PRKAR1A and Thyroid Tumors

Subjects: Oncology

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Thyroid cancer is the most common endocrine tumor in the general population and the incidence continues to rise in the United States. The American Cancer Society estimates that there will be 44,280 new cases of thyroid cancer (12,150 in men and 32,130 in women) and about 2200 deaths (1050 in men and 1150 in women) in the United States in 2021. The increased incidence could be possibly attributed to the increased detection of these tumors with imaging technics (like ultrasound and computed tomography (CT)) that better characterize incidental findings of small thyroid nodules.

Keywords: thyroid carcinoma ; PKA ; Carney complex ; cAMP

1. Introduction

In the majority of patients (about 90%), well-differentiated epithelial thyroid cancer is present; this is further categorized into papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC), based on histological criteria [1][2]. The long-term survival of those patients is excellent, with 5-year relative survival rate (as of 2010–2016) being as high as 98% in all stages (>99% for local tumors and 55% for tumors with distant metastases) [3]. However, FTC tends to behave more aggressively with distant metastases and vascular invasion [4][5] being more common and thus its prognosis is poorer than PTC [6]. The rest of the thyroid carcinomas (~2–3%) include medullary thyroid carcinomas (MTCs) that originate from the calcitonin-producing parafollicular C cells, while anaplastic carcinomas (ATCs) and poorly differentiated carcinomas account for the remaining 7–8% [2]. In addition to the above tumors, benign thyroid tumors that usually present as thyroid nodules as well, include benign hyperplasia or benign follicular adenomas [1].

Thyroid malignancies are also associated with at least two syndromes with inherited tumor predisposition, Cowden syndrome (CS, OMIM# 158350) and Carney Complex (CNC, OMIM #160980). CS is a multiple hamartoma syndrome, including FTC, brain and breast cancer. It is caused by inactivating mutations in the PTEN gene, a dual-specificity phosphatase that negatively regulates PI3 Kinase/AKT pathway; mutations in this gene have been detected in 5% of FTCs [7]; however, a mouse harboring a deletion of Pten in the thyroid developed thyroid hyperplasia and not FTC [8].

2. Medullary Thyroid Cancer as Part of MEN2 Syndromes

About one-third of MTCs are hereditary, presenting as multicentric and bilateral, in contrast with sporadic cases that are a single unilateral tumor [9][10]. They present as part of MEN2A (70–80%), MEN2B (5%), or familial MTC (FMTC) (10–20%). The first inherited subtype of MTC, MEN2A, consists of primary hyperparathyroidism, pheochromocytoma and MTC in which it can occur early in life (approximately 5 years of age) in contrast with sporadic cases that presents between 15 and 20 years [10][11]. MEN2B is characterized by pheochromocytoma, MTC and non-endocrine diseases such as mucosal neuromas, intestinal tumors (most commonly ganglioneuromas) and Marfanoid habitus [11]. In the case of FMTC, only the thyroid gland is affected, but in a significant number of relatives in the same family, usually between the ages of 20 and 40 [11][12][13]. Activating germline RET mutations have been identified as the main cause of up to 98% of hereditary MTCs and up to half of sporadic cases [14]. Depending on the mutated residue within the RET protein, the phenotype may differ [15][16][17][18]. Families with two or more members with MTC are referred for genetic counseling and screening, if positive they undergo further testing for hyperparathyroidism and pheochromocytoma [3][19][20]. In the case of sporadic MTCs, somatic RET mutations, particularly M918T, has been shown to be associated with more aggressive disease and worse prognosis [20][21].

3. Anaplastic Thyroid Carcinoma

ATC is a rare (1–2%) but very aggressive type of thyroid cancer [22] with average age at diagnosis over 70 years [23]. It is considered to evolve from dedifferentiation of a pre-existing DTC caused by accumulation of several genetic alterations that lead to disruption of two signaling pathways that are involved in cell proliferation, PI3K-AKT and MAPK [24][25][26]. The most common mutations include TP53 , which is considered a genetic hallmark of ATC, as well as RAS , BRAF , PIK3CA

[27][28], mutations that have also been identified in DTC [29]. Median survival is usually less than 6 months after diagnosis and the mortality rate is >90% [30][31]. Due to its extremely aggressive nature, it is critical to be diagnosed promptly. Clinical symptoms are usually used for the diagnosis, in contrast with DTC in which diagnosis is made by FNA of a suspicious nodule [23]. The symptoms can last from 4 weeks to 11 months and usually consist of a rapidly enlarging neck mass along with vocal cord paralysis and dyspnea [23].

