ACTUALITIES IN GENETICS OF DIFFERENTIATED THYROID CANCER

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Abstract

Genetics of cancer is a hot topic, an excellent example of translational medicine. Risk stratification, selection of cases for surgery in Bethesda categories 3 & 4 FNAB are examples of the high impact of genetic evaluation in thyroid neoplasia.

Key words: Thyroid cancer, BRAF, TERT.

INTRODUCTION

Differentiated thyroid cancer (DTC) is the most frequent endocrine neoplasia and its incidence is rising, likely due to increased ultrasound detection, particularly of micropapillary thyroid carcinomas (MPTC) (1). A lot of these cancers are clinically indolent and patients generally have a good prognosis, mostly due to the effectiveness of radioiodine therapy. However, at the opposite side of the spectrum of disease are patients with radioiodine resistant tumors who have an aggressive clinical course and sometimes die of the disease.

Current management of DTC is based on the concept of risk stratification which takes into account clinical and pathology data and provides tailored treatment solutions for each individual patient, balancing the risk of recurrence and the risk of cancer-related death with the risk of treatment-related morbidity (2).

Accumulating data on thyroid cancer genetics has provided an increasingly clear picture of the processes of cancer initiation and progression, suggesting that the molecular signature of the tumor might better reflect clinical behaviour and treatment outcomes (3), although this has not yet been included in the current risk assessment algorithms.

Genetic landscape of differentiated thyroid cancer

As we now understand it, cancer initiation

and progression occur through a step-wise accumulation of genetic and epigenetic alterations. The molecular alterations involve activating or inactivating point mutations, copy number variations or gene rearrangements in the genes responsible for cell differentiation, proliferation and apoptosis (4). These genetic alterations generally involve the MAPK (mitogen-activated protein kinase) and PI3-K (phosphoinositid 3 kinase) signalling pathways and lead to increased constitutive activation, either through activating mutations in the receptor tyrosine kinases (RTKs) or mutations in BRAF (B type Raf kinase) or RAS (rat sarcoma), or inactivating mutations in tumor suppressor genes (4, 5).

The initial event in tumorigenesis is generally an activating somatic mutation involving an effector in the MAPK pathway (5). Mutually exclusive driving mutations lead to specific histological subtypes of papillary thyroid cancer with distinct signalling and behaviour consequences (3). In the large scale study of well-differentiated papillary thyroid carcinomas performed as part of The Cancer Genome Atlas Project (3) two distinct molecular signatures were identified: “BRAF-like” and “RAS-like” PTC.

“BRAF V600E-like” mutations lead to intense constitutive activation of the MAPK pathway, associated with decreased expression of the genes involved in iodine metabolism, potentially leading to radioiodine resistance and a more poorly differentiated phenotype. Histologically, BRAFV600E mutation is associated with tall-cell and classical PTC (3).

“RAS-like” tumors have lower levels of activation of the MAPK pathway, associated with preserved expression of the genes involved in iodine metabolism. Histologically, “RAS-like” tumors tend to be highly differentiated, usually associated with follicular variant PTC (3).

A similar genetic background was identified in micropapillary thyroid carcinomas, suggesting that

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they have the potential to evolve toward large PTC (6). In the late stages of tumorigenesis the accumulation of additional genetic alterations (Telomerase Reverse Transcriptase (TERT) promoter mutations, PIK3CA, AKT1 and EIF1AX mutations) contributes to further disruption of cell adhesion, cell cycle and apoptosis processes. This generally leads to a more poorly differentiated phenotype, an aggressive clinical course and poor outcomes (7, 8). Poorly differentiated thyroid cancers (PDTC) and anaplastic thyroid cancers (ATC) are usually characterised by several different mutations that contribute to the simultaneous dysregulation of multiple pathways (5). ATCs generally have a higher mutation burden compared to PDTC (9) and typically harbour mutations in tumor suppressors (TP53, CDKN2A mutations) (8). Defining the genetic landscape of ATC has significant therapeutic implications as it has led to the development of biomarker driven targeted therapies which are being tested in clinical and preclinical trials (10).

Clinical outcomes – molecular prognostic markers

In the light of the accumulating knowledge on the genetic determinants of differentiated thyroid cancer, specific somatic mutations have been investigated for their value as prognostic biomarkers for DTC.

