Review

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Omics sciences and precision medicine in thyroid cancer

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Abstract

Background. Thyroid cancer, a heterogeneous disease originating from the thyroid gland, stands as the predominant endocrine malignancy worldwide. Despite advances in diagnosis and treatment, some patients still experience recurrence and mortality, which highlights the need for more personalized approaches to treatment. Omics sciences, encompassing genomics, transcriptomics, proteomics, and metabolomics, offer a high-throughput and impartial methodology for investigating the molecular signatures of thyroid cancer.

Methods. In the course of this review, we have adopted a focused research strategy, meticulously selecting the most pertinent and emblematic articles related to the topic. Our methodology included a systematic examination of the scientific literature to guarantee a thorough and precise synthesis of the existing sources.

Results. These techniques enable the identification of molecular markers that can aid in diagnosis, prognosis, and treatment selection. As an illustration, through genomics studies, numerous genetic alterations commonly discovered in thyroid cancer have been identified, such as mutations in the BRAF and RAS genes. Through transcriptomics studies, distinctively expressed genes in thyroid cancer have been uncovered, playing roles in diverse biological processes, including cell proliferation, invasion, and metastasis. These genes can serve as potential targets for novel therapies. Proteomics studies have unveiled differentially expressed proteins intricately involved in thyroid cancer pathogenesis, presenting promising biomarkers for early detection and disease progression monitoring. Metabolomics studies have identified alterations in metabolic pathways linked to thyroid cancer, offering promising avenues for potential therapeutic targets.

Conclusions. Precision medicine in thyroid cancer involves the integration of omics sciences with clinical data to develop personalized treatment plans for patients. Employing targeted therapies guided by molecular markers has exhibited promising outcomes in enhancing the prognosis of thyroid cancer patients. Notably, those with advanced thyroid cancer carrying BRAF mutations have displayed substantial responses to specific targeted therapies, such as vemurafenib and dabrafenib. ***Clin Ter 2023; 174 Suppl. 2 (6):11-20 doi: 10.7417/CT.2023.2467***

Key words: *thyroid cancer, biomarker, genomics, metabolomics, precision medicine, diagnosis, treatment*

Introduction

The thyroid gland, the initial endocrine gland to develop in humans, is a well-vascularized structure situated in the base of neck. With a soft and reddish appearance, it assumes the shape of an H. Utilizing iodine, the thyroid gland synthesizes essential hormones (T3, T4) responsible for regulating vital bodily functions, including heart rate, blood pressure, body temperature, and basal metabolic rate (1).

Thyroid cancer stands as the most frequently diagnosed form of endocrine cancer, surpassing all other types of endocrine cancer combined in its impact on mortality (2): in fact, it accounts for the majority (95%) of all endocrine-related cancers (3). Symptoms of thyroid cancer encompass a neck lump or swelling, difficulties in swallowing or breathing, and changes in voice hoarseness (4). Despite its relative rarity, constituting approximately 2% of all cancers (3), thyroid cancer can affect individuals of all ages, genders, and ethnicities.

As thyroid cancer is not very frequent, it is difficult to pinpoint its exact etiology (5). Nevertheless, numerous risk factors have been identified, including radiation exposure, a family history of thyroid cancer, and specific inherited genetic abnormalities (6). Thyroid cancer, second only to

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ovarian cancer, ranks as the most lethal form of cancer originating in the endocrine system. Despite comprising only 1% of all cancer-related deaths, it still remains a substantial concern (7). The objective of this review is to present an encompassing overview of the current state of knowledge in the field of omics sciences and precision medicine in thyroid cancer, incorporating the most recent research and advancements.

Various types of thyroid carcinomas and their histological characteristics

Thyroid cancer is conventionally categorized into two main groups, determined by clinical and morphological characteristics: differentiated cancer—which encompasses papillary (PTC), follicular (FTC), and medullary carcinomas (MTC)—and undifferentiated thyroid cancer, referred to as anaplastic thyroid carcinoma (ATC) (6). Over the last thirty years, there has been a rapid surge in the worldwide incidence of thyroid cancer (8). Roughly two-thirds of all cases, in both males and females, fall under the category of papillary thyroid cancer. Follicular thyroid cancer constitutes 10-20% of cases, while medullary thyroid cancer accounts for 5-10% of the total cases. Anaplastic thyroid cancer is the least common, comprising less than 5% of all cases (9). Papillary (PTC), follicular (FTC), and anaplastic (ATC) thyroid cancers arise from the thyroid follicular epithelial cells, whereas medullary thyroid cancer (MTC) originates from the parafollicular C-cells (10).