4. Systemic Treatments for Thyroid Cancer

Two multikinase inhibitors (MKI), lenvatinib and sorafenib, are currently approved by the US Food and Drug Administration (FDA) for the treatment of advanced DTC. Sorafenib was approved based on the favorable results of a placebo-controlled phase 3 clinical trial (DECISION) [32]. The positive results of the lenvatinib phase 3 SELECT trial [33] as well as a phase 2 study led to the approval of that drug [34]. Cabozatinib and vandetanib are approved by the FDA for the treatment of MTC. Vandetanib is approved for symptomatic, unresectable, locally advanced, or metastatic MTC in patients based on a phase 3 trial (ZETA) [35]. Cabozantinib was studied in a phase 3 clinical trial (EXAM) [36] and showed good results while another clinical trial in MTC patients is still active (EXAMINER, NCT01896479). RET-inhibitors have been studied as well for thyroid cancers that harbor *RET* mutations (NCT03157128, NCT04211337, NCT03906331, NCT04280081, NCT03037385).

4.1. Immunotherapy

In the recent years, immunotherapy has emerged as a new transformative approach into the body's natural antitumor defenses. To date, there is no approved immunotherapy for advanced thyroid cancer. A few clinical trials using novel immunotherapy agents like programmed cell death protein 1 (PD-1) checkpoint inhibitors are ongoing. Pembrolizumab in an Ib phase trial (KEYNOTE) showed a tumor size reduction of 35–50% in PTC and FTC. The use of another anti-PD1 agent (spartalizumab) was evaluated in progressive ATC that responded to therapy [37]. In an ongoing phase 2 clinical trial (NCT03246958), the efficacy of the combination of nivolumab (anti-PD1-1) and ipilimumab (anti-CTLA-4- cytotoxic T-lymphocyte-associated protein 4) was evaluated in patients with aggressive thyroid cancer. In addition, multiple clinical trials with VEGF and/or VEGF inhibitor and immune checkpoint inhibitors have been designed. Pemproblizumab plus lenvatinib was investigated in a phase 2 trial for unresectable ATC (NCT04171622) as well as in a randomized study in a small group of advanced ATC and PDTC [38]. The same combination is under study in DTC and PDTC naïve or progressing after lenvatinib patients (NCT02973997). Triple combined therapy (cabozantinib plus nivolumab and ipilimumab) is under evaluation for DTC and PDTC (NCT03914300).

4.2. Treatment for PRKAR1A-Associated Thyroid Tumors

To date, there is no medical treatment targeting cAMP/PKA signaling in CNC. Surgical treatment is the treatment of choice in patients with PRKAR1A-associated thyroid tumor [39].

5. Clinical Surveillance in Patients with PRKAR1A-Associated Thyroid Tumors

Human studies in CNC underly the importance of investigating thyroid nodules in these patients. Multiple thyroid nodules are present in up to 75% of patients with CNC on thyroid ultrasound; the majority of them are non-functioning follicular adenomas [40]. However, thyroid carcinomas are common as well. Early detection is vital and CNC patients should be followed with long-term clinical and/or ultrasound surveillance with biopsy of suspicious nodules, for early detection of carcinomas [40].

Because CNC is inherited in an autosomal dominant manner, each child of an affected individual has a 50% chance of inheriting the pathogenic variant. Most of the affected patients (approximately 70%) have an affected parent. In the case that the pathogenic variant is known in a family, prenatal testing may be recommended [40].

6. Conclusions

In summary, recent advances in molecular mechanisms of thyroid cancer have improved cancer prognosis and detection. *PRKAR1A*, a regulator of PKA activity, is possibly involved in the molecular events that contribute to thyroid cancer. Identifying the genetic basis of *PRKAR1A*-associated thyroid tumors is important as it will provide better clinical management to these patients.

