein, which promotes cell proliferation and tumorigenesis. This mutation also upregulates hexokinase-2 (HK2), which inhibits upstream tyrosine kinases, thereby further contributing to PTC growth (15). The BRAF V600E mutation enhances cell proliferation and tumor growth by activating the MAPK signaling pathway.

Additional genes, such as METTL3, METTL6 and METTL7B, are associated with the proliferation and migration of PTC (11,12). Overexpression of METTL3 and METTL7B has been shown to facilitate tumor progression, while METTL16 interacts with stearoyl-CoA desaturase 1 to activate lipid metabolism pathways and with YT521-B homology domain-containing protein 2, which inhibits PTC progression (13). By contrast, transducin-like enhancer of split 4 negatively associates with the proliferation, migration and invasion of PTC cells, while promoting the activation of the JAK/STAT signaling pathway (14).

The potassium calcium-activated channel subfamily N member 4 (KCNN4) gene serves an essential role in modulating the proliferation, migration and invasion of PTC cells. Low expression levels of KCNN4 not only hamper tumor progression but also enhance the expression of apoptosis-related genes, which suppresses epithelial-mesenchymal transition (EMT) (16). By contrast, the expression of PDZ domain-containing kidney-specific protein 1-interacting protein 1 (PDZK1IP1) enhances the proliferation and migration

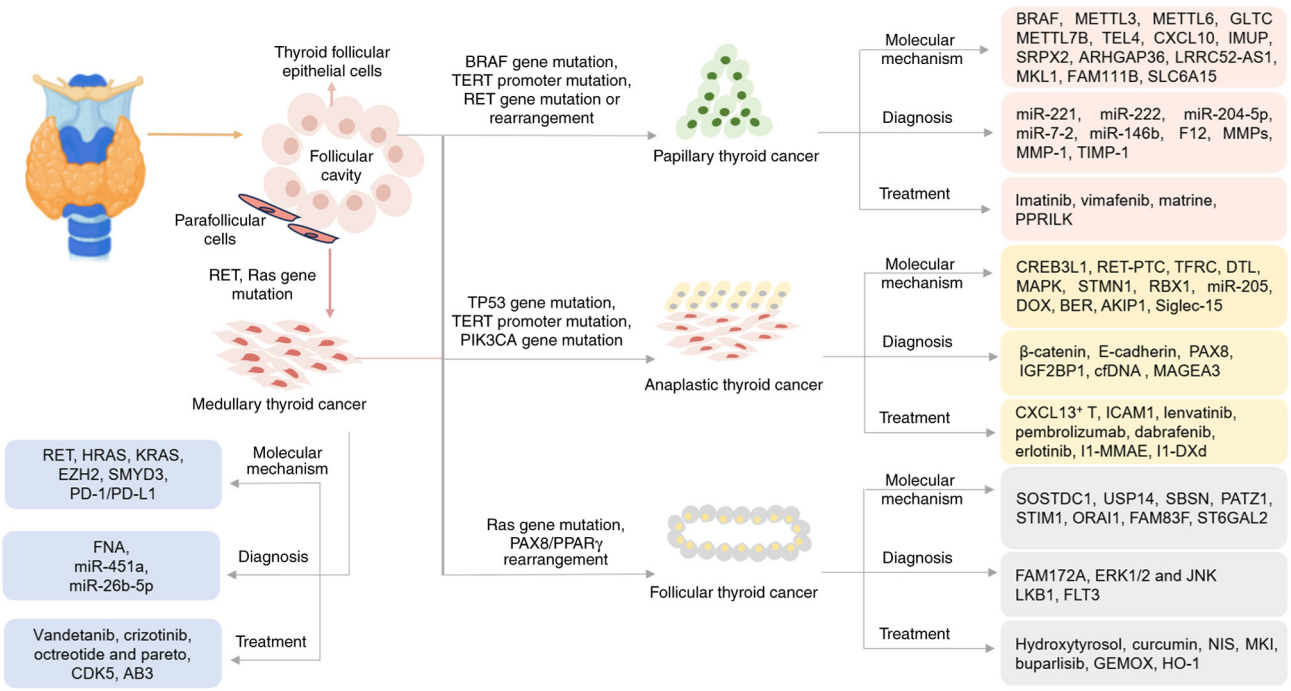

Figure 1. Emerging regulatory nodes across molecular mechanisms, diagnostic biomarkers and therapeutic targets in papillary, follicular, medullary and anaplastic thyroid carcinomas. RET, rearranged during transfection; HRAS, Harvey rat sarcoma viral oncogene homolog; miR, microRNA; TP53, tumor protein 53; TERT, telomerase reverse transcriptase; FNA, fine needle aspiration; METTL, methyltransferase-like protein; IMUP, immortalization-upregulated protein; USP14, ubiquitin-specific protease 14; TIMP-1, tissue inhibitor of MMP-1; BRAF, B-Raf proto-oncogene, serine/threonine kinase; MKL1, megakaryoblastic leukemia 1; RET, rearranged during transfection proto-oncogene; KRAS, Kirsten rat sarcoma viral oncogene homolog; RAS, rat sarcoma virus; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α; FLT3, FMS-like tyrosine kinase 3; EZH2, enhancer of zeste homolog 2; SMYD3, SET and MYND domain containing 3; ARHGAP36, Rho GTPase activating protein 36; AKIP1, A kinase interacting protein 1; E-cadherin, epithelial cadherin; IGF2BP1, insulin-like growth factor 2 mRNA-binding protein 1; TFRC, transferrin receptor; DTL, denticleless E3 ubiquitin protein ligase homolog; RBX1, ring-box 1; CDK5, cyclin-dependent kinase 5; LKB1, liver kinase B1; ETV4, ETS variant transcription factor 4; PAX8, paired box 8; PATZ1, POZ/BTB and AT hook containing zinc finger 1; CREB3L1, CAMP responsive element binding protein 3 like 1; CXCL10, C-X-C motif chemokine ligand 10; ICAM1, intercellular adhesion molecule 1; SRPX2, sushi repeat containing protein X-linked 2F12, coagulation factor XII; MMP, matrix metalloproteinase; SOSTDC1, sclerostin domain containing 1; SBSN, Suprabasin; ST6GAL2, ST6 β-galactoside α-2,6-sialyltransferase 2; FAM172A, family with sequence similarity 172 member A; FAM83F, family with sequence similarity 83 member F; Siglec-15, sialic acid-binding Ig-type lectin 15; SLC6A15, solute carrier family 6 member 15; STIM1, stromal interaction molecule 1; ORAI1, ORAI calcium release-activated calcium modulator 1; RET-PTC, RET/papillary thyroid carcinoma; PAX8/PPARγ, PAX8/peroxisome proliferator-activated receptor gamma; LRRC52-AS1, LRRC52 antisense RNA 1; cfDNA, cell-free DNA; MAGEA3, melanoma associated antigen A3; CXCL13+ T, CXCL13-positive T cells; MKI, multikinase inhibitor; MAPK, mitogen-activated protein kinase; Erk1/2, extracellular signal-regulated kinases 1 and 2; JNK, c-Jun N-terminal kinase.

of PTC while inhibiting apoptosis (17). Furthermore, C-X-C motif chemokine ligand 10 expression is downregulated in PTC, which has been closely associated with immunity and cellular defense mechanisms (18). C-X-C chemokine receptor type 4 gene upregulation in PTC tissues provides a potential therapeutic target (19). Furthermore, the downregulation of Bcl-2-like protein 11 in PTC results in increased microRNA (miRNA/miR)-300 expression, which influences PTC activity and behavior (20).

Lastly, the genes immortalization-upregulated protein (IMUP), sushi repeat-containing protein, X-linked 2 (SRPX2), ϱ GTPase-activating protein 36, leucine-rich repeat-containing protein 52 antisense RNA 1 and megakaryoblastic leukemia 1 are positively associated with the progression of PTC. High expression levels of these genes contributed to the proliferation, migration and invasion of PTC cells, which suggests their utility as potential therapeutic targets (21-25). In glutamine-affinity PTC, the inhibition of glutamine breakdown can reduce mitochondrial respiration, thereby inhibiting PTC activity (26). The family with sequence similarity 111 member B (FAM111B) motif inhibits the glycolytic process in PTC, which in turn prevents its proliferation, migration and invasion (27). As a tumor suppressor, solute carrier family 6 member 15 (SLC6A15) serves a key role in inhibiting the migration and invasion of PTC. The effect of SLC6A15 on PTC cells was associated with intercellular adhesion molecule-1 (ICAM-1). SLC6A15 functions as a tumor suppressor gene and may represent a potential target for the treatment of PTC in the future (28).

Non-coding RNAs, including lncRNAs and miRNAs, are emerging as key regulators in the pathogenesis of PTC Among the lncRNAs, glycolysis-associated regulator of lactate dehydrogenase A (LDHA) post-transcriptional modification 1 (GLTC), which interacts with LDHA, serves an essential role in aerobic glycolysis and enhances cell viability in PTC (29-31). Elevated expression levels of GLTC in PTC tissues correlates with more extensive metastasis, larger tumor size and worse prognosis. Inhibition of GLTC negates the effects of K155-succinylated LDHA, particularly on radioiodine iodine refractory, which suggests its potential as an oncogenic target in PTC (32). Bioinformatic analyses of miRNA-mRNA regulatory networks reveal that miR-204-5p exhibits the broadest

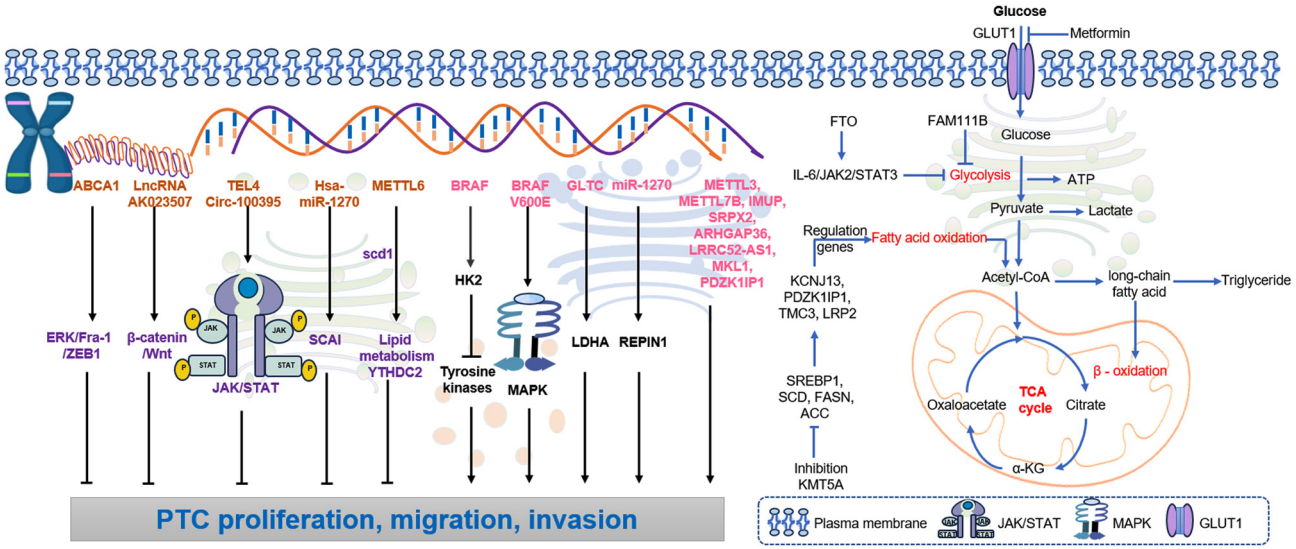

Figure 2. Dysregulated signaling pathways and non-coding RNA networks drive PTC pathogenesis at the molecular level. The schematic delineates the integrated molecular network driving PTC proliferation, migration and invasion. Key signaling cascades include the ERK/Fra-1/ZEB1 axis and JAK/STAT pathway, modulated by non-coding RNAs (lncRNA AK023507 and circ-100395) and epigenetic regulators (KMT5A). The BRAF V600E mutation activates MAPK signaling, upregulating glycolytic enzymes (HK2 and LDHA) and lipid metabolism mediators (SCD1 and FASN). GLUT1-mediated glucose uptake and metformin-sensitive pathways coordinate metabolic reprogramming, involving glycolysis-derived pyruvate, fatty acid oxidation and TCA cycle dynamics. Regulatory nodes such as SREBP1 and YTHDC2 orchestrate lipid biosynthesis, while miR-1270 and TEL4 fine-tune tumor progression. These interconnected mechanisms collectively sustain PTC malignancy through proliferative signaling and microenvironment adaptation. The black arrows indicate conventional signaling pathway interactions; blue arrows specifically denote metabolic pathway relationships. PTC, papillary thyroid cancer; Fra-1, Fos-related antigen 1; ZEB1, Zinc finger E-box binding homeobox 1; JAK, Janus kinase; lncRNA, long non-coding RNA; KMT5A, lysine methyltransferase 5A; HK2, hexokinase 2; LDHA, lactate dehydrogenase A; SCD1, stearoyl-CoA desaturase 1; FASN, fatty acid synthase; GLUT1, glucose transporter 1; TCA, tricarboxylic acid; SREBP1, sterol regulatory element-binding protein 1; YTHDC2, YT521-B homology domain-containing protein 2; miR, microRNA TEL4, translocation-Ets-leukemia 4; ABCA1, ATP-binding cassette subfamily A Member 1; SCAI, suppressor of cancer cell invasion; SCD1, tearoyl-CoA desaturase 1; REPIN1, replication initiator 1; GLTC, glucose transporter 4; FTO, fat mass and obesity-associated gene; FAM111B, family with sequence similarity 111 member B; KCNJ13, potassium inwardly rectifying channel subfamily J member 13; PDZK1IP1, PDZK1-interacting protein 1; TMC3, transmembrane channel-like 3; LRP2, low-density lipoprotein receptor-related protein 2; SREBP1, sterol regulatory element-binding protein 1; ACC, acetyl-CoA carboxylase; α-KG, α-ketoglutarate; METTL, methyltransferase-like; IMUP, immuno-upregulated protein; SRPX2, sushi repeat-containing protein X-linked 2; ARHGAP36, Rho GTPase-activating protein 36; LRRC52-AS1, LRRC52 antisense RNA 1; MKL1, megakaryoblastic leukemia 1.

regulatory capacity, targeting multiple genes, including tumor necrosis factor receptor superfamily member 12A (TNFRSF12A). Furthermore, miR-146b, miR-204 and miR-7-2 demonstrate stage-specific expression patterns in PTC, while elevated TNFRSF12A and claudin-1 levels correlate with adverse prognostic outcomes in this malignancy (23,33). The expression level of lncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is also upregulated in PTC, suggesting that MALAT1 may serve a carcinogenic role and could potentially serve as a diagnostic marker for PTC (34).

Hsa-miR-1270 is significantly upregulated in PTC cell lines (such as TPC-1 and K1) and human PTC tumors. The regulatory mechanism of hsa-miR-1270 in PTC appears to be primarily associated with the suppressor of cancer cell invasion (SCAI) gene. hsa-miR-1270 can bind to SCAI and negatively regulate the expression of the SCAI gene in PTC cells. Downregulation of hsa-miR-1270 expression inhibits the development of PTC cells both *in vitro* and *in vivo* (35). By contrast, overexpression of miR-1270 promotes the proliferation, migration and invasion of PTC cells by targeting REPIN1 (36). Circ-0011058 positively regulates yes-associated protein 1 (YAP1), thereby enhancing PTC proliferation, angiogenesis and radioresistance by acting as a sponge for miR-335-5p (37). Furthermore, miR-106a has been implicated in the carcinogenesis of the lncRNA highly upregulated in liver cancer (HULC). Both HULC and miR-106a are positively associated with cell viability, proliferation, migration, invasion capacity, and the volume and weight of PTC tumors (38). HULC overexpression enhances the activity of the PI3K/AKT and Wnt/β-catenin signaling pathways by upregulating the expression of miR-106a. A positive correlation exists between the expression levels of HOXA3 and HOXA-AS2, with HOXA-AS2 being notably expressed in the cytoplasm of PTC cells (39). Furthermore, FOXD2-AS1 upregulates HOXA3 expression by binding to miR-15a-5p. The global function of the HOXA-AS2/miR-15a-5p/HOXA3 axis serves a notable role in the progression of PTC (40).

In summary, the dysregulation of both coding and non-coding genes significantly contributes to the molecular mechanisms of PTC. These insights not only enhance current understanding of PTC biology but also open the door for novel diagnostic and therapeutic strategies targeting specific genes and pathways involved in PTC progression.

Signaling pathway. PTC involves a variety of signaling pathways that regulate its development, proliferation and invasiveness. IMUP and eva-1 homolog A (EVA1A), along with the key effectors of the Hippo pathway, YAP1 and transcriptional coactivator with PDZ-binding motif, can inhibit the proliferation, migration and invasion of PTC cells, while also inducing apoptosis. EVA1A promotes the progression and EMT of PTC through the Hippo signaling pathway (41). lncRNA AK023507

inhibits the proliferation and metastasis of PTC cells by targeting the β-catenin/Wnt signaling pathway (42). In PTC cell lines, the tumor-suppressive effect of Tektin-4 (TEKT4) downregulation was associated with the silencing of the PI3K/AKT pathway. The downregulation of TEKT4 expression inhibited cell proliferation, colony formation, migration and invasion (43). Overexpression of circ-100395 significantly reduced aerobic glycolysis, proliferation, migration and invasion, while downregulating the PI3K/AKT/mTOR pathway, an effect that was reversed by the PI3K activator 740Y-P. Circ-100395 may exert an anticancer effect in PTC cells by inhibiting the PI3K/AKT/mTOR signaling pathway (44).

SRPX2 promotes proliferation and migration of PTC. SRPX2 serves a role in the malignant development of PTC by activating the PI3K/AKT signaling pathway (22). ATP-binding cassette transporter A1 serves a key role in inhibiting PTC lung metastasis through the ERK/Fos-related antigen 1/zinc finger E-box binding homeobox 1 (ZEB1) pathway (45). METTL3 inactivates the NF-κB pathway through cellular reticuloendotheliosis viral oncogene homolog and v-rel reticuloendotheliosis viral oncogene homolog A, regulates tumor growth together with YT521-B homology domain-containing family protein 2 and tumor-associated neutrophil infiltration, and serves a key tumor suppressor role in PTC carcinogenesis, which expands current understanding of the relationship between N6-methyladenosine (m6A) modification and tumor microenvironment (TME) plasticity (46).

FTO can inhibit glycolysis and the growth of PTC, and its expression has been significantly downregulated in PTC tissues. FTO suppresses the expression of apolipoprotein E (APOE) through insulin-like growth factor 2 mRNA-binding protein 2 (IGF2BP2)-mediated m6A modification and may inhibit glycolytic metabolism in PTC by regulating the IL-6/JAK2/STAT3 signaling pathway, thereby impeding tumor growth (47). Insulin-like growth factor 1 (IGF1) promotes the proliferation and invasion of PTC via the STAT3 signaling pathway (36,47). Key oncogenes, including leucine-rich repeat kinase 2, solute carrier family 34 member 2, mucin 1, forkhead box protein Q1 and keratin 19, are upregulated in BRAF-enriched subtypes and are associated with oncogenic MAPK and PI3K/AKT signaling pathways (48).

The present review provides a key appraisal of the oncogenic signaling network architecture underlying PTC pathogenesis. Emerging evidence demonstrates that a complex interplay of mitogenic pathways, including MAPK/ERK and PI3K/AKT cascades, coordinately regulates malignant phenotype evolution through modulation of proliferation kinetics, metastatic competence, apoptotic resistance and epithelial-mesenchymal plasticity in PTC models. Particular emphasis has been placed on delineating pathway crosstalk mechanisms that create therapeutic vulnerabilities, with concurrent discussion of preclinical validation strategies for molecularly targeted interventions.

Metabolism. Thyroid cancer is a prevalent malignant tumor within the endocrine system, and its occurrence and progression are closely associated with various metabolic processes. Recent studies have demonstrated that the metabolomic profiles of serum samples from patients with thyroid cancer differ significantly from those of healthy adults. These differences encompass multiple metabolic pathways, including glucose metabolism, lipid metabolism and amino acid metabolism (49,50).

FAM111B expression is negatively associated with glucose uptake and inhibits the growth, migration, invasion and glycolysis of PTC. Methylation of FAM111B mediated by DNA (cytosine-5)-methyltransferase 3β (DNMT3B) accelerates the growth, migration, invasion and glycolysis of PTC cells. The estradiol/DNMT3B/FAM111B axis is a key regulator of PTC growth and progression (27). FTO functions as a tumor suppressor gene in PTC, inhibiting tumor glycolysis. Research has demonstrated that FTO suppresses the expression of APOE through IGF2BP2-mediated mRNA modification and may inhibit glycolytic metabolism in PTC by modulating the IL-6/JAK2/STAT3 signaling pathway, thereby restraining tumor growth (51). Pyruvate carboxylase influences the proliferation and motility of thyroid cell lines. PTC demonstrates metabolic reprogramming characterized by enhanced tricarboxylic acid (TCA) cycle flux that sustains oncogenic bioenergetic demands while generating biosynthetic precursors (52). Mitochondrial oxidative metabolism is elevated in thyroid cancer cells compared with stromal cells. PiggyBac transposable element derived 5 (PGBD5), a gene associated with glucose metabolism, is enriched in inflammatory response pathways and has been correlated with high levels of immune cell infiltration in groups sensitive to paclitaxel and anti-PD-1 treatment. Therefore, PGBD5 may serve as a therapeutic target to inhibit the progression of PTC (53).

Emerging evidence highlights the pivotal role of metabolic reprogramming in PTC progression, with glucose and lipid metabolism emerging as key regulatory axes. In glucose metabolism, pharmacological modulation using metformin suppresses HK2 and glucose transporter 1 (GLUT1) expression, impairing glycolytic flux in PTC models both *in vitro* and *in vivo*, which suggests its therapeutic potential as a metabolic adjuvant (54). This effect is synergistically enhanced by BTB domain and CNC homology 1 knockdown, which induces metabolic inflexibility by inhibiting mitochondrial respiration, thereby sensitizing cancer cells to metformin-mediated cytotoxicity (55). Complementary strategies targeting glucose transport (SGLT2 inhibitors) and mitochondrial energetics (mitochondrial glycerol-3-phosphate dehydrogenase inhibition) further demonstrate metabolic vulnerabilities in PTC, associating glucose uptake restriction with oxidative stress-mediated apoptosis and energy crisis (56,57).

Lipid metabolic rewiring similarly contributes to PTC pathogenesis. Obesity-associated PTC progression associates with METTL16-mediated lipid metabolic activation, while lysine methyltransferase 5A (KMT5A) regulates oncogenic lipogenesis through sterol regulatory element-binding protein 1/SCD/fatty acid synthase (FASN) signaling, modulating redox balance and chemotherapy response (13,58). Prognostically relevant lipid signatures involving PDZK1IP1, transmembrane channel-like 3, low-density lipoprotein receptor-related protein 2 and potassium inwardly-rectifying channel subfamily J member 13 genes underscore the clinical implications of lipid metabolism in tumor evolution (59). Beyond canonical pathways, metabolic crosstalk between tumors and microenvironmental adipocytes drives local lipid restructuring,

characterized by elevated very long chain saturated fatty acids and polyunsaturated fatty acid metabolism in peritumoral thyroid tissue (60). These findings collectively identify metabolic plasticity, characterized by predominant aerobic glycolysis activity, glutamine dependency and enhanced lipid anabolism, as a hallmark feature of PTC malignancy, with both diagnostic significance and therapeutic potential (61).

Current understanding of metabolic reprogramming in PTC remains predominantly focused on glucose and lipid homeostasis, with amino acid metabolism representing a key knowledge gap in PTC pathobiology. The present review systematically examines therapeutically exploitable mechanisms in glycolytic and lipogenic pathways, while Table I delineates emerging insights into amino acid metabolic networks that warrant further mechanistic interrogation (26,51,53,58,61-101). The paucity of comprehensive studies on glutaminolysis, serine-glycine axis modulation and branched-chain amino acid utilization underscores an urgent need for multi-omics investigations to map the complete metabolic landscape of PTC.

Progress in diagnosis. Increased expression of Stanniocalcin 1 (STC1) in PTC tissues has been associated with an elevated risk of lymph node metastasis. Furthermore, elevated STC1 expression in thyroid lesions may aid in the diagnosis of PTC, which makes it a potentially valuable marker for predicting disease prognosis (102). miRNAs such as miR-221, miR-222, miR-204-5p, miR-7-2 and miR-146b have been identified as potential biomarkers for staging PTC. Furthermore, fibronectin 1, claudin-1, TNFRSF12A, ribosomal protein S6 kinase B1, cyclin T1, specificity protein 1 and chromodomain helicase DNA-binding protein 4 may serve as novel prognostic biomarkers for PTC. The expression of coagulation factor XII (F12) may influence the overall survival (OS) of patients with PTC by modulating metabolic pathways, suggesting that F12 could be a reliable diagnostic and prognostic biomarker for PTC (103). Downregulation of Alu-mediated CDKN1A/p21 transcriptional regulator (APTR) has been associated with tumorigenesis and suggests the potential diagnostic value of APTR in patients with PTC and ATC (104). Lectin microarray analysis of salivary glycoproteins in patients with PTC revealed postoperative normalization of six lectin-binding patterns to levels comparable with healthy volunteers. These findings highlight the potential utility of salivary glycome profiling as a non-invasive prognostic biomarker for PTC. Quantitative alterations in specific lectin-reactive glycostructures may enable clinical stratification of disease progression and therapeutic monitoring in PTC management (55). Matrix metalloproteinases and their inhibitors play a role in PTC cervical metastasis, therefore high expression of matrix metalloproteinase-1 (MMP-1) and its tissue inhibitors in tumor tissue can serve as predictive indicators for tumor metastasis (105). In PTC detection diagnosis, immunohistochemical results demonstrated that E-cadherin negativity, and p53 and BRAF positivity are notable risk factors, while radioiodine refractory therapy can reduce the risk of recurrence (106). A six-gene diagnostic panel incorporating transient receptor potential cation channel subfamily C member 5, teneurin transmembrane protein 1, neural EGFL-like 2, Duchenne muscular dystrophy, solute carrier family 35 member F3 and autism susceptibility candidate 2 demonstrated robust discriminative capacity for differentiating PTC from benign thyroid tissues (107).

