Advances in transcriptomics and proteomics in differentiated thyroid cancer: An updated perspective (Review)

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Abstract. Thyroid cancer (TC) is a broad classification of neoplasms that includes differentiated thyroid cancer (DTC) as a common histological subtype. DTC is characterized by an increased mortality rate in advanced stages, which contributes to the overall high mortality rate of DTC. This progression is mainly attributed to alterations in molecular driver genes, resulting in changes in phenotypes such as invasion, metastasis and dedifferentiation. Clinical management of DTC is challenging due to insufficient diagnostic and therapeutic options. The advent of-omics technology has presented a promising avenue for the diagnosis and treatment of DTC. Identifying molecular markers that can predict the early progression of DTC to a late adverse outcome is essential for precise diagnosis and treatment. The present review aimed to enhance our understanding of DTC by integrating big data with biological systems through-omics technology, specifically transcriptomics and proteomics, which can shed light on the molecular mechanisms underlying carcinogenesis.

Contents

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1. Introduction

Thyroid cancer (TC) is among the most prevalent endocrine malignancies globally, with epidemiological data indicating a 20% annual increase in incidence and a 1.1% annual mortality rate (1-3). This trend is primarily due to the rising occurrence and heightened mortality of papillary thyroid carcinoma (PTC), which, together with follicular thyroid carcinoma (FTC), comprises differentiated thyroid cancer (DTC), accounting for >95% of all TC cases (4,5). The completion of the Human Genome Project in 2003 ushered in the post-genomic era, characterized by the emergence of functional genomics, which seeks to uncover the functions and regulatory mechanisms of the genome (6). Following the advent of the post-genomic era, medical research transitioned into the precision medicine era, leveraging various-omics technologies to elucidate the molecular mechanisms underpinning human malignancies in numerous publications (7,8). DTC is fundamentally a genetic disease, with its development being protracted, multifaceted, staged and intricate, inextricably connected to multiple molecular and environmental factors (5,8). Transcriptomics and proteomics involve the comprehensive study of gene transcription or proteins in living organisms. The vast amount of data generated by high-throughput transcriptome sequencing enables the identification of gene-specific characteristics by analyzing genes correlated with phenotypic information. By contrast, proteomics, as a functional translation of the genome, offers direct insight into the mechanisms that instigate pathogenic effects at the genomic level (9). Consequently, transcriptomics and proteomics can be employed to identify molecular markers of DTC, monitor its progression and select and validate therapeutic targets, demonstrating their long-term potential in clinical diagnostics and treatment. The present review examined the crucial transcriptomic and proteomic data of DTC identified recently, offering novel perspectives for the advancement of DTC diagnosis and therapy.

2. Transcriptome analysis of DTC

Recent advancements in transcriptomics-based sequencing analysis have led to the identification of potential molecular markers for DTC at various levels, such as pathogenic risk (10,11), early diagnosis (12-14), metastasis and progression (15-19), prognosis prediction (20-25) and therapeutic

targets (26-32) (Table I). This progress has increased our understanding of the molecular mechanisms underlying DTC and has helped resolve complex issues. However, only a few of these molecules have proved useful in clinical settings. The present review focused on the molecular classification of DTC and radioactive iodine (^{131}I) refractory (RAIR)-DTC, which is DTC that does not respond to radioactive iodine.

Molecular subtypes. DTC is categorized into distinct subtypes according to their gene expression levels, revealing differences in clinicopathological features, intracellular mechanisms and mutational profiles that contribute to a deeper understanding of TC. The initial integrative study by the Cancer Genome Atlas (TCGA) in 2014 (33) classified PTC into two molecular subtypes: BRAF-like (BVL) and RAS-like (RL), which are associated with BRAF or RAS mutations, respectively. BVL exhibits more aggressive clinical features compared with RL. This research marked the first transcriptome-based classification of PTC molecular subtypes. The study employed unsupervised clustering methods on four genomic datasets, each producing distinct subtypes that supported the overarching separation of BVL-PTC and RL-PTC. Patients in the RL-PTC group exhibited follicular variant histology, a relatively low recurrence risk and highly differentiated tumors associated with younger patients. By contrast, the different datasets divided the BVL-PTC group into varying numbers of subtypes that did not overlap, resulting in an inconsistent lower-level partitioning of BVL-PTC. To investigate signaling and differentiation in PTC, researchers developed a BRAF^{V600E}-RAS score (BRS) and a thyroid differentiation score (TDS). The BRS quantifies the extent to which the gene expression profile of a given tumor resembles either the BRAF^{V600E}- or RAS-mutant profiles, providing a continuous reference scale from most BVL to most RL to examine the signaling consequences of other, less common mutations. The TDS, derived from the expression levels of 16 highly correlated thyroid metabolic and functional genes within this cohort, plays a central role in TC. Based on the TDS and BRS results, the study (30) found that all BRAF fusions were BVL. Among the six EIF1AX mutations, four were RL, one was neutral and one was weakly BVL. All PAX8/peroxisome proliferator activated receptor γ (PPARG) fusions were RL, in line with their prevalence in follicular-patterned tumors. Almost all Ret Proto-Oncogene (RET) fusions were weakly BVL, while non-invasive follicular thyroid neoplasm (NTRK)1/3 and anaplastic lymphoma receptor tyrosine kinase (ALK) fusions were predominantly neutral. In conclusion, the comprehensive multi-platform molecular data and large sample size in this study offer an opportunity to refine the classification of PTC into molecular subtypes and correlate them with clinically relevant parameters. The BRS and TDS measures were utilized to elucidate the relationships between tumor cluster, histology, genotype, signaling and differentiation.

