Nanotechnology Perceptions
ISSN 1660-6795
www.nano-ntp.com

Significant Impact of Prognostic Molecular Markers in Papillary Thyroid Carcinoma

Samar Usama Hassan[1], Sabah A.M. fadel[2], Mahmoud Abdelhameid Mahmoud[3], Asmaa M Ahmed[2]

[1]Pathology department, faculty of medicine, South Valley University, Qena, Egypt.
[2]Pathology department, faculty of Medicine, Assuit University, Assuit, Egypt
[3]General Surgery Department, Faculty of Medicine, South Valley University, Qena, Egypt

Papillary thyroid carcinoma (PTC) is the most common subtype of thyroid cancer and is the most prevalent one in the endocrine system. According to worldwide reports, its incidence has been increasing in recent decades. The discovery of DNA sequencing methods and molecular diagnostic techniques provides an insight into the understanding of PTC molecular biology which opens a new perspective in finding molecular markers. Expanded studies have been executed on identifying the genes involved in PTC development and their prognosis. Currently, clinical and pathological features of tumor (such as size, extra thyroid extension, lymph node invasion, and capsular invasion) are used to predict the prognosis of PTC. The present article provides an updated condensed overview of PTC molecular alterations involved and recent biomarker investigations.

Keywords: Papillary Thyroid Carcinoma, Molecular Markers, Prognostic Biomarkers, Genetic Mutations, Thyroid Cancer Prognosis.

1. Introduction

Papillary thyroid carcinoma (PTC), the most common form of thyroid cancer, presents a diverse range of biological behaviors and prognostic outcomes. Molecular profiling has become a pivotal component in understanding the pathogenesis and progression of PTC, offering insights that are crucial for diagnostic precision and therapeutic strategies. Among these, the identification and characterization of specific genetic alterations have shown significant promise in predicting disease aggressiveness and patient prognosis. The present article delves into the prognostic implications of key molecular markers such as RET/PTC rearrangements, RAS and BRAF mutations, and TERT promoter mutations. By exploring

their roles within the cellular pathways and their impact on clinical outcomes [1].

RET rearrangements and PTC:

RET is a proto-oncogene which encodes membrane tyrosine kinase receptor, which is located on chromosome 10 and is expressed in thyroid parafollicular C cells [2]. It is possible for ligand-independent, constitutive dimerization to occur when the intracellular domain of RET, which possesses tyrosine kinase activity, merges with the N-terminus of the activating gene [3] This rearrangement causes RET to be

under the transcriptional control of its fusion partner gene promoters, and allows the aberrated expression of chimeric protein of the receptor in epithelial follicular thyroid cells. The fusion leaves the tyrosine kinases domain of the RET receptor intact, and enables the RET/PTC chimeric oncoprotein to hold SHC protein adapter which leads to stimulation of the RAS-RAF-MAPK signaling pathway . As a consequence of the rearrangement,the MAPK cascade becomes unrestricted and chronically activated . figure 1. As a result of the fact that these rearrangements were initially discovered in PT, they were given the name RET/PTC. The occurrence of RET/PTC rearrangements is five to twenty-five percent in patients with spontaneous PTC , while it exceeds eighty percent in individuals with radiation-induced PTC [4]. When it occurs radiation-related tumors, RET rearrangement is linked to aggressive characteristics such as increased tumor size, Extrathyroidal extension(ETE), and Lymph node metastasis(LNM) [5]. RET/PTC rearrangement is associated with well-differentiated, tiny, slow-growing PTC that has a more indolent course [6]. This is an association that occurs in sporadic PTC. An indication that RET is a favorable prognostic biomarker [7] is provided by the fact that the prevalence of RET rearrangements in poorly differentiated TC is only 6%, and that these rearrangements are not present in anaplastic TC. The presence of RET rearrangement was reported to be more prevalent in younger patients (45-60%) [8], which is indicative of its ability to operate as an initiating event of papillary tumors [9].