Our current routine diagnostic practice for PTC conforms to established medical pathological standards. However, the diagnosis in most early-stage cases is typically established using ultrasound (108-110) and subsequently confirmed by a series of more complex tests (111,112), such as ultrasound-guided fine-needle aspiration biopsy for the definitive diagnosis of PTC. Therefore, the present study summarized the relevant literature on the diagnosis of PTC, with the aim of enhancing current capabilities in the prevention and diagnosis of this condition.

Treatment. In terms of tumor growth, the combination of imatinib and vemurafenib resulted in nearly complete tumor disappearance, with a reduction of ~90%. However, monotherapy was significantly less effective in BCPAP cells expressing platelet-derived growth factor receptor (PDGFR) α (11). Matrine has been shown to induce apoptosis in PTC cells *in vitro* and inhibit tumor growth by downregulating miR-182-5p *in vivo*. Matrine, a natural product derived from marine sources, has emerged as a promising alternative for the treatment of various types of cancer, including exerting inhibitory effects in liver cancer and colorectal cancer. Emerging pharmacological evidence demonstrates that Matrine exerts potent anti-neoplastic effects in PTC through multi-modal pro-apoptotic mechanisms (113,114). In PTC-derived TPC-1 and B-CPAP cell models, Matrine induces mitochondrial apoptotic pathway activation characterized by Bcl-2 suppression and caspase-3 activation cascade. Mechanistically, this alkaloid compound mediates tumor growth inhibition via epigenetic regulation of oncogenic miR-182-5p, establishing this miRNA as a therapeutically actionable node in the anti-PTC activity of Matrine (115). The dual regulatory capacity of Matrine in modulating canonical apoptotic signaling pathways and epigenetic RNA networks establishes this alkaloid as a novel therapeutic agent for combination therapies targeting molecular vulnerabilities in PTC.

BRAF inhibitors (BRAFi), including vemurafenib and dabrafenib, have demonstrated notable therapeutic efficacy in the treatment of PTC harboring the BRAF V600E mutation (92,116). However, the development of drug resistance is primarily attributed to the adaptive reactivation of the MAPK signaling pathway, exemplified by mechanisms such as neuroblastoma Ras viral oncogene homolog mutations or the presence of BRAF splice variants that sustain continuous ERK phosphorylation (117). Furthermore, compensatory activation of parallel signaling pathways, notably the IGF-1 receptor (IGF-1R)-mediated PI3K/AKT pathway, contributes to resistance (118). In this context, Sui *et al* (119) identified nerve/glial antigen 2 (NG2) as a key quaternary structural component implicated in BRAF inhibitor resistance within BRAF V600E-mutant PTC. NG2 modulates the activity of multiple receptor tyrosine kinases (RTKs), including EGFR, fibroblast growth factor receptor (FGFR), human EGFR2, insulin-like growth factor 1 receptor (IGF-1R), vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR), via the RTK signaling axis, thereby promoting resistance to BRAFi through the activation of ERK and AKT signaling cascades. These findings indicated

Table I. PTC therapeutic targets with functional and clinical profiles.

First author, year	Key target	Function	Clinical significance	(Refs.)
Abooshahab *et al*, 2020	Sucrose metabolism	Altered sucrose metabolism in plasma of patients with thyroid nodule	Potential circulating biomarker for distinguishing between malignancy and benignity in indeterminate thyroid nodules	(62)
Ambrosi *et al*, 2017	Hobnail variant of PTC	Aggressive clinical behavior, EMT	Indicated a more aggressive form of papillary thyroid carcinoma, highlighting the need for targeted therapies	(63)
Aprile *et al*, 2023	BRAF-mutated thyroid carcinomas	Glycolytic phenotype, HIF-1α stabilization	Combination of BRAFi and diclofenac restrained glycolytic phenotype, providing a novel therapeutic approach to reduce drug resistance and toxicity	(64)
Badziong *et al*, 2017	MCT8	Marker of thyroid differentiation	Downregulation of MCT8 in thyroid cancer, useful for diagnosing and understanding cancer progression	(65)
Bai *et al*, 2020	CDK12	Regulated c-Myc/β-catenin pathway	Promoted PTC progression; potential therapeutic target to inhibit cancer proliferation and metastasis	(66)
Chen *et al*, 2021	circKIF4A	Facilitated malignant progression, suppresses ferroptosis	Potential therapeutic target for PTC by targeting the circKIF4A-miR-1231-GPX4 axis	(67)
Chen *et al*, 2021	circRAD18	Reprogrammed glucose metabolism	Promoted tumor growth and metastasis; potential therapeutic target by targeting the circRAD18-miR-516b-PDK1 axis	(68)
Chong *et al*, 2019	IL13RA2	Enhanced EMT	Associated with advanced tumor stage and lymph node metastasis; potential therapeutic target	(69)
Davis *et al*, 2020	T4	Stimulated proliferation via integrin αVβ3	Cancer-stimulating activity of T4 suggested it as a potential therapeutic target for modulating tumor invasiveness, apoptosis and angiogenesis	(70)
Fan and Zhao 2019	miR-451a	Inhibited proliferation, EMT, and induces apoptosis	Targets proteasome subunit β type-8; potential therapeutic target for PTC	(71)
Feng *et al*, 2019	miRNA genes	Regulated cell adhesion molecules, immune response	Potential therapeutic targets for PTC development	(72)
Gunjača *et al*, 2023	ST6GAL1	Glycosyltransferase involved in thyroid malignancies	High mRNA levels associated with lymph node metastasis and reduced survival; potential prognostic marker	(73)
Ha *et al*, 2017	Myricetin	Induced mitochondrial dysfunction-mediated apoptosis	Potential therapeutic agent for human PTC	(74)
Hińcza *et al*, 2020	DIRC3	No significant association with histo-pathological or clinical featuresss	No clear clinical significance as a prognostic factor	(75)
Hu *et al*, 2023	miR-96-5p	Regulated GPC3 expression	Potential therapeutic target for the prevention and treatment of PTC	(76)

Table I. Continued.

First author, year	Key target	Function	Clinical significance	(Refs.)
Hu *et al*, 2020	hsa_circ_0011290	Regulated proliferation, apoptosis, and glycolytic phenotype	Potential therapeutic target by targeting the hsa_circ_0011290-miR-1252-FSTL1 axis	(77)
Huang *et al*, 2022	FTO	Suppressed glycolysis and growth via m6A modification	Potential therapeutic target to inhibit tumor growth and glycolysis by targeting the FTO/APOE axis	(51)
Jeon *et al*, 2020	PHGDH	Induced stemness and aggressiveness	Promoted tumor growth and stemness markers; potential therapeutic target	(78)
Jin *et al*, 2022	GLR	Predictor of preoperative central lymph node metastasis	Useful for determining appropriate treatment strategies for patients with PTC with type 2 diabetes mellitus	(79)
Kang *et al*, 2019	Iodine avidity	Associated with thyroglobulin expression, Ki-67 index	Helps in adapting radioiodine dosage for enhanced efficacy	(80)
Li *et al*, 2021	OGT/O-GlcNAcylation	Promoted malignancy via YAP activation	Potential therapeutic target for manipulating OGT/YAP activity in PTC	(81)
Li *et al*, 2018	Glycolysis-related proteins	Involved in glucose metabolism	Differential expression associated with worse prognosis in various thyroid cancer subtypes	(82)
Lu *et al*, 2021	LPL, FATP2, CPT1A	Key enzymes in fatty acid metabolism	Enhanced fatty acid metabolism promoted tumor progression; potential therapeutic targets	(83)
Mardente *et al*, 2023	HHV-6A	Induced effects associated with cancer progression	Increased genomic instability and pro-inflammatory cytokine secretion; potential therapeutic target	(84)
Nahm *et al*, 2017	Glucose metabolism	Involved in glucose metabolism	Differential expression associated with worse prognosis in various thyroid cancer subtypes	(85)
Nilsson *et al*, 2021	Thyroglobulin expression	Associated with iodine avidity	Helped in adapting radioiodine dosage for enhanced efficacy	(86)
Parascandolo *et al*, 2017	Extracellular SOD3	Stimulated cancer cell proliferation, inhibits migration	Potential therapeutic target for modulating cancer cell behavior	(87)
Piana *et al*, 2019	NOTCH1	Regulated cell-cell interactions	Predominantly associated with papillary carcinomas; potential therapeutic target	(88)
Sekhar *et al*, 2023	GPX4	Regulates ferroptosis	Potential therapeutic target for inducing ferroptosis in thyroid cancer cells	(89)
Song *et al*, 2023	HIF-1α/YAP signaling	Rewrites glucose/iodine metabolism	Promoted cancer progression; potential therapeutic target for aggressive PTC	(90)
Sun *et al*, 2018	RAI therapy	Improved overall survival	Beneficial for patients with PTC and cervical lymph node metastases	(91)

Table I. Continued.

First author, year	Key target	Function	Clinical significance	(Refs.)
Valvo *et al*, 2021	ACC2	Rate-limiting enzyme for *de novo* lipid synthesis	Potential therapeutic target for overcoming resistance to BRAF (V600E) inhibitors	(92)
Wen *et al*, 2021	PDZK1IP1, TMC3, LRP2, KCNJ13	Lipid metabolism-related genes	Potential prognostic indicators for recurrence in PTC	(58)
Wu *et al*, 2020	miR-1256	Inhibited cell proliferation and cell cycle progression	Potential therapeutic target by targeting HTR3A in PTC	(93)
Xia *et al*, 2023	Lactate metabolism-related lncRNAs	Involved in lactate metabolism	Potential prognostic indicators for PTC prognosis, mutation and tumor microenvironment	(94)
Xie *et al*, 2022	Glucose metabolism-related genes	Involved in glucose metabolism	Constructed prognostic prediction model for PTC; potential therapeutic targets for guiding immunotherapy	(53)
Xu and Feng 2019	HOXD-AS1	Oncogenic lncRNA	Potential biomarker for the prediction of clinical progression in PTC	(95)
Yu *et al*, 2018	GLS	Mediated glutamine dependence	Potential therapeutic target for the inhibition of glutaminolysis and reducing mitochondrial respiration	(26)
Yun *et al*, 2022	Anticancer drug sensitivity-related genetic differences	Affected therapeutic approaches	Potential for the development of novel combination therapies for refractory PTC	(96)
Zarkesh *et al*, 2018	MMP-9	Prognostic biomarker	Elevated levels associated with malignant factors; potential biomarker for differentiating PTC from MNG	(97)
Zeng *et al*, 2019	HSDL2	Regulated lipid metabolism and cell proliferation	Promotes tumor progression; potential therapeutic target	(98)
Zhang *et al*, 2019	Bcl-2, hsa-miR-181a-5p	Regulatory networks in PTC	Potential biomarkers for PTC pathogenesis	(99)
Zhang *et al*, 2021	Amino acid metabolomics	Involved in amino acid metabolism	Potential biomarkers for early diagnosis of PTC in saliva	(100)
Zhao *et al*, 2023	DNA methylation	Associated with lymph node metastasis	Potential biomarkers for PTC lymph node metastasis	(101)

PTC, papillary thyroid cancer; MCT8, monocarboxylate transporter 8; circKIF4A, circular kinesin family member 4A; miR, microRNA; GPX4, glutathione peroxidase 4; circRAD18; PDK1, 3-phosphoinositide-dependent protein kinase-1; IL13RA2, interleukin-13 receptor subunit α-2; ST6GAL1, β-galactoside α2,6-sialyltransferase 1; DIRC3, disrupted in renal carcinoma 3; FSTL1, follistatin-like 1; FTO, fat mass and obesity-associated gene; APOE, apolipoprotein E; PHGDH, phosphoglycerate dehydrogenase; OGT, O-linked N-acetylglucosamine transferase; YAP, yes-associated protein; LPL, lipoprotein lipase; FATP2, fatty acid transport protein 2; CPT1A, carnitine palmitoyltransferase 1A; HHV-6A, human herpesvirus 6A; HIF-1α, hypoxia inducible factor-1α; RAI, radioactive iodine; ACC2, acetyl-CoA carboxylase 2; PDZK1IP1, PDZ domain-containing kidney-specific protein 1-interacting protein 1; TMC3, transmembrane channel-like 3; LRP2, low-density lipoprotein receptor-related protein 2; KCNJ13, potassium inwardly rectifying channel subfamily J member 13; HTR3A, 5-hydroxytryptamine; HOXD-AS1, HOXD cluster antisense RNA 1; MNG, multinodular goiter; GLS, glutaminase; lncRNA, long non-coding RNA; HSDL2, hydroxysteroid dehydrogenase-like 2; T4, L-thyroxine; SOD3, superoxide dismutase; GLR, glucose-to-lymphocyte ratio; Ki-67, antigen Kiel 67; EMT, epithelial-mesenchymal transition; BRAFi, BRAF inhibitor.

that treatment approaches with triple targeted inhibition (such as simultaneously blocking BRAF, MEK and EGFR) or combined immunotherapies might be needed to address drug resistance challenges in this setting (119).

While surgical resection remains the cornerstone of PTC management, emerging multimodal strategies address key limitations in recurrence prevention and metastatic control. Recent advances in nano-theranostics have yielded TME-responsive platforms such as the polypyrrole (Ppy)-poly(vinylimine)-siILK nanocomplex, which integrates photothermal ablation with gene silencing for synergistic anti-PTC efficacy (120). This system leverages near-infrared-activated gelatin-stabilized Ppy for precise photothermal conversion while exploiting pH-responsive charge inversion to mediate lysosomal escape of siILK payloads, achieving dual suppression of primary tumor growth and lymphatic metastasis. Real-time visualization of tumor-specific Ppy localization further enhances therapeutic precision.

Complementary to such technological innovations, clinical optimization requires consideration of endocrine-metabolic variables. Thyroglobulin antibody dynamics, modulated by iodine homeostasis in thyroid TMEs, may serve as both prognostic biomarkers and therapeutic adjuvants, which necessitates personalized dietary iodine regulation during intervention (121).

Collectively, these developments underscore the paradigm shift toward precision multimodality in PTC care. Although radical surgery remains primary for tumor debulking, its combination with photothermal-gene therapy and metabolic modulation provides a multimodal strategy against locoregional recurrence and systemic dissemination, which are key unmet needs in advanced PTC management.

3. FTC

FTC is a notable type of thyroid cancer and its incidence exhibits distinct trends (122-124) across various regions (125). The incidence rate of FTC in the United States increased significantly from 3.98 in 1980-1984 to 9.88 in 2005-2009. In the United States, non-Hispanic whites have the highest incidence rate of thyroid cancer, followed by Asian/Pacific islanders, Hispanics and non-Hispanic blacks. The pathogenesis of FTC is highly complex, involving numerous genetic and epigenetic alterations. Of these, mutations in the Ras gene are among the most prevalent molecular events associated with FTC (126), with the highest Ras mutation rate (61.5%). Ras gene mutations primarily disrupt the Ras-MAPK signaling pathway, which leads to the abnormal activation of several downstream proteins, such as Raf. This disruption results in aberrant cell proliferation, impaired differentiation and tumor formation (127,128). Previous studies have demonstrated that Ras gene mutations are not only associated with the pathogenesis of FTC but that they are also closely associated with the invasiveness, risk of recurrence and overall prognosis of the disease (129,130).

Molecular mechanisms. lncRNAs may regulate the progression of FTC by influencing cell proliferation, apoptosis, EMT and miRNA expression (131). 1-[1-2,5-dimethyl-1H-pyrrol-3-yl]-2-pyrrolidin-1-ylethanone (IU1) inhibits FTC proliferation and migration by targeting ubiquitin-specific protease 14 (USP14), a deubiquitinating enzyme that affects various cellular processes, including cell survival, DNA repair, endoplasmic reticulum stress, endocytosis and inflammatory responses. IU1 induces autophagy and proteasomal stimulation in a cell type-dependent manner, increasing autophagy in ML1 cancer cells and resulting in decreased proliferation and migration of these cells (132). Piperonine induces apoptosis and autophagy in human FTC cells through the reactive oxygen species (ROS)/AKT signaling pathway (133). Aberrant regulation of suprabasin (SBSN) has been implicated in the development of cancer and immune disorders. The most abundant evidence regarding SBSN comes from cancer research. SBSN expression is the response of cancer cells to anti-tumor T-cell activity. The role of SBSN in adapting to stress conditions, activating pro-survival signaling pathways and angiogenesis is often associated with carcinogenic effects. SBSN influences tumor cell migration, proliferation, angiogenesis, immune cell infiltration and the cancer immune cycle (134). The infiltration of M2 macrophages and regulatory T cells (Tregs) was significantly increased in tumor tissues with high SBSN expression. SBSN may serve a key role in the development of thyroid cancer, tumor dedifferentiation and immunosuppression as an important regulator of tumor immune cell infiltration. The pox virus and zinc finger protein/BTB and AT-hook-containing zinc finger protein 1 gene can inhibit the malignant phenotype of thyroid follicular epithelial cells and thyroid cancer cells, and it participates in the dedifferentiation process of thyroid cancer (135,136).

The knockdown of stromal interaction molecule 1 (STIM1) can reduce the invasion and proliferation of human FTC cells while enhancing the expression of thyroid-specific proteins. STIM1 and ORAI calcium release-activated calcium modulator 1 (ORAI1) calcium channels mediate store-operated calcium entry (SOCE) and regulate various cellular functions. The presence of STIM1 or ORAI1 enhances SOCE in thyroid cancer ML-1 cells, which promotes invasion and the expression of primary sphingosine-1-phosphate and VEGF-2 receptors (137,138). Compared with that in normal tissues, STIM1 protein was upregulated in thyroid cancer tissues, inhibiting the expression of the thyroid-stimulating hormone receptor and thyroid-specific proteins, while increasing iodine absorption (139).

Emerging evidence highlights key molecular drivers in FTC pathogenesis, with dysregulated signaling networks and intercellular communication mechanisms emerging as key therapeutic targets (140,141). The transcription factor prospero homeobox 1 orchestrates angiogenic programming during metastatic dissemination through vascular remodeling mechanisms (142). Similarly, exosome-mediated tumor-stromal crosstalk facilitates malignant progression, as demonstrated by annexin A1-enriched vesicles from SW579 cells inducing proliferative activation and EMT in recipient Nthy-ori3-1 cells via paracrine signaling (143).

Regarding the MAPK signaling pathway, sclerostin domain containing 1 (SOSTDC1) inhibits the proliferation, migration and EMT of FTC cells by inhibiting the PI3K/AKT and MAPK/ERK signaling pathways (144). By contrast, family with sequence similarity 83 member F upregulation serves a pro-cancer role by cross-activating follicular cell

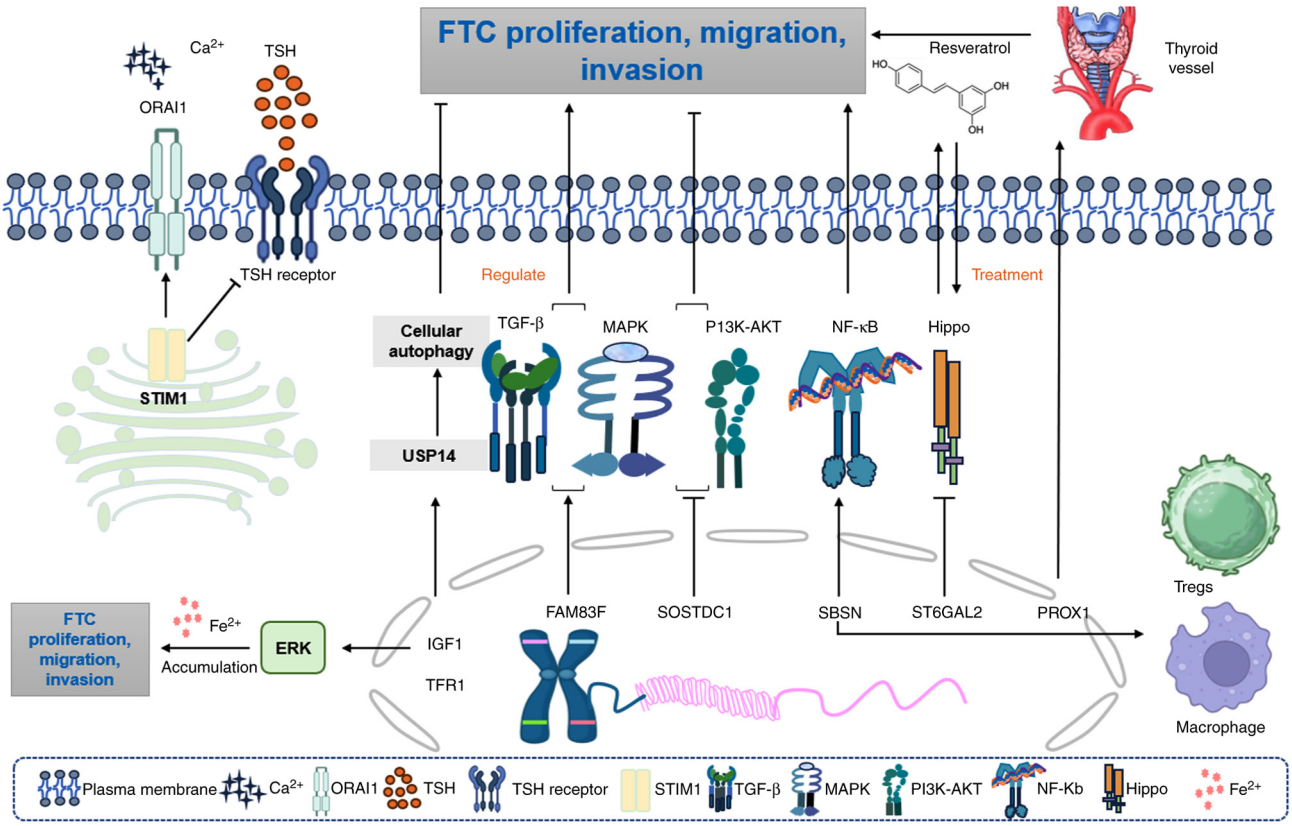

Figure 3. Molecular mechanisms underlying FTC progression. The diagram systematically delineates: i) Calcium signaling through ORAI calcium release-activated calcium modulator 1/STIM1 channels; ii) TSH receptor activation; and iii) core regulatory pathways (TGF-β, MAPK, PI3K/AKT, NF-κB and Hippo) coordinating cellular proliferation, migration and invasion. Key components include USP14-mediated autophagy regulation, ERK activation through the IGF1/TFR1 axis and iron accumulation facilitated by the FAM83F/SOSTDC1/SBSN/ST6GAL network. Immune microenvironment interactions featuring Tregs and tumor-associated macrophages are indicated in the lower right quadrant. Resveratrol is presented as a potential therapeutic agent targeting these molecular pathways. The black arrows indicate conventional signaling pathway interactions. FTC, follicular thyroid cancer; STIM1, stromal interaction molecule 1; TSH, thyroid stimulating hormone; USP14, ubiquitin-specific protease 14; IGF1, insulin-like growth factor 1; TFR1, transferrin receptor 1; SOSTDC1, sclerostin domain-containing protein 1; SBSN, suprabasin; ST6GAL2, β-galactoside α-2,6-sialyltransferase 2; Tregs, regulatory T cells; ORAI, ORAI calcium release-activated calcium modulator 1; PROX1, prospero homeobox 1; FAM83F, family with sequence similarity 83 member F.

transformation through synergizing with the MAPK/TGFβ pathway, which activates thyroid cell migration and causes resistance to chemotherapy (145). Furthermore, β-galactoside α-2,6-sialyltransferase 2 (ST6GAL2)-mediated glycosylation perturbation inhibits Hippo tumor suppressor signaling, establishing a dual-drug node in FTC tumorigenesis (146). Pharmacological modulation using resveratrol reverses ST6GAL2-Hippo axis dysfunction, which highlights the therapeutic potential of pathway-specific inhibitors (146). Concurrently, iron homeostasis disruption via transferrin receptor 1 (TFR1)-dependent ERK hyperactivation creates metabolic vulnerabilities exploitable through iron chelation strategies (147). Cell cycle control mechanisms further contribute to FTC pathobiology. The BRCA1/cyclin-dependent kinase inhibitor 2C tumor suppressor axis constrains cyclin D-CDK4/6 signaling, with CDK4 inhibitor sensitivity demonstrating clinical potential in cyclin D-dysregulated FTC subtypes (148). Genomic landscape analyses reveal recurrent mutations in chromatin remodelers (for example, nuclear receptor corepressor 1), mRNA processing factors [e.g., poly(A) binding protein cytoplasmic 1/3] and mitotic regulators (e.g., cell division cycle 27), which suggests epigenetic vulnerabilities (149). TME reprogramming via fibroblast-mediated signaling amplifies FTC aggressiveness, highlighting stromal co-targeting strategies as promising therapeutic frontiers (150).

