

Special Article - Thyroid Gland

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: Phosphatidylinositol 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/PPAR γ* : 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 FNMTTC.

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

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/PPAR γ* 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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References

- Guilmette J, Nose V. Hereditary and familial thyroid tumours. *Histopathology*. 2018; 72: 70-81.
- Peiling Yang S, Ngeow J. Familial non-medullary thyroid cancer: unraveling the genetic maze. *Endocrine-related cancer*. 2016; 23: 577-595.
- Vriens MR, Suh I, Moses W, Kebebew E. Clinical features and genetic predisposition to hereditary nonmedullary thyroid cancer. *Thyroid: official journal of the American Thyroid Association*. 2009; 19: 1343-1349.
- Xing M. Molecular pathogenesis and mechanisms of thyroid cancer. *Nature reviews Cancer*. 2013; 13: 184-199.
- Charis Eng, Jessica M. Multiple Endocrine Neoplasia Type 2. 2015.
- Eng C. RET proto-oncogene in the development of human cancer. *Journal of clinical oncology*. 1999; 17: 380-393.
- Tufano RP, Noureldine SI, Angelos P. Incidental thyroid nodules and thyroid cancer: considerations before determining management. *JAMA otolaryngology-- head & neck surgery*. 2015; 141: 566-572.
- Ruiz-Ferrer M, Fernandez RM, Navarro E, Antinolo G, Borrego S. G534E Variant in *HABP2* and Nonmedullary Thyroid Cancer. *Thyroid: official journal of the American Thyroid Association*. 2016; 26: 987-988.
- Ye F, Gao H, Xiao L, Zuo Z, Liu Y, Zhao Q, et al. Whole exome and target sequencing identifies *MAP2K5* as novel susceptibility gene for familial non-medullary thyroid carcinoma. *International journal of cancer*. 2019; 144: 1321-1330.
- Accardo G, Conzo G, Esposito D, Gambardella C, Mazzella M, Castaldo F, et al. Genetics of medullary thyroid cancer: An overview. *International journal of surgery (London, England)*. 2017; 41: S2-S6.
- Eng C, Clayton D, Schuffenecker I, Lenoir G, Cote G, Gagel RF, et al. The relationship between specific RET proto-oncogene mutations and disease phenotype in multiple endocrine neoplasia type 2. *International RET mutation consortium analysis*. *Jama*. 1996; 276: 1575-1579.
- Fernandez RM, Navarro E, Antinolo G, Ruiz-Ferrer M, Borrego S. Evaluation of the role of RET polymorphisms/haplotypes as modifier loci for MEN 2, and analysis of the correlation with the type of RET mutation in a series of Spanish patients. *International journal of molecular medicine*. 2006; 17: 575-581.
- Sanchez B, Antinolo G, Navarro E, Japon MA, Conde AF, Astorga R, et al. Cys 634 mutations in the RET proto-oncogene in Spanish families affected by MEN 2A. *Human Mutation*. 1998; 1: 72-73.
- Sanchez B, Robledo M, Biarnes J, Saez ME, Volpini V, Benitez J, et al. High prevalence of the C634Y mutation in the RET proto-oncogene in MEN 2A families in Spain. *Journal of medical genetics*. 1999; 36: 68-70.
- Hansford JR, Mulligan LM. Multiple endocrine neoplasia type 2 and RET: from neoplasia to neurogenesis. *Journal of medical genetics*. 2000; 37: 817-827.
- Wells SA, Pacini F, Robinson BG, Santoro M. Multiple endocrine neoplasia type 2 and familial medullary thyroid carcinoma: an update. *The Journal of clinical endocrinology and metabolism*. 2013; 98: 3149-3164.
- Bolino A, Schuffenecker I, Luo Y, Seri M, Silengo M, Tocco T, et al. RET mutations in exons 13 and 14 of FMTC patients. *Oncogene*. 1995; 10: 2415-2419.
- Eng C, Mulligan LM, Smith DP, Healey CS, Frilling A, Raue F, et al. Low frequency of germline mutations in the RET proto-oncogene in patients with apparently sporadic medullary thyroid carcinoma. *Clinical endocrinology*. 1995; 43: 123-127.
- Pasini A, Geneste O, Legrand P, Schlumberger M, Rossel M, Fournier L, et al. Oncogenic activation of RET by two distinct FMTC mutations affecting the tyrosine kinase domain. *Oncogene*. 1997; 15: 393-402.
- Maliszewska A, Leandro-Garcia LJ, Castelblanco E, Macia A, de Cubas A, Gomez-Lopez G, et al. Differential gene expression of medullary thyroid carcinoma reveals specific markers associated with genetic conditions. *The American journal of pathology*. 2013; 182: 350-362.
- Hofstra RM, Landsvater RM, Ceccherini I, Stulp RP, Stelwagen T, Luo Y, et al. A mutation in the RET proto-oncogene associated with multiple endocrine neoplasia type 2B and sporadic medullary thyroid carcinoma. *Nature*. 1994; 367: 375-376.
- Mulligan LM, Gardner E, Smith BA, Mathew CG, Ponder BA. Genetic events in tumour initiation and progression in multiple endocrine neoplasia type 2. *Genes, chromosomes & cancer*. 1993; 6: 166-177.
- Drost M, Putzer BM. Mechanisms of Disease: cancer targeting and the impact of oncogenic RET for medullary thyroid carcinoma therapy. *Nature clinical practice Oncology*. 2006; 3: 564-574.
- Kodama Y, Asai N, Kawai K, Jijiwa M, Murakumo Y, Ichihara M, et al. The RET proto-oncogene: a molecular therapeutic target in thyroid cancer. *Cancer science*. 2005; 96: 143-148.
- Ruiz A, Antinolo G, Fernandez RM, Eng C, Marcos I, Borrego S. Germline sequence variant S836S in the RET proto-oncogene is associated with low level predisposition to sporadic medullary thyroid carcinoma in the Spanish population. *Clinical endocrinology*. 2001; 55: 399-402.
- Fernandez RM, Pecina A, Antinolo G, Navarro E, Borrego S. Analysis of RET polymorphisms and haplotypes in the context of sporadic medullary thyroid carcinoma. *Thyroid: official journal of the American Thyroid Association*. 2006; 16: 411-417.

