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Indian Journal of Pharmacy and Pharmacology

Journal homepage: <https://www.ijpp.org.in/>

Review Article

Papillary thyroid cancer and its gene polymorphism; A molecular mechanistic perspective

Mudassir Jan Makhdoomi¹, Abid Hussain Rather^{1,2}, Tasleem Arif Lone³, Nisar Ahmad Syed⁴, Abid Ali Sheikh^{5*}¹All India Institute of Medical Sciences, New Delhi, India²Dept. of Biochemistry, Shri Nanak Medical Institute of Health Sciences Jammu, Jammu and Kashmir, India³Dept. of Clinical Research, Sher - I - Kashmir Institute of Medical Sciences, Srinagar, Jammu and Kashmir, India⁴Dept. of Medical Oncology, Sher - I - Kashmir Institute of Medical Sciences Srinagar, Jammu and Kashmir, India⁵Trg. Division, National Institute of Biologicals, Noida, Uttar-Pradesh, India

ARTICLE INFO

Article history:

Received 02-03-2024

Accepted 02-04-2024

Available online 07-05-2024

Keywords:

Thyroid Cancer

Mutation

BRAF

PTC

RAS

RAF

ABSTRACT

Thyroid cancer stands as the predominant malignancy within the endocrine system, comprising about 1% of newly identified cancer instances. Papillary Thyroid Cancer (PTC) is the predominant form of thyroid cancer, representing 80% or more of thyroid malignancies. Thyroid carcinoma harbours assorted genetic alterations which are highly prevalent, several of these characteristics are unique to this form of cancer. The conventional oncogenic genetic modifications frequently observed in thyroid carcinoma encompass RAS mutations RET/PTC rearrangements and PAX8-peroxisome proliferator-activated receptor g (PPARg) fusion oncogene. The lately discovered activating mutation in BRAF (the gene for the B-type RAF kinase, BRAF) the most widespread genetic modification in thyroid cancer (30-83%). RKIP (RAF kinase inhibitory protein) had formerly been delineated as a phospholipid binding protein. Mammalian RKIP/PEBP differs from other identified proteins and its role is still being clarified. RKIP over-expression can inhibit MEK interaction with RAF-1 and B-RAF. It plays a role in thyroid cancer progression and lymph node metastasis. So, elucidating mutational profile and protein expression of above cell signalling molecules will be very useful in determining a proper therapeutic target for anti-cancer molecules. Given that tumors often possess numerous genetic and cell signalling abnormalities, thus inhibiting a single signalling pathway is often therapeutically inefficacious, more success could be foreseen with agents directed against multiple cellular pathways.

By determining the genetic profile and protein expression of mentioned MAP Kinase pathway molecules new targets can be identified for chemotherapeutic drugs and novel strategies will be charted out to make modifications in the map kinase pathway with the aim to stop the occurrence and distant metastasis of thyroid cancer.

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1. Introduction

Tumors originating from thyroid epithelial cells manifest varied neoplastic phenotypes, encompassing benign follicular adenomas, well-differentiated papillary and

follicular carcinomas, as well as aggressive anaplastic carcinomas. Among these, Papillary Thyroid Carcinoma (PTC) emerges as the utmost prevalent thyroid malignancy, constituting 80% or more of thyroid malignancies.

The thyroid is a complicated and interesting endocrine organ with diverse functionalities, including the control of calcium equilibrium and modulation of resting metabolism.

* Corresponding author.

E-mail address: abidalis2007@gmail.com (A. A. Sheikh).

