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A Review of Driver Genetic Alterations in Thyroid Cancers

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ABSTRACT

Thyroid cancer is a frequent endocrine related malignancy with continuous increasing incidence. There has been moving development in understanding its molecular pathogenesis recently mainly through the explanation of the original role of several key signaling pathways and related molecular distributors. Central to these mechanisms are the genetic and epigenetic alterations in these pathways, such as mutation and DNA rearrangements. That does not mean, however, that all the somatic abnormalities here in a cancer genome have been involved in development of the cancer and just driver mutations are concerned in tumor initiation. By way of illustrations, *MAPK* pathway which is motivated by $BRAF^{V600E}$ and *RAS* and *RET / PTC* rearrangements are suggesting driver genetic alterations in follicular derived thyroid cancers which are considered in this review.

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Introduction

Thyroid cancer is the most common endocrine related cancer that its incidence has continuously increased in the last three decades all over the world (1-5). Thyroid carcinomas are heterogeneous groups of neoplasm with typical histopathological features like other tumors (6).

The thyroid gland is composed of two main types of epithelial cells: the follicular cells, which convert iodine into thyroxine, also known as T4, and Triiodothyronine, also known as T3. The thyroid hormones, triiodothyronine (T3) and its prohormone, thyroxine (T4), are tyrosine-based hormones produced by the thyroid gland that are primarily responsible for regulation of metabolism. Another type of epithelial cells is parafollicular or C-cells, which secrete calcitonin. Primary thyroid cancers initiate from thyroid follicular cells (epithelial tumors) mostly and develop three main pathological types of carcinomas: papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC) and anaplastic thyroid carcinoma (ATC) contrary to medullary thyroid carcinoma (MTC) that arises from thyroid parafollicular (C) cells (7-9). Because of well differentiation and indolent tumor growth, PTC and FTC are classified as differentiated thyroid cancer (DTC). PTC consists of 85-90% of all thyroid cancer cases, followed by FTC (5-10%) and MTC (about 2%), while ATC accounts for a smaller amount than 2% of thyroid cancers and usually happens in the aged people (10).

The classic treatment for thyroid cancer is thyroidectomy and adjuvant radioiodine ablation that most patients can be cured, but still surgically inoperative recurrence, refractoriness to radioiodine in DTC, poorly differentiated thyroid carcinoma and ATC are unsolved. In the same way to other solid cancers, thyroid cancer is commenced by genetic alterations and epigenetic changes in driver oncogenes or tumor suppressor genes (11-14). Recent advancement of molecular technologies has brought a new insight to the thyroid tumors diagnosis and prognosis. In this re-

view, we are mainly focused on the follicular thyroid cell derived cancers genetics in order to shed light on driver genetic alterations and their importance in thyroid tumor genesis.

Molecular genetics of thyroid cancer

Thyroid cancer comes up as a result of multiple genetic and epigenetic alterations in the DNA of cancer cells. There are numerous somatic point mutations and chromosomal rearrangements have been recognized in of different steps follicular cell-derived thyroid cancer (Figure 1) (15,16) whose are mainly belonging to the *MAPK* signaling pathway and *RET/PTC* rearrangements (17).