A number of studies have supported the notion that there are three molecular subtypes of DTC: BVL, RL and non-BRAF-non-RAS (NBNR) (34,35). Yoo *et al* (34) conducted a study on follicular thyroid tumors, including CV-PTC, FV-PTC, minimally invasive FTC and FA, using molecular typing by TCGA. In addition to expanding the RL subtype, they analyzed and proposed another molecular subtype, NBNR. The BVL subtype consisted of BRAF^{V600E} and fusion genes, including phosphatidylinositol binding clathrin assembly protein-BRAF, nuclear transcription factor y subunit α-BRAF, staphylococcal nuclease and tudor domain containing 1-BRAF, fibroblast growth factor receptor (FGFR) 2-tryptophanyl-tRNA synthetase, ETS variant transcription factor 6 (ETV6)-NTRK3, sequestosome 1-NTRK1, coiled-coil domain containing (CCDC)6-RET, nuclear receptor coactivator 4-RET and ring finger protein 213-solute carrier family (SLC) 26 member 11. The RL subtype consisted of H/K/NRAS and fusion genes, including Striatin-ALK, Ezrin-Erb-B2 receptor tyrosine kinase 4, fibroblast growth factor receptor 2-KIAA1598, ETV6-NTRK3 and CCDC6-RET. The NBNR subtype was associated with dicer 1, ribonuclease III, EIF1AX, isocitrate dehydrogenase [NADP(+)] 1, phosphatase and tensin homolog, PAX8-PPARG and other driver gene candidates. The study (32) also implemented TDS and ERK scores to explore tumor signaling and differentiation and clinical risk factors were integrated to obtain a progression model of TC. A similar perspective was obtained in a study by Song *et al* (36). Mutations in SPOP P94R and EZH1 Q571R in nonmalignant thyroid nodules were associated with BVL transcriptomic characteristics, further supporting the proposal of a third molecular subtype (12). Due to its inert biological behavior and molecular profile, enveloped PTC has been reclassified as non-invasive follicular thyroid neoplasm (NIFTP), which exhibits papillary nuclear characteristics (36-39). This reclassification demonstrates that stratification medicine can be achieved by reclassifying TC based on its mutational and transcriptional characteristics, regardless of its histological classification.

Yoo *et al* (40) proposed an updated view on the progression of DTC to advanced DTC and degenerative interstitial types using previous approaches for anaplastic thyroid cancer (ATC), poorly differentiated thyroid carcinoma, widely invasive FTC and metastatic PTC. The results showed that TERT, AKT1, PIK3CA and EIF1AX were frequently co-mutated with driver genes (BRAF^{V600E} and RAS) in advanced DTCs similar to ATC, while tumor suppressors (e.g., TP53 and CDKN2A) were predominantly altered in ATC. CDKN2A loss was significantly associated with poor disease-specific survival in patients with ATC or advanced DTC and upregulation of programmed cell death 1 ligand (PDCD1LG) 1 and PDCD1LG 2. This led to the proposal of a fourth molecular subtype of TC, ATC-like (AL) and paved the way for targeted therapy of highly invasive and fatal TCs.

Since the 2014 publication of TCGA research on PTC (33), genomic studies of DTC using more advanced massively parallel sequencing have suggested that diverse subtypes involve different mutations, which coupled with their clinical and molecular features, show progressive activation from NBNR to RL to BVL and then to AL, leading to a series of more aggressive behaviors (8,14,33,34,40) (Fig. 1). The molecular subtypes of DTC correspond to different cell signaling and differentiation characteristics, allowing for more accurate pathological classification and diagnosis. However, only a few studies have investigated this topic and further large-scale validation is necessary.