Papillary thyroid cancer stands as the most common type, with a generally favorable prognosis. This form of cancer tends to metastasize more frequently to the lymph nodes in the neck than to the lungs. On the other hand, follicular thyroid cancer and poorly differentiated thyroid cancers are categorized as high-risk cancers due to their propensity for spreading through the bloodstream to distant sites, particularly the lungs and bones. The staging system for these types of cancers varies based on age, with patients aged 45 and older experiencing less favorable prognoses (11). Medullary thyroid cancer originates in the parafollicular cells, the neuroendocrine cells of the thyroid gland. Typically, it presents as a solitary lump in the thyroid gland, predominantly affecting individuals aged between 40 and 60 (12). In some cases, the first symptom of medullary thyroid cancer is swelling of the lymph nodes in the neck, as the disease commonly spreads to the cervical lymph nodes. Approximately 70% of patients with detectable medullary thyroid cancer exhibit signs of metastasis to the cervical lymph nodes during surgery (13). Certain patients may manifest symptoms of a thyroid nodule, alongside flushing and diarrhea, suggesting a possible cancer spread. Around 25% of medullary thyroid cancer cases are associated with patients inheriting multiple endocrine neoplasia syndrome (12).

Anaplastic thyroid cancer is an infrequent and rapidly growing type of thyroid cancer, often presenting as a sizable, firm lump in the neck (14). Common symptoms include hoarseness, difficulty swallowing, and shortness of breath. If a patient exhibits a suspicious mass, an immediate biopsy is crucial for proper diagnosis. Additional tests may indicate that the cancer has metastasized to other regions of the body, with the lungs, bones, and brain being the most prevalent sites. Anaplastic thyroid cancer may either arise from differentiated thyroid cancer or manifest independently. When a patient with a history of thyroid cancer exhibits these symptoms, anaplastic transformation should be considered as a possibility. Given the unfavorable prognosis associated with this cancer, referring patients to a specialized treatment center is advisable. Fortunately, clinical trials are actively investigating novel treatments for anaplastic thyroid cancer, holding the potential to offer hope for improved survival rates (15).

Insights into the Genetic Basis of Thyroid Carcinoma

Emerging findings from DNA sequencing studies have revealed that the MAPK signaling pathway harbors genetic mutations, predominantly contributing to the occurrence of thyroid cancers. Functioning as a vital conduit for transmitting growth signals from the cell membrane to the nucleus, this pathway plays a pivotal role in regulating cell growth and division. The identified mutations within this pathway culminate in the unbridled proliferation of thyroid cells, ultimately fostering the development of cancer (16).

Gene mutation

A specific point mutation (T1799A) in exon 15 of the BRAF gene leads to the expression of a mutant protein known as BRAF-V600E, resulting in the constitutive activation of a serine/threonine kinase (17, 18). This mutation represents one of the most prevalent genetic alterations observed in thyroid cancer, occurring in approximately 45% of sporadic papillary thyroid carcinoma (PTC) cases and up to 80-100% of tall cell variant PTC cases. The presence of the BRAFV600E mutation correlates with more aggressive pathological features and higher recurrence rates, serving as a predictor for poor clinical outcomes (19). Additionally, this mutation is recognized for causing a loss of radioiodine avidity, rendering it less responsive to radioiodine treatment.

Point mutations in RAS genes are a common occurrence not only in thyroid cancer but also in various other types of solid cancers. Among the three isoforms of RAS (HRAS, KRAS, and NRAS), NRAS is the most frequently mutated in thyroid tumors. While RAS mutations are relatively rare in typical papillary thyroid carcinoma (PTC) cases (0-20%), almost half of follicular thyroid carcinoma (FTC) and follicular variant PTC cases carry RAS mutations. Moreover, approximately 20% of follicular adenoma cases show RAS mutation, suggesting its early involvement in thyroid tumorigenesis. The RAS mutation leads to a reduction in GTPase activity, resulting in a constitutively active state. Additionally, RAS mutation activates the PI3K-AKT pathway, playing a significant role in the development of thyroid cancer.