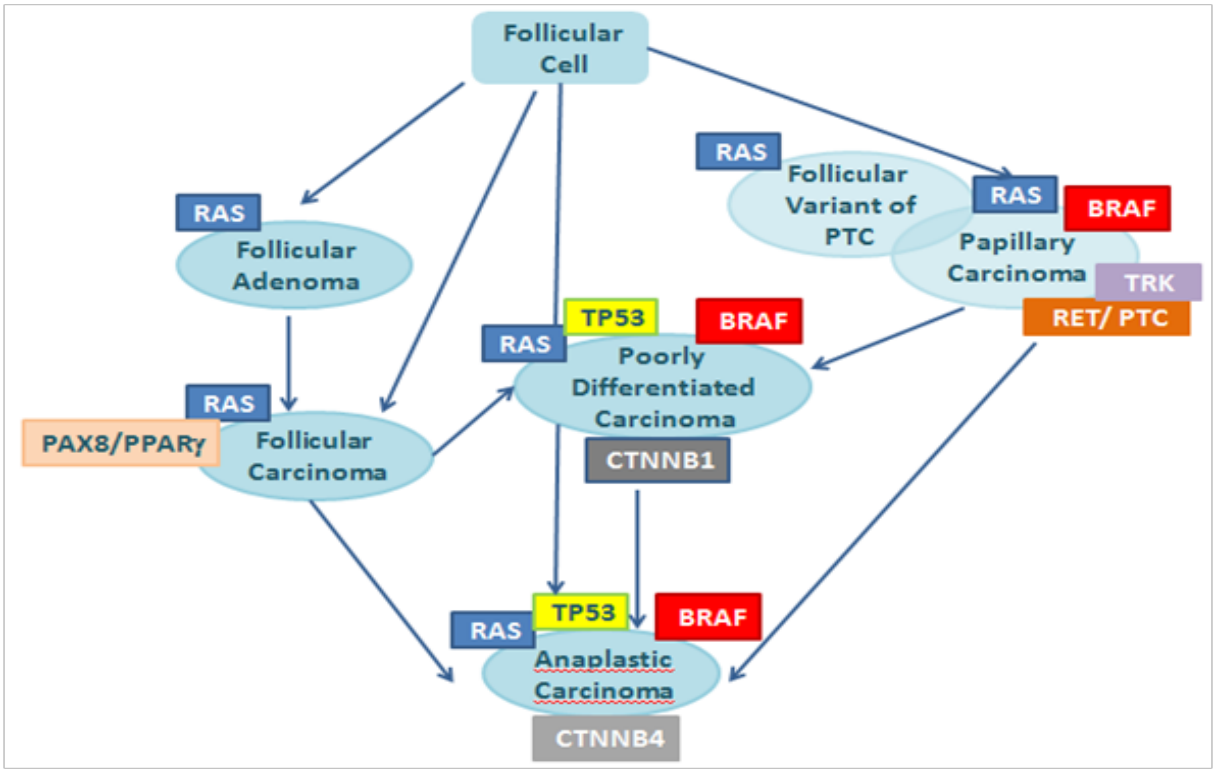

Figure 1. Stepwise dedifferentiation of follicular cell-derived thyroid cancer.

It should be kept in mind that not all the somatic abnormalities of a cancer genome have been involved in initiation of the cancer because some are the consequences of carcinogenesis, so the terms ‘driver› and ‘passenger› mutation have been made up. A driver mutation is by the way oncogenesis implication which is cancer stem cells and has been positively selected in the microenvironment of the tissue in which the cancer begins and is not needed for maintenance of the final cancer (although it often is) (18,19).

A passenger mutation has not been chosen, has not given clonally increase and has therefore not contribute to cancer development. For the reason that somatic mutations without functional consequences often happen during cell division, passenger mutations are initiated within cancer genomes (20). One of the problematic issues is discriminating driver from passenger mutations. Whole-genome sequencing, however, incorporating analysis of more than 20,000 protein-coding genes and unknown numbers of functional elements in intronic and intergenic DNA, presents a greater challenge. Investigation of the biological consequences of putative driver mutations will often consolidate the evidence implicating them in oncogenesis and will provide insight into the subverted biological processes by which they contribute to cancer development. Thyroid cancer is a genetically simple disease with a relatively low num-

ber of mutations in each tumor. Driver mutations and gene fusions are identified in most of thyroid cancers suggesting that two main cell signaling pathways are MAPK and PI3K-AKT involved in the development of thyroid tumors (17,21). The *MAPK/ERK* pathway, also known as the *Ras-Raf-MEK-ERK* pathway, is a transporter of a signal from a receptor on the cell surface to the nucleus (DNA) (Figure 2). After binding a signaling molecule to its target receptor on the cell surface, this signaling pathway initiates and when the DNA in the nucleus expresses a protein in order to make some changes in the cell, it will be terminated (22). This pathway have lots of proteins, including *MAPK* (mitogen-activated protein kinases, originally called *ERK*, extracellular signal-regulated kinases) and is connected with the cell proliferation, differentiation, migration, senescence and apoptosis Components of the *MAPK/ERK* pathway were discovered when they were found in cancer cells (6, 22-24).