RAIR-DTC. RAIR-DTC constitutes ~1/3 of distant DTC metastases, which are the primary cause of TC mortality,

Table I. Application of massively parallel sequencing methods to analyze the latest partial transcriptome studies of DTC.

Author, year	Category	Biomarkers	Expression	Regulatory target or pathway	Significance	Samples	(Refs.)
Comiskey *et al*, 2020	Diagnosis	LRRC34	-	ranBP1	Variations in LRRC34 at 3q26 revealed two independent mechanisms for predisposition to PTC, one in G protein signaling and the other in transcriptional control.	TPC1,BCPAP and 293T cell lines	(10)
Corrado *et al*, 2021		LGALS3	-	TTF-1	Polymorphism of Pro64His (rs4644) in LGALS3 serves as the risk factor for DTC, while rs4644 represents the trans-expression quantitative trait locus for modifying downstream gene transcriptional expression by modulating TTF-1.	DTC (n=1,142)	(11)
Barros-Filho *et al*, 2020	Prognosis	GADD45B	Up	FoxO/GADD45B axis	GADD45B transcript is discovered to be the new candidate prognostic biomarker for PTC cases receiving radioiodine therapy and thyroidectomy.	PTC (n=48)	(16)
Guan *et al*, 2020		ITGA7	Down	EMT	Downregulating ITGA7 promotes PTC growth, invasion and migration via EMT.	PTC (n=19), TPC1, KTC-1 and BCPAP cell lines	(22)
Ramírez-Moya *et al*, 2021		edit-CDK13	Up	ADAR1-mediated A-to-I editing/ CDK13	The ADAR1-dependent splicing can be mainly regulated through trans-acting elements such as CDK13, but not the direct cis-element editing, thus, further affecting splicing in numerous genes. CDK13 editing is the possible effective mechanism associated with cancer aggressiveness and deterioration.	PTC (n=6), Cal62 and TPC1 cell lines	(23)
Wang *et al*, 2020		MALAT1	-	miR-214/MALAT1 rs619586/CTNNB1	rs619586 SNP (G allele) within MALAT1 upregulated miR-214 and later downregulated CTNNB1, which was the possible prognostic biomarker for DTC.	PTC (n=214), FTC (n=14)	(24)
Saqcena *et al*, 2021		SWI/SNF	Down	-	SWI/SNF complexes have important effects on maintaining differentiation within TC, while the loss of such complexes induces resistance to MAPK inhibitor-based re-differentiation and radioiodine treatments.	Mice thyroid cells	(25)
Augenlicht *et al*, 2021	Treatment	miR-7-5p	Down	miR-7-5p/EGFR/ MAPK or IRS2/ PI3K signaling pathways	miR-7-5p suppresses TC growth via EGFR/ MAPK as well as IRS2/PI3K pathways.	Classical variation of PTC and FTC, LNM, adjacent to normal thyroid tissues. TPC1 and HTori-3 cell lines	(26)

Table I. Continued.

Author, year	Category	Biomarkers	Expression	Regulatory target or pathway	Significance	Samples	(Refs.)
Hou *et al*, 2021		miR-146b-3p	Up	miR-146b-3p/MUC20/MET signaling pathways	Regulating the MET pathway via miR-146b-3p can possibly target MUC20 and is associated with DTC dedifferentiation. It induces ^{131}I resistance along with failure to absorb iodine into DTC cancer foci and cancer becomes RAIR-DTC.	RAIR-DTC (n=3) and control group (n=3); WRO cell line	(27)
Huang *et al*, 2022		FTO	Down	FTO/APOE axis	FTO inhibited expression of APOE through IGF2BP2-mediated m6A modification and may inhibit glycolytic metabolism in PTC by modulating IL-6/JAK2/STAT3 signaling pathway, thus, abrogating tumor growth.	PTC (n=150); Nthy-ori3-1, TPC1, K1, IHH4 and BCPAP cell lines	(28)
Li *et al*, 2018		TBX3	Up	TBX3/p57KIP2 (CDKN1C) axis	TBX3 promotes the proliferation of PTC cells by facilitating PRC2-mediated p57KIP2 repression.	PTC (n=98), K1 and TPC1 cell lines	(29)
Long *et al*, 2020		hsa_circ_0007694	Down	hsa_circ_0007694/PI3K/AKT/mTOR or Wnt signaling pathways	The circRNA hsa_circ_0007694 is down-regulated in PTC and is, therefore, a potential therapeutic target.	PTC and adjacent to normal thyroid tissues (n=3)	(31)
Ramírez-Moa *et al*, 2022		SPTY2D1-AS1	Down	miR-221	SPTY2D1-AS1 is the strong tumor suppressor *in vivo* and *in vitro*, which shows reduced expression within many advanced TC cases and can block primary miR-221 processing.	PTC (n=8)	(32)

