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Role of RET and BRAF genes in thyroid cancer with relevance in gene therapy treatment

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Abstract

At present, cancer is a global problem, among all the types that exist, one of those that was taken into account for this research is thyroid cancer, especially associated with the predisposing genes of RET rearrangement and BRAF gene mutation, which incite the rapid exit of papillary thyroid carcinoma, from MAPK signaling pathways and conformational change by mutation in BRAF at position (V600E) and (V599E). The aim of the subsequent study is to provide recent information on the genes involved, as well as the potential impact of targeted therapies to inhibit these pathways, such as selective RET and BRAF inhibitors, providing a strategy for gene therapy and rather than the traditional approach of thyroidectomy. In addition to the way of its diagnosis by means of different genetic markers, oncogenic genes, genome sequence and generalized findings of the endocrine-genetic problem. This research also explores non-specific associations of the above-mentioned causes, generating a broader knowledge for future medical and genetic adaptation of the disease.

Keywords: Thyroid cancer; RET rearrangement; BRAF gene mutation; Papillary thyroid carcinoma; Genetic markers; Diagnosis

1. Introduction

Thyroid cancer is the endocrine cancer with the highest demand for its care, representing 2% of all cancers, and is considered the sixth most common cancer in women since they are three times more likely to acquire thyroid cancer than men. Although only 2% of thyroid cancer cases occur in children and adolescents, the five-year survival rate for these groups is approximately 98%, taking into account that survival depends on various factors starting with the type of thyroid cancer [1]. This cancer is diagnosed early, therefore, the average age at which a person is diagnosed with cancer is 51 years of age. It is less common in 40 – 50% of black people than in any other ethnic group [2].

Thyroid cancer is classified into various types based on the histological characteristics of the tumors, thus having Non-Medullary Thyroid Cancer (NMTC), which is characterized by originating from follicular cells, being responsible for 95% of all cases. This cancer is divided into four groups: Papillary Thyroid Cancer (PTC) representing more than 85% of cases, Follicular Thyroid Cancer (FTC) with a total of 10% of cases, Poorly Differentiated Thyroid Cancer (PDTC) representing 1–15% and finally Anaplastic Cancer (TCA) having less than 1% of cases [3].

Data recently obtained by the American Cancer Society show that around 44,020 new cases of thyroid cancer have been diagnosed so far this year, with 12,500 in men and 31,520 in women; while cases of death from thyroid cancer are 2,170 people corresponding to 990 men and 1,180 women. [2].

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Thyroid cancer is a disease that has shown an increase in its incidence in recent years, thus having several predisposing factors can influence its development, including genetics, exposure to radiation, and certain endocrine disorders. A family history of thyroid cancer and the presence of specific genetic mutations also play a crucial role. In addition, sex and age are relevant factors, as it is more common in women and older people. Understanding these elements is essential for the prevention and early diagnosis of this disease, which is why they are discussed in more detail in Table 1.

Table 1 Predisposing Factors

Sex And Age	Cancer can occur at any age, mostly in women more than in men, with an age range in women of 40 to 59 years, while in men it is 60 to 79 years [4]. An important factor is the higher incidence of thyroid cancer in women, because their risk increases with the presence of estrogen [5].
Familial Adenomatous Polyposis (FAP)	The presence of this syndrome, which consists of the appearance of polyps in the colon, presents an increased risk of papillary thyroid cancer.
Cowden Disease	This syndrome is characterized by defects in the PTEN gene, people with this disease have a higher risk of thyroid problems, as well as thyroid cancer that tends to be of the papillary or follicular type.
Carney Complex, Type I	It is caused by defects in the PRKAR1A gene,presents benign tumors, hormonal problems and has an increased risk of papillary and follicular cancer.
Radiation	Radiation treatments directed at the head or neck during childhood significantly increase the risk, depending on the amount of radiation given and age; the risk of suffering from it increases when higher doses are administered the younger the patient is.
Iodine In The Diet	A diet rich in iodine increases the risk of papillary thyroid cancer, while a diet low in sodium increases the risk of follicular cancer [4].
Hashimoto's Thyroiditis	People diagnosed with this disease have an increased risk of thyroid cancer
Benign Diseases	People with an enlarged thyroid (goiter) or a family history of thyroid disease increase their risk of developing thyroid disease [5].

2. Characteristic signs and symptoms

Thyroid cancer sometimes does not cause early signs or symptoms. Many times, cancer is found during a routine physical exam. Signs or symptoms usually develop as the tumor grows, such as a lump (nodule) in the neck, Shortness of breath, difficulty swallowing, pain when swallowing, hoarseness. It is critical to recognize that a thyroid nodule is formed by the abnormal proliferation of thyroid cells. The nodules can be solid or also filled with fluid [6].