Thyroid lumps frequently encountered in clinical settings, thyroid nodules are a prevalent occurrence, with the majority proving to be non-cancerous. In areas where there is an adequate supply of iodine, detectable nodules manifest in 4-7% of the overall population.^{1,2} Thyroid lumps signify an array of varied thyroid dysfunctions from the non-cancerous maladies ranging from goiter or thyroiditis to neoplastic lumps, which may be either malignant (cancerous) or benign (non-cancerous, such as follicular adenoma). At times glandular tumors and goitre are in amalgam with either an overactive thyroid (hyperthyroidism) or an underactive thyroid (hypothyroidism). Thyroid malignancies are uncommon and encompass a varied collection of malignancies spanning from the sluggish papillary micro-carcinoma that barely suggests any intimidation to existence, to a singular anaplastic carcinoma that stands out as the foremost brutal carcinoma tormenting humans. Thyroid cancers are frequently discovered unintentionally, when examinations for other thyroid abnormalities are conducted. Owing to low incidents of the papillary and thyroid adenocarcinoma, its continued survival with a relatively low fatality percentage, preplanned randomized clinical trials haven't been achievable for execution. However, patients experience significant distress due to this, plentiful experience reoccurrence, and some succumb to persistently advancing and incurable cancer. This is a disorder that is not constrained by demarcations, noticeable in all age groups. Despite the fact that approaches to diagnose and address patients have advanced as time progresses, yet numerous unanswered queries persist.³

Glandula thyroidea (Latin), the thyroid gland, is located in the cervical region anterior to the trachea, situated between the cricoid cartilage and the suprasternal notch. Prominently the thyroid organ consists of two segments attached by the isthmus. The blood is delivered primarily by the superior (the primary branch from the external carotid artery) and inferior thyroid arteries. The venal blood's return flows into the brachiocephalic vein and via the internal jugular vein. Lymphatic circulation occurs on the same side, and each segment can be considered as an independent entity, despite the presence of certain lymphatic connections between the two lobes across the isthmus. The recurring laryngeal nerve, an efferent nerve innervating the intrinsic muscles of the larynx, courses along the lateral edges of the gland. Damage results in paralysis of the vocal cord on the same side. Typically the thyroid weighs between 15 to 30 grams, conditional to body weight and iodine provision. The four parathyroid glands are positioned at the posterior aspect of each thyroid pole.⁴

2. Review of Literature

Thyroid cancer stands as the predominant malignancy within the endocrine system, comprising about 1% of

newly identified cancer instances.⁵ The occurrence of this tumour is on the rise, and is the hasty within prevalent human malignancies, it has ascended to rank as the seventh most frequently occurring tumour in females. Global incidence rates adjusted for age vary from 0.5 to 10 cases per 100K populations, happening typically between the age group of 20 and 50 in majority of the cases.⁶ Thyroid gland, the most extensive endocrine gland in humans, regulates overall metabolism via thyroid hormones. The gland consists of two distinct cell types responsible for hormone production, namely follicular cells and parafollicular C cells. The epithelium is mostly made up of follicular cells, these cells play a crucial role in the absorption of iodine and the synthesis of thyroid hormones. C cells are dispersed intra-follicular or para-follicular cells that are specialized in manufacturing the hormone calcitonin, which regulates calcium levels. Thyroid cancers originating from follicular cells (papillary and follicular thyroid carcinoma), undifferentiated thyroid carcinoma, and anaplastic thyroid carcinoma) embodies the foremost manifestation of endocrine cancer. Roughly 95% of thyroid carcinomas fall into the non-medullary category, that originate from follicular cells. Papillary carcinoma is the most frequently encountered form of thyroid cancers, constituting approximately 80-90% of all malignant cases. Medullary thyroid carcinoma (MTC) describes such tumours that arise from calcitonin-producing C thyroid cells arising from the neural crest, and represent roughly 5% of all thyroid neoplasms.^{3,4}

2.1. Genetic alterations of MAPK signalling pathway^{7,8}

Genetic modifications detected in thyroid tumors involve genes encoding receptor tyrosine kinases, specifically RET and NTRK1, and two intracellular effectors of the MAPK pathway, namely GTP-binding protein RAS and a serine-threonine kinase BRAF. Most of the thyroid carcinomas exhibit mutation of one of these genes, and they rarely overlap in the same tumour, indicating that tumour initiation occurs due to the activation of this signaling pathway and a change in a solitary mediator of the pathway is sufficient for cell metamorphosis.⁹⁻¹¹ RAF and RET (Rearranged during Transfection) the two most commonly impacted genes will be scrutinized.