27. Nikiforov YE, Nikiforova MN. Molecular genetics and diagnosis of thyroid cancer. *Nature reviews Endocrinology*. 2011; 7: 569-580.
28. Molinaro E, Romei C, Biagini A, Sabini E, Agate L, Mazzeo S, et al. Anaplastic thyroid carcinoma: from clinicopathology to genetics and advanced therapies. *Nature reviews Endocrinology*. 2017; 13: 644-660.
29. Manzella L, Stella S, Pennisi MS, Tirro E, Massimino M, Romano C, et al. New Insights in Thyroid Cancer and p53 Family Proteins. *International journal of molecular sciences*. 2017; 18.
30. Liu R, Xing M. TERT promoter mutations in thyroid cancer. *Endocrine-related cancer*. 2016; 23: 143-155.
31. Cabanillas ME, McFadden DG, Durante C. Thyroid cancer. *Lancet*. 2016; 388: 2783-2795.
32. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011; 144: 646-674.
33. Rebasmlal yi UM, Rebasmlal yi UA. Molecular genetics of thyroid cancer. *Genetics research*. 2016; 98: e7.
34. Elisei R, Cosci B, Romei C, Bottici V, Renzini G, Molinaro E, et al. Prognostic significance of somatic RET oncogene mutations in sporadic medullary thyroid cancer: a 10-year follow-up study. *The Journal of clinical endocrinology and metabolism*. 2008; 93: 682-687.
35. Deans C, Maggert KA. What do you mean, "epigenetic"? *Genetics*. 2015; 199: 887-896.
36. Luzón-Toro B FR, Martos-Martínez JM, Antiñolo G, Borrego S. Identification of new long non-coding RNAs associated with medullary thyroid cancer. *Oral Health Care*. 2019; 4: 1-3.
37. Zhang X, Ho SM. Epigenetics meets endocrinology. *Journal of molecular endocrinology*. 2011; 46: R11-32.
38. Emes RD, Farrell WE. Make way for the 'next generation': application and prospects for genome-wide, epigenome-specific technologies in endocrine research. *Journal of molecular endocrinology*. 2012; 49: R19-27.
39. Cook JD, Davis BJ, Cai SL, Barrett JC, Conti CJ, Walker CL. Interaction between genetic susceptibility and early-life environmental exposure determines tumor-suppressor-gene penetrance. *Proceedings of the National Academy of Sciences of the United States of America*. 2005; 102: 8644-8649.
40. Garcia-Carpizo V, Ruiz-Llorente L, Fraga M, Aranda A. The growing role of gene methylation on endocrine function. *Journal of molecular endocrinology*. 2011; 47: R75-89.
41. Jaenisch R, Bird A. Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. *Nature genetics*. 2003; 33: 245-254.
42. Jirtle RL, Skinner MK. Environmental epigenomics and disease susceptibility. *Nature reviews Genetics*. 2007; 8: 253-262.
43. Tang WY, Ho SM. Epigenetic reprogramming and imprinting in origins of disease. *Reviews in endocrine & metabolic disorders*. 2007; 8:173-182.
44. Rodríguez-Rodero S, Delgado-Alvarez E, Diaz-Naya L, Martín Nieto A, Menendez Torre E. Epigenetic modulators of thyroid cancer. *Endocrinología, diabetes y nutrición*. 2017; 64: 44-56.