Thyroid nodules in the adult population are extremely common, occurring in 19-68% of the population, but on rare occasions they are malignant (5-10% of all thyroid nodules in adults). In addition, neonatal thyroid carcinoma has been rarely discussed, but most cases of pediatric thyroid carcinoma occur in the second decade. A thyroid nodule in the pediatric patient usually manifests as an asymptomatic mass in the neck, may present with or without cervical lymphadenopathy, and may be accompanied by shortness of breath and/or hyperthyroidism [7].

Similarly, all patients who present with symptoms of hoarseness or a change in their voice associated with a thyroid nodule or goiter, individuals with cervical lymphadenopathy or a painless thyroid mass, which grows rapidly over a period of weeks, should be referred for urgent opinion [8].

3. Genomic of Thyroid Cancer

Currently, thyroid cancer has been the subject of multiple studies in the area of genetics due to its increasing prevalence and the innumerable differences in clinical behavior. Among thyroid cancers, PTC, FTC, TCA, and NMTC are the most extensively studied, although to a lesser extent. It is essential for the scientific community to identify specific genetic variations as a crucial part of understanding pathogenesis and making therapeutic decisions to improve patient prognosis.

The genes involved in the aforementioned carcinomas are somatic point variations in BRAF (OMIM: 164757; accelerated fibrosarcoma B), RAS (OMIM: 602209) RET (OMIM: 16476) and NTRK1/3 (OMIM: 191315) genes that promote the activation of mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) signaling pathways [9].

Importantly, there is a profound correlation between oncogenic genotype and histopathological phenotype in thyroid cancer, i.e., mutations in genes such as BRAF, PAX8 (OMIM: 167415) and PPARG (OMIM: 601487) are frequent in FTC, whereas mutations in RAS are common in both FTC and follicular variant of papillary carcinoma (fvPTC). On the other hand, global scientific studies on genomic variants, gene expression, miRNA profiles and aberrant methylation have highlighted that the most common alterations in both types of cancer include mutations in BRAF and RAS, in addition to RET-PTC gene fusions, which shows their importance in the oncogenesis of these tumors [10].

Another aspect to highlight is that recent studies have revealed the importance of single nucleotide genetic variants and other genetic changes that in some way can serve as biomarkers for both diagnosis and prognosis. This is of significance as it provides us with guidelines for personalized therapies by inhibiting specific molecular pathways that are associated with such mutations [11].

Also, the role of IncRNAs (OMIM: 617434; non-coding RNAs) in the regulation of tumor progression, and the use of technologies such as radio genomics, collaborate in the prediction of genetic mutations by imaging [12]. All these advances show a high expectation in the area of strategies for the precise treatment and identification of patients at higher risk of recurrence and metastasis.

4. RET gene

RET (OMIM: 164761) mutations influence multiple endocrine neoplasia and papillary thyroid carcinoma. Its mutations are associated with proliferation, invasion and migration of tumors. The RET gene (REarranged during Transfection) encodes a transmembrane receptor tyrosine kinase with proto-oncogene properties [13]. Currently, thyroid cancer represents 3.4% of the most common malignant endocrine neoplasia, representing 90% that includes papillary thyroid carcinoma [14].

Thyroid cancer is caused by dysregulation of the signaling pathways of mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3 kinase. When there is an inactivation of the tyrosine kinase receptor, it causes a cascade of intracellular signaling specifically of the MAPK, performing a rearrangement of the RET [15].

Several studies have shown that germline mutations of the proto-oncogene are associated with inherited cancer syndromes predominantly in endocrine neoplasia and PTC. It has also been shown that a single mutation of the RET is enough to cause changes in the germ line, however secondary events are required to induce thyroid cancer [16].

There are different factors that influence the induction of cancer, as mentioned, the rearrangement of the RET gene has relevant induction in this pathology, in this way, there are several factors including: exposure to radiation, age and the histological variant of the papillary tumor [16].

Medullary thyroid carcinoma (TMC) derives from mutations in the RET gene in the genetic codons M918 in exon 16 or in the same congener as in C364 in exon 11, due to the high rates of oncogenic formation, they provide a poor prognosis at the time of their hereditary diagnosis or sporadic (somatic), as seen in the figure 1 [17].