The tumor suppressor gene PTEN plays a crucial role in regulating the PI3K-AKT signaling pathway, acting as a significant negative regulator in opposition to PI3K. Mutation or deletion of PTEN has been linked to the tumorigenesis of follicular thyroid cells, evident in Cowden's syndrome—an autosomal inherited disease caused by germ line mutations

of the PTEN gene. Cowden's syndrome exhibits a strong correlation with an elevated risk of thyroid, breast, and endometrial cancers, as well as benign hamartomas. PTEN alterations are frequently detected in around 40% of follicular thyroid carcinoma cases. Furthermore, promoter hypermethylation has been identified as a mechanism for PTEN silencing, observed in both follicular thyroid carcinoma and anaplastic thyroid carcinoma (20). Thyroid cancers can involve mutations in various genes, including CTNNB1, TP53, IDH1, and NDUFA13 (GRIM19). CTNNB1 is a gene that plays a role in the WNT-β-catenin pathway and is frequently found to be mutated in anaplastic thyroid cancer (ATC) (21). The TP53 gene is responsible for producing the tumor suppressor protein p53 and is associated with several types of solid tumors. In cases of anaplastic thyroid cancer (ATC), TP53 mutations are commonly identified, with a frequency ranging from 70% to 80% (22, 23). CTNNB1 and TP53 mutations are predominantly observed in poorly differentiated thyroid carcinoma or anaplastic thyroid carcinoma, suggesting that these genetic alterations may occur later in the cancer progression derived from follicular cells. In contrast, Hürthle cell thyroid cancer typically lacks the typical genetic mutations seen in other types of thyroid cancer, such as BRAFV600E, RAS, or RET/PTC (24). Instead, around 15% of Hürthle cell thyroid cancer cases exhibit mutations in NDUFA13 (also known as GRIM19) (25). Thyroid carcinoma-related gene mutations and alteration are reported in Table 1.

Genetic predisposition stands as one of the factors contributing to thyroid cancer. In cases where the cancer is hereditary, there is a higher likelihood of recurrence and increased aggressiveness, often manifesting at a younger age compared to sporadic thyroid cancer (38, 39). Thyroid cancer can be categorized into two main types: medullary thyroid cancer, originating from parafollicular cells, and non-medullary thyroid cancer (NMTC), originating from follicular cells. NMTC is the most prevalent form, accounting for 95-97% of all cases. Within NMTC, there is a specific subtype called hereditary NMTC, which has a genetic basis and represents approximately 5-15% of NMTC cases and 3-9% of all thyroid cancers (40, 41). Genes that make individuals more susceptible to NMTC can also cause other diseases besides thyroid cancer. This parallels observations in other cancer syndromes, such as familial adenomatous polyposis (FAP) resulting from APC gene mutations (42), Cowden syndrome arising from PTEN gene mutations (43, 44), and Carney complex associated with PRKAR1A gene mutations (44). Regular monitoring and timely surgical intervention can help high-risk cancer patients. Genetic testing enables the identification of individuals at risk, facilitating targeted preventive treatment for the appropriate population and avoiding unnecessary treatment for others. Despite the widespread adoption of genetic testing in clinical practice, the genes that elevate susceptibility to NMTC are frequently overlooked (45), and testing for these genes is not yet a routine part of clinical settings (46).

Among individuals diagnosed with papillary thyroid cancer, at most 10% have a family member (either a first or second-degree relative) who has also experienced PTC. It is essential to highlight that PTC is not a prevalent form of cancer, ranking as the ninth most common cancer in the United States, with an estimated 44,670 new cases reported in 2010 (47). While a 10% rate of familial occurrence may seem relatively high, it's important to acknowledge that in most cases, this is based on only one or two additional cases besides the original person. Pedigrees exhibiting Mendelian-type inheritance, where a trait is clearly inherited in a predictable pattern, are exceptionally uncommon, and pedigrees with more than five affected individuals are particularly rare. Even in families where inheritance follows a Mendelian pattern, it is common for the trait to skip generations or remain unexpressed (nonpenetrance). Considering these observations, it is probable that multiple genes are involved in predisposition to PTC, exhibiting low penetrance, while environmental factors also contribute to the equation. It cannot be completely ruled out that there are Mendelian genes with high penetrance that predispose individuals to PTC; however, based on available evidence, it appears that if such genes do exist, they are not common. Such rare genes may be categorized as "common disease, rare allele," as elucidated by Bodmer and Bonilla (48). Currently, association studies are limited to identifying genes that have common variations (known as single nucleotide polymorphisms or SNPs) with a frequency of over 1% in