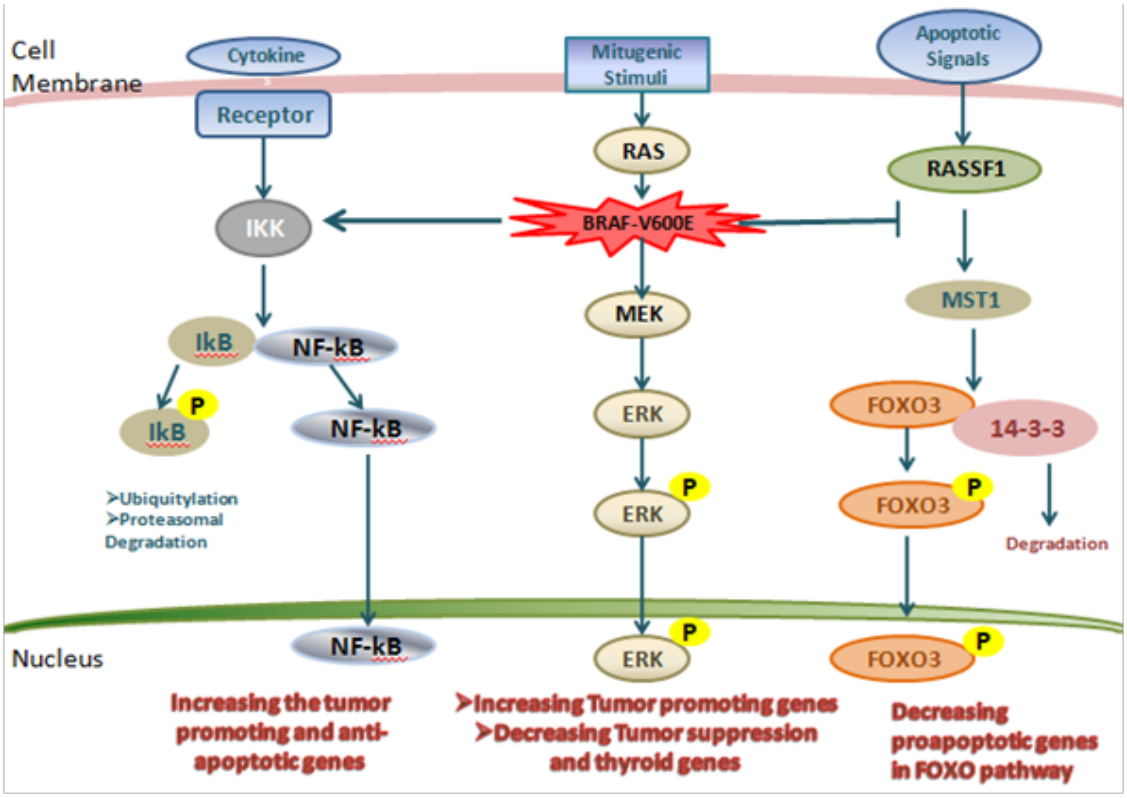

Figure 2. The MAPK and related pathways in thyroid cancer.

Nuclear factor-κB (NF-κB) pathway that is leading to activation of the inhibitor of κB (IκB) kinase (IKK), resulting in the phosphorylation of IκB and dissociation from NF-κB. Free NF-κB then enters the nucleus to promote the expression of tumor-promoting genes. On the right side of the figure is the RASSF1–mammalian STE20-like protein kinase 1 (MST1)–fork head box O3 (FOXO3) pathway and activated MST1 then phosphorylates FOXO3 on Ser207. Phosphorylated FOXO3 enters the nucleus to promote the expression of pro-apoptotic genes in the FOXO pathway. In the middle of figure is a unique and powerful mechanism of thyroid tumor genesis driven by BRAF-V600E. DAPK1, death-associated protein kinase 1; HIF1A, hypoxia-inducible factor 1α; MMP, matrix metalloproteinase; NIS, sodium–iodide symporter; TGFB1, transforming growth factor β1; TIMP3, tissue inhibitor of metallo proteinases 3; TPO, thyroid peroxidase; TSHR, thyroid-stimulating hormone receptor; TSP1, thrombospondin 1; UPA, urokinase plasminogen activator; UPAR, urokinase plasminogen activator receptor; VEGFA, vascular endothelial growth factor A (25).

In early thyroid cancer, *MAPK* pathway is motivated by mutations in *BRAF* and *RAS* or by *RET / PTC* rearrangements. A key driver mutation upsetting *MAPK* pathway is the point mutation of *BRAF*, which make the expression of $BRAF^{V600E}$ mutant protein resulting in constitutive activation of the serine/threonine kinas (26-31). In fact, amino acid substitution at position 600 in *BRAF*, from a Valine (V) to a glutamic acid (E) is the result of V600E mutation . This mutation occurs within the activation segment of the kinase dos main (Figure 3). *BRAF* mutations also are frequently found in tumors with no driver mutations in *NRAS,*

KIT, and other genes. *BRAF*^{V600E} mutation is found in about 45% of PTCs (32, 33). However, some human PTC tumors have been found to show intra-tumors heterogeneity in the *BRAF* genotype — with a minority of cells have *BRAF*^{V600E} while the majority contain wild-type *BRAF* (34).

Figure 3. Schematic of *BRAF* ^{V600E} mutation. Functional domains of *BRAF* are depicted. CR1: conserved regions 1. CR2: conserved region 2.

