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What are Telling us Genetics, Epigenetics and Environment of an Individual with Thyroid Cancer?

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Abstract

Thyroid cancer is the most common endocrine cancer. There are growing evidences about the crucial crosstalk between individual genetic background, epigenetic factors as well as specific environmental conditions in the onset and predisposition to the tumor. Although most of studies are focused on genetics, and our current knowledge of the aberrant epigenetic modifications in thyroid gland is far from complete, the role of epigenetics in the interplay genetics-environment is raising.

In this review, we describe prevailing advances and update our understanding on how genetics, epigenetics and the environment regulate the processes involved in thyroid cancer.

Keywords: Thyroid cancer; Genetics; Epigenetics; Environment

Abbreviations

FNMTC: Familial forms of Non-Medullary Thyroid Cancer; PTC: Papillary Thyroid Cancer; FTC: Follicular Thyroid Cancer; ATC: Anaplastic Thyroid Cancer; GWAS: Genome-Wide Association Studies; GWLA: Genome-Wide Linkage Analysis; MEN2: Multiple Endocrine Neoplasia type 2; *RET:* Rearranged During Transfection Protooncogene; MAPK: Mitogen-Activated Protein Kinases; PI3K-AKT: Phosphatidilinositol 3 Kinase-Serine/Threonine-Specific Protein Kinase; DNA: Deoxyribonucleic Acid; *BRAF:* Serine/Threonine-Protein Kinase B-Raf Oncogene; *RAS:* RAS type GTPase Family Gene; *RET/PTC:* RET/PTC Rearrangement in Thyroid Tumors; *PAX8/PPARy:* Paired Box8/ Peroxisome Proliferator-Activated Receptor Gamma; TERT: Telomerase Reverse Transcriptase; ncRNAs: non-coding RNAs

Introduction

Thyroid cancer is the most common endocrine cancer, with an increasing overall incidence in recent decades. It is divided into several types and histological subtypes according to the cells from which the tumor derives, with different characteristics and prognoses. Thyroid cancer originating from follicular cells is called Non-Medullary Thyroid Cancer (NMTC) and is responsible for approximately 95% of all the cases. NMTC is classified into four groups that include: 1) Papillary Thyroid Cancer (PTC), with more than 85% of cases; 2) follicular thyroid cancer (FTC; 10% of total cases) and 3) anaplastic cancer and 4) undifferentiated thyroid cancer, being groups 3 and 4 the remaining 5%. Familial forms of Non-Medullary Thyroid Cancer (FNMTC) are very rare (3-9% of all cases of thyroid cancer). Only 5% of familial forms are included within specific syndromes, such as Cowden (OMIM # 158350), Gardner (OMIM # 175100), Werner (OMIM # 277700), Li- Fraumeni (OMIM # 151623), McCune-Albright (OMIM # 174800), Carney complex (OMIM # 160980) or DICER 1 (OMIM # 138800) syndromes [1,2]. On the other hand, only 5% of cases of thyroid cancer are derived from parafollicular cells and this type is called Medullary Thyroid Cancer (MTC) [3,4]. About 75% of all MTCs are believed to be sporadic (sMTC), whereas the remaining 25% correspond to inherited cancer syndromes known as Multiple Endocrine Neoplasia type 2 (MEN2). MEN2 includes 3 clinically differentiable types: MEN2A (OMIM#171400), MEN2B (OMIM#162300) and familial thyroid cancer (FMTC, OMIM#155240) [5,6].

The subjacent mechanisms of thyroid cancer etiology remain unsolved, although it is known that being woman, exposition to external radiation, living in iodine deficit regions or having a family history of thyroid cancer are risk factors [7]. Except under some circumstances, cancer cannot be explained by a single genetic mutation or influence of a special environment. Indeed, a specific environment facilitates that epigenetics and genetics lead to cancer development.