Table 1. Thyroid Carcinoma-Related Gene Mutations and Alteration

Genes Involved	OMIM	Correlated Pathology	Inheritance	References
RET	164761	Papillary Thyroid Carcinoma	Autosomal Dominant	(26)
BRAF	164757	Papillary Thyroid Carcinoma	Sporadic	(27)
NTRK1	191315	Papillary Thyroid Carcinoma	Sporadic	(28)
TP53	191170	Anaplastic Thyroid Carcinoma	Autosomal Dominant	(29)
PTEN	601728	Follicular Thyroid Carcinoma	Autosomal Dominant	(30)
NKX2-1	600635	Poorly Differentiated Thyroid Carcinoma	Autosomal Dominant	(31)
RAS	190070	Differentiated Thyroid Carcinoma	Sporadic or Autosomal Dominant	(32)
TERT	187270	Differentiated Thyroid Carcinoma	Sporadic	(33)
TP53	191170	Follicular thyroid carcinoma, Papillary thyroid carcinoma	Autosomal dominant	(34)
MET	164860	Papillary thyroid carcinoma	Autosomal dominant	(35)
p16	600160	Papillary thyroid carcinoma	Autosomal dominant	(36)

the population. However, certain genes with rare variations that are only present in a few families cannot be detected through these studies. In the pursuit of these genes, researchers employ a technique called linkage analysis, involving the examination of the DNA of extensive families. This approach has proven fruitful in the case of PTC, leading to the identification of several potential gene locations (49).

Somatic mutations

The development of papillary thyroid cancer (PTC) is influenced by diverse genetic factors. Notably, mutations within the BRAF and RAS genes are involved, activating the MAPK signaling pathway and present in 40% and 15% of PTC cases, respectively (RAS mutations are exclusively found in the follicular variant). Moreover, rearrangement of the RET/PTC gene is detected in 18% of PTC cases. These mutations are mutually exclusive and correspond to distinct characteristics and behaviors of the tumors (50). Follicular thyroid carcinoma (FTC) diverges from papillary thyroid carcinoma (PTC) in terms of genetic mutations. FTC is frequently associated with mutations in either the RAS or PTEN genes, or rearrangements in the PAX8/PPAR genes. These genetic abnormalities are prevalent in a significant percentage of FTC tumors, ranging from 50% to 80% (51). RAS mutations are not limited to malignant follicular carcinoma alone, as they can also be found in benign follicular adenomas. Nevertheless, the mechanisms underlying the progression of follicular adenomas to follicular carcinoma remain poorly understood (51).

Epigenetic modifications

Initially, the term "epigenetic" was coined to describe the way genes interact with the environment, resulting in observable traits. Over time, its scope has expanded to encompass the study of mechanisms controlling changes in gene expression that can be transmitted through somatic cells or even germ cells. These changes cannot be attributed to alterations in DNA sequence (52). The process of epigenesis is extensively studied, particularly concerning the addition of a methyl group to the 5-carbon position of cytosine. This modification is carried out by a group of enzymes known as methyltransferases, which target cytosines within a CpG dinucleotide sequence. The methyl group is provided by S-adenosyl-L-methionine. In vertebrates, cytosine methylation represents the sole known methylation reaction (53). The process of epigenesis is most extensively studied in relation to the addition of a methyl group to the 5-carbon position of cytosine. This process is carried out by a group of enzymes called methyltransferases, which target cytosines that are part of a CpG dinucleotide sequence. The methyl group is provided by S-adenosyl-L-methionine. In vertebrates, methylation of cytosine is the only known methylation reaction that occurs (54). During the process of development, specific patterns of gene expression that are unique to each tissue are established. These patterns are closely linked to specific patterns of methylation or demethylation of CpG islands that are located near the gene promoters (55). Research findings suggest a correlation between the expression of the thyroglobulin gene in thyroid tissue and the unmethylated state of its promoter, indicating the absence of chemical modifications to the DNA that could suppress gene expression. In simpler terms, the regulation of this gene's expression in thyroid tissue hinges on the unmethylated status of its promoter region, which is essential for enabling appropriate expression (56).

Research has demonstrated that GABP, a transcription factor widely present in the body, is involved in regulating the transcription of the TSHR gene in a manner dependent on methylation. Specifically, certain CpG sites within the TSHR promoter region must be methylated for GABP to effectively regulate gene expression. In rat FRT thyroid cells, which do not express the TSHR gene, the lack of expression appears to be influenced by both the methylation of these specific CpG sites and the methylation sensitivity of GABP. However, in rat thyroid cells (FRTL-5) expressing the TSHR gene, these CpG sites are entirely demethylated, enabling GABP to bind and effectively regulate the expression of the TSHR gene (57).

