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Review Article

Recent Advances in Molecular Diagnosis of Thyroid Cancer

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Recent molecular studies have described a number of abnormalities associated with the progression and dedifferentiation of thyroid carcinoma. These distinct molecular events are often associated with specific stages of tumor development. In particular, remarkable advances have occurred in several major biological areas of thyroid cancer, including the molecular alterations for the loss of radioiodine avidity of thyroid cancer, the pathogenic role of the MAP kinase and PI3K/Akt pathways and their related genetic alterations, and the aberrant methylation of functionally important genes in thyroid tumorigenesis and pathogenesis. Recognition of these features is crucial to the management of patients with thyroid cancer. Novel treatments are being designed based on our enhanced understanding of this disease process.

1. Introduction

The incidence of thyroid cancer, the most common endocrine malignancy, has been rising gradually over the past decade. The major histological types of the follicular cell-derived thyroid cancer are papillary thyroid cancer (PTC), follicular thyroid cancer (FTC), and anaplastic thyroid cancer (ATC) [1–4]. Benign thyroid adenoma (BTA) is a common endocrine tumor. On the other hand, medullary thyroid cancer arises from the parafollicular or C cells and is not of follicular cell origin. For that reason, it is not presented in this paper.

Accumulating evidence indicates that follicular cell-derived thyroid carcinomas constitute a biological continuum progressing from the highly curable well-differentiated thyroid carcinoma (WDTC) to the often fatal undifferentiated or anaplastic thyroid carcinoma (ATC) [5, 6]. Poorly differentiated thyroid carcinoma (PDTC) and aggressive variants of WDTC, such as tall cell and columnar cell, frequently serve as intermediates in this progression model.

Clinical, epidemiologic, and pathologic evidence supports the concept of stepwise progression and dedifferentiation [7]. For example, the gradual loss of papillary and follicular growth patterns and the simultaneous increase in a solid growth pattern, with increased mitoses, necrosis, and nuclear pleomorphism, are often observed in aggressive thyroid carcinomas [8, 9]. A majority of these tumors exhibit residual foci of differentiated thyroid carcinoma.

There are also several diagnostic challenges that are often encountered in the clinical management of thyroid cancer. One is the diagnostic dilemma associated with "indeterminate cytology" on the widely used fine needle aspiration biopsy (FNAB) in the evaluation of thyroid nodules. For example, in the United States, about 300,000 cases of thyroid nodules, which are mostly BTA, are diagnosed annually [10]. Moreover, 20–30% of these FNAB cases show "indeterminate" cytological findings, a pattern that has been reported to remain essentially unchanged over the last two decades [11, 12]. These patients currently virtually all pursue thyroid surgery to definitely reveal the nature of the nodules although vast majority of them will surgically prove to have benign nodules.

Careful risk stratification is a key step in the decision making for appropriate surgical and medical managements of patients with thyroid cancer. This risk evaluation is conventionally based on clinicopathological factors, which

are often unreliable and are mostly unavailable prior to thyroid surgery.

Most thyroid cancer patients have an excellent outcome, and standard treatment usually consists of total thyroidectomy, often with lymph node resection, thyroid hormone suppressive therapy, and in more advanced staged disease, radioactive iodine (I-131) for either remnant ablation or therapeutic treatment [13–15]. These standard therapies are dependent on the tumor exhibiting a differentiated phenotype similar to normal thyrocytes consisting of responsiveness to the growth factor TSH via the presence of the TSH receptor and expression of the sodium-iodide symporter (NIS) [16, 17]. Surveillance for these patients typically consists of combination of anatomical imaging such as neck ultrasound [18, 19], radioiodine whole body scans, and serum measurement of the thyroid-specific protein thyroglobulin with antithyroglobulin antibody levels [20, 21].

On the other hand, thyroid cancer patients with recurrent or metastatic disease can have mortality rates approaching 50% [22]. Dedifferentiation of thyroid cancer may consist of loss of expression of the TSH receptor, NIS, and loss of thyroglobulin production. In the process of a tumor losing NIS expression, the clinician loses the ability to use radioiodine for monitoring and treatment. However, this subset of tumors frequently become visible with 18F-fluorodeoxyglucose positron emission tomography scans (FDG-PET) [23]. Clinically, these FDG-PET positive, noniodine avid tumors have limited treatment options which may include observation, additional surgery, external beam radiation, conventional chemotherapy like the US FDA-approved agent doxorubicin, and clinical trials.

The recent introduction of targeted therapeutic agents that have multiple targets, including the receptor tyrosine kinases, nonreceptor tyrosine kinases, and serine-threonine kinases, has shown much promise in trials for thyroid cancer patients with advanced disease [24].