BRAF: BRAF is member of the RAF protein family (ARAF, BRAF, CRAF), that serve as intracellular mediators of the MAPK signaling cascade. Following initiation induced by RAS interaction and protein recruited to the cell membrane, these serine-threonine kinases phosphorylate and initiate the activation of MAPK cascade. Within the trio of functional human RAF proteins, BRAF has the highest inherent kinase activity and is the most effective activator of MAPK.¹²⁻¹⁴ Over 40 alterations have been documented in the BRAF gene, of these alterations the T1799A point mutation in the BRAF gene is the most widespread one

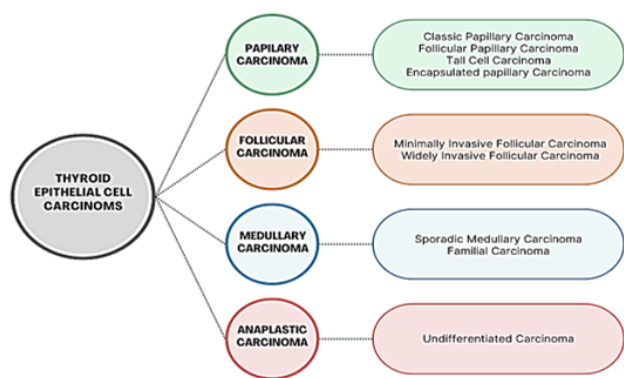


Figure 1: Classification of carcinomas arising from thyroid epithelial cells

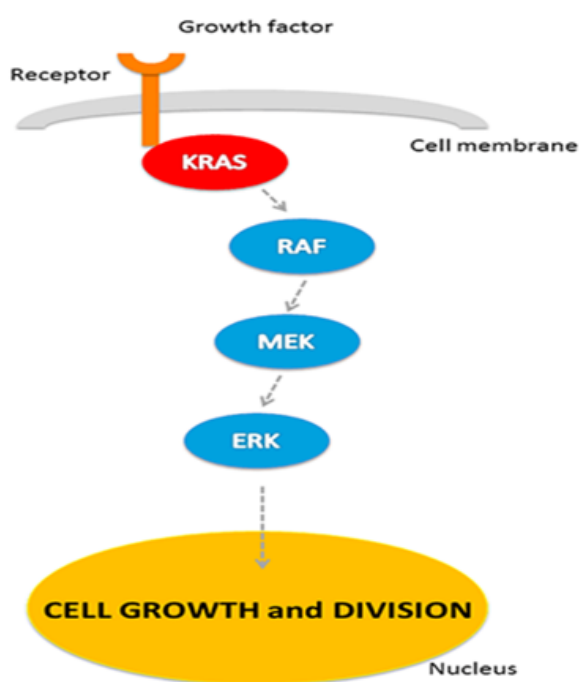


Figure 2: Schematic representation of the MAPK pathway

and making up 90% of all the mutations identified in the BRAF gene.¹⁵ This mutation has been commonly seen in thyroid cancer.¹⁵⁻¹⁷ The V600E amino acid of the BRAF protein is altered by the T1799. A mutation in the BRAF gene, and this results in a persistent and carcinogenic activation of the mutant BRAF kinase.¹⁴⁻¹⁸ In family thyroid cancer, the BRAF mutation is a somatic genetic change rather than a germline mutation.¹⁹ One important finding about BRAF mutations in thyroid cancer is that they are limited in three types of thyroid cancer: papillary thyroid carcinoma (PTC), tall cell variant of PTC, and anaplastic thyroid carcinoma derived from PTC. Crucially, these mutations are not present in any other type of thyroid

Table 1: Incidence and mortality of thyroid cancer by continent and country

Continent/Country	Thyroid Cancer Incidence Number	Thyroid Cancer Mortality Number
Asia	349897	25668
Republic Korea	17788	386
Europe	87162	6399
Latin America and The Caribbean	63368	4406
North America	62256	2420
USA	52912	2161
Africa	18457	4443
Ethiopia	3203	927
Egypt	2661	472
Oceania	5062	310

Table 2: Distribution and frequency of known somatic mutations in different histotypes of thyroid cancer