After *BRAF* mutations in thyroid cancer *RAS* mutations are the most important driver genetic alteration (35, 36) . *RAS* is in bound with GTP and when intrinsic GTPase of *RAS* hydrolyses GTP and converts *RAS* into an inactive GDP-bound state the RAS signaling terminated (Figure 4) (37). There are three isoforms of *RAS: HRAS, KRAS* and *NRAS*, and *NRAS* is predominantly mutated in thyroid tumors, mostly involving codons 12 and 61(30,38). The *RAS* mutations in follicular thyroid adenoma (FTA), a supposed premalignant lesion, suggests that activated *RAS* may have a role in early follicular thyroid cell tumor genesis and higher aggressive tumor behaviors (38,39). The expression of mutant *HRAS* was induced in resulted in differentiated colonies (39-41). Moreover, in the thyroid gland of transgenic mouse studies with conditional physiological expression of a *KRAS* had no transformation, but simultaneous KRAS mutant expression and *PTEN* deletion induced a rapid occurrence of aggressive FTC (42-44).

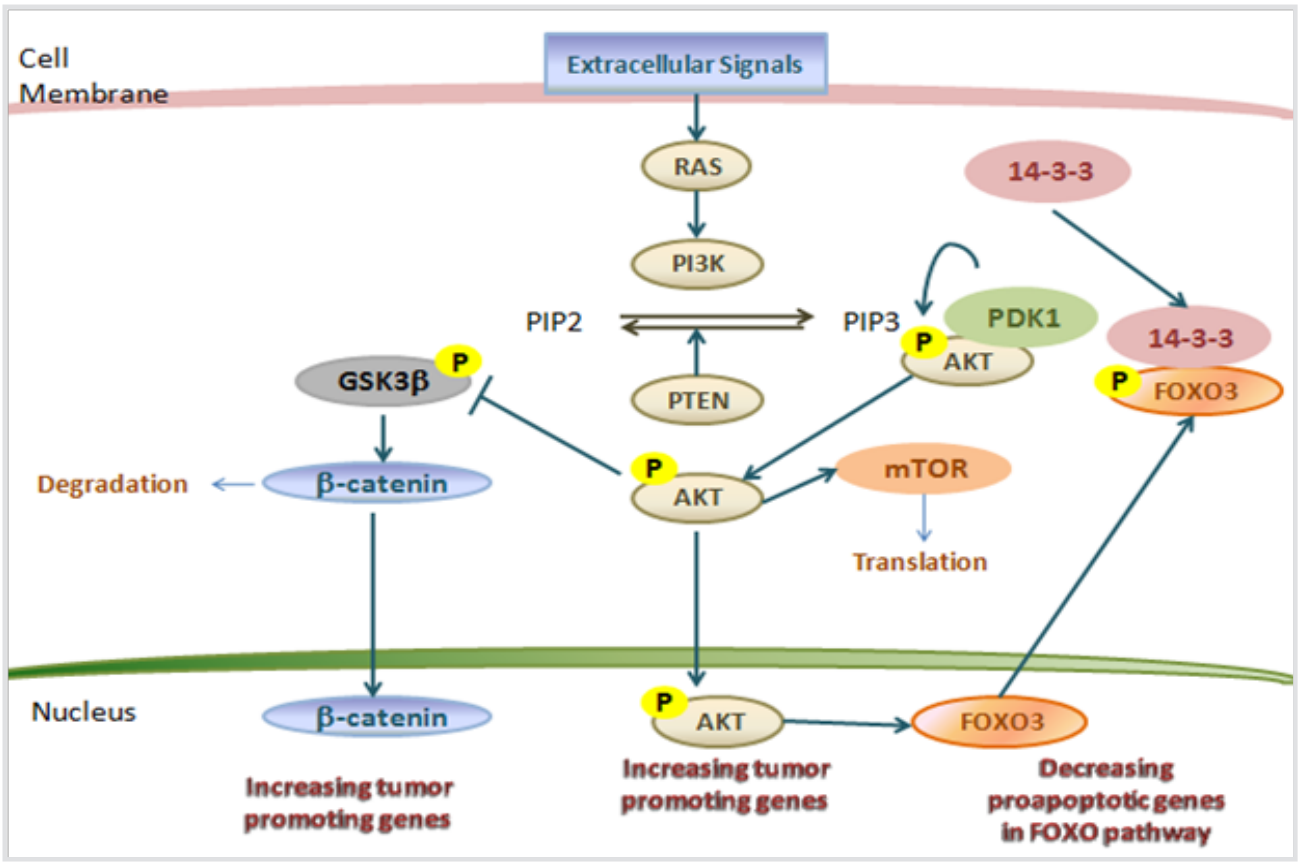

Figure 4. The PI3K–AKT and related pathways in thyroid cancer (37).