References

1. Raman, P.; Koenig, R.J. Pax-8-PPAR-gamma fusion protein in thyroid carcinoma. Nat. Rev. Endocrinol. 2014, 10, 616–623.
2. Younis, E. Oncogenesis of Thyroid Cancer. Asian Pac. J. Cancer Prev. 2017, 18, 1191–1199.
3. Eng, C.; Mulligan, L.M.; Smith, D.P.; Healey, C.S.; Frilling, A.; Raue, F.; Neumann, H.P.; Ponder, M.A.; Ponder, B.A. Low frequency of germline mutations in the RET proto-oncogene in patients with apparently sporadic medullary thyroid carcinoma. Clin. Endocrinol. 1995, 43, 123–127.
4. Besic, N.; Auersperg, M.; Golouh, R. Prognostic factors in follicular carcinoma of the thyroid—A multivariate survival analysis. Eur. J. Surg. Oncol. 1999, 25, 599–605.
5. Nguyen, X.V.; Roy Choudhury, K.; Tessler, F.N.; Hoang, J.K. Effect of Tumor Size on Risk of Metastatic Disease and Survival for Thyroid Cancer: Implications for Biopsy Guidelines. Thyroid 2018, 28, 295–300.
6. Sugino, K.; Ito, K.; Nagahama, M.; Kitagawa, W.; Shibuya, H.; Ohkuwa, K.; Yano, Y.; Uruno, T.; Akaishi, J.; Kameyama, K.; et al. Prognosis and prognostic factors for distant metastases and tumor mortality in follicular thyroid carcinoma. Thyroid 2011, 21, 751–757.
7. Nagy, R.; Ganapathi, S.; Comeras, I.; Peterson, C.; Orloff, M.; Porter, K.; Eng, C.; Ringel, M.D.; Kloos, R.T. Frequency of germline PTEN mutations in differentiated thyroid cancer. Thyroid 2011, 21, 505–510.
8. Yeager, N.; Klein-Szanto, A.; Kimura, S.; Di Cristofano, A. Pten loss in the mouse thyroid causes goiter and follicular adenomas: Insights into thyroid function and Cowden disease pathogenesis. Cancer Res. 2007, 67, 959–966.
9. Block, M.A.; Jackson, C.E.; Greenawald, K.A.; Yott, J.B.; Tashjian, A.H., Jr. Clinical characteristics distinguishing hereditary from sporadic medullary thyroid carcinoma. Treatment implications. Arch. Surg. 1980, 115, 142–148.
10. Kouvaraki, M.A.; Shapiro, S.E.; Perrier, N.D.; Cote, G.J.; Gagel, R.F.; Hoff, A.O.; Sherman, S.I.; Lee, J.E.; Evans, D.B. RET proto-oncogene: A review and update of genotype-phenotype correlations in hereditary medullary thyroid cancer and associated endocrine tumors. Thyroid 2005, 15, 531–544.
11. Brandi, M.L.; Gagel, R.F.; Angeli, A.; Bilezikian, J.P.; Beck-Peccoz, P.; Bordi, C.; Conte-Devolx, B.; Falchetti, A.; Gheri, R.G.; Libroia, A.; et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. J. Clin. Endocrinol. Metab. 2001, 86, 5658–5671.