Tumor genomics (tumor-typical somatic mutations and circulating tumor DNA)

Most of the genetic alterations underlying different types of thyroid cancer have been elucidated. These changes fall into two categories: somatic mutations or somatic copy number alterations (SCNAs), and they display an inverse relationship, with tumors often exhibiting either a high number of somatic mutations or a high number of SCNAs, but rarely both. Somatic mutations in thyroid tumors mainly affect crucial elements of three primary oncogenic pathways: (i) RTK-RAS-RAF, (ii) PI3K-AKT-mTOR, and (iii) components of the cell cycle or the DNA repair machinery. In thyroid tumors, there is a relatively high proportion of somatic mutations, indicating numerous genetic changes occurring in the DNA of non-reproductive cells throughout a person's lifetime. On the other hand, the percentage of somatic copy number alterations (SCNAs) is low, comprising only about 30% of genetic alterations in these tumors (58). While copy number alterations (SCNAs) are not prevalent in thyroid cancer, they play a substantial role in approximately one-third of papillary thyroid carcinomas (PTCs) lacking gene fusions or driver mutations. This suggests that SCNAs alone can be oncogenic. Likewise, in poorly differentiated and anaplastic thyroid carcinomas (PDTC and ATC, respectively), SCNAs are more frequent in patients without driver mutations. SCNAs can activate oncogenes and suppress tumor suppressor genes, as they often encompass large DNA regions containing multiple genes.

As an illustration, the loss of the 22q region is present in around 10% of PTCs, with the majority of these cases being part of the follicular variant, which is enriched in RAS mutations. SCNAs can influence different gene regions in cancer cells, and one such region that may be affected is the chromosomal region 1q, which is gained in approximately 15% of all papillary thyroid carcinomas (PTCs). This gain has been correlated with the presence of BRAF mutations and is linked to a heightened risk of cancer recurrence and a

poorer prognosis in poorly differentiated thyroid carcinoma (PDTC). However, despite the association, no specific genes linked to this particular region have been identified. On the other hand, in anaplastic thyroid carcinoma (ATC), the loss of 8p and 17p regions, along with gains in the 20q region, are commonly observed. These SCNAs have been correlated with a more unfavorable prognosis for ATC patients (59).

Cell-free DNA (cfDNA) consists of small fragments of DNA released by cells, present in the bloodstream. Under normal circumstances, cfDNA originates from the natural breakdown of blood cells (60). However, in cancer patients, a portion of cfDNA is produced due to the death of cancer cells, known as circulating tumor DNA (ctDNA) (61). ctDNA possesses unique properties, such as its size and stability, and contains genetic and epigenetic information that reflects the tumor's characteristics (62). This renders ctDNA a valuable source of information for cancer detection and monitoring, as well as for devising personalized treatments (63).

Assessing the amount, quality, genetic alterations, and epigenetic modifications of cf-DNA can be beneficial in determining the diagnosis of disseminated tumor cells (64). It seems that individuals who have been diagnosed with differential thyroid cancer (DTC) have higher levels of cf-DNA quantity and quality as compared to those who have not been affected by the disease (65). Conversely, the amount of mitochondrial cell-free DNA (mcf-DNA) is reduced in the same group of patients (66).

Extensive research has focused on the presence of the BRAFV600E mutation in various human cancers, with melanoma and thyroid cancer being the most common types where it is observed. However, recent studies have revealed its detection in lung cancer as well (67). Investigations indicate that the BRAFV600E mutation may be associated with advanced thyroid cancer, elevating the likelihood of nodal and distant metastasis (68). The majority of studies on thyroid cancer cfDNA have concentrated on using PCR to detect specific point mutations in circulating DNA. However, two studies have explored the methylation of specific genes in cfDNA, deemed a more reliable indicator due to its relative stability compared to point mutations. Moreover, there exists a wide range of mutations associated with each cancer type, each occurring with relatively low incidence (69). Studies have demonstrated that the average detection rate of the BRAFV600E mutation in circulating cfDNA among DTC patients is 10%. This rate rises to 19.3% when patients with non-BRAFV600E tumors are excluded. However, the relatively low detection rate may be attributed to the inclusion of tumors at different stages, with early-stage tumors potentially not shedding sufficient tumor DNA into the circulation to be detectable using current techniques. Encouragingly, promising evidence for the potential use of cfDNA as a diagnostic tool in thyroid cancer comes from Pupilli et al., who discovered a substantially higher proportion of BRAFV600E cfDNA in PTC patients compared to those with benign nodules. They also found a higher proportion in individuals with suspicious cytology in comparison to those with benign cytology (11).