LRRC34, leucine rich repeat containing 34; ranBP1, RAN binding protein 1; PTC, papillary thyroid carcinoma; LGALS3, lectin, galactoside-binding, soluble; TTF-1, thyroid transcription factor-1; DTC, differentiated thyroid cancer; GADD45B, growth arrest and DNA damage inducible β; ITGA7, integrin subunit α 7; EMT, epithelial-mesenchymal transition; CDK13, cyclin dependent kinase 13; ADAR, adenosine deaminase acting on RNA; MALAT1, metastasis associated lung adenocarcinoma transcript 1; miR, microRNA; CTNNB1, catenin β 1; FTC, follicular thyroid carcinoma; SWI/SNF, SWI/SNF complexes; TC, thyroid carcinoma; IRS2, insulin receptor substrate 2; LNM, lymph node metastases; MUC20, mucin 20, cell surface associated; RAIR-DTC, radioactive iodine-refractory DTC; FTO, α-ketoglutarate dependent dioxygenase; APOE, apolipoprotein E; TBX3, T-box transcription factor 3; PRC2, polycomb repressive complex 2.

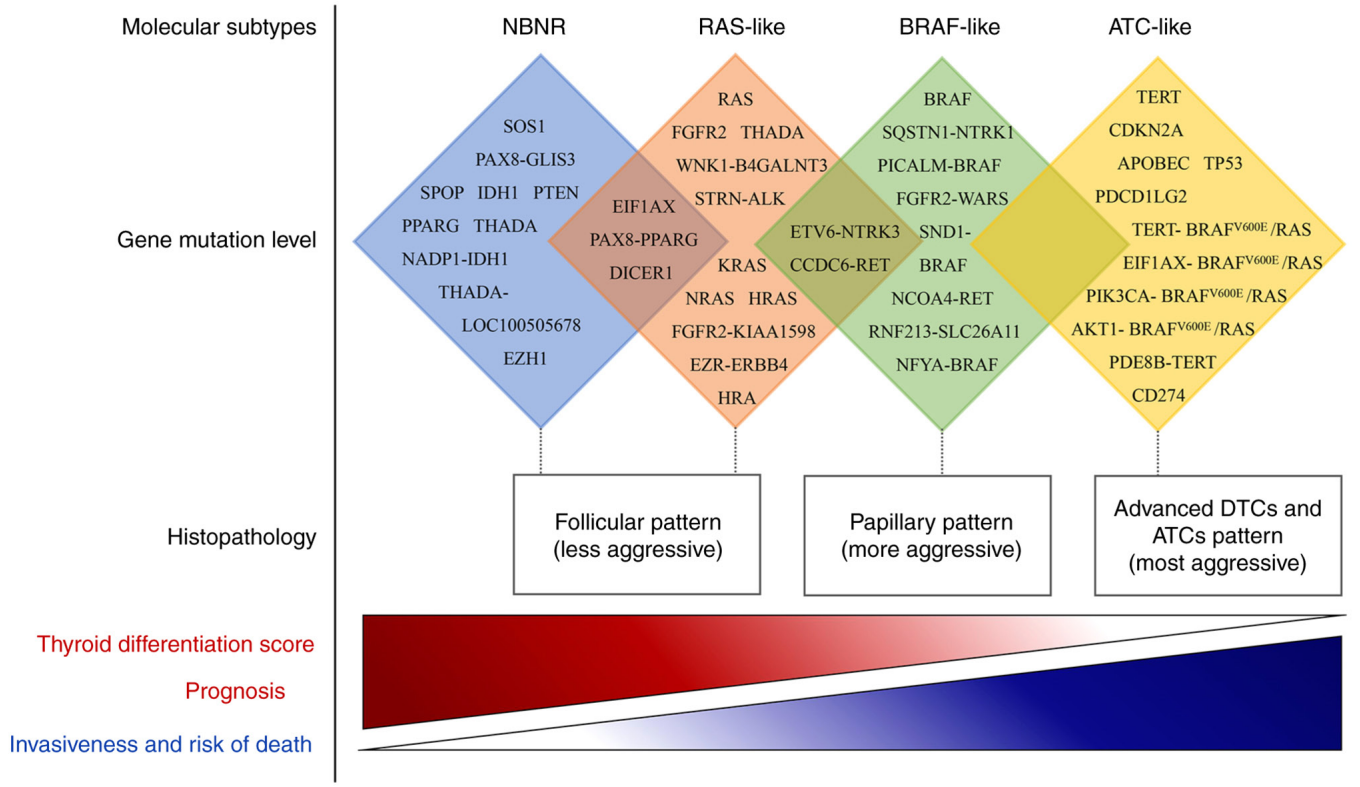

Figure 1. Schematic model of DTC progression. DTC, differentiated thyroid cancer; NBNR, non-BRAF-non-RAS; ATC, anaplastic thyroid cancer.