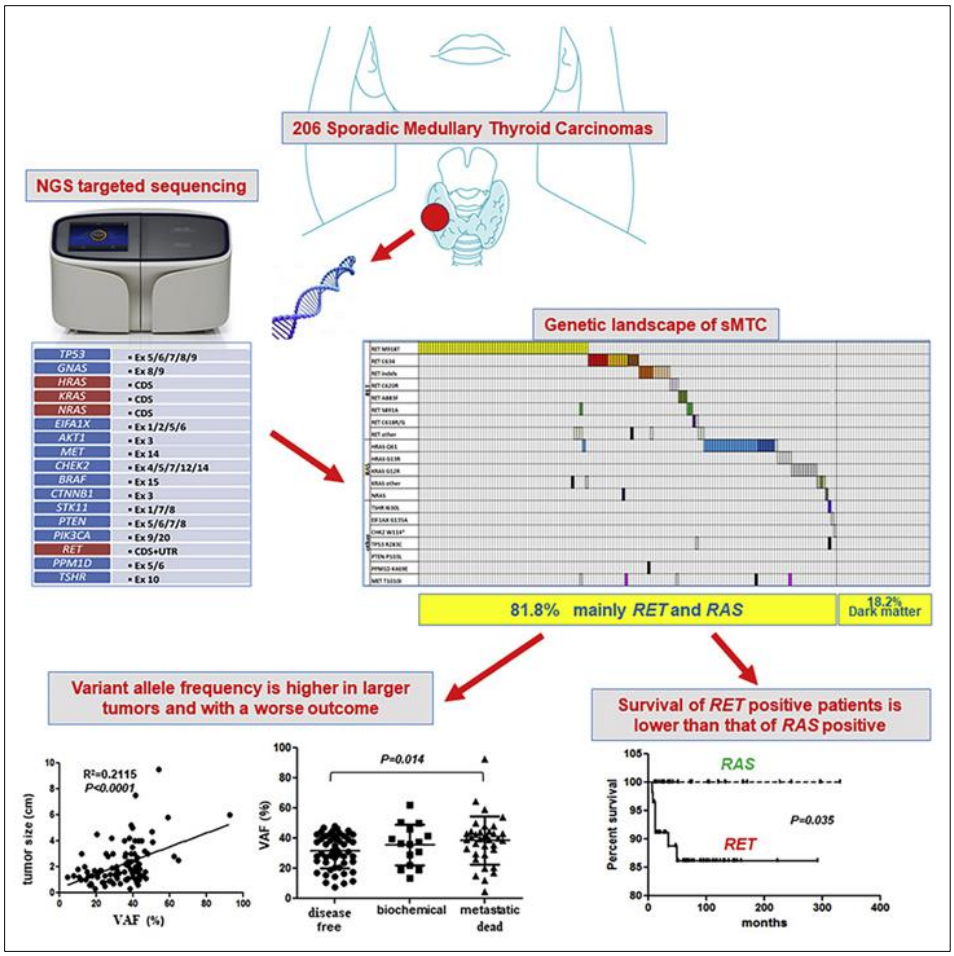

Figure 1 Genetic Landscape of Somatic Mutations in a Large Cohort of Sporadic Medullary Thyroid Carcinomas Studied by Next-Generation Targeted Sequencing [17]

5. BRAF gene

The BRAF gene (OMIM: 164757) is a member of the RAF family of serine/threonine protein kinases, which play a major role in cell proliferation, differentiation, and programmed cell death. Raf kinase type B is a cytoplasmic protein kinase, a major subtype of the Raf kinase, which triggers tumorigenesis by activating the MAPK pathway. Because RAF proteins activate the mitogen-activated protein kinase pathway, inappropriate activation of the mitogen activated protein kinase pathway following a BRAF mutation may result in abnormal proliferation and differentiation [18].

Mutations in a V600E substitution in BRAF and consequent constitutive activation occur in about 45% of PTCs in adults. Apart from the V600E mutation, foreign thyroid tumors with mutations in locations 599 and 601 have been reported, which also result in constitutive activation of the BRAF kinase [19].

The BRAF V600E mutation is related to the presence of extrathyroidal extension (TEE) and cervical lymph node metastasis (CLNM) in patients with PTC, suggesting invasion [20].

Risk Factors and Links Related to the BRAF V600E Mutation in Patients with PTC age (≥45 years), sex (male), multiple factors, non-metastatic malignant tumor, vascular invasion, endometriosis, and advanced TNM stage (stages III and IV) [18].

Most PTC are safely treated with surgical removal alone or, for high-risk cases, followed by radioactive iodine (RAI) treatment. The particular use of RAI is supported by the intrinsic ability of thyroid follicular cells to take up iodine (necessary for the physiological synthesis of thyroid hormones) by the sodium-iodine importing transporter (NIS) [21].