Research has revealed that the quantity of cfDNA (cell-free DNA) in the bloodstream is associated with the stage of various cancers. Moreover, the rate of cfDNA release into the bloodstream corresponds to the size of the primary tumor (70). A study indicates that the levels of circulating cfDNA with BRAFV600E mutation seem to be correlated with the occurrence of nodal and distant metastasis in PTC (71). A meta-analysis revealed a correlation between the BRAFV600E mutation and advanced clinical stage in various medical conditions (72). The identification of BRAFV600E in ctDNA holds promise as a non-invasive marker for identifying aggressive thyroid cancer. Detecting BRAFV600E in a patient's blood could indicate the presence of aggressive disease. Additionally, cfDNA can serve as a target for developing new methods to detect cancer recurrence after treatment.

At present, surveillance for thyroid cancer recurrence involves neck ultrasound scans and measuring thyroglobulin levels. However, this can be challenging due to the presence of antibodies in a substantial number of patients, which may interfere with accurate thyroglobulin measurements (73). Scientists researching various types of cancer have reported that a decrease in the amount of total cfDNA in a patient's body during treatment can be indicative of their response to the administered therapy (74). This statement indicates that the research conducted on thyroid cancer measured the levels before and after the treatment, and the results remained consistent in both instances (75).

Pharmacogenomics for thyroid cancer

Tumor pharmacogenomics is the investigation of how a person's genetic makeup affects their reaction to various cancer medications. These genetic alterations may also impact the efficacy of radiation therapy, and it is crucial to comprehend the role of pharmacogenomics in determining which patients are suitable for treatment when developing new radiopharmaceutical therapies for cancer patients (76).

For more than 40 years, the main treatment for well-differentiated thyroid cancer has involved surgery followed by ^{131}I therapy (when deemed appropriate). However, in some patients, ^{131}I therapy may not work, and some metastatic lesions may not take up the radioactive iodine. This could be due to a reduction in the NaI symporter in tumor cells. In such cases, inducing NaI expression and restoring responsiveness to ^{131}I therapy through redifferentiation therapy may be effective. Research has demonstrated that drugs targeting tyrosine kinases in tumors with NRAS and BRAFV600E mutations can facilitate the administration of successful ^{131}I treatment in affected patients (77).

An alternative treatment approach for thyroid cancers is external beam radiation (EBM) therapy, utilizing high-energy beams or particles to eliminate cancerous cells or hinder their growth (78). Typically, radiation therapy is not recommended for patients with differentiated thyroid cancers (DTCs) who respond well to radioactive iodine (RAI) therapy. However, in the case of patients with medullary thyroid cancer (MTC) or anaplastic thyroid cancer (ATC), EBM and chemotherapy are commonly employed in their treatment. Chemotherapy involves administering anti-cancer drugs through injection, infusion, or orally, which then travel through the bloodstream to target and eliminate cancer cells. Nonetheless, chemotherapy is generally not effective for most types of thyroid tumors and is typically used in

conjunction with EBM therapy for ATC or for advanced thyroid cancer patients who have not responded to other treatments.

In recent years, significant progress has been made in the development of new medications tailored to specifically target the molecules responsible for tumor formation, known as targeted therapy (79). Distinguishing themselves from traditional chemotherapy drugs, targeted therapy drugs focus on specific molecular pathways in cancer cells, rather than simply attacking fast-growing cells. Within the realm of thyroid cancer therapies, various small molecules have been identified as potential targets, falling into three main categories: oncogenic kinases, signaling kinases, and vasculature/angiogenesis processes. Furthermore, there are other molecules that target epigenetic mechanisms (such as Fosbretabulin, Romidepsin, Celecoxib, Vorinostat, Valproic acid, Azacytidine, and Decitabine) as well as nuclear receptors.

Vandetanib (Caprelsa) is a medication prescribed to manage symptomatic and aggressive medullary thyroid cancer (MTC). This targeted therapy is available in the form of a 300mg biconvex, oval-shaped tablet. Cabozantinib (Cometriq), on the other hand, is a small molecule targeted therapy used to treat MTC and as a second-line treatment for renal cell carcinoma. It predominantly inhibits tyrosine kinases c-Met and VEGFR2, exerting greater effects on these targets compared to AXL and RET (80, 81). Cabozantinib has demonstrated its effectiveness in inhibiting cancer growth in MTC patients, with a duration of approximately seven months longer than a placebo. In the treatment of radioiodine-refractory differentiated thyroid cancer, two targeted therapy drugs, Lenvatinib (Lenvima®) and sorafenib (Nexavar®), function as kinase inhibitors and have been utilized (82, 83). Dabrafenib and Trametinib are combined medications utilized to treat advanced melanoma and anaplastic thyroid carcinoma (ATC). They function by inhibiting the formation of new blood vessels in cancer cells and targeting essential proteins crucial for cancer cell growth (84, 85). This combination therapy proves to be a viable treatment option for ATC patients with a specific type of positive BRAF gene mutation and for those who have not undergone complete tumor removal through surgery (86).