with an average survival of 3-5 years and a 10-year survival rate of ~10% (41). However, molecular-level investigations on RAIR-DTC have been scarce due to the complexity and heterogeneity of RAIR-DTC development, the instability and irreproducibility of the methods employed and the challenges in acquiring clinical samples (42-44). Capdevila *et al* (45) questioned the limitations of DNA mutation profiles in stratifying prognostic factors. They correlated RNA expression patterns and patient survival in cases enrolled in the DECISION trial, discovering that although RNA expression patterns were associated with DNA mutation patterns and tumor histology, they exhibited considerable differences in multivariate analysis, correlating with prognosis while the other two factors did not. Notably, the RNA expression profiles of BVL and RL revealed 7-9% of BRAF or RAS mutated tumors with 'unexpected' expression profiles, suggesting that these classical driver mutations did not dictate the final RNA gene expression profile in these instances. Additionally, ~40% of cases in BVL and RL expression profiles lacked mutations in BRAF or RAS genes, necessitating the identification of potential genomic/epigenomic aberrations that might influence the final expression profile. These findings imply that prognostic biomarkers associated with DTC may become prevalent in individuals with RAIR status. Therefore, it is essential to identify genomic/epigenomic mutations that could potentially affect the eventual expression patterns, as a genome-only stratified prognostic analysis of RAIR-DTC is insufficient. This study (45) also has a limitation due to the use of formalin-fixed and paraffin-embedded (FFPE) samples, which, although representing most tumor sample materials, lack information such as TERT promoter mutations in the prognostic genome.

Another study supports the view of the RAI refractory state. Colombo *et al* (46) investigated gene/miRNA and molecular expression profiles of PTC primary foci, synchronous lymph node metastases (LNM) and RAI-LNM, noting that patient characteristics with RAI+/D+ (metastatic site with initial RAI uptake and disease persistence) and RAI-/D+ (metastatic site without RAI uptake and disease persistence) still possessed driving lesions (particularly $BRAF^{V600E}$) of BRAF-/RAS-like subtypes with TDS. These results suggest that DTC maintains its classification as a molecular subtype based on transcriptome expression profiles, even in an RAIR environment. Furthermore, the study found transcriptome similarity in $BRAF^{V600E}$ mutation samples from primary and post-RAI LNM, indicating that RAI treatment has minimal influence on the expression profile of RAIR LNMs compared with primary tumors. This observation may offer a fresh perspective on the challenge of sample accessibility in future RAIR-DTC research.

A recent study utilizing whole-exome sequencing of matched sixty-six iodine-refractory and ninety-two iodine uptake PTC samples identified the APOBEC SBS13 mutation nomogram as an independent predictor of radioiodine resistance in PTC (47). When combined with SBS13 and TERTp mutations, this nomogram significantly increases the likelihood of prediction.

In contrast to adult PTC, molecular characterization of pediatric PTC is crucial for the development of molecule-targeted therapies for progressive RAIR PTC. A genome-wide and transcriptomic study comparing 106 RAIR-DTC children with adults (48) revealed a significant tumor response with the restoration of radioactive iodine uptake when exposed to

NTRK and RET fusion-targeted drug therapy. The study also identified age-related drivers of pediatric PTC, thus, supporting fusion-targeted therapy for RAIR-DTC re-differentiation.

Research on RAIR-DTC is currently limited and more molecular studies are necessary to address this bottleneck as quickly as possible.

3. Proteome analysis of DTC

Recent technological advancements in molecular research have enabled scientists to analyze protein information in various specimens, such as cells, tissues, cell lines and body fluids, using different mass spectrometry techniques, thereby increasing proteome coverage. This has led to the replacement of 2D gel electrophoresis by mass spectrometry coupled with other techniques. DTC proteomics research has made significant strides in improving the accuracy of fine needle aspiration biopsy in diagnosing indeterminate thyroid nodule cases before surgery, as well as in predicting diagnosis and prognosis by identifying biomarkers (Fig. 2; Table II). These advances have facilitated a better understanding of the pathogenic molecular mechanisms associated with the occurrence and progression of DTC, thereby aiding in guiding treatment decisions' (49).