Molecular Genetics of Thyroid Cancer

Alterations at germline level

Around 10% of total cases of NMTC occurs during the first two decades of life with a more favorable prognostic than later forms [4]. NMTC is one of the most heritable forms, with an increased risk of 8-10 times for first-degree relatives of patients (around a 5% are familial forms and 95% are sporadic).

Regarding non-syndromic family forms, some GWAS or GWLA have led to the identification of some associated genes although not all have been validated in additional populations [1,2,8,9]. Nevertheless, the studies carried out to date are scarce and inconclusive, so new approaches are needed to identify loci associated with FNMTC.

More than 95% of MEN2 cases have germline mutations in the *RET* proto-oncogene, which lead to a gain of function of the receptor. In the specific case of MEN2A, 98% of patients have mutations

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grouped in a hot-spot that corresponds to five cysteine codons present in the extracellular domain of the protein [10,11]. Around 87% of MEN2A mutations affect to codon 634, where p.Cys634Arg has been detected in more than 50% of cases [11]. In Spain, there is a higher prevalence of the p.Cys634Tyr mutation, which suggests a founder effect [12-14]. Biochemical studies on mutated proteins in cysteine codons indicate that these mutations lead to a constitutive activation of the metabolic pathways of *RET* signaling [15]. Although more than 100 *RET* point mutations, duplications, insertions, deletions, and fusions have been found in patients with MEN2A, only two *RET* mutations (918 and 883) have been linked to MEN2B [16]. Regarding FMTC, two missense mutations (amino acids E768 or V804) [17,18] that change glutamate 768 and valine 804 (located in the tyrosine kinase domain) for an aspartate and a leucine respectively, have been described. Both are gain of function mutations and result in aberrant signaling mediated by RET [19].

The etiology of sMTC remains elusive, although the major genetic events seem to reside in several different *RET* loci, but knowledge of pathways related with non-*RET*-mutated sMTC remains unclear [20]. MTC somatic mutations in *RET* (mainly at codon 918) [6,11,18,21] and loss of heterozygosity at various loci corresponding to deletions of tumor suppressor genes, have been described in a variable number of sMTC [22]. A germline *RET* S836S variant has been highly correlated with somatic RET^{M918T} mutation in exon 16, which it is associated with aggressive sMTC [23-25]. In addition, at least two sMTC loci, linked to S836S (c.2508C>T, rs1800862)-IVS1-126G>T (c.74-126G>T, rs2565206), or to G691S (c.2071G>A, rs1799939)-S904S (c.2712C>G, rs1800863) has been related with the disease [26].

Concerning germinal mutations, point mutations of the *BRAF* and *RAS* genes and *RET/PTC* and *PAX8/PPARγ* chromosomal rearrangements are common mutations found in thyroid cancer patients [27]. In ATC, which accounts for most of deaths related to thyroid cancer, the accumulation of several oncogenic alterations is equivalent to an increased level of dedifferentiation and aggressiveness [28]. Although the role of *P53* in thyroid carcinogenesis is well established, the implication of the remaining *P53* family members in thyroid cancer needs to be fully clarified. In either way, increasing evidences indicates that *P53* family members favor the development of multiple thyroid cancer variants and they are being used as future therapeutical targets [29]. Furthermore, the appearance of *BRAF* mutation (p.Val600Glu; commonly known as V600E), or other genetic markers (e.g. *RAS* mutations) together with *TERT* promoter mutations have been linked to more aggressive and recurrent thyroid tumor and patient mortality, especially in PTC cases. All of this makes *TERT* with promoter mutations in a new oncogene in thyroid cancer and those mutations as promising in clinical management of thyroid cancer [30].

Alterations at somatic level

The genetic basis for most thyroid tumors have been unraveled through DNA sequencing studies. Regarding somatic mutations, most of thyroid tumors harbor mutations leading to the activation of the MAPK and PI3K-AKT signaling pathways, which play a critical role in the regulation of cellular proliferation [31-33]. Additionally, somatic *RET* mutations are detected in 40-50% of sporadic MTCs and correlates with a worse outcome of these patients. Furthermore, the presence of a somatic *RET* mutation is associated with the presence of lymph node metastases at diagnosis, that is a known bad prognostic factor for the definitive cure of these patients [34].