Metabolomic and microbiomic prognostic indicators

Metabolomics is a burgeoning field of research in thyroid cancer, still in its early stages compared to genomics and proteomics, resulting in fewer studies. The most commonly utilized techniques include mass spectrometry and NMR spectrometry, with HRMAS NMR demonstrating potential in identifying various thyroid lesions (87). Most studies have primarily focused on analyzing tissue specimens, with limited research on less invasive biological fluids (such as serum, plasma, or urine) as diagnostic biomarkers for thyroid cancer (88). Despite this, all studies have successfully distinguished between cancerous and normal tissues, as well as benign and malignant lesions.

In a study by Shang et al., they aimed to profile the metabolites of 25 papillary carcinoma tissues and compared them to 25 healthy controls, employing both targeted and untargeted approaches. For untargeted analysis of 15 cancerous and normal samples, they utilized gas chromatography-time of flight mass spectrometry (GC-TOF-MS), while for targeted analysis of 10 paired samples, they utilized ultra-high-performance liquid chromatography-triple-quadrupole mass spectrometry (UHPLC-QqQ-MS) and GC-TOF-MS. In their untargeted analysis, they successfully identified 45 significant metabolites, such as oleic acid, sorbitol, galactinol, arachidic acid, glutaric acid, melibiose, glucose, linolenic acid, uridine, and melatonin. To validate these findings, the subsequent targeted analysis confirmed the significance of certain metabolites, with sorbitol, glucose, galactinol, melibiose, and melatonin standing out as the most notable (89). In this study, a non-targeted approach involving gas chromatography and mass spectrometry was employed to compare thyroid tissues from 16 patients with papillary thyroid carcinoma (PTC) and normal thyroid tissues. To confirm the metabolic changes observed, an RT-qPCR experiment was conducted to assess enzyme genes. The results revealed several significant alterations in metabolites. Notably, there was a decrease in carbohydrates such as glucose, fructose, galactose, mannose, and rhamnose, along with reduced malonic acid and increased inosine concentration related to nucleotide metabolism. Moreover, lipid metabolism showed an increase in cholesterol and arachidonic acid. The study also highlighted notable elevations in mRNA levels of G6PD, PGK1, LDHA, PHGDH, and PTGS2 (90).

In a particular study, researchers conducted a comparison between benign and malignant thyroid tissues, which revealed distinct metabolic differences. Malignant tissues exhibited elevated levels of phosphocholine, glycerophosphocholine, phosphoethanolamine, lactate, and various amino acids, while showing decreased levels of citrate, scyllo- and myo-inositol, inosine, and uridine. Moreover, when comparing malignant and benign nodules, the study identified increased levels of uracil, hypoxanthine, xanthine, and amino acids, with decreased levels of choline. The observed alterations mainly involved changes in energy metabolism, such as glycolysis, lipid metabolism, and the TCA cycle, as well as in protein turnover, nucleotide biosynthesis, and phosphatidylcholine biosynthesis (91).

The serum biomarkers that have been identified demonstrate a remarkable ability to accurately diagnose cancer patients, effectively distinguishing them from healthy individuals, and accurately differentiating between those with malignant and benign thyroid lesions. These findings highlight the potential of metabolomics to significantly advance our comprehension of the molecular mechanisms underlying thyroid cancer (TC), rendering it a highly promising research avenue for studying this disease. Furthermore, through metabolomics studies, we can gain deeper insights into cancer-related processes and uncover novel biomarkers, which have the potential to drive improvements in TC diagnosis and classification.

Microbiomics correlation with Thyroid Cancer

Microbes present in tumor tissues of papillary thyroid carcinoma (PTC), but not in adjacent normal tissues, are believed to have a significant impact on immune cell expression

and the regulation of immune and cancer pathways, thereby potentially restraining cancer growth. Notably, these microbes seem to be more abundant in tall cell and male patient groups, showing a correlation with heightened expression of mutations and tumor suppressor methylation (93).

Substantial evidence suggests that the composition of microorganisms in the gut (the gut microbiome) could increase susceptibility to certain types of cancer, alter the functioning of the human immune system, and influence the tumor microenvironment's response to treatment (94). Manipulating the microbiome in a targeted way has shown potential in enhancing the effectiveness of PD-1 blockade, indicating that the microbiome may play a role in supporting therapeutic approaches for tumors (95).