Mutation	PTC	FTC	PDTC	ATC	MTC
AKT	1%	1-2.6%	-	0-3%	-
BRAF	61.7%	1.7%	19-33%	19-45%	-
DICER1	2.7%	5.1%	-	1.1%	-
EIF1AX	1.5%	5.1%	10%	9%	0.6%
HRAS	2%	7%	5%	6%	9.3-15.8%
KRAS	1.26%	4%	2%	0-5%	3.0-6.2%
NRAS	6%	17-57%	21%	18%	0.6-1%
PAX8-PPARγ	0.8%	12-53%	4%	0	-
PI3KCA	-	5.5%	2%	18%	-
PTEN	1%	7.1%	4%	15%	1%
RET	-	-	-	-	55.8%
RET/PTC	6.8%	0	14%	0	Rare
SWI/SNF	-	-	6%	18-36%	-
TERT promoter	9.4%	-	33-40%	43-73%	-
TP53	6%	5.1-9.7%	0-8%	43-78%	1.2%

cancer, including follicular thyroid carcinomas.¹⁷ In those malignancies, regions of the tumour that are Anaplastic or poorly differentiated as well as well-differentiated can both be found to contain mutant BRAF. Numerous researches have looked into the connection between the BRAF mutation and the clinicopathological features of PTC.^{20,21} Even though the outcomes aren't totally constant, majority of research from different racial and geographic origins shows a strong correlation of BRAF mutation along with one or more typical high-risk clinicopathological traits of PTC, such as patient's advanced age, increased frequency

of extra thyroidal extension, advanced stage of the tumour at presentation, as well as tumour recurrence.^{22,23} In a sizable, thorough, multinational, multicenter study, Xing et al.^{24,25} revealed a strong correlation between the BRAF mutation and lymph node metastases, extra-thyroidal invasion, and progressed ailment phases. Importantly, BRAF genetic alterations have also been linked to the diminished capacity of tumors to capture I-131 and therapeutic ineffectiveness in the relapsed condition.^{26,27} Lately, an additional pathway for the activation of BRAF has been uncovered. It entails chromosomal 7q reversal, which causes BRAF and the AKAP9 gene to fuse in-frame.²⁸ This fusion is more frequent in tumors linked to radiation exposure than it is in spontaneous papillary carcinomas.

3. RET/PTC Rearrangements

The RET proto-oncogene resides on chromosome 10q11.2 and encodes the tyrosine kinase, serving as a cell membrane receptor.^{5,6} It has three different domains of functionality: an extracellular ligand binding domain, a hydrophobic Trans-membrane domain, and an intracellular tyrosine kinase (TK) domain. The growth factors that are ligands of the RET receptor are members of the family of glial cell line derived neurotrophic factors. (GDNF).⁹ Tyrosine residue autophosphorylation and receptor dimerization are brought about by ligand binding. Within the intracellular domain, and activation of the signaling cascade. RET is highly expressed in parafollicular C-cells of the thyroid gland but not in follicular cells, where a chromosomal rearrangement can activate it, culminating in the fusion of the 3' portion of the RET gene to the 5' portion of several unconnected genes, known as RET/PTC rearrangement. The Ret gene, which also contributes to numerous endocrine neoplasm 2A and B, encoding a receptor-type tyrosine kinase, which is an enzyme for neurotropic compounds that are part of the family of neurotropic factors produced from glial cell lines. There is a direct correlation between the radiation exposure levels of patients and the development of RET/PTC and it has a greater role in papillary carcinomas in people who have had radiation exposure in the past, including individuals who have received radiation therapy or unintentional exposure.

4. Genomic Instability

Chromosome instability falls within the wide category of microsatellite instability (MIN) linked to the mutator phenotype, and gross chromosomal abnormalities are indicative of chromosome instability (CIN). Genetic instability has been proposed as a major contributing element to the development of thyroid neoplasms.²⁹ The PCCL3 rat thyroid cell line experiences genomic instability upon transfection with either mutant BRAFV600E or mutant HRASV12 appearing as chromosomal material loss,

mitotic bridge formation, and mismatched chromosomes.³⁰ According to these results, constitutive oncogenic activation of the mitogen-activated protein kinase (MAPK) signaling pathway may increase thyroid carcinoma cells' genomic instability and lead to new somatic mutations as the malignancy progresses.^{31,32}