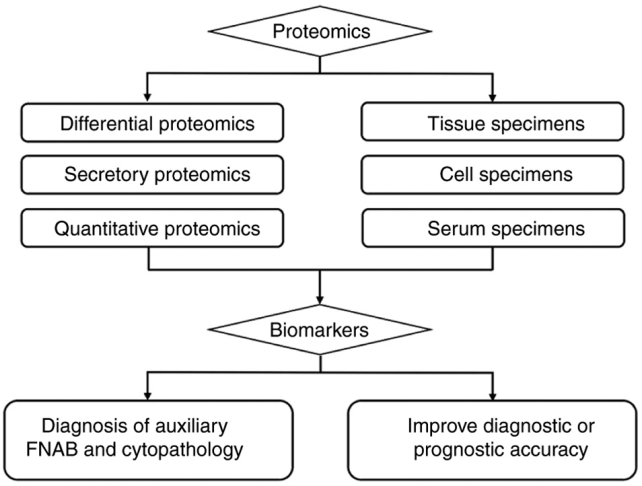

Figure 2. Application of proteomics in DTC. DTC, differentiated thyroid cancer; FNAB, fine-needle aspiration biopsy.

Diagnosis of auxiliary fine-needle aspiration biopsy (FNAB) and cytopathology. The study of biomarkers in DTC tissues poses a challenge due to the heterogeneous cellular components that can mask the aberrant expression of tumor proteins. Mass spectrometry imaging (MSI) can resolve certain limitations by accurately and locally determining protein levels within tissues (50), which is vital in classifying indeterminate lesions that cannot be correctly identified by FNAB and cytopathological examination.

Ucal *et al* (51) used MSI-based label-free quantitative methods to investigate the roles of IQGAP proteins, actin cytoskeletal proteins and energy metabolism alterations in follicular and classical variants of PTC. Another study (52) evaluated the discriminatory ability of matrix-assisted laser desorption/ionization (MALDI) combined with MSI to classify classical variants of PTC using FFPE samples from CV-PTC, FV-PTC and NIFTP. The signal intensities of S100-A6, cytoplasmic actin 1 and vimentin were enhanced within FV-PTC, while 60S ribosomal protein L6/L8 and Prelamin A/C were enhanced in NIFTP and CV-PTC, respectively. The results revealed that the peptide profiles of NIFTP showed significant differences compared with invasive FV-PTC, supporting the renaming of non-invasive FV-PTC to 'non-invasive follicular thyroid neoplasms with papillary nuclear features' (NIFTP).

A study using liquid chromatography-tandem mass spectrometry to explore novel protein biomarkers found that upregulated mitochondrial proteins, particularly SUVLG2, differentiate follicular carcinoma (FC) from follicular adenoma (FA) with a sensitivity and specificity of 75 and 80% respectively (53). Furthermore, using mass spectrometry, molecular similarities were observed between seven thyroid specimens, including the major types of thyroid malignancies (FV-PTC, CV-PTC, FTC, ATC, medullary thyroid carcinoma and FA, as well as non-carcinoma thyroid tissue (54,55), demonstrating the high feasibility of MSI combined with various techniques in testing cancer types.

Serum samples offer a readily available, easily monitored and less invasive means of detecting biomarkers for pathological diagnosis in DTC (56). Zhang *et al* (57) used label-free analysis to identify and quantify the overall proteome, complete N-glycopeptides and desialic acid N-glycopeptides within urine and plasma samples of females with PTC, thus, establishing an integrated, highly reproducible and rapid approach for exploring potential non-invasive diagnostic and prognostic biomarkers and therapeutic targets for PTC. Wang *et al* (58) discovered that serum-based proteomic profiles showed significantly lower levels of CA4 and plasminogen (PLG) in the PTC group compared with the nodular goiter group. C4A and PLG were identified as excellent diagnostic biomarkers for PTC cases, with sensitivities of 91.67 and 87.50% and specificities of 83.33 and 75.00%, respectively. Another study combining the expression of oncogene NRASQ61R within Nthy-ori 3-1 cells (based on blood and cell lines) with a multi-dimensional proteomics technology DISER, the combination of 2D-difference gel electrophoresis (2D-DIGE) and serological proteome analysis (SERPA), established a comprehensive way to identify disease-related tumor-associated antigens (TAAs) in thyroid tumors, enabling the identification of both cell-based and TAA biomarkers. Among these biomarkers, autoantibodies against CNN3 and PGK1 were identified as tumor-specific biomarkers of the thyroid envelope follicular type/RAS-like phenotype (EFP/RLP), which can be used to differentiate tumors of diverse malignancy grades (59).