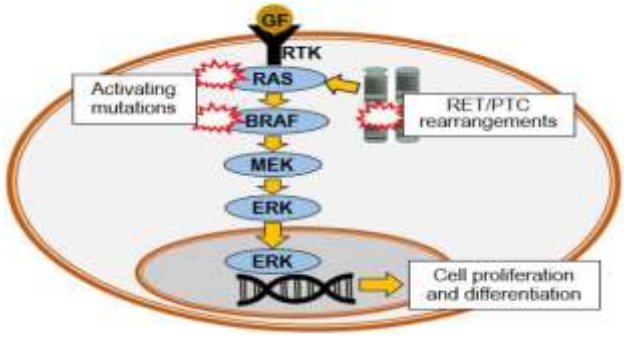

Figure 1. Oncogenic activation of MAPK pathway. The pathway is triggered by binding of growth factor (GF) to a receptor tyrosine kinase (RTK),which activates the RAS, BRAF, MEK and ERK phosphorylation cascade. [10].

MEK: MAPK kinase; ERK: extracellular-signal-regulated kinase.

RAS oncogenes and PTC:

RAS, which is upstream of BRAF, is a family of GTP-binding proteins that control cell

growth via the MAPK and PI3K-AKT cascades. In TC RAS mutation appear to affect substantially the PI3K pathway [4]. They are set up in a broad variety of thyroid tumors involving follicular adenomas, follicular carcinomas, poorly differentiated carcinomas, undifferentiated carcinomas as well as papillary carcinomas. Three members of the RAS gene family (HRAS, NRAS and KRAS) have been demonstrated to be mutated in thyroid cancer. The most common RAS mutations were detected is the NRAS gene, followed by HRAS, and least frequently, KRAS. However, later it became clear that the RAS mutations are predominantly related to poorly differentiated thyroid carcinomas and anaplastic thyroid cancers than PTC , which suggests the role of RAS is more inclined to the progression rather than the initiation of tumors. 10% to 20% of patients with PTC, most commonly follicular variant PTC, have RAS mutations [11].

BRAF oncogene and PTC

BRAF a member of the RAF family (A, B, and C) of serine/threonine kinases, is located in chromosome 7. These proteins relay signals from membrane-bound receptors to downstream regulators of the MAPK pathway that control the expression of several genes responsible for cell proliferation, differentiation, migration and apoptosis [12]. BRAF is recognized as the most potent stimulator of the MAPK/extracellular signal-regulated kinase (MAPK/ERK) pathway. Tumor transformation occurs as a result of the aberrant activation of the MAPK/ERK pathway [13]. The predominant BRAF mutations arise from a specific genetic alteration called the 1796T-A mutation, which occurs in exon 15 of the BRAF gene. The mutation results in the replacement of glutamic acid with valine at position 600, and it is known as BRAF V600E [14]. The mutation causes the ERK [8, 9] to become activated and the inhibitory loop [15] to be deleted, resulting in the formation of a constantly active BRAF kinase. BRAF mutation is specifically connected with some types of thyroid cancer, particularly papillary thyroid carcinoma (PTC), where it is observed in around 32-73% of cases. However, it is rarely found in other types of follicular lesions, regardless of whether they are benign or malignant. A BRAF point mutation at position 601 (BRAFK601E) has been found in patients with follicular thyroid adenoma and follicular variant PTC [16]. Since its first description, BRAF has been extensively studied as a biological marker to assess the aggressiveness and prognosis of cancers [17].