The gut microbiome has emerged as a crucial regulator of thyroid function as a host factor. Research has demonstrated that germ-free rats, raised in a sterile environment without gut bacteria, exhibit smaller thyroid glands compared to conventionally raised rats, highlighting the substantial influence of gut microbes on thyroid health (96). Furthermore, imbalances in the intestines have been linked to both low thyroid function and autoimmune thyroid conditions, further underlining the association between gut microbiota and thyroid-related disorders (97). The gut microbiome has been linked to both thyroid cancer (TC) and the development of thyroid nodules, indicating its potential role in thyroid health (98). Specifically, individuals with high-grade thyroid nodules have shown a gut microbiome with increased amino acid breakdown and decreased butyrate production, implying a connection between gut bacteria and thyroid problems through host-microbe metabolite interactions (99). Moreover, gut bacteria contribute to the conversion of thyroxine (T4) to triiodothyronine (T3) in the intestine and can modulate the immune response of T helper 1 (Th1) and Th2 cells (100). Microorganisms also influence thyroid hormone levels by regulating iodine cycling, highlighting their impact on thyroid function within the body and the intricate interactions between the host and gut microbiome (97).

Proteomic Studies

Proteomics has gained popularity in the search for novel protein biomarkers for cancer diagnosis and prognosis (101). In PTC research, scientists frequently employ techniques such as two-dimensional electrophoresis, differential in-gel electrophoresis, and liquid chromatography to separate intricate protein mixtures. The identified proteins are then analyzed using mass spectrometry and database searches. Proteomics methods are often complemented by other techniques, including northern and western blotting, as well as immunohistochemical staining. For more precise quantification of protein levels, enzyme-linked immunosorbent assay (ELISA) is commonly utilized. These integrated approaches offer valuable insights into the study of PTC and its potential biomarkers.

Scientists use a comparative approach to identify differentially expressed proteins in tissue and serum samples of PTC patients compared to healthy individuals or those with benign thyroid goiter, using proteomics methods (102). Additionally, proteomics has been applied to analyze proteins produced by PTC cell lines, as well as cyst fluid and urine samples. Among the early proteomics studies on PTC, researchers reported an upregulation of prohibitin and ATP synthase D chain in tissue samples of patients compared to controls (102). These findings highlight the potential of proteomics in unraveling the protein signatures associated with PTC and its various sample sources, facilitating the discovery of new biomarkers and therapeutic targets.

In recent advances, researchers have successfully obtained protein profiles of thyroid cancer in humans by employing specific tumor cell lines. The process involves subjecting glycoproteins to precise denaturation procedures, followed by digestion and solid-phase extraction for extraction purposes. Identification of these proteins is achieved through electrospray ionization tandem mass spectrometry (ESI-MS/MS) analysis. Preliminary results have unveiled variations in the protein composition of thyroid cancer, contingent upon the particular type of cancer under investigation (103). These protein profiling techniques offer valuable insights into the molecular intricacies of thyroid cancer and hold promise for developing targeted therapies and personalized treatment approaches.

It was discovered that thyroid cell lines do not exhibit the same traits as in vivo tumors. Although these cell lines were derived from various tumor types, they have developed phenotypes and gene expression profiles that are similar to undifferentiated tumors due to in vitro evolution. This has led to the absence of expression of most thyrocyte-specific genes, non-responsiveness to thyrotropin, and a high number of chromosomal abnormalities. While thyroid cell lines retain certain properties of the cells they originated from, such as genetics, epigenetics, and gene expression, they differ significantly from in vivo tumors. Therefore, when interpreting thyroid cell line studies, it's important to consider these findings (104).

Conclusion

In conclusion, omics sciences have brought about a paradigm shift in the diagnosis, treatment, and control of thyroid cancer. The advent of diverse omics technologies has significantly enhanced our comprehension of the molecular underpinnings of thyroid cancer, fueling the advancement of precision medicine. By leveraging omics sciences, we have successfully pinpointed specific gene mutations and somatic alterations, enabling the development of targeted interventions like pharmacogenomics and biological therapies. Furthermore, the identification of protein biomarkers and of metabolomic and microbiomic prognostic indicators has improved the accuracy of thyroid cancer diagnosis and prognosis.

In summary, omics sciences have provided new routes for research and improved the clinical management of thyroid cancer, leading to better outcomes for patients.

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Conflicts of interest statement

Authors declare no conflict of interest.

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