MALDI-MSI has shown promise in cytopathology for diagnosing thyroid nodules, using FNAB needle washes as a sample source (60). Furthermore, new diagnostic tools, such as nanoparticle-assisted proteomics approaches, are constantly being developed (61). Taken together, proteomics appears to be a very promising alternative for diagnosing thyroid nodules that are difficult for cytopathologists to identify.

Identification of biomarkers to improve diagnostic or prognostic accuracy. The progression of DTC is marked by

Table II. Application of high-throughput sequencing methods to analyze the latest partial proteomics of DTC.

Author, year	Category	Biomarkers	Expression	Significance	Samples	(Refs.)
Lai X *et al*, 2017	Diagnosis	SUCLG2	Up	SUCLG2, a mitochondrial protein upregulated in FC, distinguishes FC from FA and has a sensitivity of 75% and a specificity of 80% for the diagnosis of FC.	FA, FC(FFPE, n=54, 52)	(53)
Wang Y *et al*, 2021		C4A	Down	Low serum levels of CA4 and PLG in the PTC group could be used as early diagnostic biomarkers for PTC, with sensitivities of 91.67 and 87.50% and specificities of 83.33 and 75.00%, respectively.	NG, PTC(serum, n=29)	(58)
		PLG				
Dai J *et al*, 2020	Prognosis	SLC27A6	Up	SLC27A6 was a specifical upregulated protein in iPTC and may be significantly associated with the metastasis and staging of PTC.	PTC, iPTC and adjacent to normal thyroid tissues (n=3)	(62)
Zhan, S *et al*, 2019		LAMC2	Up	They played a role in PTC lymph node metastasis and more importantly, their elevated mRNA expression in tumorous tissues showed a positive relationship with unfavorable variables, including larger tumor size, LNM, high AJCC staging, $BRAF^{V600E}$ mutation and poor prognosis.	PTC and adjacent to normal thyroid tissues (n =48)	(63)
		MYO1G				
Wei X *et al*, 2018		PDLIM5	Up	PDLIM5 is highly expressed in PTC and could promote the migration, invasion and proliferation of PTC cells through the Ras-ERK pathway.	PTC and adjacent to normal thyroid tissues (n =75)	(64)
Orlandella FM *et al*, 2019		JAM-A	Down	Silencing of JAM-A enhances the proliferation and motility of thyroid cancer cells, which is closely associated with the phosphorylation of P53 and GSK3α/β proteins.	PTC, ATC, NT(n=11, 9, 9)	(65)
Lin P *et al*, 2019		ISG15	Up	ISG15 is highly expressed in PTMC with lymph node metastasis and thus can be used as a candidate biomarker for prognosis of lymph node metastatic PTMC.	PTMC with or without CLNM (FNAB, n=60)	(72)
Krishnan, A *et al*, 2020	Treatment	TFG-RET fusion	Up	Targeting HUWE1 or DUBs is a promising strategy to prevent RET-induced tumors.	PTC, adjacent to normal thyroid tissues and LNM	(74)

SUCLG2, succinate-CoA ligase GDP-forming subunit β; FA, follicular adenoma; FC, follicular carcinoma; FFPE, formalin-fixed and paraffin-embedded; C4A, complement C4A; PLG, plasminogen; PTC, papillary thyroid carcinoma; NG, nodular goiter; SLC27A6, solute carrier family 27 member 6; PTC, papillary thyroid carcinoma; iPTC, invasive PTC phenotype; LAMC2, laminin subunit Gamma 2; MYO1G, myosin IG; LNM, lymph node metastases; AJCC, American Joint Committee on Cancer; PDLIM5, PDZ and LIM domain 5; JAM-A, junctional adhesion molecule A; ATC, anaplastic thyroid cancer; NT, normal thyroid; ISG15, ISG15 Ubiquitin Like Modifier; PTMC, papillary thyroid microcarcinoma; CLNM, central lymph node metastasis; FNAB, fine-needle aspiration biopsy; DUB, deubiquitinating enzyme.

invasion and metastasis events, particularly LNM in PTC, which heighten the risk of relapse and result in a dismal prognosis. The discovery of novel protein biomarkers for improved prediction of DTC prognostic risk is of utmost importance.