BRAF potentially play role in TC proliferation independently of the oncogenic activation, suggesting a role of wild-type BRAF also in RET/PTC and activated RAS signaling pathways. The presence of BRAF mutation in PMC indicates its role in the initiation of thyroid tumors [18]. Identifying BRAF mutations in FNAB specimens significantly improving the accuracy of PTC cytological diagnosis to nearly 100% [19] BRAF mutation role in tumor aggressiveness and prognosis is still debatable, Lin et al reported that no significant correlation between BRAF mutation and poor prognostic clinicopathological characteristics and recurrence in PTC [20]. According to Valvo et al., BRAF mutation is significantly associated with increased mortality and poorer clinicopathological features, risk of recurrence, loss of radioiodine avidity and therapy failure PTC [21]. In addition, they discovered a correlation between BRAF mutation and the alteration of the microenvironment, which enhances the advancement and aggressiveness of the tumor [22].

TERT promotor mutation and PTC :

The TERT gene encodes the reverse transcriptase subunit of the telomerase complex, that elongates the telomere portion of chromosomes adding repeated sequences. Usually absent/low in normal cells telomerase activation is known to be a hallmark of cancer, being detected in 80% to 90% of malignant tumors [23] and not being detected in benign thyroid lesions . TERT promoter (TERT p) mutations are a late event in thyroid tumorigenesis, are more prevalent in poorly differentiated TC (40%) and anaplastic TC (70%) (30) t. In PTC, TERT p mutation has been associated with larger tumor size, older patients, male gender [16], advanced tumor stage and poor prognosis [24]. TERTp mutations may occur combined with BRAF mutation and RAS mutation in poorly differentiated TC and anaplastic TC [25]. Tumors with combined TERTp mutation and BRAF mutation have been described as having increased recurrence rate[26], poor clinicopathological features and increased mortality in comparison to tumors who lack both mutations [27].

MicroRNA and PTC:

MicroRNAs (miRNAs) are small endogenous non-coding RNAs of approximately 22 nucleotides in length. They have major roles in post-transcriptional control of genes by repressing translation and/or degrading their messenger RNA targets in the cytosol, also in the alteration of gene expression in the nucleus . since of their ubiquitous role in gene regulation, miRNAs are included in numerous intracellular regulatory processes, such as differentiation, proliferation and apoptosis. Thus, dysregulation of miRNAs has been correlated with several pathological disorders, involving varoius types of cancer. The altered levels of many different miRNAs have been associated with the metastases and invasion of cancers . Compared to the genetic analyses, studies on the applications of miRNAs as biomarkers for PTC are relatively more recent. Currently, there have been many reports confirming that PTC is consistently associated with overexpression of specific miRNAs such as mir-146b, miR-221 and miR-222 compared to normal thyroid tissues. The expression of these miRNAs was apparently associated with features of tumour aggressiveness such as extrathyroidal extension, recurrence, lymph node or distant metastasis and BRAFV600E mutation . PTC tumors were also demonstrated to have alterations in the process of miRNA biogenesis. Compared with benign thyroid lesions and normal thyroid tissues, the transcription of RNA endonuclease Dicer, which is included in the biogenesis and targeting of miRNAs in PTC tissues, was reported to be downregulated. This alteration was associated with the same tumour aggressiveness features [28].

Furthermore, these levels were shown to have a direct association with the size of the tumor and a higher TNM stage. [29].

PIM1 and PTC :

an important PIM family member, Pim-1 was originally identified as a proviral integration site for Moloney murine leukemia virus 1 In addition to the induction of cytokines, mitogens, hypoxia, hormones, and infection factors, the expression of Pim-1 is also regulated and activated through upstream signaling pathways, such as JAK-STAT,and NF-κB. Studies have unveiled that Pim-1 is widely involved in the occurrence and development of multiple human cancers. Pim-1also take part in mediating the redistribution of mitosis and

accelerating cell division progression [30]

PIM-1 kinase regulates the tricarboxylic acid (TCA) cycle and mitochondrial oxidative phosphorylation. The significance of PIM-1 in PTC, in relation to OS, is crucial due to the function OS plays in the carcinogenesis of PTC [31].