12. Romei, C.; Pardi, E.; Cetani, F.; Elisei, R. Genetic and clinical features of multiple endocrine neoplasia types 1 and 2. J. Oncol. 2012, 2012, 705036.
13. Wohllk, N.; Schweizer, H.; Erlic, Z.; Schmid, K.W.; Walz, M.K.; Raue, F.; Neumann, H.P. Multiple endocrine neoplasia type 2. Best Pract. Res. Clin. Endocrinol. Metab. 2010, 24, 371–387.
14. Eng, C.; Clayton, D.; Schuffenecker, I.; Lenoir, G.; Cote, G.; Gagel, R.F.; van Amstel, H.K.; Lips, C.J.; Nishisho, I.; Takai, S.I.; 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.
15. Lodish, M.B.; Stratakis, C.A. RET oncogene in MEN2, MEN2B, MTC and other forms of thyroid cancer. Expert Rev. Anticancer Ther. 2008, 8, 625–632.
16. Wells, S.A., Jr. Advances in the management of MEN2: From improved surgical and medical treatment to novel kinase inhibitors. Endocr. Relat. Cancer 2018, 25, T1–T13.
17. Romei, C.; Ciampi, R.; Elisei, R. A comprehensive overview of the role of the RET proto-oncogene in thyroid carcinoma. Nat. Rev. Endocrinol. 2016, 12, 192–202.
18. Mulligan, L.M. RET revisited: Expanding the oncogenic portfolio. Nat. Rev. Cancer 2014, 14, 173–186.
19. Elisei, R.; Tacito, A.; Ramone, T.; Ciampi, R.; Bottici, V.; Cappagli, V.; Viola, D.; Matrone, A.; Lorusso, L.; Valerio, L.; et al. Twenty-Five Years Experience on RET Genetic Screening on Hereditary MTC: An Update on The Prevalence of Germline RET Mutations. Genes 2019, 10, 698.
20. Romei, C.; Ugolini, C.; Cosci, B.; Torregrossa, L.; Vivaldi, A.; Ciampi, R.; Tacito, A.; Basolo, F.; Materazzi, G.; Miccoli, P.; et al. Low prevalence of the somatic M918T RET mutation in micro-medullary thyroid cancer. Thyroid 2012, 22, 476–481.
21. Romei, C.; Casella, F.; Tacito, A.; Bottici, V.; Valerio, L.; Viola, D.; Cappagli, V.; Matrone, A.; Ciampi, R.; Piaggi, P.; et al. New insights in the molecular signature of advanced medullary thyroid cancer: Evidence of a bad outcome of cases with double RET mutations. J. Med. Genet. 2016, 53, 729–734.
22. Molinaro, E.; Romei, C.; Biagini, A.; Sabini, E.; Agate, L.; Mazzeo, S.; Materazzi, G.; Sellari-Franceschini, S.; Ribechini, A.; Torregrossa, L.; et al. Anaplastic thyroid carcinoma: From clinicopathology to genetics and advanced therapies. Nat.