This integrated framework (Fig. 3) delineates the molecular architecture of FTC, emphasizing oncogenic drivers across signal transduction, metabolic adaptation and microenvironmental crosstalk, thereby informing precision therapeutic development for thyroid malignancies in the future.

Progress in diagnosis. As a marker for FTC, family with sequence similarity 172 member A (FAM172A) promotes the development of this malignancy. FAM172A serves a key role in the pathogenesis of FTC through the ERK1/2 and JNK signaling pathways. The downregulation of FAM172A can inhibit the proliferation, invasion and migration of FTC cells via these pathways (151). Emerging insights into FTC pathogenesis reveal paradoxical oncogenic signaling activation within canonical tumor suppressor pathways. Mechanistic studies demonstrated that protein kinase A-mediated adenosine monophosphate-activated protein kinase activation via liver kinase B1 (LKB1) phosphorylation exhibits context-dependent tumorigenic effects, with accumulating preclinical and clinical evidence associating LKB1 pathway hyperactivation to FTC progression (152-154). Concurrently, genomic profiling of thyroid malignancies identifies feline McDonough

sarcoma-like tyrosine kinase 3 domain mutations as recurrent targetable alterations, although their functional contribution to FTC oncogenesis and clinical utility for precision kinase inhibition therapies remains to be fully elucidated (155).

Treatment. Current therapeutic strategies for advanced FTC encompass diverse advanced modalities, including radioactive iodine (131I) therapy, multikinase inhibitors (MKIs) and RET/NTRK/ALK inhibitors. These approaches target key molecular pathways and resistance mechanisms to enhance therapeutic efficacy in refractory cases.

Targeted therapeutic approaches primarily involve multikinase inhibitors and PI3K pathway modulation. The treatment of advanced FTC primarily relies on indirect evidence derived from clinical trials of MKIs, which are associated with notable toxicity and may adversely affect quality of life in patients. The antitumor effect of the pan-class I PI3K inhibitor buparlisib on refractory follicular carcinoma and poorly differentiated thyroid cancer (PDTC) dysregulation was investigated, given that PI3K pathway dysregulation is commonly observed in advanced FTC and PDTC, and has been associated with tumorigenesis and disease progression. The efficacy of buparlisib in the treatment of advanced FTC and PDTC has been found to be limited. However, the observed reduction in tumor growth rate may suggest that oncogenic pathways and/or escape mechanisms are not entirely inhibited (156).

Natural compounds demonstrate antitumor effects through redox modulation and signaling pathway regulation. Hydroxytyrosol, a prominent phenolic compound present in olive oil, exhibits antitumor effects attributed to its pro-oxidative properties, as well as its capacity to inhibit cell proliferation and promote apoptosis in various tumor cell lines, including MCF-7 and MDA-MB-231 (157). Notably, high doses of hydroxytyrosol have been shown to induce apoptosis in papillary and FTC cells (158). Curcumin induces ferroptosis in FTC through heme oxygenase-1 (HO-1) upregulation (159). Mechanistic studies have revealed that HO-1 serves as a key mediator of oxidative stress regulation, with its abnormal upregulation observed in FTC vs. adjacent tissues. By contrast, elevated HO-1 levels reduce cellular viability via ferroptosis pathway activation (160,161). Curcumin exerts dual antitumor effects by enhancing HO-1 expression to suppress FTC proliferation while potentiating ferroptosis-mediated cell death. These findings position the HO-1-ferroptosis axis as a key therapeutic target in FTC pathogenesis (162). Matrine, a bioactive alkaloid derived from *Sophora flavescens*, exhibits anti-neoplastic effects in FTC by modulating the miR-21/phosphatase and tensin homolog deleted on chromosome ten (PTEN)/AKT signaling axis. Mechanistic studies have demonstrated that matrine suppresses miR-21 expression, thereby alleviating its inhibitory effect on PTEN (163). The subsequent upregulation of PTEN inactivates AKT phosphorylation, which induces caspase-dependent apoptosis and proliferation arrest in FTC-133 cells. This dual regulation of miRNA and kinase signaling pathways highlights the therapeutic potential of matrine in targeting FTC pathogenesis (163).

Molecular-targeted radiosensitization represents an advanced strategy exploiting specific pathways to overcome radioactive iodine (RAI) resistance. Sorafenib and sunitinib are effective treatment options for delaying disease progression in patients with RAI-refractory metastatic DTC, both demonstrating acceptable safety profiles (164). Furthermore, sunitinib appears to exhibit some efficacy even in patients who experience disease progression following treatment with sorafenib (165). Inhibition of β-catenin expression may enhance the efficacy of radioiodine treatment in invasive FTC cells by modulating the localization of the sodium iodide symporter (NIS). Following the inhibition of β-catenin expression, FTC cells that exhibit high levels of hypoxia inducible factor-1α can be completely suppressed by radioiodine treatment. This mechanism may be associated with the regulation of NIS localization (166).

Chemotherapy remains an alternative for multi-resistant cases. Conventional chemotherapy with a gemcitabine plus oxaliplatin (GEMOX) regimen is an off-label treatment that demonstrates some efficacy and a favorable safety profile in advanced DTC. Dias *et al* (167) reported a case of metastatic FTC in a patient who developed resistance to multiple therapies. Notably, OS time appeared to be significantly prolonged by this chemotherapy due to durable responses to GEMOX. In conclusion, GEMOX may be a viable option for patients with thyroid cancer who do not respond to MKIs.

Collectively, as shown in Table II (168-190), FTC represents a clinically notable endocrine malignancy characterized by complex pathogenesis involving dysregulation of multiple signaling cascades and molecular biomarkers. The present review summarizes current insights into molecular mechanisms underlying FTC progression, particularly highlighting emerging evidence implicating FAM172A-mediated pathways as potential therapeutic targets. Contemporary management of advanced FTC necessitates consideration of molecularly targeted agents such as MKIs alongside conventional chemotherapeutic protocols, which have demonstrated measurable clinical responses in selected patient cohorts despite non-negligible toxicity profiles. Therefore, optimized therapeutic algorithms for FTC management should incorporate comprehensive biomarker profiling to enable precision medicine approaches while strategically combining multimodal interventions to maximize therapeutic efficacy.

4. MTC

MTC is a neuroendocrine tumor that originates from parafollicular cells of the thyroid gland. The molecular mechanisms underlying MTC primarily involve mutations in the RET proto-oncogene, which is the most prevalent genetic driver of this cancer (191). Mutations in the RET gene result in alterations to the protein conformation in both the inner and outer regions of cells, leading to excessive cell proliferation and carcinogenesis. In addition to RET mutations, alterations in the Ras gene also contribute to the pathogenesis of MTC, particularly in cases of sporadic MTC.

Recent studies have identified novel pathogenic genes associated with MTC, including BRAF and neurofibromatosis type 1. These findings have enhanced current understanding of the molecular pathological mechanisms underlying MTC. By analyzing the genome, transcriptome, epigenome, proteome and phosphoproteome of a substantial cohort of patients with MTC, researchers have, to the best of our knowledge, created the first comprehensive proteomic profile of MTC globally. This classification based on protein expression profiles

Table II. FTC therapeutic targets with functional and clinical profiles.

First author, year	Key target	Function	Clinical significance	(Refs.)
Heffess and Thompson, 2001	Capsular/vascular invasion	Indicators of malignancy in FTC	Diagnostic criteria for FCMI to guide conservative surgical management and improve patient outcomes	(168)
Hernandez-Prera & Wenig 2024	Ras mutations	Promoted cell proliferation and signaling pathways	Identified Ras-mutant FTCs, aiding in distinguishing between benign and malignant tumors, thus guiding appropriate treatment	(169)
Lang *et al*, 2007	Prognostic factors	Predicted survival and recurrence in PTC and FTC	Tailored staging systems for papillary and follicular thyroid carcinoma to optimize individualized treatment strategies	(170)
Levi *et al*, 2013	MMP-2 and MMP-9	Involved in tumor invasion and metastasis	Non-invasive photoacoustic imaging for early detection of FTC, enhancing early-stage diagnosis and treatment planning	(171)
Li *et al*, 2024	Circulating sEV-miRNAs	Biomarkers for FTC diagnosis	Developed a non-invasive miRNA classifier to assist in diagnosing FTC, reducing unnecessary surgeries and improving surgical strategy	(172)
Liang *et al*, 2018	lncRNA HCP5	Promoted tumor progression via miRNA sponge mechanism	Identified HCP5 as a potential diagnostic and therapeutic target for FTC, contributing to improved diagnosis and therapy	(173)
Lin *et al*, 2022	miR-199a-5p/ PD-L1 axis	Regulated cell proliferation, migration, and invasion	Investigated PD-L1 as a therapeutic target to inhibit tumor progression and metastasis in FTC	(174)
Lo *et al*, 2005	Histomorphology	Predicted survival and recurrence in FTC	Validated staging systems specifically for FTC to identify low-risk patients for conservative management	(175)
Macerola *et al*, 2022	Trk protein expression	Marker for NTRK rearrangements	Limited accuracy of Trk IHC for identifying NTRK-rearranged tumors; suggested alternative detection methods for effective targeted therapies	(176)
Park *et al*, 2022	TERT promoter mutations	Associated with tumor aggressiveness	Refined cancer-specific survival prediction in FTC, improving DFS and CSS predictability	(177)
Paulsson *et al*, 2020	DICER1	Regulated miRNA processing	Downregulation of DICER1 in FTC suggests its role as a tumor suppressor and potential early tumorigenic marker	(178)
Pulcrano *et al*, 2007	Cell proliferation markers	Predicted prognosis in PDFC	Identified prognostic indicators for PDFC, aiding in patient management and treatment decisions	(179)
Repaci *et al*, 2022	BRAF K601N mutation	Promoted tumor progression and metastasis	Reported on unusual BRAF mutations associated with widespread bone metastases, highlighting the need for further research on uncommon BRAF mutations	(180)
Romitti *et al*, 2013	MAPK, PI3K	Involved in thyroid tumorigenesis and progression	Provided insights into genetic alterations driving thyroid cancer development, informing potential therapeutic targets	(181)
Rossing *et al*, 2012	miR-199b-5p, miR-144	Regulated proliferation and tumorigenesis	Identified downregulated miRNAs as potential diagnostic markers and therapeutic targets for FTC	(182)

Table II. Continued.

First author, year	Key target	Function	Clinical significance	(Refs.)
Saburi *et al*, 2022	$CD8^+$ T cells, PD-L1	Influenced tumor invasion and immune response	Revealed unique immune profiles at the invasive front of FTC, providing insights into tumor-immune interactions	(183)
Staubitz *et al*, 2019	Surgical management strategies	Guided surgical decision-making for FTC	Discussed optimal surgical approaches for FTC, balancing preoperative diagnosis and intraoperative findings	(184)
Stenman *et al*, 2019	TERT promoter mutations	Associated with tumor aggressiveness and spatial heterogeneity	Highlighted the importance of TERT promoter mutations in FTC, influencing clinical management and molecular biology understanding	(185)
Taylor *et al*, 1998	Radioiodine therapy	Improved overall and cancer-specific mortality	Supports the use of radioiodine therapy for high-risk patients with thyroid cancer, enhancing survival outcomes	(186)
Thompson, 2023	Ki-67 labeling index	Measured proliferation rate	Differentiated between high-grade differentiated follicular cell-derived thyroid carcinoma and poorly differentiated thyroid carcinoma, aiding in prognosis and treatment	(187)
Wenter *et al*, 2021	Oncocytic carcinoma	Compared clinical outcomes with classical FTC	Identified OFTC as having a higher recurrence rate and worse disease-free survival, supporting separate categorization	(188)
Yu *et al*, 2022	Ultrasound radiomics features	Non-invasively differentiated FTC from adenoma	Developed a combined model integrating radiomics and clinical features to reduce unnecessary diagnostic thyroidectomies	(189)
Zhang *et al*, 2021	DNA methylation markers	Discriminated FTC from adenoma	Constructed a DNA methylation-based prediction model for accurate preoperative diagnosis, reducing unnecessary surgeries	(190)

FTC, follicular thyroid cancer; FCMI, minimally invasive FTC; PTC, papillary thyroid cancer; sEV-miRNAs, small extracellular vesicle-microRNA; lncRNA, long non-coding RNA; HCP5, histocompatibility leukocyte antigen complex P5; PD-L1, programmed death ligand-1; Trk, tropomyosin receptor kinase; IHC, immunohistochemistry; NTRK, neurotrophic tyrosine receptor kinase; TERT, telomerase reverse transcriptase; DICER1, dicer 1, ribonuclease III; DFS, disease-free survival; CSS, cause-specific survival; PDFC, poorly differentiated follicular thyroid carcinoma; Ki-67, antigen Kiel 67.

offers notable reference data for the precise treatment of MTC (192-194).

Furthermore, the differential expression and gene regulation of miRNA in MTC have garnered notable attention. These studies offer potential biomarkers and therapeutic strategies for the early diagnosis, accurate prognosis and gene therapy of MTC. Collectively, the molecular mechanisms underlying MTC involve the mutation and regulatory expression of multiple genes and these findings contribute to the development of novel therapeutic approaches and the enhancement of patient prognosis.

Molecular mechanisms. From a genetic perspective, RET, Harvey rat sarcoma viral oncogene homolog (HRAS) and KRAS are the most notable genes in MTC. Epigenetically, the development of MTC may be associated with the methylation of the telomerase reverse transcriptase promoter, upregulation of histone methyltransferases such as enhancer of zeste homolog 2 and SET and murine homolog of Max-domain containing 3, and notable fluctuations in non-coding RNAs, including Ras association domain family member 1A (195). Unique transcriptional and functional alterations in myeloid cells manifest prior to tumor invasion and initiate within the bone marrow, indicating their active role in shaping the tumor immune microenvironment (196). The PD-1/PD-L1 pathway is expressed in patients with MTC and has been significantly correlated with intraoperative distant metastasis, positioning it as a potential novel target for MTC treatment (197). A comprehensive understanding of PD-1/PD-L1 expression and its association with immunotherapy response may provide a key foundation to address refractory MTC.

Progress in diagnosis. The management of locally advanced or metastatic MTC necessitates a thorough workup, which includes the measurement of serum procalcitonin and carcinoembryonic antigen, assessment of their doubling times and comprehensive imaging to evaluate the extent of disease, aggressiveness and treatment requirements. Recent advances in MTC diagnostics have established multimodal approaches combining imaging guidance with molecular profiling. Ultrasound-guided fine-needle aspiration integrated with liquid-based cytology and immunocytochemical analysis demonstrates high preoperative diagnostic reliability for MTC through enhanced cellular characterization (198). Complementing this, circulating miRNA signatures (particularly miR-26b-5p and miR-451a) exhibit robust diagnostic accuracy metrics, offering non-invasive diagnostic adjuncts that synergize with conventional techniques to enable precision risk stratification (199). These complementary strategies collectively advance MTC detection paradigms by bridging cytomorphological precision with systemic molecular biomarkers, underscoring their translational potential to optimize clinical decision-making in thyroid oncology.

Treatment. MTC constitutes 1-5% of thyroid malignancies (200). Recent findings have indicated that targeted molecular therapies, which inhibit RET and other tyrosine kinase receptors involved in angiogenesis, enhance progression-free survival in patients with advanced MTC (201-203). Two drugs, vandetanib and cabozantinib, have been approved for the treatment of progressive or symptomatic MTC, while several others (selpercatinib and pralsetinib) have demonstrated variable efficacy (204). Emerging therapeutic strategies for MTC target oncogenic signaling vulnerabilities through multimodal pharmacological interventions. Somatostatin analogs (octreotide/pasireotide) demonstrate selective anti-proliferative effects in RET-driven MTC subsets by modulating neuroendocrine signaling cascades, demonstrating synergistic potential with mitochondrial-targeting agents when combined with kinase inhibitors, such as vandetanib or cabozantinib (205). Notably, ceritinib maintains durable clinical efficacy with favorable toxicity profiles in pretreated MTC cohorts, which suggests ALK-independent therapeutic utility (205).

At the molecular level, mTOR pathway dysregulation in MTC involves protein interacting with carboxyl terminus 1-mediated spliceosomal control, where its upregulation counteracts everolimus-induced cytotoxicity via PTEN suppression and AKT-serine (Ser)473 hyperphosphorylation, revealing novel resistance mechanisms in neuroendocrine neoplasms (206). Concurrently, the glial cell line-derived neurotrophic factor (GDNF)/RET/CDK5/STAT3 signaling axis emerged as a key driver of MTC progression. Mechanistic studies reported that GDNF-induced RET phosphorylation activates cyclin-dependent kinase 5 (CDK5), which phosphorylates STAT3 at Ser727 to sustain proliferative signaling (207-209). This pathway is enhanced by a unique feature of MTC biology, such as direct RET-CDK5 interaction (207).

These findings collectively map therapeutic vulnerabilities across three dimensions: Neuroendocrine receptor modulation, mTOR-AKT crosstalk and RET-kinase network targeting. The identification of CDK5 as a RET-interacting kinase partner particularly highlights its promise as a druggable node for precision intervention strategies in advanced MTC management.

MTC often exhibits resistance to standard therapies, which highlights the need for alternative treatment options. AB3, a novel histone deacetylase inhibitor, has demonstrated efficacy in inhibiting the proliferation of MTC cells *in vitro*. However, its clinical application *in vivo* is hindered by poor water solubility and stability, rapid clearance and insufficient tumor targeting ability. Recent advancements in MTC nanotheranostics have yielded precision-targeted delivery systems to optimize therapeutic efficacy (210,211). Engineered single-molecule micelles incorporating AB3 chemotherapeutic payloads with KE108 peptide-directed active targeting demonstrated enhanced tumor-selective accumulation, achieving 2.3-fold greater cytotoxicity in MTC models compared with free drug formulations. This nanoplatform significantly suppresses tumor biomarker expression while mitigating off-target effects key for patients with comorbidities, particularly those with cardiovascular complications requiring blood pressure stability (212). Furthermore, these micelles demonstrated optimal anticancer effects *in vivo* without notable systemic toxicity, which offers a promising strategy for targeted therapy in MTC.

As shown in Fig. 4, current evidence delineates that the molecular pathogenesis of MTC arises from convergent oncogenic pathways encompassing both genetic drivers (notably the RET proto-oncogene and Ras family members,

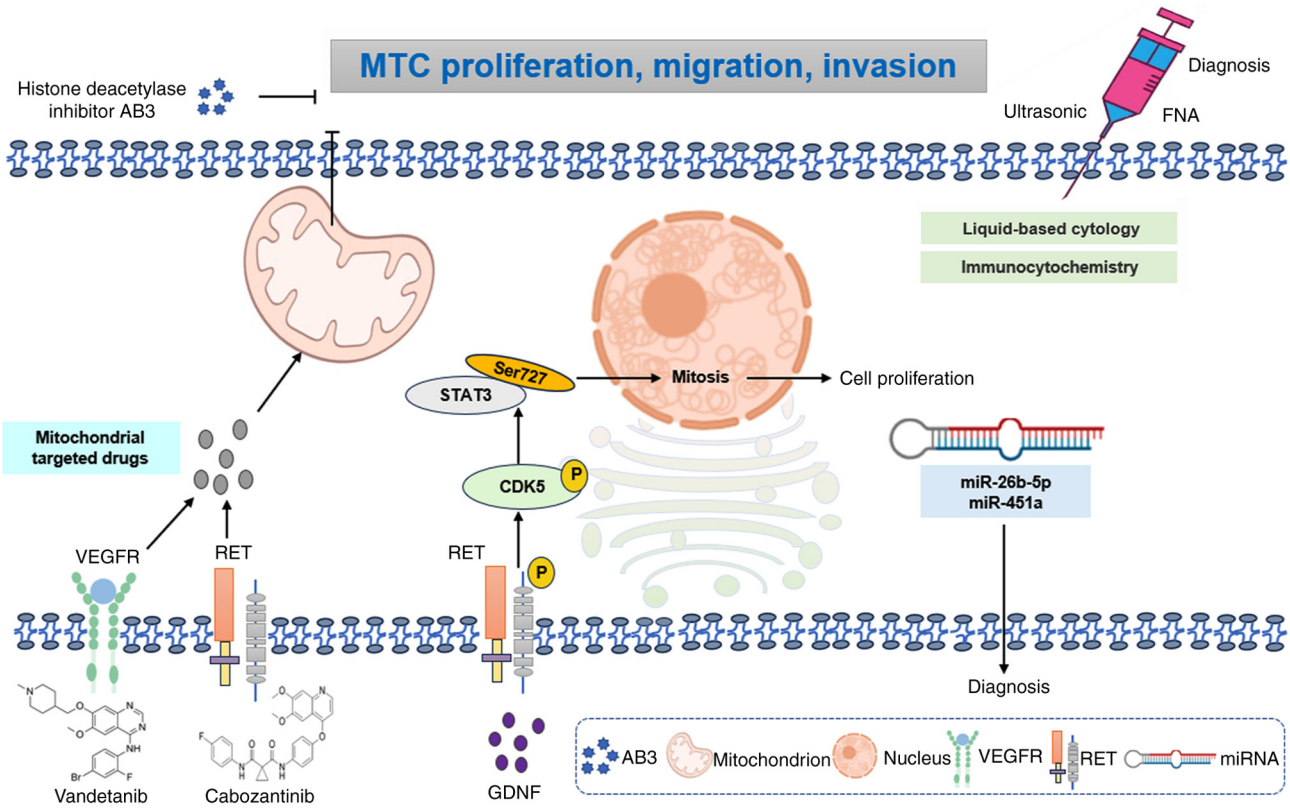

Figure 4. Schematic illustrating the therapeutic and diagnostic mechanisms in MTC. The schematic is structured as: i) Targeted therapy with tyrosine kinase inhibitors (vandetanib, cabozantinib and GDNK) blocking RET/VEGFR signaling; ii) diagnostic workflow exhibiting ultrasound-guided FNA followed by liquid-based cytology and immunocytochemical analysis; and iii) molecular mechanisms involving CDK5-mediated STAT3 phosphorylation at Ser727 (P). The histone deacetylase inhibitor AB3 is shown in the epigenetic regulation domain (upper left). Mitochondrial-targeted agents are indicated interacting with membrane receptors (green, VEGFR; orange, RET). Directional arrows denote signaling amplification. MTC, medullary thyroid cancer; FNA, fine-needle aspiration; RET, rearranged during transfection; Ser727, serine 727; miR, microRNA; P, phosphorylation; GDNF, glial cell line-derived neurotrophic factor; AB3, A new histone deacetylase inhibitor.

including HRAS/KRAS) and epigenetic regulators, such as chromatin-modifying enzymes and non-coding RNA networks. Furthermore, the PD-1/PD-L1 pathway is emerging as a promising therapeutic target. From a diagnostic standpoint, ultrasound-guided thyroid fine-needle aspiration combined with liquid-based cytology and immunocytochemistry provides a reliable preoperative diagnostic approach. Furthermore, circulating miRNA profiles have emerged as promising non-invasive biomarkers enabling molecular subtyping in clinical practice. Targeted therapeutic agents, particularly MKIs, have been approved by regulatory agencies or demonstrated clinical efficacy in controlled trials. Recent mechanistic investigations have delineated oncogenic signaling networks governing malignant proliferation, exemplified by CDK5-mediated phosphorylation events that regulate cell cycle progression, providing a mechanistic rationale for novel therapeutic strategies. Notably, targeted delivery of therapies using single-molecule micelles has demonstrated promising anticancer effects both *in vitro* and *in vivo*.

5. ATC

ATC is a rare malignancy, accounting for 1-2% of all thyroid cancer cases (7). Despite its rarity, ATC accounts for the majority of thyroid cancer-related deaths (213). The median overall survival of ATC is 3-5 months, and the disease-specific mortality rate is close to 100%. Typically, ATC arises from pre-existing thyroid cancer lesions, as evidenced by the co-existence of differentiated or PDTC regions. Characterized by the accumulation of multiple oncogenic alterations, previous studies have indicated that an increase in the number of these alterations is correlated with a heightened degree of dedifferentiation and invasiveness (214,215). The clinical management of ATC necessitates a multidisciplinary approach, with treatment modalities such as surgery, radiotherapy or chemotherapy being considered in accordance with the latest guidelines from the American Thyroid Association (216). In addition to conventional therapies, novel molecular targeted therapies represent a promising area of emerging treatment (214). These agents frequently include multiple receptor tyrosine kinase inhibitors (TKIs), such as lenvatinib, sorafenib, cabozantinib and vandetanib, several of which have demonstrated notable results in clinical trials (217). Therefore, clinical trials are currently underway to assess the safety, efficacy and effectiveness of these novel pharmacological agents. The present review presents the most recent clinical and pathological features of ATC and explores the molecular biology underlying this disease. Furthermore, the present review discusses the latest literature on traditional therapies, newly available treatments and potential future therapies for ATC (Table III) (218-255).

Table III. Available treatment options in previously published literature for MTC and ATC.