Survivin and PTC:

Survivin is a unique bifunctional protein in the family of baculovirus inhibitors of apoptosis proteins that regulate cell death. Survivin involved on cell cycle regulation and apoptosis inhibition. In the G2/N phase of the cell cycle survivin accelerates cell division . It has shown to have role in tumor angiogenesis . Survivin expression correlated with tumor size , regional lymph node metastasis and distant metastasis.Survivin expression was significantly associated with the tumor size in PTC consisting of different variants and lymph vascular invasion indicating that surviving is a marker for poor prognosis in PTC. [32].

Components of the Urokinase Plasminogen Activating System and PTC:

The urokinase plasminogen activating system (uPAS) involves the urokinase plasminogen activator , the plasminogen activator inhibitors 1 and 2, and the uPA cell membrane receptor (uPAR). A number of studies proved the ability of the uPAS to alter cellular proliferation, migration, adhesion, and tumor neoangiogenesis, and significantly affect tumor invasion and metastasis. furthermore, high tumor tissue levels of one or more uPAS components correlate with poor prognosis in multiple human malignancies [33]

An increased uPA, uPAR, and PAI-1 expression was documented in PTC tissues compared to normal thyroid tissues. furthermore, a correlation has been reported between tumor size and uPA expression, and higher levels of uPA and uPAR were found in metastatic PTC. Also reported significantly higher uPA and uPAR expression in BRAFV600E-positive PTC compared to those bearing the wild type BRAF [34]. it is demonstrated that the increased gene expression of uPA and uPAR in PTC tissues was associated with tumor invasiveness and advanced stages. , these findings indicate a correlation between the increased expression of one or more uPAS components and a worst prognosis in TC patients. [35].

2. Conclusion :

Recently , significant progress has been made in deciphering the genetic landscape of papillary thyroid carcinoma that is complex disease in its nature and affected by multiple genetics and epigenetics alteration, these alteration play crucial roles in PTC progression. Therefore targeting these genetics alterations holds promise for the development of effective therapies for PTC. So further researches are needed to identify and validate molecular markers to improve outcomes for PTC patients and assist in the early diagnosis.

References

1. Valderrabano, P., Eszlinger, M., Stewardson, P., & Paschke, R. (2023). Clinical value of molecular markers as diagnostic and prognostic tools to guide treatment of thyroid cancer. Clinical endocrinology, 98(6), 753-762.