6. Other related genes

PAX8-PPARy (OMIM: 167415) PAX8 is a transcription factor important for organogenesis and development of the thyroid gland, urogenital tract, placenta and inner ear. This protein is practically expressed in follicular and papillary thyroid carcinomas in most of the findings [22].

This protein is practically expressed in CFT and PTC in most of the findings. The gene plays an extremely important cellular function for thyrocyte cell differentiation, as well as expression of thyroid genes such as modulation of thyroglobulin, thyroid peroxidase and sodium iodide symporter channel and a terminal differentiatior of TSH. Thus, the gene coding error leads to disastrous events, one of which is thyroid cancer by blocking or highly activating its activity [23].

The PPARy they are nuclear receptors with a function in the expression of target genes after binding to ligands. Where the binding with PAX8 derives from a chromosomal alteration and where this translocation is found in FTC and PTC and benign follicular adenomas [24]. This created binding PPFP has an erroneous function where it acts as an inhibitor of PPARy and represses PAX8 genes.

Given that PPARγ is expressed at very low levels in the normal thyroid, an overexpression of this same gene in the thyroid detected by an analysis, can generate evidence that the PPFP is present in the thyroid [23]. The activity of PPFP in PAX8 could generate a mechanism for the creation of tumorigenesis. The promoter driving PAX8 modulates the expression of PPFP, being likewise that an alteration of PPFP would mark an erroneous state of differentiation in thyroid tumors [25]

7. TERT promotor

The importance of TERT (OMIM:187270) is that it is not activated after cell differentiation has finished, unless it has stem cell properties, so if it does it would be by mutation excluding the primary cause [26]. The TERT mutation brings the activation of BRAF V600E genes so that instead of giving rise to cancer, it promotes it [27].

Studies have shown that they assist tumorigenesis by interaction with other genetic factors such as nuclear factor kB, the Wnt pathway, FOXO3a or MYC and since their reactivation occurs through mutation of the promoter in the C228T and C250T region or gene amplification [26].

A very important gene at this stage for the reason that it has been detected in more than 90% of cancers and not only of the thyroid, opening a guideline for its observation and possible treatment with target to these target cells. As if that were not enough, there are also biological parameters in thyroid cancer and it has been shown that there is an association with mutations in the TERT promoter and the advanced age of the patients and with male sex [27]. It cannot be silenced at an early stage because it causes serious adverse conditions such as bone marrow failure and cardiovascular damage [26].

8. RAS

The RAS gene has been taken into account as the second exponential marker for thyroid neoplasms. The gene has known isoforms such as NRAS (OMIM:164790), HRAS (OMIM:190020) and KRAS (OMIM: 190070), in general it is involved in signal transduction of tyrosine kinase and G protein-coupled receptors, where it affects MAPK and PI3-AKT signaling pathways that control differentiation, proliferation and survival at the cellular level [28].

Its regulated condition in turn is controlled by hydrolysis by GTP giving the inactivated RAS bound to GDP subsequently its mutant condition is related to oncogenic production by GTP predilection or inhibition of autocatalytic function of GTP-ase codon 12,13 and 61 giving its activation by MAPK and PI3-AKT signaling pathways [28].

However, the same error can be produced by gene amplification and develop human neoplasia. Although all three are fundamental and have oncogenic properties, NRAS is more associated with a major cause of thyroid cancer [29].

The generation of late genetic events in tumors by positive RAS gives opening to oncogenic capacities, in which a mutation of this gene promotes molecular alterations that can cause the disease by error in its fundamental activities, overexpressing or inhibiting itself.

Since its isoforms are dependent on the site where they are generated and develop the type of cancer for its ability to be in a large number of cancers around the body, studies show that NRAS gene mutations are 6.2% followed by HRAS 3.9% and KRAS 2.0%. The RAS gene is found in 40-50% of follicular carcinomas and 20-40% in follicular adenomas and with a high incidence in MTC [29].

9. Diagnosis

There are international stratification systems based on ultrasound with the aim of reducing unnecessary biopsies. Less invasive and lower-risk alternatives, such as active surveillance, have been explored. It is important to mention that there are microcarcinomas or asymptomatic thyroid cancer that are detected during physical examination or incidentally in diagnostic imaging studies [30].

Normally the diagnosis and treatment involves the exposure of radioactive iodine, since iodine is essential for the synthesis of thyroid hormones, normally there is a co-transporter NIS that carries out the process of organizing iodine.