BRAF V600E mutation was associated in some studies with a more aggressive clinical course and a higher risk of recurrence (11), but this observation was not always noted. Moreover, BRAF V600E is generally considered to be highly prevalent in DTC, although a recent study revealed a low prevalence in a Greek population (12), and by itself it has a limited prognostic value. Interestingly, obesity is associated with a greater risk of BRAF V600E mutated PTC, although BRAF V600E mutation was not significantly associated with features of adverse prognosis in these patients (13).

TERT (Telomerase Reverse Transcriptase) promoter mutation is frequently identified in poorly differentiated and anaplastic carcinomas (51-61%) (7-9) compared to the 9.4% prevalence in the well differentiated papillary carcinomas of the TCGA (3). Increased TERT expression occurs in cancer due to several genetic anomalies: point mutations in the TERT promoter (C228T, C250T), increased number of copies or aberrant methylation of certain regions of the TERT promoter (14, 15). In differentiated thyroid cancer, these mutations are frequently associated with aggressive clinical and pathological features (older age, tumor

size, extra-thyroidal extension, lymph node invasion, vascular invasion, metastatic disease) (3, 16) and are less prevalent in micropapillary thyroid carcinomas (6). In multiple prospective studies TERT promoter mutations were associated with advanced age, features of tumor aggression (advanced stage, extra-thyroidal extension, metastatic disease), persistent or recurrent disease and increased disease-specific mortality (16). Even in PTC patients without pathological features of aggressive and metastatic disease, TERT promoter mutations can select the subgroup of patients with a poorer prognosis (17).

At a molecular level, BRAF V600E and TERT promoter mutations were shown to work synergistically to increase TERT expression (18). From a clinical perspective, co-existent BRAF V600E and TERT promoter mutations are particularly associated with high-risk clinical and pathological features (lymph node invasion, extra-thyroidal invasion, metastatic disease) and a higher disease-specific mortality compared to either mutation alone, suggesting a strong value as prognostic markers for this oncogene duet (19, 20).

Perspectives

There is increasing more evidence that a wide integrative molecular classification of thyroid cancer, including gene mutations/ fusions, gene expression and methylation, better reflects thyroid cancer clinical behaviour and prognosis.

Genetic profiling of thyroid cancer is expected to reduce un-necessary treatment of indolent cases and identify patients with aggressive forms that require careful management. This sets the stage for precision oncology, in which novel therapies are developed, targeting specific molecular alterations implicated in tumorigenesis. This in turn will improve the prognosis and quality of life of patients with advanced differentiated thyroid cancer, poorly differentiated thyroid cancer and anaplastic cancer.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Wiltshire JJ, Drake TM, Uttley L, Balasubramanian SP. Systematic Review of Trends in the Incidence Rates of Thyroid Cancer. *Thyroid*. 2016; 26:1541-1552.
2. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM,