First author, year	Key target	Function	Clinical significance	(Refs.)
Al-Mohanna *et al*, 2023	PAC (curcumin analogue)	Induced apoptosis via mitochondrial pathway	Potential therapeutic agent for ATC by overcoming resistance to conventional therapies	(218)
Anderson *et al*, 1978	Calcitonin	Marker for familial MTC	Early detection marker for MTC, enabling timely surgical intervention	(219)
Ballal *et al*, 2022	SA.FAPi	Targeted FAP in aggressive MTC	Provided a theranostic approach for high-grade MTC refractory to standard treatments, improving quality of life	(220)
Bao *et al*, 2024	Siglec-15	Promoted immunosuppression and tumor progression in ATC	Emerging target for immunotherapy in ATC, aiming to enhance T cell activation and reduce immunosuppression	(221)
Biermann *et al*, 2011	TKIs, somatostatin receptors	Inhibited tyrosine kinases; target somatostatin receptors	Palliative strategies for advanced thyroid malignancies, addressing ineffective radioiodine therapy and conventional chemotherapies	(222)
Ceolin *et al*, 2019	RET proto-oncogene	Key driver in MTC tumorigenesis; mutations lead to hereditary and sporadic MTC	Identified RET as a therapeutic target for advanced MTC, focusingon multikinase inhibitors and next-generation small-molecule TKIs	(223)
Chintakuntlawar *et al*, 2019	Multimodal therapy	Combination of chemora-diotherapy and surgery for ATC	Preferred initial treatment for ATC, associated with improved overall survival	(224)
Choi *et al*, 2024	CPA4	Mediated crosstalk between M2 macrophages and ATC cells; promotes proliferation, migration, and invasion	Potential therapeutic target for ATC, aiming to disrupt the positive feedback loop between macrophages and cancer cells	(225)
Contarino *et al*, 2022	Capsule presence	Encapsulation associated with improved prognosis and absence of nodal metastases	Indicated favorable prognosis in MTC, guiding surgical and follow-up strategies	(226)
Cristinziano *et al*, 2020	NETs	Released by viable neutrophils in response to ATC	Potential target for therapeutic intervention in ATC, addressing chronic inflammation and cancer progression	(227)
D'Aprile *et al*, 2023	CD71	Involved in iron internalization; contributes to iron overload tolerance in ATC	Potential target to address ferroptosis resistance in ATC, improving therapeutic outcomes	(228)
Doolittle *et al*, 2022	CDK7-NOTCH1-cMYC	Regulated CSC activity in ATC	Targeting this signaling axis can inhibit CSC activity, providing a promising therapeutic strategy for ATC	(229)
Egan *et al*, 2021	CSPG4	Transmembrane proteoglycan with increased expression in aggressive thyroid cancer	Potential immunotherapeutic target for ATC, correlating with poor prognosis	(230)

Table III. Continued.

First author, year	Key target	Function	Clinical significance	(Refs.)
Harach & Williams 1983	Calcitonin	Marker for medullary carcinoma with glandular differentiation	Essential for accurate diagnosis of medullary carcinoma, even in cases with glandular features	(231)
Hu *et al*, 2023b	Alantolactone	Induced apoptosis and pyroptosis via ROS-mediated mitochondria-dependent caspase activation	Potential therapeutic agent for ATC, promoting immunogenic cell death	(232)
Li *et al*, 2022	Inflammatory markers	Predictive of clinicopathological features and postoperative calcitonin progression in MTC	Useful prognostic biomarkers for MTC, aiding in risk stratification and treatment planning	(233)
Li *et al*, 2023	NIS	Restored radioiodine uptake in ATC	Enhanced the therapeutic efficacy of radioactive iodine, serving as a promising adjunctive therapy for ATC	(234)
Li, 2021	Pyrvinium pamoate	Inhibited Wnt signaling, overcoming artemisinin resistance in ATC	Combination therapy with artemisinin for managing ATC, addressing drug resistance	(235)
Lu *et al*, 2023	Single-cell transcriptomics	Revealed anaplastic transformation process and identifies key milestones in ATC	Provided insights into intratumor transformation, highlighting novel therapeutic opportunities	(236)
Lu *et al*, 2021	Wee1	Regulated G_2/M progression; key for DNA damage repair	Potential therapeutic target for ATC, combining with other inhibitors to suppress tumor growth	(237)
Ma *et al*, 2023	LINC00886	Negatively regulated malignancy in ATC by interacting with PKR	Potential biomarker and therapeutic target for ATC, focusing on LINC00886/PKR/eIF2α signaling	(238)
Matrone *et al*, 2022	RET inhibitors, radionuclide therapy	Target RET mutations and somatostatin receptors	Systemic treatments for advanced and metastatic sporadic MTC, addressing rapid disease progression	(239)
Niccoli-Sire *et al*, 2001	RET mutations	Driver mutations in familial MTC; associated with late-onset disease	Guided optimal timing for thyroidectomy in familial MTC, considering delayed C cell disease appearance	(240)
Pan *et al*, 2023	IL2RA$^+$ VSIG4$^+$ macrophages	Key subpopulation in immunosuppressive microenvironment of ATC	Potential therapeutic target to disrupt immunosuppression and enhance antitumor immunity	(241)
Pozdeyev *et al*, 2018	CDKN2A, CDKN2B, KDR, KIT, PDGFRA	Genes involved in genetic alterations associated with ATC	Identified genetic alterations associated with anaplastic transformation, offering diagnostic and therapeutic insights	(242)
Pusztaszeri *et al*, 2014	RET mutation	Key molecular alteration in MTC; enables early detection and specific therapies	Facilitated early detection and targeted therapies in MTC, improving patient outcomes	(243)

Table III. Continued.

First author, year	Key target	Function	Clinical significance	(Refs.)
Rougier *et al*, 1983	External radiotherapy, surgery	Treats locally advanced or metastatic MTC	Highlighted the importance of combined modalities for optimal treatment outcomes in MTC	(244)
Shakiba *et al*, 2024	MicroRNAs	Modulate fundamental cancer pathways; serve as therapeutic targets and biomarkers	Promising tools for evaluating medical outcomes and potential therapeutic targets in TC and MTC	(245)
Sherman *et al*, 2023	Paclitaxel + pazopanib	Combination therapy for ATC	Feasible and safe combination therapy, generating hypothesis-generating data for further investigation	(246)
Subbiah *et al*, 2018	Dabrafenib + trametinib	Targeted BRAF V600E mutation in ATC	Robust clinical activity and well-tolerated regimen for BRAF V600E-mutated ATC	(247)
Sugarman *et al*, 2023	SHMT2	Key enzyme in mitochondrial one-carbon metabolism	Targetable vulnerability in ATC, inhibiting cell proliferation and colony formation	(248)
Tang *et al*, 2022	USP26	Deubiquitylated and stabilized TAZ in ATC	Potential therapeutic target for ATC, focusing on Hippo pathway regulation	(249)
Wang *et al*, 2023	Lactylation (H4K12La)	Epigenetic mark translating metabolic signals into transcriptional regulation	Targeting lactylation can sensitize mutant ATC to BRAF V600E inhibitors, enhancing therapeutic efficacy	(250)
Wu *et al*, 2023	Autophagy-ferroptosis pathway	Regulated cell death mechanisms in ATC	Synergistic combination therapy to enhance antitumor effects in ATC	(251)
Zaballos *et al*, 2022	ERK dimerization	Key for Ras-to-ERK signaling in ATC	Inhibited ERK dimerization provides therapeutic benefits, particularly for BRAF-mutant ATC	(252)
Zhang *et al*, 2019	miR-155/SOCS1	miR-155 targets SOCS1, promoting ATC progression	Potential therapeutic target for ATC, focusing on miR-155/SOCS1 axis	(253)
Zhao *et al*, 2022	GSDMD and GSDME	Mediate pyroptosis in ATC	Two-way positive feedback interaction providing novel prospects for targeted therapy in ATC	(254)
Zhao *et al*, 2020	Clinicopathological characteristics	Compares pediatric and adult MTC	Indicated improved prognosis in pediatric MTC, guiding tailored treatment strategies	(255)

FAP, fibroblast activation protein; PAC, 3,5-bis (4-hydroxy-3-methoxybenzylidene)-N-methyl-4-piperidone; MTC, medullary thyroid cancer; SA.FAPi, squaramide-conjugated fibroblast activation protein inhibitor; Siglec-15, sialic acid-binding Ig-like lectin 15; TKIs, tyrosine kinase inhibitors; CPA4, carboxypeptidase A4; NETs, neutrophil extracellular traps; CSPG4, chondroitin sulfate proteoglycan 4; ROS, reactive oxygen species; NIS, sodium iodide symporter; Wee1, Wee1 G_2 checkpoint kinase; LINC00886, long intergenic non-protein coding RNA 886; PKR, protein kinase R; eIF2α, eukaryotic initiation factor-2α ; IL2RA, interleukin-2 receptor subunit α; VSIG4, V-set and immunoglobulin domain containing 4; KDR, kinase insert domain receptor; KIT, KIT proto-oncogene, receptor tyrosine kinase; PDGFRA, platelet-derived growth factor receptor α; RET, rearranged during transfection; TC, thyroid cancer; SHMT2, serine hydroxymethyltransferase 2; USP26, ubiquitin specific peptidase 26; TAZ, transcriptional coactivator with PDZ-binding motif; miR, mciroRNA; SOCS1, suppressor of cytokine signaling 1; GSDMD, gasdermin D.

Molecular mechanisms. ATC is a highly aggressive endocrine malignancy frequently presenting with extrathyroidal extension or distant metastasis, ~70% of ATC spreads to nearby tissues such as the trachea, esophagus and throat. The lungs, bones, and brain are also common sites of ATC metastasis (256), although its pathogenesis remains to be elucidated. Mechanistic studies have identified cAMP-responsive element-binding protein 3-like 1 (CREB3L1) as a key regulator maintaining cancer-associated fibroblast-like phenotypes in ATC through extracellular matrix (ECM) signaling activation, thereby remodeling TMEs to facilitate malignant progression (257,258). The MAPK pathway, activated via Ras/BRAF mutations or RET-PTC fusions, has been established as a central oncogenic driver and therapeutic target for TKIs, while secondary genomic alterations, including telomerase reverse transcriptase (TERT) promoter and tumor protein p53 (TP53) mutations, are correlated with advanced tumor evolution (259).

Molecular profiling analyses have revealed distinct protein expression patterns in ATC, characterized by marked upregulation of miRNA-regulated oncogenes, such as transferrin receptor TFRC or CD71, and E3-ubiquitin ligase denticleless, enabling reliable differentiation from PDTC (260). Angiogenesis and EMT are suppressed by miR-205 through dual targeting of VEGF-A and ZEB1 (261). Epigenetic and transcriptional regulators include sialic acid-binding Ig-like lectin 15 (Siglec-15) (STAT1/STAT3-mediated proliferation/apoptosis) (262), CCCTC-binding factor/hematological and neurological expressed 1 (HN1; chromatin remodeling of thyroid differentiation genes) (263), REGγ (TGF-β activation via SMAD7 degradation) (264) and HOXD9 (PI3K/AKT-driven proliferation/EMT through miR-451a/proteasome 20S subunit β8 axis) (265). The miR-17-92 cluster has been implicated in differentiation blockade, with CRISPR/caspase 9-mediated knockdown restoring thyrocyte-specific gene expression (266).

The stepwise molecular progression from DTC to ATC entails early MAPK pathway alterations, including BRAF V600E and Ras mutations, with subsequent acquisition of TERT and TP53 mutations driving dedifferentiation (267).

Cellular invasion mechanisms in ATC are regulated through multiple molecular axes: HN1 stabilizes stathmin 1 (STMN1) mRNA and prevents its ubiquitin-mediated degradation, thereby enhancing invasiveness (268). RING-box protein 1 (RBX1) modulates pyruvate kinase M1/2 splicing via scaffold/matrix attachment region binding protein 1/histone deacetylase 6 complex disruption, promoting metastasis and aerobic glycolysis (269) and type 2 deiodinase depletion induces cellular senescence (270).

Capsaicin exemplifies the multimodal mechanisms of pharmacological interventions, where transient receptor potential vanilloid 1 activation initiates mitochondrial calcium overload culminating in apoptosis (271). Berberine induces ROS-dependent apoptosis/autophagy via PI3K/AKT/mTOR pathway modulation and synergizes with doxorubicin (272). A-kinase interacting protein 1 knockdown enhances chemosensitivity through PI3K/AKT/β-catenin inactivation (273). Gli-antagonist 61 inhibits EMT via AKT/mTOR and JAK/STAT3 pathway suppression (274).

Taken together, ATC pathogenesis involves multilevel dysregulation spanning CREB3L1-mediated ECM remodeling, MAPK/TERT/TP53 genetic evolution and coordinated control of invasion/metastasis by HN1/STMN1/RBX1. Therapeutic vulnerabilities were identified in calcium signaling, redox balance, epigenetic reprogramming and kinase cascades, which provides a molecular framework for targeted intervention strategies.

Progress in diagnosis. Total residual disease remains the most key prognostic indicator for ATC. Factors such as the capsule, marginal status, percentage and size of the primary ATC are associated with prognosis. Pure thyroid squamous cell carcinoma can be classified as ATC if it shares a similar BRAF V600E genotype and prognosis. Both BRAF-mutated and Ras-mutated ATC exhibit comparable metastatic spread. The coexistence of BRAF or Ras mutations alongside TERT mutations is correlated with a poor prognosis (7,275,276). Current diagnostic algorithms for ATC incorporate three cardinal immunohistochemical features: i) Aberrant nuclear β-catenin accumulation with membranous expression loss, indicative of Wnt pathway activation; ii) disrupted E-cadherin localization patterns reflecting EMT; and iii) paired box 8 nuclear expression deficiency marking thyroid differentiation loss, collectively serving as histopathological hallmarks for ATC confirmation (277).

Optical imaging has been shown to effectively visualize cellular and tissue architectures through optical absorption, refraction and scattering properties, enabling functional assessment across organ systems and facilitating diagnostic applications. This modality further demonstrates therapeutic potential for targeted and non-invasive precision treatment in thyroid carcinoma (278). Concurrently, contrast-enhanced CT-based radiomics analysis exhibits notable discriminative capacity in distinguishing ATC and PDTC from DTC in patients with advanced thyroid malignancies (279).

IGF2 mRNA-binding protein 1 (IGF2BP1) is currently regarded as the most promising single-gene marker for ATC, followed by melanoma-associated antigen 3 (MAGEA3), representing an advancement over existing techniques (280), like application of single-cell sequencing technology and epigenetic analysis. The expression levels of IGF2BP1 and MAGEA3 can effectively differentiate ATC from PDTC. Furthermore, IGF2BP1 has the capability to identify ATC foci within poorly differentiated FTC. Reliable markers are key for distinguishing this high-grade malignancy (ATC) from other types of thyroid cancer subtypes, thereby informing surgical decisions, treatment options and post-resection or therapeutic monitoring strategies (280).

Circulating cell-free DNA (cfDNA) has emerged as a key biomarker for characterizing tumor molecular profiles in ATC. Comparative analyses have demonstrated high concordance between cfDNA-derived genetic alterations and tumor tissue-based next-generation sequencing results, which supports the utility of cfDNA in dynamically monitoring actionable mutations. These findings underscore the clinical relevance of cfDNA in guiding therapeutic decisions and prognostic stratification in ATC management (281).

Treatment. Emerging evidence suggests that C-X-C motif chemokine 13 $(CXCL13)^+$ T lymphocytes are enriched in ATC TMEs, correlating with the formation of early tertiary lymphoid structures (TLSs) that potentially enhance

immunotherapeutic responsiveness in this aggressive malignancy (282). The involvement of $CXCL13^+$ T cells within the tumor immune microenvironment and their investigative advancements in ATC have emerged as key areas of focus in tumor immunotherapy research. ATC, recognized as the most aggressive form of thyroid malignancy, is typified by a notably immunosuppressive TME characterized by limited lymphocyte infiltration (283,284). However, recent investigations have identified an enrichment of $CXCL13^+$ T cells in ATC, which may represent a pivotal target for immunotherapeutic intervention. $CXCL13^+$ T cells demonstrate a bifunctional role in tumor biology. Firstly, in ATC, these cells facilitate the recruitment of B lymphocytes and promote the early development of TLS through the secretion of the chemokine CXCL13, thereby potentiating the antitumor immune response (283,284). By contrast, $CXCL13^+$ T cells may also engage with immunosuppressive populations, including Tregs and M2-polarized tumor-associated macrophages, or exhibit functional impairment characterized by elevated expression levels of exhaustion markers, such as PD-1 and T cell immunoglobulin and mucin-domain containing-3 (285-288). Furthermore, emerging evidence indicates that CXCL13 can disseminate systemically to the lungs, where it activates macrophages to release prothrombotic vesicles, thus elevating the risk of thrombosis and metastatic progression (289,290).

Similarly, previous studies in non-small cell lung cancer have demonstrated that combined radiotherapy and anti-PD-L1 treatment induces the formation of spatially adjacent synergistic units comprising $CXCL13^+CD8^+$ T cells and $CXCL9^+$ macrophages, whose effector molecules, including granzyme B and IFN-γ, directly suppress tumor growth (291,292). Similarly, in lung adenocarcinoma associated with chronic obstructive pulmonary disease, $CXCL13^+CD8^+$ T cells cooperate with tumor cells exhibiting high HLA class I expression to enhance immunotherapy response rates (293). By contrast, within clear cell renal cell carcinoma, $CXCL13^+CD8^+$ T cells predominantly display a terminally exhausted phenotype associated with unfavorable clinical outcomes. The high infiltration of $CXCL13^+CD8^+$T cells can also demonstrate the immune escape structure of $CD8^+$T cells, characterized by immune damage, increased tumor promoting cells and reduced anti-tumor factors (294). These observations underscore that the functional role of $CXCL13^+$ T cells is highly contingent upon the specific TME context, including the composition and spatial arrangement of coexisting immune cell populations. Therefore, in ATC, $CXCL13^+$ T cells both promote immune activation by augmenting antitumor responses through TLS formation and may increase risk of malignancy due to their exhausted phenotype and associated systemic complications.

In therapeutic investigations, combination regimens targeting both angiogenesis and immune checkpoints, such as lenvatinib with pembrolizumab, demonstrated favorable clinical outcomes. A retrospective study involving 6 metastatic ATC patients receiving combination therapy with lenvatinib and pembrolizumab and 2 PDTC patients confirmed. These regimens achieved durable complete remissions in subsets of patients with ATC and PDTC (295). Notably, BRAF-targeted strategies continue to evolve. A subset of patients with BRAF-mutant ATC exhibited significant tumor regression when treated with neoadjuvant pembrolizumab followed by BRAF/MEK inhibitor combinations, enabling subsequent curative resection (296). Mechanistic studies further revealed that dabrafenib combined with erlotinib synergistically suppresses MAPK/EGFR signaling pathways, as evidenced by downregulation of p-MEK, p-ERK and p-EGFR in preclinical models (297). This dual inhibition strategy overcomes monotherapy resistance and significantly reduces tumor burden in xenograft models (298).

Clinical trials evaluating PD-1 blockade in ATC demonstrated durable responses across BRAF mutation statuses. Spartalizumab, an anti-PD-1 monoclonal antibody, achieved a 52.1% 1-year survival rate in patients who were $PD\text{-}L1^+$, with objective responses observed in both BRAF mutant and wild-type cohorts (299). PD-L1 was significantly upregulated in a subset of patients with advanced ATC. Notably, PD-L1 expression in immune cells was detected in 11.1% of ATC cases (300). Furthermore, monoclonal antibodies targeting PD-L1 have demonstrated notable efficacy in inhibiting ATC tumor growth *in vivo* (301). Siglec-15 has emerged as a promising immunotherapeutic target in ATC, whose function is to suppress T-cell activation by downregulating nuclear factor of activated T cells (NFAT)1, NFAT2 and NF-κB signaling pathways. Inhibition of Siglec-15 has been shown to enhance the secretion of IFN-γ and IL-2 both *in vitro* and *in vivo* (218). Furthermore, the combination therapy of dabrafenib and trametinib has notably transformed the treatment landscape for BRAF V600E-mutant ATC. Despite initial responses, resistance to this targeted therapy inevitably develops, leading to disease progression. Furthermore, neoadjuvant BRAF-targeted therapy administered preoperatively has demonstrated improvements in patient survival outcomes (302).

These findings underscore the potential of immunotherapy as a backbone for multimodal treatment paradigms in ATC. ICAM1 is a promising target for the treatment of ATC and PTC. Two ICAM1-targeted antibody-drug conjugates (I1-MMAE and I1-DXd) have been developed, exhibiting selective cytotoxicity against proliferating ATC and PTC cells *in vitro*, while maintaining minimal impact on non-proliferative cell populations (303). Preclinical evaluation further demonstrated notable tumor regression in ATC and PTC xenograft models following ADC administration (304). Similarly, a CD44-directed nanodelivery system was engineered through tyrosine-hyaluronic acid-polyethylenimine self-assembly, enabling simultaneous 131I/125I radiolabeling and encapsulation of p53 reactivation and induction of massive apoptosis-1 (Prima-1), a p53 mutation-targeted therapeutic agent. The ^{125}I-labeled nanocomposites achieved sustained tumor visualization and prolonged radiosensitivity, while 131I-conjugated nanoparticles exerted synergistic antitumor effects in ATC models through Prima-1-mediated p53 reactivation and radiation potentiation (305).

Recent advances in ATC therapeutics have revealed several promising strategies. Emerging evidence suggests that $CXCL13^+$ T cell infiltration and nascent TLS formation may serve as biomarkers for immunotherapy responsiveness. The combined regimen of lenvatinib and pembrolizumab, when integrated with BRAF/MEK inhibition, has demonstrated therapeutic efficacy in molecularly defined ATC subsets. Notably, neoadjuvant applications of pembrolizumab remain under clinical investigation (282,295,296). Pharmacodynamic

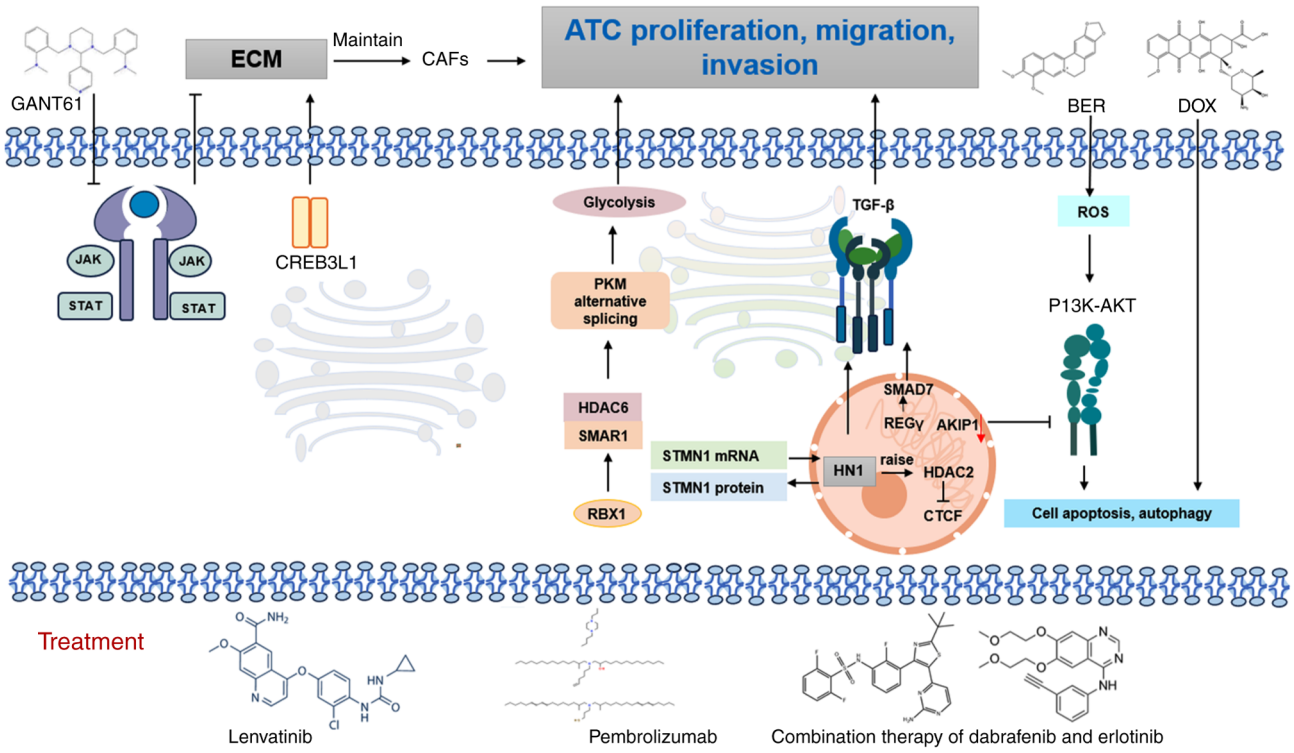

Figure 5. Molecular circuitry and therapeutic targeting in ATC pathogenesis. This schematic illustrates the molecular mechanisms driving ATC proliferation and metastasis, alongside therapeutic strategies. CAFs remodel the ECM through the CREB3L1/miR-205 axis and JAK-STAT signaling modulated by GANT61. Metabolic reprogramming involves HDAC6/SMAR1-mediated PKM splicing and RBX1-STMN1 regulation. DOX triggers ROS-dependent apoptosis via PI3K-AKT, while targeted therapies include lenvatinib (multikinase inhibitor), pembrolizumab (anti-PD-1) and BRAF/EGFR inhibitors (dabrafenib + erlotinib). ATC, anaplastic thyroid cancer; CAFs, cancer-associated fibroblasts; ECM, extracellular matrix; CREB3L1, cAMP-responsive element-binding protein 3-like 1; miR, microRNA; JAK, Janus kinase; GANT61, Gli-antagonist 61; HDAC6, histone deacetylase 6; SMAR1, scaffold/matrix attachment region binding protein 1; PKM, pyruvate kinase M1/2; RBX1, RING-box protein 1; STMN1, stathmin 1; DOX, doxorubicin; ROS, reactive oxygen species; PD-1, programmed cell death protein-1; HN1, hematological and neurological expressed 1; CTCF, CCCTC-binding factor; REGγ, proteasome activator subunit 3; AKIP1, A kinase-interacting protein 1; BER, base excision repair.

studies have indicated that dabrafenib-erlotinib co-administration achieves synergistic tumor suppression through circumventing monotherapy resistance mechanisms. PD-1 blockade via spartalizumab has induced objective responses across diverse ATC histological variants, including spindle cell variant, giant cell variant, and epithelioid variant. Preclinical models further highlight the therapeutic potential of CD44-directed nanocarriers co-delivering ^{131}I radiotherapy and Prima-1-mediated p53 reactivation (298,300,305). These multimodal approaches collectively expand the therapeutic landscape for this aggressive malignancy (Fig. 5).