This carrier is of utmost importance for the diagnosis of thyroid cancer, since it can be used immunohistochemistry with anti-NIS antibodies, lower NIS can be detected in neoplastic thyroid tissues, in addition to its detection it is important to know its location in the cell membrane to know if it is fully functional or cancer can be detected through it [31].

A successful example for diagnosis, molecular mutations are used, which are tests in which more than 400 genes are detected to individualize therapeutic management. In thyroid cancer, altered parafollicular cells tell us about one of the first neoplastic manifestations in individuals [32].

With greater ease for detection, we can detect it through palpation of a non-painful isolated thyroid nodule, or by growth of a cervical ganglion. Ultrasound and fine needle aspiration cytology can confirm the diagnosis [33].

In Mexico, the diagnosis is also based on the detection of serum levels of calcitonin > 10pg/mL and of the carcinoembryonic antigen. Fortunately, there is RET molecular testing at the Mexican social security institute, which consists of a multidisciplinary research team focused on the detection of the RET Gene in relation to thyroid cancer [32].

An additional consideration in diagnosis and treatment planning is the identification of potential that may derive from an altered thyroid nodule since the treatment depends on the patient's symptoms [34].

Knowing the state of thyroid function is only useful to rule out that the nodule is functioning, the same for the evaluation of the medical history, since normally this cancer is asymptomatic and is often confused with endocrinological diseases due to the detection of some failure in thyroid hormones [35].

That is why today the definitive diagnosis is made by minimally invasive techniques, specifically ultrasound with puncture aspiration with fine needle for cytological study, the advantage is that it allows a preoperative assessment of thyroid lesions [36].

10. Treatment

The treatment of thyroid cancer has advanced considerably in recent years thanks to a better understanding of the molecular genetics underlying the disease, as we have seen in this review article. New targeted therapies, drugs against specific genetic mutations and emerging immunotherapies offer patients more personalized options.

Targeted therapies have transformed the approach to thyroid cancer treatment, especially in advanced stages. Multi-tyrosine kinase inhibitors (multi-TKIs) are at the forefront of these treatments. Multi-TKIs, such as sorafenib and lenvatinib, work by blocking multiple signaling pathways involved in tumor growth and proliferation. By inhibiting these pathways, multi-TKIs can slow cancer progression and potentially reduce tumor size [37]. The only drawback with this form of treatment is the side effects associated with it, such as fatigue, hypertension and skin reactions, so careful monitoring is essential.

Another option is BRAF and RET inhibitors. For example, BRAF V600E and RET mutations are common in the most aggressive types of thyroid cancer, such as ATC and MTC. Drugs such as dabrafenib and trametinib, which target BRAF mutations, have shown promising results, particularly in patients whose tumors harbor the BRAF V600E mutation.

These drugs block the BRAF protein, which is involved in the MAPK/ERK signaling pathway that promotes cancer cell growth [37].

Similarly, RET-specific inhibitors, such as pralsetinib and selpercatinib, are used in patients with RET mutations. These inhibitors have demonstrated efficacy in reducing tumor size and are approved for use in patients with RET-disrupted thyroid cancers. The specificity of these drugs helps minimize the impact on healthy cells, resulting in fewer side effects compared to non-specific therapies [38].

Finally, immunotherapy represents a promising area in cancer treatment, although it remains less common in thyroid cancer due to the low number of mutations in these tumors. Drugs such as pembrolizumab, an anti-PD-1 (or programmed death protein 1) therapy, a protein found on the surface of immune cells, mainly T cells, that plays a key role in regulating the immune system, are currently being investigated for their potential in the treatment of advanced cases of thyroid cancer, particularly in patients who have not responded to the treatments mentioned above [37]. Immunotherapies act by stimulating the immune system to stimulate the immune response of thyroid cells.

Immunotherapies work by stimulating the body's immune system to recognise and attack cancer cells, which are often adept at evading immune detection. Despite the paucity of data on the efficacy of immunotherapy in thyroid cancer, initial studies are promising and ongoing trials are exploring how best to use these drugs, although more research is needed in this area.

11. Conclusion

Multiple investigations of the *RET* and *BRAF* genes have yielded molecular mechanisms that drive thyroid cancer, specifically papillary carcinoma. Apart from being one of the main factors for tumor development, there is also a record of therapeutic objective. Such as the inhibitors of the *RET* and *BRAF* genes, demonstrating efficacy in the control of tumor growth. Radiogenomics has enhanced the diagnostic capacity and therapeutic bases, giving rise to combinations of molecular diagnosis and innovative therapies, which drives more research on the genetic panorama of thyroid cancer to improve clinical results and find prevention strategies.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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