Rev. Endocrinol. 2017, 13, 644–660.

23. Deeken-Draisey, A.; Yang, G.Y.; Gao, J.; Alexiev, B.A. Anaplastic thyroid carcinoma: An epidemiologic, histologic, immunohistochemical, and molecular single-institution study. Hum. Pathol. 2018, 82, 140–148.
24. Wreesmann, V.B.; Ghossein, R.A.; Patel, S.G.; Harris, C.P.; Schnaser, E.A.; Shaha, A.R.; Tuttle, R.M.; Shah, J.P.; Rao, P.H.; Singh, B. Genome-wide appraisal of thyroid cancer progression. Am. J. Pathol. 2002, 161, 1549–1556.
25. Charles, R.P.; Silva, J.; Iezza, G.; Phillips, W.A.; McMahon, M. Activating BRAF and PIK3CA mutations cooperate to promote anaplastic thyroid carcinogenesis. Mol. Cancer Res. 2014, 12, 979–986.
26. Garcia-Rostan, G.; Costa, A.M.; Pereira-Castro, I.; Salvatore, G.; Hernandez, R.; Hermsem, M.J.; Herrero, A.; Fusco, A.; Cameselle-Teijeiro, J.; Santoro, M. Mutation of the PIK3CA gene in anaplastic thyroid cancer. Cancer Res. 2005, 65, 10199–10207.
27. Gauchotte, G.; Philippe, C.; Lacomme, S.; Leotard, B.; Wissler, M.P.; Allou, L.; Toussaint, B.; Klein, M.; Vignaud, J.M.; Bressenot, A. BRAF, p53 and SOX2 in anaplastic thyroid carcinoma: Evidence for multistep carcinogenesis. Pathology 2011, 43, 447–452.
28. Landa, I.; Ibrahimpasic, T.; Boucai, L.; Sinha, R.; Knauf, J.A.; Shah, R.H.; Dogan, S.; Ricarte-Filho, J.C.; Krishnamoorthy, G.P.; Xu, B.; et al. Genomic and transcriptomic hallmarks of poorly differentiated and anaplastic thyroid cancers. J. Clin. Investig. 2016, 126, 1052–1066.
29. Tiedje, V.; Ting, S.; Herold, T.; Synoracki, S.; Latteyer, S.; Moeller, L.C.; Zwanziger, D.; Stuschke, M.; Fuehrer, D.; Schmid, K.W. NGS based identification of mutational hotspots for targeted therapy in anaplastic thyroid carcinoma. Oncotarget 2017, 8, 42613–42620.
30. Baloch, Z.W.; LiVolsi, V.A. Special types of thyroid carcinoma. Histopathology 2018, 72, 40–52.
31. Aschebrook-Kilfoy, B.; Ward, M.H.; Sabra, M.M.; Devesa, S.S. Thyroid cancer incidence patterns in the United States by histologic type, 1992–2006. Thyroid 2011, 21, 125–134.
32. Brose, M.S.; Nutting, C.M.; Jarzab, B.; Elisei, R.; Siena, S.; Bastholt, L.; de la Fouchardiere, C.; Pacini, F.; Paschke, R.; Shong, Y.K.; et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: A randomised, double-blind, phase 3 trial. Lancet 2014, 384, 319–328.
33. Schlumberger, M.; Tahara, M.; Wirth, L.J.; Robinson, B.; Brose, M.S.; Elisei, R.; Habra, M.A.; Newbold, K.; Shah, M.H.; Hoff, A.O.; et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N. Engl. J. Med. 2015, 372, 621–630.
34. Cabanillas, M.E.; Schlumberger, M.; Jarzab, B.; Martins, R.G.; Pacini, F.; Robinson, B.; McCaffrey, J.C.; Shah, M.H.; Bodenner, D.L.; Topliss, D.; et al. A phase 2 trial of lenvatinib (E7080) in advanced, progressive, radioiodine-refractory, differentiated thyroid cancer: A clinical outcomes and biomarker assessment. Cancer 2015, 121, 2749–2756.
35. Wells, S.A., Jr.; Robinson, B.G.; Gagel, R.F.; Dralle, H.; Fagin, J.A.; Santoro, M.; Baudin, E.; Elisei, R.; Jarzab, B.; Vasselli, J.R.; et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: A randomized, double-blind phase III trial. J. Clin. Oncol. 2012, 30, 134–141.
36. Elisei, R.; Schlumberger, M.J.; Muller, S.P.; Schoffski, P.; Brose, M.S.; Shah, M.H.; Licitra, L.; Jarzab, B.; Medvedev, V.; Kreissl, M.C.; et al. Cabozantinib in progressive medullary thyroid cancer. J. Clin. Oncol. 2013, 31, 3639–3646.
37. Capdevila, J.; Wirth, L.J.; Ernst, T.; Ponce Aix, S.; Lin, C.C.; Ramlau, R.; Butler, M.O.; Delord, J.P.; Gelderblom, H.; Ascierto, P.A.; et al. PD-1 Blockade in Anaplastic Thyroid Carcinoma. J. Clin. Oncol. 2020, 38, 2620–2627.
38. Dierks, C.; Seufert, J.; Aumann, K.; Ruf, J.; Klein, C.; Kiefer, S.; Rassner, M.; Boerries, M.; Zielke, A.; la Rosee, P.; et al. Combination of Lenvatinib and Pembrolizumab Is an Effective Treatment Option for Anaplastic and Poorly Differentiated Thyroid Carcinoma. Thyroid 2021, 31, 1076–1085.
39. Bouys, L.; Bertherat, J. Management of Endocrine Disease: Carney complex: Clinical and genetic update 20 years after the identification of the CNC1 (PRKAR1A) gene. Eur. J. Endocrinol. 2021, 184, R99–R109.
40. Stratakis, C.A.; Raygada, M. Carney Complex. In GeneReviews(R); Adam, M.P., Ardinger, H.H., Pagon, R.A., Wallace, S.E., Bean, L.J.H., Mirzaa, G., Amemiya, A., Eds.; University of Washington: Seattle, WA, USA, 1993.

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