45. Bisarro Dos Reis M, Barros-Filho MC, Marchi FA, Beltrami CM, Kuasne H, Pinto CAL, et al. Prognostic Classifier Based on Genome-Wide DNA Methylation Profiling in Well-Differentiated Thyroid Tumors. *The Journal of clinical endocrinology and metabolism*. 2017; 102: 4089-4099.
46. Ceolin L, Goularte APP, Ferreira CV, Romitti M, Maia AL. Global DNA methylation profile in medullary thyroid cancer patients. *Experimental and molecular pathology*. 2018; 105: 110-114.
47. Zhang K, Li C, Liu J, Tang X, Li Z. DNA methylation alterations as therapeutic prospects in thyroid cancer. *Journal of endocrinological investigation*. 2019; 42: 363-370.
48. Feinberg AP. Phenotypic plasticity and the epigenetics of human disease. *Nature*. 2007; 447: 433-440.
49. Leeman-Neill RJ, Brenner AV, Little MP, Bogdanova TI, Hatch M, Zurnadzy LY, et al. RET/PTC and PAX8/PPARgamma chromosomal rearrangements in post-Chernobyl thyroid cancer and their association with iodine-131 radiation dose and other characteristics. *Cancer*. 2013; 119: 1792-1799.
50. Moysich KB, Menezes RJ, Michalek AM. Chernobyl-related ionising radiation exposure and cancer risk: an epidemiological review. *The Lancet Oncology*. 2002; 3: 269-279.
51. Vu-Phan D, Koenig RJ. Genetics and epigenetics of sporadic thyroid cancer. *Molecular and cellular endocrinology*. 2014; 386: 55-66.
52. Hamatani K, Eguchi H, Ito R, Mukai M, Takahashi K, Taga M, et al. RET/PTC rearrangements preferentially occurred in papillary thyroid cancer among atomic bomb survivors exposed to high radiation dose. *Cancer research*. 2008; 68: 7176-7182.
53. Barcellos-Hoff MH, Nguyen DH. Radiation carcinogenesis in context: how do irradiated tissues become tumors? *Health physics*. 2009; 97: 446-457.
54. Nettore IC, Albano L, Ungaro P, Colao A, Macchia PE. Sunshine vitamin and thyroid. *Reviews in endocrine & metabolic disorders*. 2017; 18: 347-354.
55. Albi E, Kruger M, Hemmersbach R, Lazzarini A, Cataldi S, Codini M, et al. Impact of Gravity on Thyroid Cells. *International journal of molecular sciences*. 2017; 18.
56. Ahmed M, Rauf M, Mukhtar Z, Saeed NA. Excessive use of nitrogenous fertilizers: an unawareness causing serious threats to environment and human health. *Environmental science and pollution research international*. 2017; 24: 26983-26987.
57. Hoffman K, Sosa JA, Stapleton HM. Do flame retardant chemicals increase the risk for thyroid dysregulation and cancer? *Current opinion in oncology*. 2017; 29: 7-13.
58. Maqbool F, Mostafalou S, Bahadar H, Abdollahi M. Review of endocrine disorders associated with environmental toxicants and possible involved mechanisms. *Life sciences*. 2016; 145: 265-273.
59. Marcello MA, Malandrino P, Almeida JF, Martins MB, Cunha LL, Bufalo NE, et al. The influence of the environment on the development of thyroid tumors: a new appraisal. *Endocrine-related cancer*. 2014; 21: 235-254.