6. Problems and challenges in thyroid research

In the field of thyroid cancer research, notable progress has been made in recent years; however, several limitations persist. Firstly, studies investigating the molecular mechanisms and gene mutations associated with thyroid cancer have identified the roles of various key genes (such as BRAF, RET and Ras) (306-309). However, these studies do not fully elucidate the occurrence and developmental processes of all types of thyroid cancer. The intricate interactions between multiple genetic mutations and environmental factors remain inadequately understood, such as ionizing radiation induces DNA double strand breaks, leading to RET/PTC rearrangements; excessive iodine can promote BRAF V600E mutation, which increases the risk of PTC. These poses presenting challenges in the pursuit of more effective prevention and treatment strategies.

In the research and treatment of thyroid cancer, it is imperative to focus on the early screening of high-risk groups, the application of molecular markers in diagnosis and treatment, and the development of individualized treatment strategies tailored to the various pathological types of thyroid cancer (310). Concurrently, for advanced and refractory cases, overcoming drug resistance and enhancing treatment efficacy remain key areas of investigation. For instance, in the case of highly malignant subtypes, such as ATC, treatment options are currently limited and survival rates are dismal, which necessitates the urgent identification of novel therapeutic targets and strategies. Furthermore, despite the generally favorable prognosis for DTC, the monitoring and management of recurrence and metastasis continue to pose notable challenges in clinical practice (311).

Targeted drug therapy has demonstrated notable therapeutic potential in the management of thyroid cancer, particularly for advanced or refractory cases. These therapies inhibit tumor progression by focusing on specific molecular targets that promote cancer cell proliferation. Common targeted drugs include VEGFR inhibitors, such as pazopanib and sorafenib, which primarily inhibit new angiogenesis and restrict tumor blood supply (312-314). Furthermore, EGFR inhibitors,

including gefitinib and erlotinib (315), mainly function to inhibit tumor cell proliferation and survival. Targeting the prevalent BRAF V600E driver mutation in thyroid cancer subtypes, BRAFi, including vemurafenib and dabrafenib, represent a mechanistically grounded therapeutic strategy. Furthermore, RET inhibitors, such as pralsetinib and selpercatinib, primarily inhibit key drivers of MTC, such as RET gene fusion or mutation (316). Targeted therapies are characterized by their high specificity, resulting in less impact on normal cells and fewer side effects compared with conventional chemotherapy; they can effectively control disease progression and prolong progression-free survival, which makes them particularly suitable for advanced cases that are not amenable to surgical or radiotherapeutic interventions. However, the cost of targeted drugs is typically high, which can impose economic burdens on patients over the long term. Furthermore, drug resistance may develop, as tumor cells can evolve novel mechanisms to evade treatment. Potential side effects, including hypertension, diarrhea and rash (317), necessitate long-term management and continuous monitoring.

Challenges of drug resistance in BRAF V600E-mutant PTC. Drug resistance in BRAF V600E-mutant PTC to BRAFi is characterized by a multifaceted mechanism encompassing epigenetic regulation, signaling pathway reprogramming and metabolic adaptation. For instance, Pit-Oct-Unc class 5 homeobox 1B contributes to dabrafenib resistance by promoting stem cell-like properties and activating the Taste 1 Receptor Member 1 signaling axis (318). Similarly, NG2 (chondroitin sulfate proteoglycan 4) diminishes the efficacy of BRAFi through feedback activation of the ERK/AKT pathway mediated by multiple RTKs, including EGFR and FGFR (119). Furthermore, aberrant activation of the JAK/STAT pathway exacerbates resistance via IFN regulatory factor 1-driven immune evasion mechanisms, such as upregulation of human leukocyte antigen A2 and ICAM-1 (118). Transcription factors Forkhead box protein P2 and Src homology-2 domain-containing protein tyrosine phosphatase 2 sustain the resistant phenotype by cross-activating the lysophosphatidic acid receptor (LPAR)3/PI3K-AKT and MAPK/PI3K pathways, respectively (319,320). At the metabolic level, myeloid cell leukemia-1 inhibits apoptosis by maintaining mitochondrial membrane stability, while resistance to ferroptosis mediated by the arylsulfatase I-STAT3-epiregulin axis restricts the therapeutic efficacy of sorafenib (321). Collectively, these findings indicate that monotherapy targeting BRAF is readily circumvented by compensatory mechanisms, which underscores the urgent need for combinatorial therapeutic strategies.

Pan-drug resistance phenomenon in ATC. The mechanisms underlying drug resistance in ATC are notably complex, frequently involving widespread dysregulation of the transcriptome and epigenetic landscape. NOP2/Sun RNA methyltransferase family member 2 (NSUN2)-mediated 5-methylcytosine modification stabilizes ATP-binding cassette transporters via the serine/arginine-rich splicing factor 6/UDP-N-acetylglucosamine pyrophosphorylase 1 axis, thereby promoting multidrug resistance (322). Furthermore, N-Myc proto-oncogene (MYCN) induces paclitaxel resistance through transcriptional reprogramming (323). Microenvironmental factors, such as glutamate accumulation, inhibit lysophosphatidic acid receptor 1, which results in persistent activation of the MAPK pathway and reduced sensitivity to anlotinib (117). These interconnected mechanisms collectively establish a 'pan-drug resistance' barrier, rendering conventional chemotherapy and targeted therapies largely ineffective in ATC.

Limitations of current clinical trials and unmet clinical needs. Although BRAF/MEK inhibitors, including dabrafenib and trametinib, have demonstrated high objective response rates (ranging from 54 to 89%) in BRAF V600E-mutant thyroid cancer, their long-term efficacy is compromised by the development of acquired resistance (324,325). Combination immunotherapy approaches, such as BRAFi combined with atezolizumab, have extended the median survival time in patients with ATC to ~43 months; however, the associated cumulative toxicities, including dysphoria and fatigue, limit broader clinical application (326).

Additional challenges include histological variability in response to targeted therapies. For instance, lenvatinib only achieved an 11.9% 1-year survival rate in ATC (327), while pazopanib combined with chemoradiotherapy failed to significantly improve survival outcomes, underscoring the limitations of VEGFR monotherapy (219). The feasibility and safety of metabolic interventions remains a challenge. Although melittin combined with apatinib enhances antitumor efficacy by inducing pyroptosis, optimizing the therapeutic-toxicity balance persists as a key concern (220). A lack of reliable predictive biomarkers complicates treatment. No current biomarkers adequately forecast patient responses to NSUN2- or MYCN-targeted therapies, which hampers patient stratification and treatment personalization (322,323).

Future studies may continue to investigate the molecular mechanisms underlying thyroid cancer, with particular emphasis on key signaling pathways and gene variants in ATC. This research will encompass the examination of oncogenes, tumor suppressor genes, cell cycle regulatory genes and molecules that interact with the TME. Further understanding of the molecular heterogeneity of thyroid cancer will shift the focus of future research towards personalized treatment strategies. This approach can involve the selection of appropriate targeted therapies and immunotherapy regimens based on the molecular characteristics of individual tumors. For instance, the identification of driver genes, such as the BRAF V600E mutation and RET/neurotrophic tyrosine receptor kinase fusion, has informed the application of targeted therapeutic agents (328). Concurrently, research may also prioritize the development of novel targeted drugs and immunotherapy techniques, as well as the integration of these treatments with established methods such as surgery, radioiodine therapy and TKIs to enhance treatment efficacy and improve patient survival.

Through multi-omics studies, researchers may aim to identify precise molecular markers of thyroid cancer, which could potentially enhance patient stratification and risk assessment, leading to more refined management strategies. Furthermore, advancements in bioinformatics and artificial intelligence technologies are expected to serve an increasingly vital role

in the diagnosis, treatment planning and prognostic evaluation of thyroid cancer. For instance, artificial intelligence-based models can assist in determining lymph node metastasis in DTC, thereby improving diagnostic accuracy (329).

Research on thyroid cancer encompasses multiple disciplines, including genetics, pathology, imaging, endocrinology and oncology. Effectively integrating the resources and expertise from these fields to establish a comprehensive interdisciplinary research system is key to enhance the quality of thyroid cancer research and its clinical applications. Clinical research must persist in advancing efforts to validate the efficacy and safety of novel treatment strategies and medications for patients. Furthermore, translational research can facilitate the swift application of laboratory findings to clinical settings, ensuring that research outcomes benefit patients at the earliest opportunity.

7. Conclusion

Thyroid cancer represents a highly heterogeneous endocrine malignancy with significant differences in molecular mechanisms, clinical presentations and therapeutic approaches across its subtypes (PTC, FTC, MTC and ATC). This review delineates key molecular characteristics of these four categories: PTC is predominantly characterized by BRAF V600E mutations, FTC is frequently associated with RAS mutations and MTC primarily originates from RET proto-oncogene mutations, while ATC demonstrates profound genomic instability evidenced by TP53 and TERT promoter mutations. These molecular markers not only facilitate disease diagnosis and prognostic stratification but also provide foundational insights for targeted therapy development.

In diagnostic practice, integrating ultrasound, fine-needle aspiration biopsy and molecular profiling, including BRAF, RET and RAS mutation analysis substantially enhances preoperative diagnostic precision. Regarding therapeutic management, surgical resection remains the primary intervention for localized tumors. For advanced or metastatic disease, however, targeted therapies such as RET inhibitor selpercatinib and BRAF/MEK inhibitor combinations alongside immunotherapy demonstrate transformative potential. Particularly for aggressive ATC, multimodal regimens combining surgery, radiotherapy, chemotherapy and targeted agents may extend survival in selected patient cohorts.

Notwithstanding substantial research advancements in thyroid oncology, persistent challenges warrant attention. Certain resistance mechanisms in FTC and ATC remain incompletely elucidated. Comprehensive evaluation of long-term efficacy and toxicity profiles for targeted therapies is imperative. Furthermore, molecular stratification-guided personalized treatment paradigms require validation through large-scale clinical trials. Future investigations should prioritize novel biomarker discovery, optimization of combination therapies and multi-omics exploration of TME dynamics in disease progression, ultimately aiming to enhance patient survival outcomes and quality of life.

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Authors' contributions

ZL, NW, XL and HX collected related literature and drafted the manuscript. ZD, YL, YX, YS, TF and GW participated in the design of the review and draft of the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 74: 229-263, 2024.
2. Wan Y, Li G, Cui G, Duan S and Chang S: Reprogramming of thyroid cancer metabolism: From mechanism to therapeutic strategy. Mol Cancer 24: 743, 2025.
3. Myung SK, Lee CW, Lee J, Kim J and Kim HS: Risk factors for thyroid cancer: A hospital-based case-control study in Korean adults. Cancer Res Treat 49: 70-78, 2017.
4. Li M, Li Q, Zou C, Huang Q and Chen Y: Application and recent advances in conventional biomarkers for the prognosis of papillary thyroid carcinoma. Front Oncol 15: 1598934, 2025.
5. Badulescu CI, Piciu D, Apostu D, Badan M and Piciu A: Follicular thyroid carcinoma-clinical and diagnostic findings in a 20-year follow up study. Acta Endocrinol (Buchar) 16: 170-177, 2020.
6. Huai JX, Wang F, Zhang WH, Lou Y, Wang GX, Huang LJ, Sun J and Zhou XQ: Unveiling new chapters in medullary thyroid carcinoma therapy: Advances in molecular genetics and targeted treatment strategies. Front Endocrinol (Lausanne) 15: 1484815, 2024.
7. Cleere EF, Prunty S and O'Neill JP: Anaplastic thyroid cancer: Improved understanding of what remains a deadly disease. Surgeon 22: e48-e53, 2024.

8. Singarayer R, Mete O, Perrier L, Thabane L, Asa SL, Van Uum S, Ezzat S, Goldstein DP and Sawka AM: A systematic review and meta-analysis of the diagnostic performance of BRAF V600E immunohistochemistry in thyroid histopathology. Endocr Pathol 30: 201-218, 2019.
9. Grabellus F, Worm K, Schmid KW and Sheu SY: The BRAF V600E mutation in papillary thyroid carcinoma is associated with glucose transporter 1 overexpression. Thyroid 22: 377-382, 2012.
10. Zou M, Baitei EY, Alzahrani AS, BinHumaid FS, Alkhafaji D, Al-Rijjal RA, Meyer BF and Shi Y: Concomitant RAS, RET/PTC, or BRAF mutations in advanced stage of papillary thyroid carcinoma. Thyroid 24: 1256-1266, 2014.
11. Kang N, Zhao Z, Wang Z, Ning J, Wang H, Zhang W, Ruan X, Gao M and Zheng X: METTL3 regulates thyroid cancer differentiation and chemosensitivity by modulating PAX8. Int J Biol Sci 20: 3426-3441, 2024.
12. Li Q, Wang Y, Meng X, Wang W, Duan F, Chen S, Zhang Y, Sheng Z, Gao Y and Zhou L: METTL16 inhibits papillary thyroid cancer tumorigenicity through m^{6}A/YTHDC2/SCD1-regulated lipid metabolism. Cell Mol Life Sci 81: 81, 2024.
13. Zhu J, Wang Y, Yang C, Feng Z, Huang Y, Liu P, Chen F and Deng Z: circ-PSD3 promoted proliferation and invasion of papillary thyroid cancer cells via regulating the miR-7-5p/METTL7B axis. J Recept Signal Transduct Res 42: 251-260, 2022.
14. Lin J, Cai B, Lin Q, Lin X, Wang B and Chen X: TLE4 downregulation identified by WGCNA and machine learning algorithm promotes papillary thyroid carcinoma progression via activating JAK/STAT pathway. J Cancer 15: 4759-4776, 2024.
15. Wagner M, Wuest M, Lopez-Campistrous A, Glubrecht D, Dufour J, Jans HS, Wuest F and McMullen TPW: Tyrosine kinase inhibitor therapy and metabolic remodelling in papillary thyroid cancer. Endocr Relat Cancer 27: 495-507, 2020.
16. Wen J, Lin B, Lin L, Chen Y and Wang O: KCNN4 is a diagnostic and prognostic biomarker that promotes papillary thyroid cancer progression. Aging (Albany NY) 12: 16437-16456, 2020.
17. Wang K, Liu S, Tian Y, Liu C, Gui Z, Yu T and Zhang L: PDZK1 Interacting Protein 1 promotes the progression of papillary thyroid cancer. J Clin Endocrinol Metab 107: 2449-2461, 2022.
18. Qin XJ, Lin X, Xue G, Fan HL, Wang HY, Wu JF and Pei D: CXCL10 is a potential biomarker and associated with immune infiltration in human papillary thyroid cancer. Biosci Rep 41: BSR20203459, 2021.
19. Sirakriengkrai K, Tepmongkol S, Keelawat S and Techavijit U: Clinical association of CXCR4 in primary tumor of papillary thyroid cancer and response to iodine-131 treatment. Nucl Med Commun 42: 396-401, 2021.
20. Shen Y, Li X, Xie R, Chen Y, Hu X, Liu Y and Ma H: Expression levels of MicroRNA-300/BCL2L11 in papillary thyroid cancer and their clinical diagnostic values. Eur Surg Res 64: 342-351, 2023.
21. Lin L, Wen J, Lin B, Bhandari A, Zheng D, Kong L, Wang Y, Wang O and Chen Y: Immortalization up-regulated protein promotes tumorigenesis and inhibits apoptosis of papillary thyroid cancer. J Cell Mol Med 24: 14059-14072, 2020.
22. Guo H, Liu R, Wu J, Li S, Yao W, Xu J, Zheng C, Lu Y and Zhang H: SRPX2 promotes cancer cell proliferation and migration of papillary thyroid cancer. Clin Exp Med 23: 4825-4834, 2023.
23. Yan T, Qiu W, Song J, Fan Y and Yang Z: ARHGAP36 regulates proliferation and migration in papillary thyroid carcinoma cells. J Mol Endocrinol 66: 1-10, 2021.
24. Zhou Y, Xiang J, Bhandari A, Wen J, Lin B, Kong L and Wang O: LRRC52-AS1 is associated with clinical progression and regulates cell migration and invasion in papillary thyroid cancer. Clin Exp Pharmacol Physiol 47: 696-702, 2020.
25. Cheng X, Xu S, Pan J, Zheng J, Wang X, Yu H, Bao J, Xu Y, Guan H and Zhang L: MKL1 overexpression predicts poor prognosis in patients with papillary thyroid cancer and promotes nodal metastasis. J Cell Sci 132: jcs231399, 2019.
26. Yu Y, Yu X, Fan C, Wang H, Wang R, Feng C and Guan H: Targeting glutaminase-mediated glutamine dependence in papillary thyroid cancer. J Mol Med (Berl) 96: 777-790, 2018.
27. Zhu X, Xue C, Kang X, Jia X, Wang L, Younis MH, Liu D, Huo N, Han Y, Chen Z, *et al*: DNMT3B-mediated FAM111B methylation promotes papillary thyroid tumor glycolysis, growth and metastasis. Int J Biol Sci 18: 4372-4387, 2022.
28. Chen Y, Li H, Liang W, Guo Y, Peng M, Ke W, Xiao H, Guan H and Li Y: SLC6A15 acts as a tumor suppressor to inhibit migration and invasion in human papillary thyroid cancer. J Cell Biochem 122: 814-826, 2021.
29. Ratti M, Lampis A, Ghidini M, Salati M, Mirchev MB, Valeri N and Hahne JC: MicroRNAs (miRNAs) and Long Non-coding RNAs (lncRNAs) as new tools for cancer therapy: First steps from bench to bedside. Target Oncol 15: 261-278, 2020.
30. Zhu Y, Jin L, Shi R, Li J, Wang Y, Zhang L, Liang CZ, Narayana VK, De Souza DP, Thorne RF, *et al*: The long noncoding RNA glycoLINC assembles a lower glycolytic metabolon to promote glycolysis. Mol Cell 82: 542-554.e6, 2022.
31. Peng X, Li S, Zeng A and Song L: Regulatory function of glycolysis-related lncRNAs in tumor progression: Mechanism, facts, and perspectives. Biochem Pharmacol 229: 116511, 2024.
32. Shi L, Duan R, Sun Z, Jia Q, Wu W, Wang F, Liu J, Zhang H and Xue X: LncRNA GLTC targets LDHA for succinylation and enzymatic activity to promote progression and radioiodine resistance in papillary thyroid cancer. Cell Death Differ 30: 1517-1532, 2023.
33. Qiu J, Zhang W, Zang C, Liu X, Liu F, Ge R, Sun Y and Xia Q: Identification of key genes and miRNAs markers of papillary thyroid cancer. Biol Res 51: 45, 2018.
34. Liu J, Dong H, Yang Y, Qian Y, Liu J, Li Z, Guan H, Chen Z, Li C, Zhang K, *et al*: Upregulation of long noncoding RNA MALAT1 in papillary thyroid cancer and its diagnostic value. Future Oncol 14: 3015-3022, 2018.
35. Yi T, Zhou X, Sang K, Zhou J and Ge L: MicroRNA-1270 modulates papillary thyroid cancer cell development by regulating SCAI. Biomed Pharmacother 109: 2357-2364, 2019.
36. Sun Y, Sun W, Hua H, Zhang J, Yu Q, Wang J, Liu X and Dong A: Overexpression of miR-127 predicts poor prognosis and contributes to the progression of papillary thyroid cancer by targeting REPIN1. Horm Metab Res 53: 197-203, 2021.
37. Zhang Z, Wang W, Su Z, Zhang J and Cao H: Circ_0011058 facilitates proliferation, angiogenesis and radioresistance in papillary thyroid cancer cells by positively regulating YAP1 via acting as miR-335-5p sponge. Cell Signal 88: 110155, 2021.
38. Yang Z, Li G, Ding C, Sun W and Zhang J: Long non-coding RNA HULC exerts oncogenic activity on papillary thyroid cancer in vitro and in vivo. Artif Cells Nanomed Biotechnol 48: 326-335, 2020.
39. Xia F, Chen Y, Jiang B, Du X, Peng Y, Wang W, Huang W, Feng T and Li X: Long Noncoding RNA HOXA-AS2 promotes papillary thyroid cancer progression by regulating miR-520c-3p/S100A4 pathway. Cell Physiol Biochem 50: 1659-1672, 2018.
40. Jiang L, Wu Z, Meng X, Chu X, Huang H and Xu C: LncRNA HOXA-AS2 facilitates tumorigenesis and progression of papillary thyroid cancer by modulating the miR-15a-5p/HOXA3 axis. Hum Gene Ther 30: 618-631, 2019.
41. Lin BY, Wen JL, Zheng C, Lin LZ, Chen CZ and Qu JM: Eva-1 homolog A promotes papillary thyroid cancer progression and epithelial-mesenchymal transition via the Hippo signalling pathway. J Cell Mol Med 24: 13070-13080, 2020.
42. Yang M, Huang S, Zhao Y, Xie B, Hu X and Cai Y: Novel LncRNA AK023507 inhibits cell metastasis and proliferation in papillary thyroid cancer through β-catenin/Wnt signaling pathway. Biochem Biophys Res Commun 655: 104-109, 2023.
43. Zheng Z, Zhou X, Cai Y, Chen E, Zhang X, Wang O, Wang Q and Liu H: TEKT$_4$ promotes papillary thyroid cancer cell proliferation, colony formation, and metastasis through activating PI3K/Akt pathway. Endocr Pathol 29: 310-316, 2018.
44. Chen L, Zhuo D and Yuan H: Circ_100395 impedes malignancy and glycolysis in papillary thyroid cancer: Involvement of PI3K/AKT/mTOR signaling pathway. Immunol Lett 246: 10-17, 2022.
45. Park JH, Myung JK, Lee SJ, Kim H, Kim S, Lee SB, Jang H, Jang WI, Park S, Yang H, *et al*: ABCA1-Mediated EMT promotes papillary thyroid cancer malignancy through the ERK/Fra-1/ZEB1 Pathway. Cells 12: 274, 2023.
46. He J, Zhou M, Yin J, Wan J, Chu J, Jia J, Sheng J, Wang C, Yin H and He F: METTL3 restrains papillary thyroid cancer progression via m^{6}A/c-Rel/IL-8-mediated neutrophil infiltration. Mol Ther 29: 1821-1837, 2021.
47. Yang L, Tan Z, Li Y, Zhang X, Wu Y, Xu B and Wang M: Insulin-like growth factor 1 promotes proliferation and invasion of papillary thyroid cancer through the STAT3 pathway. J Clin Lab Anal 34: e23531, 2020.
48. Hong S, Xie Y, Cheng Z, Li J, He W, Guo Z, Zhang Q, Peng S, He M, Yu S, *et al*: Distinct molecular subtypes of papillary thyroid carcinoma and gene signature with diagnostic capability. Oncogene 41: 5121-5132, 2022.