Epigenetics of Thyroid Cancer

It seems that only genetic approaches do not fully explain the onset of thyroid cancer. Epigenetic alterations are heritable changes that influence on gene expression without modifying the DNA sequence [35]. They include changes on DNA methylation, histone modifications, Polycomb Repression (PCR), ATP dependent chromatin remodeling, and non-coding RNA (ncRNAs). These factors, together with exogenous environmental changes and developmental stages, could finally explain population endocrine diversity and thyroid cancer in particular [36,37].

Concerning the epigenetics alterations in thyroid cancer, a limited number of studies have been performed to discern the role beyond the genetic changes. Cells of endocrine organs, such as thyroid, are susceptible to epigenetic alterations, leading to tumor development [38]. Thus, some authors reinforce the consensus opinion that epigenetics may be a pivotal mechanism of interaction between genes and the environment [37,39-43].

The growing interest on the epigenetic influence on thyroid cancer, has risen the number of studies to evaluate processes such as the DNA methylation, histone modifications and ncRNAs on this tumor [44]. DNA methylation and miRNAs present the most promising features for tumor prognosis and thus, new therapies are focused on them for the most aggressive forms. Regarding global DNA methylation levels, it seems that overall DNA methylation profile is histologically dependent. The differentiated thyroid tumors are preferentially hypermethylated *versus* healthy samples, while the non-differentiated tumors are hypomethylated [44-46].

The 10-year survival rate of individuals with differentiated thyroid cancer is around 90% after using classical treatments, with patients presenting tumor recurrence or drug resistance. Zhang K et al have recently described new and promising approaches based on the interplay among genetic (*BRAF*/V600E) and epigenetic changes (gene methylation changes) in thyroid cancer [47].

Environmental Influence on Thyroid Cancer

The environmental factors play a very important role in determining human phenotype [48]. One of the classical agents affecting thyroid function is radiation. Different epidemiological studies on the survivors of the nuclear disasters in Japan and Chernobyl, support acute radiation exposure as a risk factor of thyroid cancer development [49,50]. Moreover, if the environment-epigenetic alteration-cancer hypothesis would be evidenced, then an early cancer diagnosis, personalized treatment and prevention to nuclear plant workers could be provided [51]. Some mutations found on thyroid tumors are chromosomal rearrangements, which present a strong association with exposure to ionizing radiation and then with DNA fragility, while point mutations probably originate through chemical mutagenesis [49,52]. It is also important to identify specific patterns of epigenetic alterations after radiation exposure, to predict carcinogens, and to clarify the association among chronic exposure to low concentration of radiation and thyroid cancer

[53]. Furthermore, a potential role of dietary iodine excess in the occurrence of *BRAF* point mutations has also been described [27]. It is also worth of mention the role that plays the vitamin D on the onset of thyroid cancer, where mutations in the main genes involved in its metabolic transport have been linked to this pathology [54]. Gravity also impacts on thyroid cells, inducing severe morphological and functional changes in thyroid gland which is influenced by the pituitary gland [55]. Flame retardant chemicals and excessive use of nitrogenous fertilizers have been also associated with thyroid cancer [56,57]. Other factors such as tobacco smoking, eating habits, living in a volcanic area, xenobiotics and viruses are also been related with the onset of this cancer [58,59].

Conclusion

Based on the thyroid cancer incidence in the last two decades, which has risen worldwide more than any other cancer, helpful diagnostic biomarkers are urgently needed.

Apart from genetic aberration, epigenetic changes that are potentially reversible, are promising therapeutic drug targets. Studies to establish if epigenetic changes induced by today's lifestyles or environmental influences could be inherited would facilitate the application of our current knowledge about genetics, epigenetics and the environmental influence on the prevention and treatment of thyroid cancer. In detail, research is applying high throughput technologies to uncover global epigenetic changes defining the interplay among genetics and environment to produce biologically relevant data and conclusions.

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