Another main driver genetic alteration in thyroid cancer is the rearranged during transfusion (*RET*) proto-oncogene. *RET* is (rearranged during transfection), is localized on chromosome 10 (10q11.2) and have 21 exons (45). The natural alternative splicing of the *RET* gene consequences in the making of three different isoforms of the protein RET; RET51, RET43, and RET9 which have 51, 43 and 9 amino acids in their C-terminal tail respectively (46) . Each protein is divided into three domains: an N-terminal extracellular domain with four cadherin-like repeats and a cysteine-rich region, a hydrophobic trans membrane domain and a cytoplasmic tyrosine kinase domain, which is split by an insertion of 27 amino acids (47). As a result of its capability to transform *NIH/3T3* cells by DNA rearrangement, the RET proto-oncogene was first recognized in 1985 (48). The proteins that RET encodes is a cellular tyrosine kinase transmembrane receptor that is separated into the three main domains: an N-terminal extracellular domain containing four cadherin-like regions; a cysteine-rich region with a transmembrane domain; and a cytoplasmic domain with tyrosine kinase activity (47, 49-51). Four diverse ligands have been described: Glial Derived Neurotrophic (*GDN*) factors, Neurturin (*NRTN*), Artimin (*ARTN*), and Persepin (*PSPN*), respectively (47, 52, 53) . DNA rearrangements are a result of homologous recombination, gene conversion, and illegitimate recombination. During homologous recombination in a cell containing more than one copy of a given chromosome one copy can combine with corresponding segments of the other. This kind of recombination is ultimately dependent upon the DNA sequence homology between the two copies. Several types of *RET/PTC* rearrangements have been reported (Table 1) (54,55). The presence of *RET/PTC* rearrangement in microcarcinoma powerfully support the hypothesis of a driving role of this oncogene in the tumor transformation (56).

Table 1. Different types of RET/PTC rearrangements in thyroid tumors according to Nikiforov YE (57)

Oncogene	Donor gene	Chromosomal location
RET/PTC1	CCD6(formerly H4)	10q21
RET/PTC2	PRKAR1A	17q23
RET/PTC3	NCO4 (formerly Ele 1)	10q11.2
RET/PTC4	NCO4 (formerly Ele1)	10q11.2
RET/PTC5	Golgas	14q
RET/PTC6	TRIM24	7q32-34
RET/PTC7	TRIM33	1p13
RET/PTC8	KTN1	14q22.1
RET/PTC9	RFG9	18q21-22
ELKS-RET	ELKS	12p13.3
PCM1-RET	PCM1	8p21-22
RFP-RET	TRIM27	6p21
HOOK3-RET	HOOK3	8p11.21

The described *RET/PTC* prevalence in thyroid tumors varies greatly in different studies (58-65). However, this difference can be the consequence of Tumor heterogeneity, ethnical and geographic variations, and dissimilar sensitivities of detection methods (66-68). *RET/PTC* rearrangements are more often in thyroid cancers after radiation exposure (50-80%) (69-72). The biological mechanisms of radiation carcinogenesis related to *RET/PTC* rearrangements have been studied several times. It has been shown that damage to cellular DNA is responsible for mutagenesis and carcinogenesis and those double-strand breaks

is the most important event for the direct generation of gene translocations and rearrangements (21, 73-77). Thanks to the recent advanced next generation sequencing, and whole genome sequencing the number of candidate genetic changes in thyroid cancer has increased (78). But it is really important to discriminate between driver and passenger ones. Other genetic changes that are considered as passenger mutations include: *PI3K* (phosphatidylinositol-3 kinase), β-catenin (*CTNNB1*), TP53, isocitrate dehydrogenase 1 (*IDH1*), anaplastic lymphoma kinase (*ALK*) and epidermal growth factor receptor (*EGFR*) (79-89). The preferential occurrences of these mutations in PDTC and ATC, which are the most aggressive thyroid cancers, indicate to the fact that they may have a role in the progression and aggressiveness of thyroid cancer.

Conclusions

While diverse oncogenes have been brought into being involved in thyroid tumor genesis, *BRAF* and *RAS* mutations, and *RET/PTC* rearrangements are the most frequently involved as a driver changes. Notwithstanding all these observations, there are not still strong supporting data showing a classic prognostic role for *BRAF* and *RAS* mutations, and *RET/PTC* rearrangements. But it is clear that *RET/PTC* rearrangements are connected to radiation exposure and are more recurrent in patients with radio induced PTC.

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Conflict of Interest

The authors declare that there was no conflict of interest.

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