49. Carnazza M, Quaranto D, DeSouza N, Moscatello AL, Garber D, Hemmerdinger S, Islam HK, Tiwari RK, Li XM and Geliebter J: The current understanding of the molecular pathogenesis of papillary thyroid cancer. Int J Mol Sci 26: 4646, 2005.
50. Ju SH, Song M, Lim JY, Kang YE, Yi HS and Shong M: Metabolic reprogramming in thyroid cancer. Endocrinol Metab (Seoul) 39: 425-444, 2024.
51. Huang J, Sun W, Wang Z, Lv C, Zhang T, Zhang D, Dong W, Shao L, He L, Ji X, *et al*: FTO suppresses glycolysis and growth of papillary thyroid cancer via decreasing stability of APOE mRNA in an N6-methyladenosine-dependent manner. J Exp Clin Cancer Res 41: 42, 2022.
52. Strickaert A, Corbet C, Spinette SA, Craciun L, Dom G, Andry G, Larsimont D, Wattiez R, Dumont JE, Feron O, *et al*: Reprogramming of energy metabolism: Increased expression and roles of pyruvate carboxylase in papillary thyroid cancer. Thyroid 29: 845-857, 2019.
53. Xie W, Zeng Y, Hu L, Hao J, Chen Y, Yun X, Lin Q and Li H: Based on different immune responses under the glucose metabolizing type of papillary thyroid cancer and the response to anti-PD-1 therapy. Front Immunol 13: 991656, 2022.
54. Shen CT, Wei WJ, Qiu ZL, Song HJ, Zhang XY, Sun ZK and Luo QY: Metformin reduces glycometabolism of papillary thyroid carcinoma in vitro and in vivo. J Mol Endocrinol 58: 15-23, 2017.
55. Ren X, Shu J, Wang J, Guo Y, Zhang Y, Yue L, Yu H, Chen W, Zhang C, Ma J and Li Z: Machine learning reveals salivary glycopatterns as potential biomarkers for the diagnosis and prognosis of papillary thyroid cancer. Int J Biol Macromol 215: 280-289, 2022.
56. Wang Y, Yang L, Mao L, Zhang L, Zhu Y, Xu Y, Cheng Y, Sun R, Zhang Y, Ke J and Zhao D: SGLT2 inhibition restrains thyroid cancer growth via G1/S phase transition arrest and apoptosis mediated by DNA damage response signaling pathways. Cancer Cell Int 22: 74, 2022.
57. Thakur S, Daley B, Gaskins K, Vasko VV, Boufraqech M, Patel D, Sourbier C, Reece J, Cheng SY, Kebebew E, *et al*: Metformin targets mitochondrial glycerophosphate dehydrogenase to control rate of oxidative phosphorylation and growth of thyroid cancer in vitro and in vivo. Clin Cancer Res 24: 4030-4043, 2018.
58. Wen S, Luo Y, Wu W, Zhang T, Yang Y, Ji Q, Wu Y, Shi R, Ma B, Xu M and Qu N: Identification of lipid metabolism-related genes as prognostic indicators in papillary thyroid cancer. Acta Biochim Biophys Sin (Shanghai) 53: 1579-1589, 2021.
59. Xu M, Sun T, Wen S, Zhang T, Wang X, Cao Y, Wang Y, Sun X, Ji Q, Shi R and Qu N: Characteristics of lipid metabolism-related gene expression-based molecular subtype in papillary thyroid cancer. Acta Biochim Biophys Sin (Shanghai) 52: 1166-1170, 2020.
60. Liao T, Wang YJ, Hu JQ, Wang Y, Han LT, Ma B, Shi RL, Qu N, Wei WJ, Guan Q, *et al*: Histone methyltransferase KMT5A gene modulates oncogenesis and lipid metabolism of papillary thyroid cancer *in vitro*. Oncol Rep 39: 2185-2192, 2018.
61. Zwara A, Hellmann A, Czapiewska M, Korczynska J, Sztendel A and Mika A: The influence of cancer on the reprogramming of lipid metabolism in healthy thyroid tissues of patients with papillary thyroid carcinoma. Endocrine 87: 273-280, 2024.
62. Abooshahab R, Hooshmand K, Razavi SA, Gholami M, Sanoie M and Hedayati M: Plasma metabolic profiling of human thyroid nodules by gas Chromatography-mass spectrometry (GC-MS)-based untargeted metabolomics. Front Cell Dev Biol 8: 385, 2020.
63. Ambrosi F, Righi A, Ricci C, Erickson LA, Lloyd RV and Asioli S: Hobnail variant of papillary thyroid carcinoma: A literature review. Endocr Pathol 28: 293-301, 2017.
64. Aprile M, Cataldi S, Perfetto C, Federico A, Ciccodicola A and Costa V: Targeting metabolism by B-raf inhibitors and diclofenac restrains the viability of BRAF-mutated thyroid carcinomas with Hif-1α-mediated glycolytic phenotype. Br J Cancer 129: 249-265, 2023.
65. Badziong J, Ting S, Synoracki S, Tiedje V, Brix K, Brabant G, Moeller LC, Schmid KW, Fuhrer D and Zwanziger D: Differential regulation of monocarboxylate transporter 8 expression in thyroid cancer and hyperthyroidism. Eur J Endocrinol 177: 243-250, 2017.
66. Bai N, Xia F, Wang W, Lei Y, Bo J and Li X: CDK12 promotes papillary thyroid cancer progression through regulating the c-myc/β-catenin pathway. J Cancer 11: 4308-4315, 2020.
67. Chen W, Fu J, Chen Y, Li Y, Ning L, Huang D, Yan S and Zhang Q: Circular RNA circKIF4A facilitates the malignant progression and suppresses ferroptosis by sponging miR-1231 and upregulating GPX4 in papillary thyroid cancer. Aging (Albany NY) 13: 16500-16512, 2021.
68. Chen W, Zhang T, Bai Y, Deng H, Yang F, Zhu R, Chen Y, He Z, Zeng Q and Song M: Upregulated circRAD18 promotes tumor progression by reprogramming glucose metabolism in papillary thyroid cancer. Gland Surg 10: 2500-2510, 2021.
69. Chong ST, Tan KM, Kok CYL, Guan SP, Lai SH, Lim C, Hu J, Sturgis C, Eng C, Lam PYP, *et al*: IL13RA2 is differentially regulated in papillary thyroid carcinoma vs follicular thyroid carcinoma. J Clin Endocrinol Metab 104: 5573-5584, 2019.
70. Davis PJ, Lin HY, Hercbergs A and Mousa SA: Actions of L-thyroxine (T4) and tetraiodothyroacetic acid (Tetrac) on gene expression in thyroid cancer cells. Genes (Basel) 11: 755, 2020.
71. Fan X and Zhao Y: miR-451a inhibits cancer growth, epithelial-mesenchymal transition and induces apoptosis in papillary thyroid cancer by targeting PSMB8. J Cell Mol Med 23: 8067-8075, 2019.
72. Feng Z, Song Y, Qian J, Chen T, Yang C, Jia L, Liu C, Liu P, Lv J and Deng Z: Differential expression of a set of microRNA genes reveals the potential mechanism of papillary thyroid carcinoma. Ann Endocrinol (Paris) 80: 77-83, 2019.
73. Gunjača I, Benzon B, Pleić N, Babić Leko M, Pešutić Pisac V, Barić A, Kaličanin D, Punda A, Polašek O, Vukojević K, *et al*: Role of ST6GAL1 in thyroid cancers: Insights from tissue analysis and genomic datasets. Int J Mol Sci 24: 16334, 2023.
74. Ha TK, Jung I, Kim ME, Bae SK and Lee JS: Anti-cancer activity of myricetin against human papillary thyroid cancer cells involves mitochondrial Dysfunction-mediated apoptosis. Biomed Pharmacother 91: 378-384, 2017.
75. Hińcza K, Kowalik A, Pałyga I, Walczyk A, Gąsior-Perczak D, Mikina E, Trybek T, Szymonek M, Gadawska-Juszczyk K, Zajkowska K, *et al*: Does the TT variant of the rs966423 polymorphism in DIRC3 affect the stage and clinical course of papillary thyroid cancer? Cancers (Basel) 12: 423, 2020.
76. Hu H, Quan G, Yang F, Du S, Ding S, Lun Y and Chen Q: MicroRNA-96-5p is negatively regulating GPC3 in the metastasis of papillary thyroid cancer. SAGE Open Med 11: 20503121231205710, 2023.
77. Hu Z, Zhao P, Zhang K, Zang L, Liao H and Ma W: Hsa_circ_0011290 regulates proliferation, apoptosis and glycolytic phenotype in papillary thyroid cancer via miR-1252/ FSTL1 signal pathway. Arch Biochem Biophys 685: 108353, 2020.
78. Jeon MJ, You MH, Han JM, Sim S, Yoo HJ, Lee WK, Kim TY, Song DE, Shong YK, Kim WG and Kim WB: High phosphoglycerate dehydrogenase expression induces stemness and aggressiveness in thyroid cancer. Thyroid 30: 1625-1638, 2020.
79. Jin L, Zheng D, Mo D, Guan Y, Wen J, Zhang X and Chen C: Glucose-to-Lymphocyte ratio (GLR) as a predictor of preoperative central lymph node metastasis in papillary thyroid cancer patients with type 2 diabetes mellitus and construction of the nomogram. Front Endocrinol (Lausanne) 13: 829009, 2022.
80. Kang YE, Kim JT, Lim MA, Oh C, Liu L, Jung SN, Won HR, Lee K, Chang JW, Yi HS, *et al*: Association between Circulating Fibroblast Growth Factor 21 and Aggressiveness in Thyroid Cancer. Cancers (Basel) 11: 1154, 2019.
81. Li X, Wu Z, He J, Jin Y, Chu C, Cao Y, Gu F, Wang H, Hou C, Liu X and Zou Q: OGT regulated O-GlcNAcylation promotes papillary thyroid cancer malignancy via activating YAP. Oncogene 40: 4859-4871, 2021.
82. Li Y, Chen M, Liu C, Xia Y, Xu B, Hu Y, Chen T, Shen M and Tang W: Metabolic changes associated with papillary thyroid carcinoma: A nuclear magnetic resonance-based metabolomics study. Int J Mol Med 41: 3006-3014, 2018.
83. Lu J, Zhang Y, Sun M, Ding C, Zhang L, Kong Y, Cai M, Miccoli P, Ma C and Yue X: Multi-omics analysis of fatty acid metabolism in thyroid carcinoma. Front Oncol 11: 737127, 2021.
84. Mardente S, Romeo MA, Asquino A, Po A, Gilardini Montani MS and Cirone M: HHV-6A infection of papillary thyroid cancer cells induces several effects related to cancer progression. Viruses 15: 2122, 2023.
85. Nahm JH, Kim HM and Koo JS: Glycolysis-related protein expression in thyroid cancer. Tumour Biol 39: 1010428317695922, 2017.
86. Nilsson JN, Siikanen J, Hedman C, Juhlin CC and Ihre Lundgren C: Pre-Therapeutic measurements of iodine avidity in papillary and poorly differentiated thyroid cancer reveal associations with thyroglobulin expression, histological variants and Ki-67 index. Cancers (Basel) 13: 3627, 2021.

87. Parascandolo A, Rappa F, Cappello F, Kim J, Cantu DA, Chen H, Mazzoccoli G, Hematti P, Castellone MD, Salvatore M and Laukkanen MO: Extracellular superoxide dismutase expression in papillary thyroid cancer mesenchymal Stem/Stromal cells modulates cancer cell growth and migration. Sci Rep 7: 41416, 2017.
88. Piana S, Zanetti E, Bisagni A, Ciarrocchi A, Giordano D, Torricelli F, Rossi T and Ragazzi M: Expression of NOTCH1 in thyroid cancer is mostly restricted to papillary carcinoma. Endocr Connect 8: 1089-1096, 2019.
89. Sekhar KR, Cyr S and Baregamian N: Ferroptosis inducers in thyroid cancer. World J Surg 47: 371-381, 2023.
90. Song H, Qiu Z, Wang Y, Xi C, Zhang G, Sun Z, Luo Q and Shen C: HIF-1α/YAP signaling rewrites Glucose/Iodine metabolism program to promote papillary thyroid cancer progression. Int J Biol Sci 19: 225-241, 2023.
91. Sun Y, Gong J, Guo B, Shang J, Cheng Y and Xu H: Association of adjuvant radioactive iodine therapy with survival in node-positive papillary thyroid cancer. Oral Oncol 87: 152-157, 2018.
92. Valvo V, Iesato A, Kavanagh TR, Priolo C, Zsengeller Z, Pontecorvi A, Stillman IE, Burke SD, Liu X and Nucera C: Fine-tuning lipid metabolism by targeting Mitochondria-associated Ac92etyl-CoA-Carboxylase 2 in BRAF(V600E) papillary thyroid carcinoma. Thyroid 31: 1335-1358, 2021.
93. Wu C, Ma L, Wei H, Nie F, Ning J and Jiang T: MiR-1256 inhibits cell proliferation and cell cycle progression in papillary thyroid cancer by targeting 5-hydroxy tryptamine receptor 3A. Hum Cell 33: 630-640, 2020.
94. Xia M, Wang S, Wang L, Mei Y, Tu Y and Gao L: The role of lactate metabolism-related LncRNAs in the prognosis, mutation, and tumor microenvironment of papillary thyroid cancer. Front Endocrinol (Lausanne) 14: 1062317, 2023.
95. Xu K and Feng Y: HOXD-AS1 is a predictor of clinical progression and functions as an oncogenic lncRNAs in papillary thyroid cancer. J Cell Biochem 120: 5326-5332, 2019.
96. Yun HJ, Kim M, Kim SY, Fang S, Kim Y, Chang HS, Chang HJ and Park KC: Effects of Anti-cancer drug Sensitivity-related genetic differences on therapeutic approaches in refractory papillary thyroid cancer. Int J Mol Sci 23: 699, 2022.
97. Zarkesh M, Zadeh-Vakili A, Akbarzadeh M, Fanaei SA, Hedayati M and Azizi F: The role of matrix metalloproteinase-9 as a prognostic biomarker in papillary thyroid cancer. BMC Cancer 18: 1199, 2018.
98. Zeng J, Ma X, Wang J, Liu R, Shao Y, Hou Y, Li Z and Fang Y: Down-regulated HSDL2 expression suppresses cell proliferation and promotes apoptosis in papillary thyroid carcinoma. Biosci Rep 39: BSR20190425, 2019.
99. Zhang C, Bo C, Guo L, Yu P, Miao S and Gu X: BCL2 and hsa-miR-181a-5p are potential biomarkers associated with papillary thyroid cancer based on bioinformatics analysis. World J Surg Oncol 17: 221, 2019.
100. Zhang J, Wen X, Li Y, Zhang J, Li X, Qian C, Tian Y, Ling R and Duan Y: Diagnostic approach to thyroid cancer based on amino acid metabolomics in saliva by ultra-performance liquid chromatography with high resolution mass spectrometry. Talanta 235: 122729, 2021.
101. Zhao F, Zhu S, Fang J, Dong H and Zhu C: Correlation of DNA methylation and lymph node metastasis in papillary thyroid carcinoma. Head Neck 45: 1654-1662, 2023.
102. Sengun S, Korkmaz H, Ciris M, Yüceer RO, Boyluboy SM and Kiran M: Diagnostic and prognostic value of Stanniocalcin 1 expression in papillary thyroid cancer. Endocrine 78: 95-103, 2022.
103. Luo JH, Zhang XX and Sun WH: F12 as a reliable diagnostic and prognostic biomarker associated with immune infiltration in papillary thyroid cancer. Aging (Albany NY) 14: 3687-3704, 2022.
104. Zhang K, Li C, Liu J, Li Z and Ma C: Down-regulation of APTR and it's diagnostic value in papillary and anaplastic thyroid cancer. Pathol Oncol Res 26: 559-565, 2020.
105. Bumber B, Marjanovic Kavanagh M, Jakovcevic A, Sincic N, Prstacic R and Prgomet D: Role of matrix metalloproteinases and their inhibitors in the development of cervical metastases in papillary thyroid cancer. Clin Otolaryngol 45: 55-62, 2020.
106. Ali KM, Awny S, Ibrahim DA, Metwally IH, Hamdy O, Refky B, Abdallah A and Abdelwahab K: Role of P53, E-cadherin and BRAF as predictors of regional nodal recurrence for papillary thyroid cancer. Ann Diagn Pathol 40: 59-65, 2019.
107. Wang Y, Song W, Li Y, Liu Z, Zhao K, Jia L, Wang X, Jiang R, Tian Y and He X: Integrated analysis of tumor microenvironment features to establish a diagnostic model for papillary thyroid cancer using bulk and single-cell RNA sequencing technology. J Cancer Res Clin Oncol 149: 16837-16850, 2023.
108. Boucai L, Zafereo M and Cabanillas ME: Thyroid cancer: A review. JAMA 331: 425-435, 2024.
109. Levine RA: History of thyroid ultrasound. Thyroid 33: 894-902, 2023.
110. Mitchell AL, Gandhi A, Scott-Coombes D and Perros P: Management of thyroid cancer: United kingdom national multidisciplinary guidelines. J Laryngol Otol 130 (Suppl): S150-S160, 2016.
111. Hou ZK, Zhao J, Zhang M, Hou W, Li Y, Yang Y, Liu Y, Ye Z, Cai Q, Wei X, *et al*: Preoperative identification of papillary thyroid carcinoma subtypes and lymph node metastasis via deep Learning-Assisted Surface-enhanced raman spectroscopy. ACS Nano 19: 21807-21819, 2025.
112. Su X, Shang L, Yue C and Ma B: Ultrasound-guided fine needle aspiration thyroglobulin in the diagnosis of lymph node metastasis of differentiated papillary thyroid carcinoma and its influencing factors. Front Endocrinol (Lausanne) 15: 1304832, 2024.
113. Zhao L, Zhang X and Cui S: Matrine inhibits TPC-1 human thyroid cancer cells via the miR-21/PTEN/Akt pathway. Oncol Lett 16: 2965-2970, 2018.
114. Fu S, Ma C, Tang X, Ma X, Jing G, Zhao N and Ran J: MiR-192-5p inhibits proliferation, migration, and invasion in papillary thyroid carcinoma cells by regulation of SH3RF3. Biosci Rep 41: BSR20210342, 2021.
115. Fu S, Zhao N, Jing G, Yang X, Liu J, Zhen D and Tang X: Matrine induces papillary thyroid cancer cell apoptosis in vitro and suppresses tumor growth in vivo by downregulating miR-182-5p. Biomed Pharmacother 128: 110327, 2020.
116. Wen SS, Wu YJ, Wang JY, Ni ZX, Dong S, Xie XJ, Wang YT, Wang Y, Huang NS, Ji QH, *et al*: BRAFV600E/p-ERK/p-DRP1(Ser616) promotes tumor progression and reprogramming of glucose metabolism in papillary thyroid cancer. Thyroid 34: 1246-1259, 2024.
117. Liu B, Peng Y, Su Y, Diao C, Cha L and Cheng R: Glutamate activates the MAPK pathway by inhibiting LPAR1 expression and promotes anlotinib resistance in thyroid cancer. Discov Oncol 16: 1082, 2025.
118. Limberg J, Egan CE, Gray KD, Singh M, Loewenstein Z, Yang Y, Riascos MC, Al Asadi H, Safe P, El Eshaky S, *et al*: Activation of the JAK/STAT pathway leads to BRAF inhibitor resistance in BRAFV600E positive thyroid carcinoma. Mol Cancer Res 21: 397-410, 2023.
119. Sui F, Wang G, Liu J, Yuan M, Chen P, Yao Y, Zhang S, Ji M and Hou P: Targeting NG2 relieves the resistance of BRAF-mutant thyroid cancer cells to BRAF inhibitors. Cell Mol Life Sci 81: 238, 2024.
120. Xu M, Zhao D, Chen Y, Chen C, Zhang L, Sun L, Chen J, Tang Q, Sun S, Ma C, *et al*: Charge reversal polypyrrole nanocomplex-mediated gene delivery and photothermal therapy for effectively treating papillary thyroid cancer and inhibiting lymphatic metastasis. ACS Appl Mater Interfaces 14: 14072-14086, 2022.
121. Pearce EN and Caldwell KL: Urinary iodine, thyroid function, and thyroglobulin as biomarkers of iodine status. AmJ Clin Nutr 104 (Suppl 3): 898S-901S, 2016.
122. Sørensen SM, de la Cour CD, Maltesen T, Urbute A and Kjaer SK: Temporal trends in papillary and follicular thyroid cancer incidence from 1995 to 2019 in adults in denmark according to education and income. Thyroid 32: 972-982, 2022.
123. Aschebrook-Kilfoy B, Grogan RH, Ward MH, Kaplan E and Devesa SS: Follicular thyroid cancer incidence patterns in the United states 1980-2009. Thyroid 23: 1015-1021, 2013.
124. Kitahara CM and Sosa JA: The changing incidence of thyroid cancer. Nat Rev Endocrinol 12: 646-653, 2016.
125. Aschebrook-Kilfoy B, Kaplan EL, Chiu BC, Angelos P and Grogan RH: The acceleration in papillary thyroid cancer incidence rates is similar among racial and ethnic groups in the United States. Ann Surg Oncol 20: 2746-2753, 2013.
126. Liu LP, Hao JY, Pan H, Wang C and Yue P: Mutation of RAS gene in follicular-differentiated thyroid tumors and its significance. Zhonghua Bing Li Xue Za Zhi 49: 256-261, 2020 (In Chinese).
127. Yang X and Wu H: RAS signaling in carcinogenesis, cancer therapy and resistance mechanisms. J Hematol Oncol 17: 108, 2024.

128. Tartaglia M and Gelb BD: Disorders of dysregulated signal traffic through the RAS-MAPK pathway: Phenotypic spectrum and molecular mechanisms. Ann N Y Acad Sci 1214: 99-121, 2010.
129. Bahar ME, Kim HJ and Kim DR: Targeting the RAS/RAF/MAPK pathway for cancer therapy: From mechanism to clinical studies. Signal Transduct Target Ther 8: 455, 2023.
130. Takács T, Kudlik G, Kurilla A, Szeder B, Buday L and Vas V: The effects of mutant Ras proteins on the cell signalome. Cancer Metastasis Rev 39: 1051-1065, 2020.
131. De Martino M, Esposito F, Capone M, Pallante P and Fusco A: Noncoding RNAs in thyroid-follicular-cell-derived carcinomas. Cancers (Basel) 14: 3079, 2022.
132. Srinivasan V, Asghar MY, Zafar S, Törnquist K and Lindholm D: Proliferation and migration of ML1 follicular thyroid cancer cells are inhibited by IU1 targeting USP14: Role of proteasome and autophagy flux. Front Cell Dev Biol 11: 1234204, 2023.
133. Lin TH, Kuo CH, Zhang YS, Chen PT, Chen SH, Li YZ and Lee YR: Piperlongumine induces cellular apoptosis and autophagy via the ROS/Akt signaling pathway in human follicular thyroid cancer cells. Int J Mol Sci 24: 8048, 2023.
134. Pribyl M, Hodny Z and Kubikova I: Suprabasin-A review. Genes (Basel) 108: 12, 2021.
135. Tan H, Wang L and Liu Z: Role of suprabasin in the dedifferentiation of follicular epithelial Cell-derived thyroid cancer and identification of related immune markers. Front Genet 13: 810681, 2022.
136. Iesato A, Nakamura T, Izumi H, Uehara T and Ito KI: PATZ1 knockdown enhances malignant phenotype in thyroid epithelial follicular cells and thyroid cancer cells. Oncotarget 8: 82754-82772, 2017.
137. Yoshida J, Iwabuchi K, Matsui T, Ishibashi T, Masuoka T and Nishio M: Knockdown of stromal interaction molecule 1 (STIM1) suppresses store-operated calcium entry, cell proliferation and tumorigenicity in human epidermoid carcinoma A431 cells. Biochem Pharmacol 84: 1592-1603, 2012.
138. Kuang CY, Yu Y, Guo RW, Qian DH, Wang K, Den MY, Shi YK and Huang L: Silencing stromal interaction molecule 1 by RNA interference inhibits the proliferation and migration of endothelial progenitor cells. Biochem Biophys Res Commun 398: 315-320, 2010.
139. Asghar MY, Lassila T, Paatero I, Nguyen VD, Kronqvist P, Zhang J, Slita A, Löf C, Zhou Y, Rosenholm J and Törnquist K: Stromal interaction molecule 1 (STIM1) knock down attenuates invasion and proliferation and enhances the expression of Thyroid-specific proteins in human follicular thyroid cancer cells. Cell Mol Life Sci 78: 5827-5846, 2021.
140. Cai X, Sun R, Yang L, Yao N, Sun Y, Zhang G, Ge W, Zhou Y, Gui Z, Wang Y, *et al*: Proteomic analysis reveals modulation of key proteins in follicular thyroid cancer progression. Chin Med J (Engl): May 21 doi: 10.1097/CM9.0000000000003645 (Epub ahead of print).
141. Goenka A, Khan F, Verma B, Sinha P, Dmello CC, Jogalekar MP, Gangadaran P and Ahn BC: Tumor microenvironment signaling and therapeutics in cancer progression. Cancer Commun (Lond) 43: 525-561, 2023.
142. Rudzińska M, Mikula M, Arczewska KD, Gajda E, Sabalińska S, Stępień T, Ostrowski J and Czarnocka B: Transcription factor prospero Homeobox 1 (PROX1) as a potential angiogenic regulator of follicular thyroid cancer dissemination. Int J Mol Sci 20: 5619, 2019.
143. Li Q, Liu W, Wang Z, Wang C and Ai Z: Exosomal ANXA1 derived from thyroid cancer cells is associated with malignant transformation of human thyroid follicular epithelial cells by promoting cell proliferation. Int J Oncol 59: 104, 2021.
144. Zhou Q, Chen J, Feng J, Xu Y, Zheng W and Wang J: SOSTDC1 inhibits follicular thyroid cancer cell proliferation, migration, and EMT via suppressing PI3K/Akt and MAPK/Erk signaling pathways. Mol Cell Biochem 435: 87-95, 2017.
145. Fuziwara CS, Saito KC, Leoni SG, Waitzberg Â FL and Kimura ET: The highly expressed FAM83F protein in papillary thyroid cancer exerts a Pro-oncogenic role in thyroid follicular cells. Front Endocrinol (Lausanne) 10: 134, 2019.
146. Xu G, Chen J, Wang G, Xiao J, Zhang N, Chen Y, Yu H, Wang G and Zhao Y: Resveratrol inhibits the tumorigenesis of follicular thyroid cancer via ST6GAL2-Regulated activation of the hippo signaling pathway. Mol Ther Oncolytics 16: 124-133, 2020.
147. Campisi A, Bonfanti R, Raciti G, Bonaventura G, Legnani L, Magro G, Pennisi M, Russo G, Chiacchio MA, Pappalardo F and Parenti R: Gene silencing of Transferrin-1 receptor as a potential therapeutic target for human follicular and anaplastic thyroid cancer. Mol Ther Oncolytics 16: 197-206, 2020.
148. Bai F, Liu X, Zhang X, Mao Z, Wen H, Ma J and Pei XH: p18INK4C and BRCA1 inhibit follicular cell proliferation and dedifferentiation in thyroid cancer. Cell Cycle 22: 1637-1653, 2023.
149. Erinjeri NJ, Nicolson NG, Deyholos C, Korah R and Carling T: Whole-exome sequencing identifies two discrete druggable signaling pathways in follicular thyroid cancer. J Am Coll Surg 226: 950-959.e5, 2018.
150. Fozzatti L, Alamino VA, Park S, Giusiano L, Volpini X, Zhao L, Stempin CC, Donadio AC, Cheng SY and Pellizas CG: Interplay of fibroblasts with anaplastic tumor cells promotes follicular thyroid cancer progression. Sci Rep 9: 8028, 2019.
151. Xu PP, Zeng S, Xia XT, Ye ZH, Li MF, Chen MY, Xia T, Xu JJ, Jiao Q, Liu L, *et al*: 2020: FAM172A promotes follicular thyroid carcinogenesis and may be a marker of FTC. Endocr Relat Cancer 27: 657-669, 2020.
152. Liu JL, Mao Z, Gallick GE and Yung WK: AMPK/TSC2/mTOR-signaling intermediates are not necessary for LKB1-mediated nuclear retention of PTEN tumor suppressor. Neuro Oncol 13: 184-194, 2011.
153. Pringle DR, Vasko VV, Yu L, Manchanda PK, Lee AA, Zhang X, Kirschner JM, Parlow AF, Saji M, Jarjoura D, *et al*: Follicular thyroid cancers demonstrate dual activation of PKA and mTOR as modeled by thyroid-specific deletion of Prkar1a and Pten in mice. J Clin Endocrinol Metab 99: E804-E812, 2014.
154. Kari S, Vasko VV, Priya S and Kirschner LS: PKA activates AMPK through LKB1 signaling in follicular thyroid cancer. Front Endocrinol (Lausanne) 10: 769, 2019.
155. Borowczyk M, Szczepanek-Parulska E, Dębicki S, Budny B, Janicka-Jedyńska M, Gil L, Verburg FA, Filipowicz D, Wrotkowska E, Majchrzycka B, *et al*: High incidence of FLT3 mutations in follicular thyroid cancer: Potential therapeutic target in patients with advanced disease stage. Ther Adv Med Oncol 12: 1758835920907534, 2020.
156. Borson-Chazot F, Dantony E, Illouz F, Lopez J, Niccoli P, Wassermann J, Do Cao C, Leboulleux S, Klein M, Tabarin A, *et al*: Effect of buparlisib, a Pan-class I PI3K inhibitor, in refractory follicular and poorly differentiated thyroid cancer. Thyroid 28: 1174-1179, 2018.
157. El-Azem N, Pulido-Moran M, Ramirez-Tortosa CL, Quiles JL, Cara FE, Sanchez-Rovira P, Granados-Principal S and Ramirez-Tortosa M: Modulation by hydroxytyrosol of oxidative stress and antitumor activities of paclitaxel in breast cancer. Eur J Nutr 58: 1203-1211, 2019.
158. Toteda G, Lupinacci S, Vizza D, Bonofiglio R, Perri E, Bonofiglio M, Lofaro D, La Russa A, Leone F, Gigliotti P, *et al*: High doses of hydroxytyrosol induce apoptosis in papillary and follicular thyroid cancer cells. J Endocrinol Invest 40: 153-162, 2017.
159. Son Y, Lee JH, Chung HT and Pae HO: Therapeutic roles of heme oxygenase-1 in metabolic diseases: Curcumin and resveratrol analogues as possible inducers of heme oxygenase-1. Oxid Med Cell Longev 2013: 639541, 2013.
160. Li R, Zhang J, Zhou Y, Gao Q, Wang R, Fu Y, Zheng L and Yu H: Transcriptome investigation and in vitro verification of Curcumin-induced HO-1 as a feature of ferroptosis in breast cancer cells. Oxid Med Cell Longev 2020: 3469840, 2020.
161. Kwon MY, Park E, Lee SJ and Chung SW: Heme oxygenase-1 accelerates erastin-induced ferroptotic cell death. Oncotarget 6: 24393-24403, 2015.
162. Chen H, Li Z, Xu J, Zhang N, Chen J, Wang G and Zhao Y: Curcumin induces ferroptosis in follicular thyroid cancer by upregulating HO-1 expression. Oxid Med Cell Longev 2023: 6896790, 2023.
163. Li Q, Zhang S, Wang M, Dong S, Wang Y, Liu S, Lu T, Fu Y, Wang X and Chen G: Downregulated miR-21 mediates matrine-induced apoptosis via the PTEN/Akt signaling pathway in FTC-133 human follicular thyroid cancer cells. Oncol Lett 18: 3553-3560, 2019.
164. Marotta V, Di Somma C, Rubino M, Sciammarella C, Modica R, Camera L, Del Prete M, Marciello F, Ramundo V, Circelli L, *et al*: Second-line sunitinib as a feasible approach for iodine-refractory differentiated thyroid cancer after the failure of first-line sorafenib. Endocrine 49: 854-858, 2015.