2. Póvoa, A. A., Teixeira, E., Bella-Cueto, M. R., Batista, R., Pestana, A., Melo, M., ... & Soares, P. (2021). Genetic determinants for prediction of outcome of patients with papillary thyroid carcinoma. Cancers, 13(9), 2048.
3. Ulisse, S., Baldini, E., Lauro, A., Pironi, D., Tripodi, D., Lori, E., ... & Sorrenti, S. (2021). Papillary thyroid cancer prognosis: An evolving field. Cancers, 13(21), 5567.
4. Arora, C., Kaur, D., Naorem, L. D., & Raghava, G. P. (2021). Prognostic biomarkers for predicting papillary thyroid carcinoma patients at high risk using nine genes of apoptotic pathway. PLoS One, 16(11), e0259534.
5. Niciporuka, R., Nazarovs, J., Ozolins, A., Narbuts, Z., Miklasevics, E., & Gardovskis, J. (2021). Can we predict differentiated thyroid cancer behavior? role of genetic and molecular markers. Medicina, 57(10), 1131.
6. Sorrenti, S., Carbotta, G., Di Matteo, F. M., Catania, A., Pironi, D., Tartaglia, F., ... & Baldini, E. (2020). Evaluation of clinicopathological and molecular parameters on disease recurrence of papillary thyroid cancer patient: A retrospective observational study. Cancers, 12(12), 3637.
7. Bains, A., Mur, T., Wallace, N., & Noordzij, J. P. (2021). The role of vitamin D as a prognostic marker in papillary thyroid cancer. Cancers, 13(14), 3516.
8. Samà, M. T., Grosso, E., Mele, C., Laurora, S., Monzeglio, O., Marzullo, P., ... & Pagano, L. (2021). Molecular characterisation and clinical correlation of papillary thyroid microcarcinoma. Endocrine, 71, 149-157.
9. Hong, S., Xie, Y., Cheng, Z., Li, J., He, W., Guo, Z., ... & Xiao, H. (2022). Distinct molecular subtypes of papillary thyroid carcinoma and gene signature with diagnostic capability. Oncogene, 41(47), 5121-5132.
10. Pekova, B., Sykorova, V., Mastnikova, K., Vaclavikova, E., Moravcova, J., Vlcek, P., ... & Bendlova, B. (2021). NTRK fusion genes in thyroid carcinomas: clinicopathological characteristics and their impacts on prognosis. Cancers, 13(8), 1932.
11. Titov, S. E., Kozorezova, E. S., Demenkov, P. S., Veryaskina, Y. A., Kuznetsova, I. V., Vorobyev, S. L., ... & Ivanov, M. K. (2021). Preoperative typing of thyroid and parathyroid tumors with a combined molecular classifier. Cancers, 13(2), 237.
12. Hescot, S., Al Ghuzlan, A., Henry, T., Sheikh-Alard, H., Lamartina, L., Borget, I., ... & Leboulleux, S. (2022). Prognostic of recurrence and survival in poorly differentiated thyroid cancer. Endocrine-related Cancer, 29(11), 625-634.
13. Spirina, L. V., Chizhevskaya, S. Y., Kovaleva, I. V., & Kondakova, I. V. (2021). The association of the BRAF-V600E mutation with the expression of the molecular markers in the primary tumor and metastatic tissue in papillary thyroid cancer. Asian Pacific Journal of Cancer Prevention: APJCP, 22(7), 2017.
14. Gao, T., Zhao, L., Zhang, F., Cao, C., Fan, S., & Shi, X. (2022). Evaluate the diagnostic and prognostic value of NUSAP1 in papillary thyroid carcinoma and identify the relationship with genes, proteins, and immune factors. World journal of surgical oncology, 20(1), 207.
15. Zhao, L., Wang, L., Jia, X., Hu, X., Pang, P., Zhao, S., ... & Lyu, Z. (2020). The coexistence of genetic mutations in thyroid carcinoma predicts histopathological factors associated with a poor prognosis: a systematic review and network meta-analysis. Frontiers in oncology, 10, 540238.
16. Barros-Filho, M. C., De Mello, J. B., Marchi, F. A., Pinto, C. A., Da Silva, I. C., Damasceno, P. K., ... & Rogatto, S. R. (2020). GADD45B transcript is a prognostic marker in papillary thyroid carcinoma patients treated with total thyroidectomy and radioiodine therapy. Frontiers in Endocrinology, 11, 269.
17. Wang, Z., Li, J., Liu, Z., & Yue, L. (2023). Nrf2 as a novel diagnostic biomarker for papillary thyroid carcinoma. European Journal of Histochemistry: EJH, 67(2).
18. Ito, Y., & Miyauchi, A. (2024). Prognostic factors of papillary and follicular carcinomas based on pre-, intra-, and post-operative findings. European Thyroid Journal, 13(5).