5. Follicular Thyroid Cancer

Follicular thyroid cancer: The second most prevalent form of thyroid cancer, which makes up 15% of all cases, is more likely in women over 50years of age. A tumour marker that can be utilized for well-differentiated follicular thyroid carcinoma is thyroglobulin (Tg). The thyroid cells called follicular cells are in charge of producing and secreting thyroid hormones. Cytologically, follicular adenoma and carcinoma cannot be distinguished from one another.³³ To confirm the histological diagnosis of follicular neoplasm, thyroid lobectomy should be carried out if fine needle aspiration cytology (FNAC) suggests follicular neoplasm. The features of tumour cell invasion of the circulatory system and the capsular invasion are essential for the diagnosis of follicular carcinoma. However, foci of the capsular invasion need to be carefully assessed and separated from capsular rupture owing to FNA (Fine Needle Aspiration) penetration, which causes WHAFFT (Worrisome Histologic Changes after thyroid FNA).

1. Follicular carcinoma typically propagates through the bloodstream to the lung and bone.
2. Cervical lymph nodes are frequently affected by the metastasis of papillary thyroid cancer.

It has been proposed that HMGA2 can serve as a diagnostic marker to detect malignant tumors.³³ Follicle cell carcinoma is generally acknowledged to be a subtype of thyroid cancer that has Hurthle cell characteristics.^{34,35} Compared to follicular carcinomas, Hurthle cell types are more likely to exhibit bilaterality, multifocality, and lymph node involvement. Similar to follicular carcinoma, non-invasive diseases are treated with a unilateral hemi thyroidectomy, whereas invasive diseases are treated with a whole thyroidectomy. For follicular thyroid carcinoma, the overall 5-year survival rate is 91%, while the 10-year survival rate is 85%.³⁶

According to the general cancer staging system, follicular thyroid carcinoma has a 100% 5-year survival rate for stages I and II, 71% for stages III, and 50% for stages IV.³⁷

Approximately 50% of follicular thyroid carcinomas are caused by mutations in the oncogenes belonging to the RAS subfamily, specifically HRAS, NRAS, and KRAS.³⁴ Additionally, a chromosomal translocation between paired box gene 8 (PAX-8), a gene crucial for thyroid development, is unique to follicular thyroid

carcinomas and the gene encoding peroxisome proliferator-activated receptor γ 1 (PPAR γ 1), a nuclear hormone receptor that aids in the final stages of cell differentiation. About one-third of follicular thyroid carcinomas have the PAX8-PPAR γ 1 fusion, specifically those with a t (2; 3) (q13; p25) translocation, which allows for the juxtaposition of parts of both genes³⁸. RAS mutations or PAX8-PPAR γ 1 fusions are the most common genetic abnormalities seen in tumors; both mutations are rarely found in the same patient.³⁴ Therefore, it appears that two separate and essentially non-overlapping molecular processes give birth to follicular thyroid carcinomas.

6. Papillary Carcinoma

The most frequent type of well-differentiated thyroid cancer and the type most frequently triggered by radiation exposure is papillary carcinoma (PTC). In a normal thyroid parenchyma, papillary cancer manifests as an anomalous solid or fluid-filled mass or growth. It is necessary to see papillary/follicular carcinoma as a variation of papillary thyroid carcinoma (mixed type).³⁹

Papillary carcinoma has well-differentiated features, although it can also be obviously or barely invasive. Malignant tumors can spread quickly to other organs. Although they are less likely to enter blood vessels, papillary tumors are more likely to invade lymphatics.

Patients with this malignancy have a correlated life expectancy with their age. Patients under 45 years old exhibit a more favourable prognosis compared to those exceeding 45 years. Roughly 11% of individuals with papillary tumors show evidence of metastasis outside of the mediastinum and neck. Previously, lymph node metastases in the cervical region were believed to be irregular (supernumerary) thyroids as they harbored well-developed papillary thyroid carcinoma. However, occult cervical lymph node metastases are now recognized as a prevalent occurrence in this condition.⁴⁰⁻⁴⁵

6.1. Pathophysiology

There have been several chromosomal rearrangements linked to papillary thyroid cancer. Chromosome alterations concerning the RET proto-oncogene, which results from a paracentric inversion of chromosome 10, were the first oncogenic events linked to papillary thyroid cancer.⁴⁶ About 20% of papillary thyroid carcinomas seem to be caused by RET fusion proteins (the RET/PTC family), with RET/PTC1, RET/PTC2, and RET/PTC3 accounting for the majority of instances.^{47,48} Furthermore, there is a chance that the proto-oncogenes MET and NTRK1 will be amplified or overexpressed.^{48,49}

Additionally, evidences point to the possibility that molecules that physiologically control the growth of thyrocytes, like interleukin-1 and interleukin-8 or other

cytokines, such as insulin-like growth factor-1, transforming growth factor-beta, and epidermal growth factor, may contribute to the etiology of this cancer.