165. Sousa Santos F, Joana Santos R and Leite V: Sorafenib and sunitinib for the treatment of metastatic thyroid cancer of follicular origin: A 7-year Single-Centre experience. Eur Thyroid J 8: 262-267, 2019.
166. Lan L, Basourakos S, Cui D, Zuo X, Deng W, Huo L, Chen L, Zhang G, Deng L, Shi B, *et al*: Inhibiting β-catenin expression promotes efficiency of radioiodine treatment in aggressive follicular thyroid cancer cells probably through mediating NIS localization. Oncol Rep 37: 426-434, 2017.
167. Dias D, Damásio I, Marques P, Simões H, Rodrigues R, Cavaco BM and Leite V: Metastatic follicular thyroid cancer with a longstanding responsiveness to gemcitabine plus oxaliplatin. Eur Thyroid J 12: e220227, 2023.
168. Heffess CS and Thompson LD: Minimally invasive follicular thyroid carcinoma. Endocr Pathol 12: 417-422, 2001.
169. Hernandez-Prera JC and Wenig BM: RAS-mutant follicular thyroid tumors: A continuous challenge for pathologists. Endocr Pathol 35: 167-184, 2024.
170. Lang BH, Lo CY, Chan WF, Lam KY and Wan KY: Prognostic factors in papillary and follicular thyroid carcinoma: Their implications for cancer staging. Ann Surg Oncol 14: 730-738, 2007.
171. Levi J, Kothapalli SR, Bohndiek S, Yoon JK, Dragulescu-Andrasi A, Nielsen C, Tisma A, Bodapati S, Gowrishankar G, Yan X, *et al*: Molecular photoacoustic imaging of follicular thyroid carcinoma. Clin Cancer Res 19: 1494-1502, 2013.
172. Li G, Wang H, Zhong J, Bai Y, Chen W, Jiang K, Huang J, Shao Y, Liu J, Gong Y, *et al*: Circulating small extracellular vesicle-based miRNA classifier for follicular thyroid carcinoma: A diagnostic study. Br J Cancer 130: 925-933, 2024.
173. Liang L, Xu J, Wang M, Xu G, Zhang N, Wang G and Zhao Y: LncRNA HCP5 promotes follicular thyroid carcinoma progression via miRNAs sponge. Cell Death Dis 9: 372, 2018.
174. Lin J, Qiu Y, Zheng X, Dai Y and Xu T: The miR-199a-5p/PD-L1 axis regulates cell proliferation, migration and invasion in follicular thyroid carcinoma. BMC Cancer 22: 756, 2022.
175. Lo CY, Chan WF, Lam KY and Wan KY: Follicular thyroid carcinoma: The role of histology and staging systems in predicting survival. Ann Surg 242: 708-715, 2005.
176. Macerola E, Proietti A, Poma AM, Vignali P, Sparavelli R, Ginori A, Basolo A, Elisei R, Santini F and Basolo F: Limited accuracy of Pan-trk immunohistochemistry screening for NTRK rearrangements in Follicular-derived thyroid carcinoma. Int J Mol Sci 23: 7470, 2022.
177. Park H, Shin HC, Yang H, Heo J, Ki CS, Kim HS, Kim JH, Hahn SY, Chung YJ, Kim SW, *et al*: Molecular classification of follicular thyroid carcinoma based on TERT promoter mutations. Mod Pathol 35: 186-192, 2022.
178. Paulsson JO, Wang N, Gao J, Stenman A, Zedenius J, Mu N, Lui WO, Larsson C and Juhlin CC: GABPA-dependent down-regulation of DICER1 in follicular thyroid tumours. Endocr Relat Cancer 27: 295-308, 2020.
179. Pulcrano M, Boukheris H, Talbot M, Caillou B, Dupuy C, Virion A, De Vathaire F and Schlumberger M: Poorly differentiated follicular thyroid carcinoma: Prognostic factors and relevance of histological classification. Thyroid 17: 639-646, 2007.
180. Repaci A, Salituro N, Vicennati V, Monari F, Cavicchi O, de Biase D, Ciarrocchi A, Acquaviva G, De Leo A, Gruppioni E, *et al*: Unexpected widespread bone metastases from a BRAF K601N mutated follicular thyroid carcinoma within a previously resected multinodular goiter. Endocr Pathol 33: 519-524, 2022.
181. Romitti M, Ceolin L, Siqueira DR, Ferreira CV, Wajner SM and Maia AL: Signaling pathways in follicular cell-derived thyroid carcinomas (review). Int J Oncol 42: 19-28, 2013.
182. Rossing M, Borup R, Henao R, Winther O, Vikesaa J, Niazi O, Godballe C, Krogdahl A, Glud M, Hjort-Sørensen C, *et al*: Down-regulation of microRNAs controlling tumourigenic factors in follicular thyroid carcinoma. J Mol Endocrinol 48: 11-23, 2012.
183. Saburi S, Tsujikawa T, Miyagawa-Hayashino A, Mitsuda J, Yoshimura K, Kimura A, Morimoto H, Ohmura G, Arai A, Ogi H, *et al*: Spatially resolved immune microenvironmental profiling for follicular thyroid carcinoma with minimal capsular invasion. Mod Pathol 35: 721-727, 2022.
184. Staubitz JI, Musholt PB and Musholt TJ: The surgical dilemma of primary surgery for follicular thyroid neoplasms. Best Pract Res Clin Endocrinol Metab 33: 101292, 2019.
185. Stenman A, Hysek M, Jatta K, Bränström R, Darai-Ramqvist E, Paulsson JO, Wang N, Larsson C, Zedenius J and Juhlin CC: TERT promoter mutation spatial heterogeneity in a metastatic follicular thyroid carcinoma: Implications for clinical work-up. Endocr Pathol 30: 246-248, 2019.
186. Taylor T, Specker B, Robbins J, Sperling M, Ho M, Ain K, Bigos ST, Brierley J, Cooper D, Haugen B, *et al*: Outcome after treatment of high-risk papillary and non-Hürthle-cell follicular thyroid carcinoma. Ann Intern Med 129: 622-627, 1998.
187. Thompson LDR: High grade differentiated follicular Cell-derived thyroid carcinoma versus poorly differentiated thyroid carcinoma: A clinicopathologic analysis of 41 cases. Endocr Pathol 34: 234-246, 2023.
188. Wenter V, Albert NL, Unterrainer M, Ahmaddy F, Ilhan H, Jellinek A, Knösel T, Bartenstein P, Spitzweg C, Lehner S, *et al*: Clinical impact of follicular oncocytic (Hürthle cell) carcinoma in comparison with corresponding classical follicular thyroid carcinoma. Eur J Nucl Med Mol Imaging 48: 449-460, 2021.
189. Yu B, Li Y, Yu X, Ai Y, Jin J, Zhang J, Zhang Y, Zhu H, Xie C, Shen M, *et al*: Differentiate thyroid follicular adenoma from carcinoma with combined ultrasound radiomics features and clinical ultrasound features. J Digit Imaging 35: 1362-1372, 2022.
190. Zhang H, Zhang Z, Liu X, Duan H, Xiang T, He Q, Su Z, Wu H and Liang Z: DNA methylation haplotype block markers efficiently discriminate follicular thyroid carcinoma from follicular adenoma. J Clin Endocrinol Metab 106: 1011-1021, 2021.
191. Saltiki K, Simeakis G, Karapanou O and Alevizaki M: Management of Endocrine Disease: Medullary thyroid cancer: From molecular biology and therapeutic pitfalls to future targeted treatment perspectives. Eur J Endocrinol 187: R53-R63, 2022.
192. Shi X, Sun Y, Shen C, Zhang Y, Shi R, Zhang F, Liao T, Lv G, Zhu Z, Jiao L, *et al*: Integrated proteogenomic characterization of medullary thyroid carcinoma. Cell Discov 8: 120, 2022.
193. Khan E, Hylton H, Rajan N, Bouley SJ, Siddiqui JK, Rajasekaran S, Koshre GR, Storts H, Valenciaga A, Khan M, *et al*: Proteomic profiling of medullary thyroid cancer identifies CAPN1 as a key regulator of NF1 and RET fueled growth. Thyroid 35: 177-187, 2025.
194. Navas-Carrillo D, Rodriguez JM, Montoro-García S and Orenes-Piñero E: High-resolution proteomics and metabolomics in thyroid cancer: Deciphering novel biomarkers. Crit Rev Clin Lab Sci 54: 446-457, 2017.
195. Khatami F and Tavangar SM: Genetic and epigenetic of medullary thyroid cancer. Iran Biomed J 22: 142-150, 2018.
196. Rabold K, Zoodsma M, Grondman I, Kuijpers Y, Bremmers M, Jaeger M, Zhang B, Hobo W, Bonenkamp HJ, de Wilt JHW, *et al*: Reprogramming of myeloid cells and their progenitors in patients with non-medullary thyroid carcinoma. Nat Commun 13: 6149, 2022.
197. Bi Y, Ren X, Bai X, Meng Y, Luo Y, Cao J, Zhang Y and Liang Z: PD-1/PD-L1 expressions in medullary thyroid carcinoma: Clinicopathologic and prognostic analysis of Chinese population. Eur J Surg Oncol 45: 353-358, 2019.
198. Nikas IP, Kazamias G, Vrontaki M, Rapti AS and Mastorakis E: Medullary thyroid carcinoma diagnosed with liquid-based cytology and immunocytochemistry. J Immunoassay Immunochem 43: 502-515, 2022.
199. Besharat ZM, Trocchianesi S, Verrienti A, Ciampi R, Cantara S, Romei C, Sabato C, Noviello TMR, Po A, Citarella A, *et al*: Circulating miR-26b-5p and miR-451a as diagnostic biomarkers in medullary thyroid carcinoma patients. J Endocrinol Invest 46: 2583-2599, 2023.
200. Fugazzola L: Medullary thyroid cancer-An update. Best Pract Res Clin Endocrinol Metab 37: 101655, 2023.
201. Almeida MQ and Hoff AO: Recent advances in the molecular pathogenesis and targeted therapies of medullary thyroid carcinoma. Curr Opin Oncol 24: 229-234, 2012.
202. Tomuleasa C, Tigu AB, Munteanu R, Moldovan CS, Kegyes D, Onaciu A, Gulei D, Ghiaur G, Einsele H and Croce CM: Therapeutic advances of targeting receptor tyrosine kinases in cancer. Signal Transduct Target Ther 9: 201, 2024.
203. Li J, Gong C, Zhou H, Liu J, Xia X, Ha W, Jiang Y, Liu Q and Xiong H: Kinase inhibitors and Kinase-targeted cancer therapies: Recent advances and future perspectives. Int J Mol Sci 25: 5489, 2024.
204. Patel J, Klopper J and Cottrill EE: Molecular diagnostics in the evaluation of thyroid nodules: Current use and prospective opportunities. Front Endocrinol (Lausanne) 14: 1101410, 2023.

205. Giardino E, Catalano R, Mangili F, Barbieri AM, Treppiedi D, Elli FM, Dolci A, Contarino A, Spada A, Arosio M, *et al*: Octreotide and pasireotide effects on medullary thyroid carcinoma (MTC) cells growth, migration and invasion. Mol Cell Endocrinol 520: 111092, 2021.
206. Bareli Y, Shimon I, Tobar A and Rubinfeld H: PICT-1 regulates p53 splicing and sensitivity of medullary thyroid carcinoma cells to everolimus. J Neuroendocrinol 34: e13187, 2022.
207. Pozo K, Castro-Rivera E, Tan C, Plattner F, Schwach G, Siegl V, Meyer D, Guo A, Gundara J, Mettlach G, *et al*: The role of Cdk5 in neuroendocrine thyroid cancer. Cancer Cell 24: 499-511, 2013.
208. Hedayati M, Zarif Yeganeh M, Sheikholeslami S and Afsari F: Diversity of mutations in the RET proto-oncogene and its oncogenic mechanism in medullary thyroid cancer. Crit Rev Clin Lab Sci 53: 217-227, 2016.
209. Yue CH, Oner M, Chiu CY, Chen MC, Teng CL, Wang HY, Hsieh JT, Lai CH and Lin H: RET regulates human medullary thyroid cancer cell proliferation through CDK5 and STAT3 Activation. Biomolecules 11: 860, 2021.
210. Kunte SC, Wenter V, Toms J, Lindner S, Unterrainer M, Eilsberger F, Jurkschat K, Wängler C, Wängler B, Schirrmacher R, *et al*: PET/CT imaging of differentiated and medullary thyroid carcinoma using the novel SSTR-targeting peptide [^{18}F]SiTATE-first clinical experiences. Eur J Nucl Med Mol Imaging 52: 900-912, 2025.
211. Kong Z, Li Z, Cui XY, Wang J, Xu M, Liu Y, Chen J, Ni S, Zhang Z, Fan X, *et al*: CTR-FAPI PET enables precision management of medullary thyroid carcinoma. Cancer Discov 15: 316-328, 2025.
212. Jaskula-Sztul R, Chen G, Dammalapati A, Harrison A, Tang W, Gong S and Chen H: AB3-loaded and Tumor-targeted unimolecular micelles for medullary thyroid cancer treatment. J Mater Chem B 5: 151-159, 2017.
213. Rao SN and Smallridge RC: Anaplastic thyroid cancer: An update. Best Pract Res Clin Endocrinol Metab 37: 101678, 2023.
214. Molinaro E, Romei C, Biagini A, Sabini E, Agate L, Mazzeo S, Materazzi G, Sellari-Franceschini S, Ribechini A, Torregrossa L, *et al*: Anaplastic thyroid carcinoma: From clinicopathology to genetics and advanced therapies. Nat Rev Endocrinol 13: 644-660, 2017.
215. Moreno F, Reyes C, Pineda CA, Castellanos G, Cálix F, Calderón J and Vasquez-Bonilla WO: Anaplastic thyroid carcinoma with unusual long-term survival: A case report. J Med Case Rep 16: 39, 2022.
216. Davies L and Welch HG: Increasing incidence of thyroid cancer in the united states, 1973-2002. JAMA 295: 2164-2167, 2006.
217. Fallahi P, Ferrari SM, Galdiero MR, Varricchi G, Elia G, Ragusa F, Paparo SR, Benvenga S and Antonelli A: Molecular targets of tyrosine kinase inhibitors in thyroid cancer. Semin Cancer Biol 79: 180-196, 2022.
218. Al-Mohanna M, Alraouji NN, Alhabardi SA, Al-Mohanna F, Al-Otaibi B, Al-Jammaz I and Aboussekhra A: The curcumin analogue PAC has potent anti-anaplastic thyroid cancer effects. Sci Rep 13: 4217, 2023.
219. Anderson RJ, Sizemore GW, Wahner HW and Carney JA: Thyroid scintigram in familial medullary carcinoma of the thyroid gland. Clin Nucl Med 3: 147-151, 1978.
220. Ballal S, Yadav MP, Moon ES, Rösch F, ArunRaj ST, Agarwal S, Tripathi M, Sahoo RK and Bal C: First-in-Human experience with 177Lu-DOTAGA.(SA.FAPi)2 therapy in an uncommon case of aggressive medullary thyroid carcinoma clinically mimicking as anaplastic thyroid cancer. Clin Nucl Med 47: e444-e445, 2022.
221. Bao L, Li Y, Hu X, Gong Y, Chen J, Huang P, Tan Z, Ge M and Pan Z: Targeting SIGLEC15 as an emerging immunotherapy for anaplastic thyroid cancer. Int Immunopharmacol 133: 112102, 2024.
222. Biermann K, Biersack HJ, Sabet A and Janzen V: Alternative therapeutic approaches in the treatment of primary and secondary dedifferentiated and medullary thyroid carcinoma. Semin Nucl Med 41: 139-148, 2011.
223. Ceolin L, Duval M, Benini AF, Ferreira CV and Maia AL: Medullary thyroid carcinoma beyond surgery: Advances, challenges, and perspectives. Endocr Relat Cancer 26: R499-R518, 2019.
224. Chintakuntlawar AV, Foote RL, Kasperbauer JL and Bible KC: Diagnosis and management of anaplastic thyroid cancer. Endocrinol Metab Clin North Am 48: 269-284, 2019.
225. Choi YS, Jeon MJ, Doolittle WKL, Song DE, Kim K, Kim WB and Kim WG: Macrophage-induced carboxypeptidase A4 promotes the progression of anaplastic thyroid cancer. Thyroid 34: 1150-1162, 2024.
226. Contarino A, Dolci A, Maggioni M, Porta FM, Lopez G, Verga U, Elli FM, Iofrida EF, Cantoni G, Mantovani G, *et al*: Is encapsulated medullary thyroid carcinoma associated with a better prognosis? A case series and a review of the literature. Front Endocrinol (Lausanne) 13: 866572, 2022.
227. Cristinziano L, Modestino L, Loffredo S, Varricchi G, Braile M, Ferrara AL, de Paulis A, Antonelli A, Marone G and Galdiero MR: Anaplastic thyroid cancer cells induce the release of mitochondrial extracellular DNA traps by viable neutrophils. J Immunol 204: 1362-1372, 2020.
228. D'Aprile S, Denaro S, Pavone AM, Giallongo S, Giallongo C, Distefano A, Salvatorelli L, Torrisi F, Giuffrida R, Forte S, *et al*: Anaplastic thyroid cancer cells reduce CD71 levels to increase iron overload tolerance. J Transl Med 21: 780, 2023.
229. Doolittle WKL, Zhao L and Cheng SY: Blocking CDK7-mediated NOTCH1-cMYC Signaling attenuates cancer stem cell activity in anaplastic thyroid cancer. Thyroid 32: 937-948, 2022.
230. Egan CE, Stefanova D, Ahmed A, Raja VJ, Thiesmeyer JW, Chen KJ, Greenberg JA, Zhang T, He B, Finnerty BM, *et al*: CSPG4 is a potential therapeutic target in anaplastic thyroid cancer. Thyroid 31: 1481-1493, 2021.
231. Harach HR and Williams ED: Glandular (tubular and follicular) variants of medullary carcinoma of the thyroid. Histopathology 7: 83-97, 1983.
232. Hu Y, Wen Q, Cai Y, Liu Y, Ma W, Li Q, Song F, Guo Y, Zhu L, Ge J, *et al*: Alantolactone induces concurrent apoptosis and GSDME-dependent pyroptosis of anaplastic thyroid cancer through ROS mitochondria-dependent caspase pathway. Phytomedicine 108: 154528, 2023.
233. Li C, Zhang H, Li S, Zhang D, Li J, Dionigi G, Liang N and Sun H: Prognostic impact of inflammatory markers PLR, LMR, PDW, MPV in medullary thyroid carcinoma. Front Endocrinol (Lausanne) 13: 861869, 2022.
234. Li Q, Zhang L, Lang J, Tan Z, Feng Q, Zhu F, Liu G, Ying Z, Yu X, Feng H, *et al*: Lipid-peptide-mRNA nanoparticles augment radioiodine uptake in anaplastic thyroid cancer. Adv Sci (Weinh) 10: e2204334, 2023.
235. Li Y: Pyrvinium pamoate can overcome artemisinin's resistance in anaplastic thyroid cancer. BMC Complement Med Ther 21: 156, 2021.
236. Lu L, Wang JR, Henderson YC, Bai S, Yang J, Hu M, Shiau CK, Pan T, Yan Y, Tran TM, *et al*: Anaplastic transformation in thyroid cancer revealed by single-cell transcriptomics. J Clin Invest 133: e169653, 2023.
237. Lu YL, Huang YT, Wu MH, Chou TC, Wong R and Lin SF: Efficacy of adavosertib therapy against anaplastic thyroid cancer. Endocr Relat Cancer 28: 311-324, 2024.
238. Ma B, Luo Y, Xu W, Han L, Liu W, Liao T, Yang Y and Wang Y: LINC00886 negatively regulates malignancy in anaplastic thyroid cancer. Endocrinology 164: bqac204, 2023.
239. Matrone A, Gambale C, Prete A and Elisei R: Sporadic medullary thyroid carcinoma: Towards a precision medicine. Front Endocrinol (Lausanne) 13: 864253, 2022.
240. Niccoli-Sire P, Murat A, Rohmer V, Franc S, Chabrier G, Baldet L, Maes B, Savagner F, Giraud S, Bezieau S, *et al*: Familial medullary thyroid carcinoma with noncysteine ret mutations: Phenotype-genotype relationship in a large series of patients. J Clin Endocrinol Metab 86: 3746-3753, 2001.
241. Pan Z, Bao L, Lu X, Hu X, Li L, Chen J, Jin T, Zhang Y, Tan Z, Huang P and Ge M: IL2RA+VSIG4+ tumor-associated macrophage is a key subpopulation of the immunosuppressive microenvironment in anaplastic thyroid cancer. Biochim Biophys Acta Mol Basis Dis 1869: 166591, 2023.
242. Pozdeyev N, Gay LM, Sokol ES, Hartmaier R, Deaver KE, Davis S, French JD, Borre PV, LaBarbera DV, Tan AC, *et al*: Genetic analysis of 779 advanced differentiated and anaplastic thyroid cancers. Clin Cancer Res 24: 3059-3068, 2018.
243. Pusztaszeri MP, Bongiovanni M and Faquin WC: Update on the cytologic and molecular features of medullary thyroid carcinoma. Adv Anat Pathol 21: 26-35, 2014.
244. Rougier P, Parmentier C, Laplanche A, Lefevre M, Travagli JP, Caillou B, Schlumberger M, Lacour J and Tubiana M: Medullary thyroid carcinoma: Prognostic factors and treatment. Int J Radiat Oncol Biol Phys 9: 161-169, 1983.