19. Bai, M., Ke, S., Yu, H., Xu, Y., Yu, Y., Lu, S., ... & Wu, Y. (2022). Key molecules associated with thyroid carcinoma prognosis: A study based on transcriptome sequencing and GEO datasets. Frontiers in Immunology, 13, 964891.
20. Li, X., & Kwon, H. (2020). The impact of BRAF mutation on the recurrence of papillary thyroid carcinoma: A meta-analysis. Cancers, 12(8), 2056.
21. Qin, R., Li, C., Wang, X., Zhong, Z., & Sun, C. (2021). Identification and validation of an immune-related prognostic signature and key gene in papillary thyroid carcinoma. Cancer Cell International, 21, 1-15.
22. Acar, H. Z., & Özer, N. (2021). What is the impact of serum molecular markers on the diagnosis of thyroid cancers? A comparison of serum molecular markers with invasive biopsy methods. Asian Journal of Research and Reports in Endocrinology, 4(2), 32-41.
23. Gao, X., Le, Y., Geng, C., Jiang, Z., Zhao, G., & Zhang, P. (2022). DPP4 is a potential prognostic marker of thyroid carcinoma and a target for immunotherapy. International Journal of Endocrinology, 2022(1), 5181386.
24. Buczyńska, A., Kościuszko, M., Krętowski, A. J., & Popławska-Kita, A. (2023). Exploring the clinical utility of angioinvasion markers in papillary thyroid cancer: a literature review. Frontiers in Endocrinology, 14, 1261860.
25. Wei, X., Wang, X., Xiong, J., Li, C., Liao, Y., Zhu, Y., & Mao, J. (2022). Risk and prognostic factors for BRAFV600E mutations in papillary thyroid carcinoma. BioMed Research International, 2022(1), 9959649.
26. Cao, J., Zhu, X., Sun, Y., Li, X., Yun, C., & Zhang, W. (2022). The genetic duet of BRAF V600E and TERT promoter mutations predicts the poor curative effect of radioiodine therapy in papillary thyroid cancer. European Journal of Nuclear Medicine and Molecular Imaging, 49(10), 3470-3481.
27. Lopes, N. M. D., Lens, H. H. M., Armani, A., Marinello, P. C., & Cecchini, A. L. (2020). Thyroid cancer and thyroid autoimmune disease: A review of molecular aspects and clinical outcomes. Pathology-Research and Practice, 216(9), 153098.
28. Macerola, E., Poma, A. M., Vignali, P., Basolo, A., Ugolini, C., Torregrossa, L., ... & Basolo, F. (2021). Molecular genetics of follicular-derived thyroid cancer. Cancers, 13(5), 1139.
29. Liang, T., Wu, X., Wang, L., Ni, Z., Fan, Y., Wu, P., ... & Huang, H. (2023). Clinical significance and diagnostic value of QPCT, SCEL and TNFRSF12A in papillary thyroid cancer. Pathology-Research and Practice, 245, 154431.
30. Oh, E. J., Bychkov, A., Cho, H., Kim, T. M., Bae, J. S., Lim, D. J., & Jung, C. K. (2020). Prognostic implications of CD10 and CD15 expression in papillary thyroid carcinoma. Cancers, 12(6), 1413.
31. Song, B., Lin, Z., Feng, C., Zhao, X., & Teng, W. (2023). Global research landscape and trends of papillary thyroid cancer therapy: a bibliometric analysis. Frontiers in Endocrinology, 14, 1252389.
32. Dell'Aquila, M., Fiorentino, V., Martini, M., Capodimonti, S., Cenci, T., Lombardi, C. P., ... & Rossi, E. D. (2021). How limited molecular testing can also offer diagnostic and prognostic evaluation of thyroid nodules processed with liquid-based cytology: role of TERT promoter and BRAF V600E mutation analysis. Cancer cytopathology, 129(10), 819-829.
33. Xie, Z., Li, X., Lun, Y., He, Y., Wu, S., Wang, S., ... & Zhang, J. (2020). Papillary thyroid carcinoma with a high tumor mutation burden has a poor prognosis. International immunopharmacology, 89, 107090.
34. Jung, C. K., Jung, S. H., Jeon, S., Jeong, Y. M., Kim, Y., Lee, S., ... & Chung, Y. J. (2020). Risk stratification using a novel genetic classifier including PLEKHS1 promoter mutations for differentiated thyroid cancer with distant metastasis. Thyroid, 30(11), 1589-1600.
35. Deng, C., Li, S., Yang, Z., Dou, Y., Hu, D., Zhu, J., ... & Su, X. (2021). Multi-gene assay and clinical characteristics research in papillary thyroid carcinoma. Gland Surgery, 10(1), 242.