Papillary thyroid cancer is frequently associated with mutations in the BRAF gene that produce the BRAF V600E protein. In papillary thyroid cancer, frequencies of BRAF V600E mutations increased from 1991 to 2005, according to a study conducted within a sole institution by Mathur et al. This finding raises the possibility that the rising incidence of thyroid cancer is related to this fact.⁵⁰ The aggressive clinicopathological features of papillary thyroid cancer are linked to the BRAF V600E mutation, encompassing lymph node metastasis, extrathyroidal invasion, and loss of radioiodine avidity, all of which can result in the ineffectiveness of radioiodine therapy and the recurrence of disease.⁵¹

Furthermore, a direct correlation has been observed between the occurrence of papillary thyroid cancer and radiation exposure (fallout or radiotherapy).⁵² Port et al reported that, based on gene expression patterns involving seven genes i.e. (SFRP1, MMP1, ESM1, KRTAP2-1, COL13A1, BAALC, PAGE1), papillary thyroid tumors in patients exposed to radiation from the Chernobyl accident could be fully differentiated from spontaneous papillary thyroid cancers in patients with no history of radiation exposure.⁵²

7. Conclusion

The understanding of the genetic basis of thyroid tumorigenesis has been made feasible by recent advancements in molecular diagnostics. These breakthroughs have yielded important insights into a variety of genetic disorders linked to the development of malignancies generated from papillary cells. Genetic abnormalities commonly found in thyroid cancer include RET/PTC rearrangements, RAS genetic alterations, and the PAX8-peroxisome proliferator-activated receptor-g (PPARg) fused oncogene. Individuals who live in Asian countries have significantly different mutational profiles than individuals who live in Western countries, and the frequency of each of these mutations varies significantly throughout groups. Differential mutation rates between Korean and non-Korean populations are widespread; BRAF mutation rates are the highest globally, while RET/PTC and TERT promoter mutations, as well as PAX8/PPAR γ rearrangements, are less common. Comprehending the role and frequency of each mutation may be essential for organizing future studies and may come in handy as a therapeutic or diagnostic tool later on. Research on the clinical significance of these unique mutational profiles across a range of populations should be prioritized in addition to deciphering the complex network of genetic variables that contribute to thyroid cancer. Regional prevalence and mutation frequencies may be used to inform

the development of diagnostic and treatment plans that will improve patient outcomes by increasing intervention precision. Collaborative international initiatives will play a critical role in furthering our understanding of the genetic landscape and converting our discoveries into practical personalized medicine approaches for thyroid cancer.

8. Source of Funding

None.

9. Conflict of Interest

None.

10. Acknowledgement


The Authors would like to thank their respective current organisations for nurturing a scientific and analytical vision for compiling a review on “Papillary Thyroid Cancer and its Gene Polymorphism; A Molecular Mechanistic Perspective.”


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Author biography

Mudassir Jan Makhdoomi, Researcher  <https://orcid.org/0000-0003-0026-2206>

Abid Hussain Rather, Lecturer  <https://orcid.org/0000-0002-8013-9154>

Tasleem Arif Lone, Researcher  <https://orcid.org/0009-0007-8182-0674>

Nisar Ahmad Syed, Associate Professor  <https://orcid.org/0000-0002-8013-9154>

Abid Ali Sheikh, Training Scientific Consultant  <https://orcid.org/0000-0002-8013-9154>

Cite this article: Makhdoomi MJ, Rather AH, Lone TA, Syed NA, Sheikh AA. Papillary thyroid cancer and its gene polymorphism; A molecular mechanistic perspective. *Indian J Pharm Pharmacol* 2024;11(1):3-9.