245. Shakiba E, Boroomand S, Kheradmand Kia S and Hedayati M: MicroRNAs in thyroid cancer with focus on medullary thyroid carcinoma: Potential therapeutic targets and diagnostic/prognostic markers and web based tools. Oncol Res 32: 1011-1019, 2024.
246. Sherman EJ, Harris J, Bible KC, Xia P, Ghossein RA, Chung CH, Riaz N, Gunn GB, Foote RL, Yom SS, *et al*: Radiotherapy and paclitaxel plus pazopanib or placebo in anaplastic thyroid cancer (NRG/RTOG 0912): A randomised, double-blind, placebo-controlled, multicentre, phase 2 trial. Lancet Oncol 24: 175-186, 2023.
247. Subbiah V, Kreitman RJ, Wainberg ZA, Cho JY, Schellens JHM, Soria JC, Wen PY, Zielinski C, Cabanillas ME, Urbanowitz G, *et al*: Dabrafenib and trametinib treatment in patients with locally advanced or metastatic BRAF V600-mutant anaplastic thyroid cancer. J Clin Oncol 36: 7-13, 2018.
248. Sugarman AJ, Huynh LD, Shabro A and Di Cristofano A: Anaplastic thyroid cancer cells upregulate mitochondrial one-carbon metabolism to meet purine demand, eliciting a critical targetable vulnerability. Cancer Lett 568: 216304, 2023.
249. Tang J, Luo Y and Xiao L: USP26 promotes anaplastic thyroid cancer progression by stabilizing TAZ. Cell Death Dis 13: 326, 2022.
250. Wang X, Ying T, Yuan J, Wang Y, Su X, Chen S, Zhao Y, Zhao Y, Sheng J, Teng L, *et al*: BRAFV600E restructures cellular lactylation to promote anaplastic thyroid cancer proliferation. Endocr Relat Cancer 30: e220344, 2023.
251. Wu J, Liang J, Liu R, Lv T, Fu K, Jiang L, Ma W, Pan Y, Tan Z, Liu Q, *et al*: Autophagic blockade potentiates anlotinib-mediated ferroptosis in anaplastic thyroid cancer. Endocr Relat Cancer 30: 230036, 2023.
252. Zaballos MA, Acuña-Ruiz A, Morante M, Riesco-Eizaguirre G, Crespo P and Santisteban P: Inhibiting ERK dimerization ameliorates BRAF-driven anaplastic thyroid cancer. Cell Mol Life Sci 79: 504, 2022.
253. Zhang W, Ji W and Zhao X: MiR-155 promotes anaplastic thyroid cancer progression by directly targeting SOCS1. BMC Cancer 19: 1093, 2019.
254. Zhao Q, Feng H, Yang Z, Liang J, Jin Z, Chen L, Zhan L, Xuan M, Yan J, Kuang J, *et al*: The central role of a two-way positive feedback pathway in molecular targeted therapies-mediated pyroptosis in anaplastic thyroid cancer. Clin Transl Med 12: e727, 2022.
255. Zhao Z, Yin XD, Zhang XH, Li ZW and Wang DW: Comparison of pediatric and adult medullary thyroid carcinoma based on SEER program. Sci Rep 10: 13310, 2020.
256. Alhejaily AG, Alhuzim O and Alwelaie Y: Anaplastic thyroid cancer: Pathogenesis, prognostic factors and genetic landscape (review). Mol Clin Oncol 19: 992023.
257. Zhao Y, Yu Z, Song Y, Fan L, Lei T, He Y and Hu S: The regulatory network of CREB3L1 and its roles in physiological and pathological conditions. Int J Med Sci 21: 123-136, 2024.
258. Pan Z, Xu T, Bao L, Hu X, Jin T, Chen J, Chen J, Qian Y, Lu X, Li L, *et al*: CREB3L1 promotes tumor growth and metastasis of anaplastic thyroid carcinoma by remodeling the tumor microenvironment. Mol Cancer 21: 190, 2022.
259. Haroon Al Rasheed MR and Xu B: Molecular alterations in thyroid carcinoma. Surg Pathol Clin 12: 921-930, 2019.
260. Misiak D, Bauer M, Lange J, Haase J, Braun J, Lorenz K, Wickenhauser C and Hüttelmaier S: MiRNA deregulation distinguishes anaplastic thyroid carcinoma (ATC) and supports upregulation of oncogene expression. Cancers (Basel) 13: 5913, 2021.
261. Vosgha H, Ariana A, Smith RA and Lam AK: miR-205 targets angiogenesis and EMT concurrently in anaplastic thyroid carcinoma. Endocr Relat Cancer 25: 323-337, 2018.
262. Hou X, Chen C, He X and Lan X: Siglec-15 silencing inhibits cell proliferation and promotes cell apoptosis by inhibiting STAT1/STAT3 signaling in anaplastic thyroid carcinoma. Dis Markers 2022: 1606404, 2022.
263. Pan Z, Lu X, Xu T, Chen J, Bao L, Li Y, Gong Y, Che Y, Zou X, Tan Z, *et al*: Epigenetic inhibition of CTCF by HN1 promotes dedifferentiation and stemness of anaplastic thyroid cancer. Cancer Lett 580: 216496, 2024.
264. Jiao C, Li L, Zhang P, Zhang L, Li K, Fang R, Yuan L, Shi K, Pan L, Guo Q, *et al*: REGγ ablation impedes dedifferentiation of anaplastic thyroid carcinoma and accentuates radio-therapeutic response by regulating the Smad7-TGF-β pathway. Cell Death Differ 27: 497-508, 2020.
265. Zhong Y, Yu F, Yang L, Wang Y, Liu L, Jia C, Cai H, Yang J, Sheng S, Lv Z, *et al*: HOXD9/miR-451a/PSMB8 axis is implicated in the regulation of cell proliferation and metastasis via PI3K/AKT signaling pathway in human anaplastic thyroid carcinoma. J Transl Med 21: 817, 2023.
266. Fuziwara CS, Saito KC and Kimura ET: Thyroid follicular cell loss of differentiation induced by MicroRNA miR-17-92 cluster is attenuated by CRISPR/Cas9n gene silencing in anaplastic thyroid cancer. Thyroid 30: 81-94, 2020.
267. Xu B and Ghossein RA: Advances in thyroid pathology: High grade follicular Cell-derived thyroid carcinoma and anaplastic thyroid carcinoma. Adv Anat Pathol 30: 3-10, 2023.
268. Pan Z, Fang Q, Li L, Zhang Y, Xu T, Liu Y, Zheng X, Tan Z, Huang P and Ge M: HN1 promotes tumor growth and metastasis of anaplastic thyroid carcinoma by interacting with STMN1. Cancer Lett 501: 31-42, 2021.
269. Xu D, Yu J, Yang Y, Du Y, Lu H, Zhang S, Feng Q, Yu Y, Hao L, Shao J and Chen L: RBX1 regulates PKM alternative splicing to facilitate anaplastic thyroid carcinoma metastasis and aerobic glycolysis by destroying the SMAR1/HDAC6 complex. Cell Biosci 13: 36, 2023.
270. Angela De Stefano M, Porcelli T, Ambrosio R, Luongo C, Raia M, Schlumberger M and Salvatore D: Type 2 deiodinase is expressed in anaplastic thyroid carcinoma and its inhibition causes cell senescence. Endocr Relat Cancer 30: e230016, 2023.
271. Xu S, Cheng X, Wu L, Zheng J, Wang X, Wu J, Yu H, Bao J and Zhang L: Capsaicin induces mitochondrial dysfunction and apoptosis in anaplastic thyroid carcinoma cells via TRPV1-mediated mitochondrial calcium overload. Cell Signal 75: 109733, 2020.
272. Shi XZ, Zhao S, Wang Y, Wang MY, Su SW, Wu YZ and Xiong C: Antitumor activity of berberine by activating autophagy and apoptosis in CAL-62 and BHT-101 anaplastic thyroid carcinoma cell lines. Drug Des Devel Ther 17: 1889-1906, 2023.
273. Zheng H, Lin Q and Rao Y: A-Kinase interacting protein 1 knockdown restores chemosensitivity via inactivating PI3K/AKT and β-catenin pathways in anaplastic thyroid carcinoma. Front Oncol 12: 854702, 2022.
274. Gao H, Wang W and Li Q: GANT61 suppresses cell survival, invasion and epithelial-mesenchymal transition through inactivating AKT/mTOR and JAK/STAT3 pathways in anaplastic thyroid carcinoma. Cancer Biol Ther 23: 369-377, 2022.
275. Sugitani I, Miyauchi A, Sugino K, Okamoto T, Yoshida A and Suzuki S: Prognostic factors and treatment outcomes for anaplastic thyroid carcinoma: ATC Research Consortium of Japan cohort study of 677 patients. World J Surg 36: 1247-1254, 2012.
276. Califano I, Smulever A, Jerkovich F and Pitoia F: Advances in the management of anaplastic thyroid carcinoma: Transforming a life-threatening condition into a potentially treatable disease. Rev Endocr Metab Disord 25: 123-147, 2023.
277. Kanematsu R, Hirokawa M, Tanaka A, Suzuki A, Higuchi M, Kuma S, Hayashi T and Miyauchi A: Evaluation of E-Cadherin and β-Catenin immunoreactivity for determining undifferentiated cells in anaplastic thyroid carcinoma. Pathobiology 88: 351-358, 2021.
278. Shao C, Li Z, Zhang C, Zhang W, He R, Xu J and Cai Y: Optical diagnostic imaging and therapy for thyroid cancer. Mater Today Bio 17: 100441, 2022.
279. Moon J, Lee JH, Roh J, Lee DH and Ha EJ: Contrast-enhanced CT-based radiomics for the differentiation of anaplastic or poorly differentiated thyroid carcinoma from differentiated thyroid carcinoma: A pilot study. Sci Rep 13: 4562, 2023.
280. Haase J, Misiak D, Bauer M, Pazaitis N, Braun J, Pötschke R, Mensch A, Bell JL, Dralle H, Siebolts U, *et al*: IGF2BP1 is the first positive marker for anaplastic thyroid carcinoma diagnosis. Mod Pathol 34: 32-41, 2021.
281. Qin Y, Wang JR, Wang Y, Iyer P, Cote GJ, Busaidy NL, Dadu R, Zafereo M, Williams MD, Ferrarotto R, *et al*: Clinical utility of circulating Cell-Free DNA mutations in anaplastic thyroid carcinoma. Thyroid 31: 1235-1243, 2021.
282. Han PZ, Ye WD, Yu PC, Tan LC, Shi X, Chen XF, He C, Hu JQ, Wei WJ, Lu ZW, *et al*: A distinct tumor microenvironment makes anaplastic thyroid cancer more lethal but immunotherapy sensitive than papillary thyroid cancer. JCI Insight 9: e173712, 2024.
283. Ukita M, Hamanishi J, Yoshitomi H, Yamanoi K, Takamatsu S, Ueda A, Suzuki H, Hosoe Y, Furutake Y, Taki M, *et al*: CXCL13-producing CD4+ T cells accumulate in the early phase of tertiary lymphoid structures in ovarian cancer. JCI Insight 7: e157215, 2022.

284. Wang J, Liang Y, Xue A, Xiao J, Zhao X, Cao S, Li P, Dong J, Li Y, Xu Z and Yang L: Intratumoral CXCL13+ CD160+ CD8+ T cells promote the formation of tertiary lymphoid structures to enhance the efficacy of immunotherapy in advanced gastric cancer. J Immunother Cancer 12: e009603, 2024.
285. Han D, Lee AY, Kim T, Choi JY, Cho MY, Song A, Kim C, Shim JH, Kim HJ, Kim H, *et al*: Microenvironmental network of clonal CXCL13+CD4+ T cells and Tregs in pemphigus chronic blisters. J Clin Invest 133: e166357, 2023.
286. Yang Z, Tian H, Chen X, Li B, Bai G, Cai Q, Xu J, Guo W, Wang S, Peng Y, *et al*: Single-cell sequencing reveals immune features of treatment response to neoadjuvant immunochemotherapy in esophageal squamous cell carcinoma. Nat Commun 15: 9097, 2024.
287. Liu B, Zhang Y, Wang D, Hu X and Zhang Z: Single-cell meta-analyses reveal responses of tumor-reactive CXCL13^{+} T cells to immune-checkpoint blockade. Nat Cancer 3: 1123-1136, 2022.
288. Bassez A, Vos H, Van Dyck L, Floris G, Arijs I, Desmedt C, Boeckx B, Vanden Bempt M, Nevelsteen I, Lambein K, *et al*: A single-cell map of intratumoral changes during anti-PD1 treatment of patients with breast cancer. Nat Med 27: 820-832, 2021.
289. Lucotti S, Ogitani Y, Kenific CM, Geri J, Kim YH, Gu J, Balaji U, Bojmar L, Shaashua L, Song Y, *et al*: Extracellular vesicles from the lung pro-thrombotic niche drive cancer-associated thrombosis and metastasis via integrin β2. Cell 188: 1642-1661.e24, 2025.
290. Gao SH, Liu SZ, Wang GZ and Zhou GB: CXCL13 in cancer and other diseases: Biological functions, clinical significance, and therapeutic opportunities. Life (Basel) 11: 1282, 2021.
291. Sakai SA, Oyoshi H, Nakamura M, Taki T, Nomura K, Hojo H, Hirata H, Motegi A, Nakamura Y, Zenkoh J, *et al*: Single-cell spatial analysis with Xenium reveals anti-tumour responses of CXCL13 + T and CXCL9+ cells after radiotherapy combined with anti-PD-L1 therapy. Br J Cancer: Jul 16, 2025 doi: 10.1038/s41416-025-03088-0 (Epub ahead of print).
292. Zhu J, Yuan Y, Wan X, Yin D, Li R, Chen W, Suo C and Song H: Immunotherapy (excluding checkpoint inhibitors) for stage I to III non-small cell lung cancer treated with surgery or radiotherapy with curative intent. Cochrane Database Syst Rev 12: CD011300, 2021.
293. Huang Y, Liang B, Chen X, Li Z, Deng Y, Du J, Zhong Y, Lin X, Fu J, Xie J, *et al*: Enhanced immunotherapy response in lung adenocarcinoma patients with COPD: Insights into tumor cells and immune microenvironment characteristics. Cell Commun Signal 23: 324, 2025.
294. Siyuan D, Han Z, Zhaopei L, Kaifeng J, Wenbin J, Zewei W, Zhiyuan L, Ying X, Jiajun W, Yuan C, *et al*: Intratumoral CXCL13+CD8+T cell infiltration determines poor clinical outcomes and immunoevasive contexture in patients with clear cell renal cell carcinoma. J Immunother Cancer 9: e001823, 2021.
295. Dierks C, Seufert J, Aumann K, Ruf J, Klein C, Kiefer S, Rassner M, Boerries M, Zielke A, la Rosee P, *et al*: Combination of lenvatinib and pembrolizumab is an effective treatment option for anaplastic and poorly differentiated thyroid carcinoma. Thyroid 31: 1076-1085, 2021.
296. Cabanillas ME, Ferrarotto R, Garden AS, Ahmed S, Busaidy NL, Dadu R, Williams MD, Skinner H, Gunn GB, Grosu H, *et al*: Neoadjuvant BRAF- and Immune-directed therapy for anaplastic thyroid carcinoma. Thyroid 28: 945-951, 2018.
297. Yang Y, Li S, Wang Y, Zhao Y and Li Q: Protein tyrosine kinase inhibitor resistance in malignant tumors: Molecular mechanisms and future perspective. Signal Transduct Target Ther 7: 329, 2022.
298. Choi YS, Kwon H, You MH, Kim TY, Kim WB, Shong YK, Jeon MJ and Kim WG: Effects of dabrafenib and erlotinib combination treatment on anaplastic thyroid carcinoma. Endocr Relat Cancer 29: 307-319, 2022.
299. Capdevila J, Wirth LJ, Ernst T, Ponce Aix S, Lin CC, Ramlau R, Butler MO, Delord JP, Gelderblom H, Ascierto PA, *et al*: PD-1 blockade in anaplastic thyroid carcinoma. J Clin Oncol 38: 2620-2627, 2020.
300. Ahn S, Kim TH, Kim SW, Ki CS, Jang HW, Kim JS, Kim JH, Choe JH, Shin JH, Hahn SY, *et al*: Comprehensive screening for PD-L1 expression in thyroid cancer. Endocr Relat Cancer 24: 97-106, 2017.
301. Cantara S, Bertelli E, Occhini R, Regoli M, Brilli L, Pacini F, Castagna MG and Toti P: Blockade of the programmed death ligand 1 (PD-L1) as potential therapy for anaplastic thyroid cancer. Endocrine 64: 122-129, 2019.
302. Hamidi S, Iyer PC, Dadu R, Gule-Monroe MK, Maniakas A, Zafereo ME, Wang JR, Busaidy NL and Cabanillas ME: Checkpoint inhibition in addition to Dabrafenib/Trametinib for BRAF(V600E)-Mutated anaplastic thyroid carcinoma. Thyroid 34: 336-346, 2024.
303. Min IM, Shevlin E, Vedvyas Y, Zaman M, Wyrwas B, Scognamiglio T, Moore MD, Wang W, Park S, Park S, *et al*: CAR T therapy targeting ICAM-1 eliminates advanced human thyroid tumors. Clin Cancer Res 23: 7569-7583, 2017.
304. Zhang P, Tao C, Shimura T, Huang AC, Kong N, Dai Y, Yao S, Xi Y, Wang X, Fang J, *et al*: ICAM1 antibody drug conjugates exert potent antitumor activity in papillary and anaplastic thyroid carcinoma. iScience 26: 107272, 2023.
305. Huang S, Zhang L, Xu M, Li C, Fu H, Huang J, Jin X, Liang S and Wang H: Co-Delivery of ^{131}I and Prima-1 by Self-Assembled CD44-Targeted Nanoparticles for Anaplastic Thyroid Carcinoma Theranostics. Adv Healthc Mater 10: e2001029, 2021.
306. Landa I and Cabanillas ME: Genomic alterations in thyroid cancer: Biological and clinical insights. Nat Rev Endocrinol 20: 93-110, 2024.
307. Xing M: Molecular pathogenesis and mechanisms of thyroid cancer. Nat Rev Cancer 13: 184-99, 2013.
308. Bhattacharya S, Mahato RK, Singh S, Bhatti GK, Mastana SS and Bhatti JS: Advances and challenges in thyroid cancer: The interplay of genetic modulators, targeted therapies, and AI-driven approaches. Life Sci 332: 122110, 2023.
309. Shay JW, Homma N, Zhou R, Naseer MI, Chaudhary AG, Al-Qahtani M, Hirokawa N, Goudarzi M, Fornace AJ Jr, Baeesa S, *et al*: Abstracts from the 3rd International Genomic Medicine Conference (3rd IGMC 2015): Jeddah, Kingdom of Saudi Arabia. 30 November-3 December 2015. BMC Genomics 17 (Suppl 6): S487, 2016.
310. Guo M, Sun Y, Wei Y, Xu J and Zhang C: Advances in targeted therapy and biomarker research in thyroid cancer. Front Endocrinol (Lausanne) 15: 1372553, 2024.
311. Sekihara K, Himuro H, Toda S, Saito N, Hirayama R, Suganuma N, Sasada T and Hoshino D: Recent trends and potential of radiotherapy in the treatment of anaplastic thyroid cancer. Biomedicines 12: 1286, 2024.
312. Zhong L, Li Y, Xiong L, Wang W, Wu M, Yuan T, Yang W, Tian C, Miao Z, Wang T and Yang S: Small molecules in targeted cancer therapy: Advances, challenges, and future perspectives. Signal Transduct Target Ther 6: 201, 2021.
313. Zhang Y, Xing Z, Liu T, Tang M, Mi L, Zhu J, Wu W and Wei T: Targeted therapy and drug resistance in thyroid cancer. Eur J Med Chem 238: 114500, 2022.
314. Zhang L, Feng Q, Wang J, Tan Z, Li Q and Ge M: Molecular basis and targeted therapy in thyroid cancer: Progress and opportunities. Biochim Biophys Acta Rev Cancer 1878: 188928, 2023.
315. Deshmukh VG, Sapkal SB, Gadekar SS and Deshmukh V: EGFR inhibitors across generations: Progress, challenges, and future directions. J Mol Structure: 1339, 2025.
316. Chen MF, Repetto M, Wilhelm C and Drilon A: RET Inhibitors in RET Fusion-positive lung cancers: Past, present, and future. Drugs 84: 1035-1053, 2024.
317. Krajewska J, Paliczka-Cieslik E and Jarzab B: Managing tyrosine kinase inhibitors side effects in thyroid cancer. Expert Rev Endocrinol Metab 12: 117-127, 2017.
318. Li J and Yu Y: POU5F1B is responsible for the acquired resistance to dabrafenib in papillary thyroid cancer cells with the BRAF V600E mutation. Endocrine 87: 220-233, 2025.
319. Jiang S, Huang Y, Li Y, Gu Q, Jiang C, Tao X and Sun J: Silencing FOXP2 reverses vemurafenib resistance in BRAF(V600E) mutant papillary thyroid cancer and melanoma cells. Endocrine 79: 86-97, 2023.
320. Ma W, Tian M, Hu L, Ruan X, Zhang W, Zheng X and Gao M: Early combined SHP2 targeting reverses the therapeutic resistance of vemurafenib in thyroid cancer. J Cancer 14: 1592-1604, 2023.
321. Cavallo MR, Yo JC, Gallant KC, Cunanan CJ, Amirfallah A, Daniali M, Sanders AB, Aplin AE, Pribitkin EA and Hartsough EJ: Mcl-1 mediates intrinsic resistance to RAF inhibitors in mutant BRAF papillary thyroid carcinoma. Cell Death Discov 10: 175, 2024.

322. Hou X, Dong Q, Hao J, Liu M, Ning J, Tao M, Wang Z, Guo F, Huang D, Shi X, *et al*: NSUN2-mediated m(5)C modification drives alternative splicing reprogramming and promotes multidrug resistance in anaplastic thyroid cancer through the NSUN2/SRSF6/UAP1 signaling axis. Theranostics 15: 2757-2777, 2025.
323. Molteni E, Baldan F, Damante G and Allegri L: GSK2801 reverses paclitaxel resistance in anaplastic thyroid cancer cell lines through MYCN downregulation. Int J Mol Sci 24: 5993, 2023.
324. Subbiah V, Kreitman RJ, Wainberg ZA, Gazzah A, Lassen U, Stein A, Wen PY, Dietrich S, de Jonge MJA, Blay JY, *et al*: Dabrafenib plus trametinib in BRAFV600E-mutated rare cancers: The phase 2 ROAR trial. Nat Med 29: 1103-1112, 2023.
325. Tahara M, Kiyota N, Imai H, Takahashi S, Nishiyama A, Tamura S, Shimizu Y, Kadowaki S, Ito KI, Toyoshima M, *et al*: A phase 2 study of encorafenib in combination with binimetinib in patients with metastatic BRAF-Mutated thyroid cancer in Japan. Thyroid 34: 467-476, 2024.
326. Cabanillas ME, Dadu R, Ferrarotto R, Gule-Monroe M, Liu S, Fellman B, Williams MD, Zafereo M, Wang JR, Lu C, *et al*: Anti-programmed death ligand 1 plus targeted therapy in anaplastic thyroid carcinoma: A nonrandomized clinical trial. JAMA Oncol 10: 1672-1680, 2024.
327. Higashiyama T, Sugino K, Hara H, Ito KI, Nakashima N, Onoda N, Tori M, Katoh H, Kiyota N, Ota I, *et al*: Phase II study of the efficacy and safety of lenvatinib for anaplastic thyroid cancer (HOPE). Eur J Cancer 173: 210-218, 2022.
328. Loo E, Khalili P, Beuhler K, Siddiqi I and Vasef MA: BRAF V600E mutation across multiple tumor types: Correlation between DNA-based sequencing and Mutation-specific immunohistochemistry. Appl Immunohistochem Mol Morphol 26: 709-713, 2018.
329. Cece A, Agresti M, De Falco N, Sperlongano P, Moccia G, Luongo P, Miele F, Allaria A, Torelli F, Bassi P, *et al*: Role of artificial intelligence in thyroid cancer diagnosis. J Clin Med 14: 2422, 2025.