Dai *et al* (62) employed TMT-based mass spectrometry and Gene Expression Omnibus and TCGA databases to identify differential proteins between PTC and invasive PTC phenotype (iPTC). They discovered that SLC 27 Member 6, a protein acting as a transporter mediating long-chain fatty acid uptake, was specifically upregulated in iPTC and may be significantly linked to PTC metastasis and staging. Similarly, LAMC2 and myosin IG were found to serve a role in PTC lymph node metastasis and, more importantly, their increased mRNA expression in tumor tissues demonstrated a positive correlation with unfavorable variables such as larger tumor size, LNM, high American Joint Committee on Cancer (AJCC) staging, $BRAF^{V600E}$ mutation and poor prognosis (63). Another study first revealed that PDZ and LIM domain 5 is highly expressed in PTC and could promote the migration, invasion and proliferation of PTC cells through the Ras-ERK pathway (64). Junctional adhesion molecule A, a transmembrane protein involved in various biological processes, including epithelial-to-mesenchymal transition, was shown to have its silencing enhance the proliferation and motility of TC cells, which is closely associated with the phosphorylation of P53 and GSK3α/β proteins. Each of these proteins could positively affect their potential as candidate biomarkers for predicting PTC prognosis (65). Luo *et al* (66) compared the proteomic profiles of serum purified exosomes (SPEs) of PTC cases (with and without LNM) to those of healthy individuals and observed overexpression of proteins like talin 1, SRC proto-oncogene, non-receptor tyrosine kinase, calpain small subunit 1 and integrin subunit β 2, which are associated with tumor cell migration. Furthermore, abnormal activation of integrin signaling in the SPE of PTC with LNM promoted the aggressiveness of BHT101 TC cells. These findings offer insight into the biological activities and features of serum exosomes during LNM of PTC; thus, aiding in understanding DTC-related molecular mechanisms.

The global increase in PTC morbidity is primarily associated with a rise in papillary thyroid microcarcinoma (PTMC) diagnosis. The need for surgical treatment of PTMC largely depends on LNM. Jin *et al* (67) studied PTMC with and without LNM and screened for proteins potentially associated with migration and invasion, such as α-1-antitrypsin, α-actinin-1, carbonic anhydrase 4, high mobility group protein HMGI-C and hepatocellular carcinoma-derived growth factor. ISG15 ubiquitin like modifier (ISG15), a type I interferon-regulated ubiquitin-like molecule that plays crucial roles in modulating cell growth and cancer progression, has been reported to be highly expressed in various cancers (68-71). Similarly, ISG15 was well distinguished between patients with lymph node metastatic and non-metastatic PTMC. ISG15 knockdown reduced proliferation and infiltration of human PTC-derived BCPAP cells *in vitro*. Additionally, silencing ISG15 inhibited xenografted tumor growth in immunodeficient nude mice (72).

Targeted therapy remains a primary treatment for managing advanced TC. However, resistance to multiple drugs restricts the clinical utility of targeted agents. A study by Mishall *et al* (73) highlight the need for targeting multiple pathways simultaneously. They developed TC cells resistant to four Src inhibitors (dasatinib) and proteomic analysis revealed that the MAPK and AKT/mTOR pathways were critical for resistance to single-drug Src inhibitors.

Through proteogenomic analysis of matched normal thyroid tissue, primary tumor foci and LNM in one case, Krishnan *et al* (74) discovered a novel TFG-RET gene fusion. This fusion involves the 5'-terminal of Trk fusion gene (TFG) exons 1-4 and the 3'-terminal of RET tyrosine kinase. Further studies have revealed the involvement of HUWE1 in RET-induced oncogenic conversion of PTC and suggest that targeting HUWE1 or deubiquitinating enzymes (DUBs) is a promising therapeutic strategy for preventing RET-induced tumors. Clinical trials targeting the ubiquitinome are currently underway in other tumors and appear promising for PTC (75).

Proteomics has proven to be an efficient approach to identify potential biomarkers for DTC, but further research is needed to expand our understanding of DTC at the molecular level beyond the two aspects discussed earlier.

4. Discussion

DTC is the most prevalent type of TC worldwide and early detection remains challenging due to the lack of reliable and specific markers. Thus, identifying biomarkers that can aid in better diagnostic stratification, prognosis prediction and precise treatment is crucial. Recent research has focused on exploring the molecular mechanisms of DTC at the transcript and protein abundance levels. With the advancement of high-resolution histology technologies, even small changes in transcriptional, translational and post-translational modifications have been uncovered, which were previously undetectable using genomic or proteomic approaches. These research findings can serve as a foundation for future studies aimed at translating these results into clinical practice, meeting the demand for clinical stratification of DTC management in the era of precision medicine.

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Authors' contributions

SY conceived, designed, wrote and revised the manuscript. RH, DF and JF were involved in the design and revision of the manuscript. GZ reviewed and revised the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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