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 BRAFV600E 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 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).

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-
number 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.

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 \( \text{BRAF}^{V600E} \) mutant protein resulting in constitutive activation of the serine/threonine kinases (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 domain (Figure 3). BRAF mutations also are frequently found in tumors with no driver mutations in NRAS,
KIT, and other genes. \textit{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 \textit{BRAF} genotype — with a minority of cells have \textit{BRAF}^{V600E} while the majority contain wild-type \textit{BRAF} (34).

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

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

**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 transmembrane 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), Artim in (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).

| 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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