- Wartofsky L. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 2016; 26:1-133.
3. Cancer Genome Atlas Research N. Integrated genomic characterization of papillary thyroid carcinoma. *Cell*. 2014; 159:676-690.
4. Tirro E, Martorana F, Romano C, Vitale SR, Motta G, Di Gregorio S, Massimino M, Pennisi MS, Stella S, Puma A, Giani F, Russo M, Manzella L, Vigneri P. Molecular Alterations in Thyroid Cancer: From Bench to Clinical Practice. *Genes (Basel)*. 2019; 10.
5. Acquaviva G, Visani M, Repaci A, Rhoden KJ, de Biase D, Pession A, Giovanni T. Molecular pathology of thyroid tumours of follicular cells: a review of genetic alterations and their clinicopathological relevance. *Histopathology*. 2018; 72:6-31.
6. Song YS, Kang BH, Lee S, Yoo SK, Choi YS, Park J, Park DY, Lee KE, Seo JS, Park YJ. Genomic and Transcriptomic Characteristics According to Size of Papillary Thyroid Microcarcinoma. *Cancers*. 2020; 12.
7. Pozdeyev N, Gay LM, Sokol ES, Hartmaier R, Deaver KE, Davis S, French JD, Borre PV, LaBarbera DV, Tan AC, Schweppe RE, Fishbein L, Ross JS, Haugen BR, Bowles DW. Genetic Analysis of 779 Advanced Differentiated and Anaplastic Thyroid Cancers. *Clin Cancer Res*. 2018; 24:3059-3068.
8. Yoo SK, Song YS, Lee EK, Hwang J, Kim HH, Jung G, Kim YA, Kim SJ, Cho SW, Won JK, Chung EJ, Shin JY, Lee KE, Kim JI, Park YJ, Seo JS. Integrative analysis of genomic and transcriptomic characteristics associated with progression of aggressive thyroid cancer. *Nat Commun*. 2019; 10:2764.
9. Landa I, Ibrahimipasic T, Boucai L, Sinha R, Knauf JA, Shah RH, Dogan S, Ricarte-Filho JC, Krishnamoorthy GP, Xu B, Schultz N, Berger MF, Sander C, Taylor BS, Ghossein R, Ganly I, Fagin JA. Genomic and transcriptomic hallmarks of poorly differentiated and anaplastic thyroid cancers. *J Clin Invest*. 2016; 126:1052-1066.
10. Pozdeyev N, Rose MM, Bowles DW, Schweppe RE. Molecular therapeutics for anaplastic thyroid cancer. *Seminars in cancer biology*. 2020; 61:23-29.
11. Huang Y, Qu S, Zhu G, Wang F, Liu R, Shen X, Viola D, Elisei R, Puxeddu E, Fugazzola L, Colombo C, Jarzab B, Czarniecka A, Lam AK, Mian C, Vianello F, Yip L, Riesco-Eizaguirre G, Santisteban P, O'Neill CJ, Sywak MS, Clifton-Bligh R, Bendlova B, Sykora V, Xing M. BRAF V600E Mutation-Assisted Risk Stratification of Solitary Intrathyroidal Papillary Thyroid Cancer for Precision Treatment. *J Natl Cancer Inst*. 2018; 110:362-370.
12. Argyropoulou M, Veskoukis AS, Karanatsiou PM, Manolakelli A, Kostoglou-Athanassiou I, Vilaras G, Karameris A, Liadaki K. Low Prevalence of TERT Promoter, BRAF and RAS Mutations in Papillary Thyroid Cancer in the Greek Population. *Pathology oncology research: POR*. 2020; 26:347-354.
13. Rahman ST, Pandeya N, Neale RE, McLeod DSA, Bain CJ, Baade PD, Youl PH, Allison R, Leonard S, Jordan SJ. Obesity Is Associated with BRAF(V600E)-Mutated Thyroid Cancer. *Thyroid: Official Journal of the American Thyroid Association*. 2020.
14. Juhlin CC. A Clinical Overview of Telomerase-Associated Aberrancies in Follicular Thyroid Tumors as Diagnostic and Prognostic Markers: Tert Alert! *Scand J Surg*. 2019; 1457496919850434.
15. Badiu C, Dobrescu R. Telomeres biology involvement in thyroid neoplasia: from aging clock to aggressive cancers. *Toxicol Lett*. 2019; 314:S29-S30.
16. Yang J, Gong YP, Yan SP, Chen H, Qin SQ, Gong RX. Association between TERT promoter mutations and clinical behaviors in differentiated thyroid carcinoma: a systematic review and meta-analysis. *Endocrine*. 2020; 67:44-57.
17. Bournaud C, Descotes F, Decaussin-Petrucci M, Berthiller J, de la Fouchardiere C, Giraudet AL, Bertholon-Gregoire M, Robinson P, Lifante JC, Lopez J, Borson-Chazot F. TERT promoter mutations identify a high-risk group in metastasis-free advanced thyroid carcinoma. *Eur J Cancer*. 2019; 108:41-49.
18. Liu RY, Zhang T, Zhu GW, Xing MZ. Regulation of mutant TERT by BRAF V600E/MAP kinase pathway through FOS/GABP in human cancer. *Nature Communications* 9. 2018.
19. Liu RY, Bishop J, Zhu GW, Zhang T, Ladenson PW, Xing MZ. Mortality Risk Stratification by Combining BRAF V600E and TERT Promoter Mutations in Papillary Thyroid Cancer Genetic Duet of BRAF and TERT Promoter Mutations in Thyroid Cancer Mortality. *Jama Oncol*. 2017; 3:202-208.
20. Moon S, Song YS, Kim YA, Lim JA, Cho SW, Moon JH, Hahn S, Park DJ, Park YJ. Effects of Coexistent BRAF(V600E) and TERT Promoter Mutations on Poor Clinical Outcomes in Papillary Thyroid Cancer: A Meta-Analysis. *Thyroid*. 2017; 27:651-660.