The current goal of molecular medicine is to be able to profile each patient's tumor in order to determine which treatments will achieve the maximal response with minimal side effects. There have been significant conceptual and technical advances in elucidating areas of tumor biology such as genetic and/or epigenetic regulation, but a unifying theory for thyroid carcinogenesis is lacking. This review aims to provide a framework to understand the rationale of how selected research developments may segregate tumors into different therapeutic regimens.

2. Chromosomal Rearrangements

One of the earliest genetic changes identified in papillary thyroid cancer was chromosomal alterations involving the proto-oncogene RET (rearranged during transfection) [25]. The RET (rearranged during transfection) proto-oncogene is a 21-exon gene located on the proximal long arm of chromosome 10 that encodes a tyrosine kinase receptor. It is involved in the regulation of growth, survival, differentiation, and migration of cells of neural crest origin. It is not normally expressed in the follicular cell [26]. The unique spatial proximity of translocation-prone gene loci, which may be preferentially occurring in thyrocytes in their mitotic interphase, favors RET gene rearrangements [27, 28]. This may help explain why RET rearrangements are specific for thyroid tumors [29, 30].

Although more than 10 rearrangements have been described, RET/PTC1, RET/PTC2, and RET/PTC3 account for most of the rearrangements found in PTC [31, 32]. In each of these rearrangements, the upstream (5′) component of a "housekeeping" (or ubiquitously expressed) gene drives the expression of the tyrosine kinase domain of RET. Expression of the RET/PTC chimeric proteins is facilitated by the heterologous promoters provided by the fused genes and results in constitutive, ligand-independent activation of RET receptor tyrosine kinase in papillary cancer cells [33–35].

Clinically, RET/PTC variants are often found in radiation-associated PTC. The increase in pediatric thyroid cancers following the Chernobyl nuclear plant explosion in 1986 resulted in two groups of thyroid cancer. The first was an early appearing and aggressive solid variant of PTC which contained the RET/PTC3 rearrangement while a later onset of PTC, with a more classical phenotype and clinical course, in the Chernobyl survivors contained RET/PTC1 [36].

Both transgenic mouse models and in vitro cellular work have shown these fusion proteins as capable of initiating PTC [37, 38]. RET/PTC rearrangements are less commonly found in undifferentiated thyroid cancers, suggesting that these tumors may be managed with conventional treatment [39]. Moreover, the utility of RET/PTC identification from FNA of thyroid nodules for diagnosis of PTC is beginning to be used [40].

There is evidence to support the belief that RET/PTC rearrangements represent early genetic changes leading to the development of PTC [41]. In approximately 20% of sporadic PTCs, RET/PTC rearrangements have been found [42]. Moreover, it has been also found in adenomas and other benign lesions of the thyroid [43, 44]. However, since it is present in most tumor cells, it is reasonable to consider it specific for PTCs [45].

Several studies have shown that RET/PTC rearrangements are associated with PTC that lacks evidence of progression to PDTC or ATC [46]. A recent study from Santoro et al. [47] showed that less than 10% of PDTCs were positive for RET/PTC rearrangements. They concluded that PTCs with RET/PTC rearrangements have a relatively low potential for progression to PDTC or ATC.

Recently, compounds have been identified that exhibit significant inhibitory activity on RET kinase [48]. In particular, the recent success in the treatment of chronic myelogenous leukemia with imatinib mesylate, an inhibitor of constitutively activated ABL kinase, has generated considerable interest in developing therapeutic protein kinase inhibitors. There are multiple drugs in trial with activity against RET, most notably ZD6474-Vandetanib and Bay 43-9006-Sorafenib, but these agents also target other tyrosine kinase receptors [49]. In particular, Sorafenib has now been shown in two phase II clinical trials to have achieved a partial response rate of 15 and 23% in patients [50]. Due to Vandetanib's ability to block RET signaling activity, it is primarily being used for medullary thyroid cancer patients;

however, there is an ongoing phase II trial including DTC patients [51].

3. RAS Mutations

The RAS (an abbreviation of RAt sarcoma) family of oncogenes regulates two important signaling pathways in thyroid 3 cancer, the mitogen-activated protein kinase/extracellular signal-regulated kinase (RAS/Raf/MEK/ERK) and the phosphatidylinositol-3 kinase (PI3K)/Akt signaling pathways. Ras mutations occur in both benign and malignant thyroid tumors, with variable frequency in ATCs [52].

Three RAS genes, H-RAS, K-RAS, and N-RAS, synthesize a family of 21-kDa proteins that play an important role in tumorigenesis [53]. The RAS proteins exist in two different forms: an inactive form that is bound to guanosine diphosphate (GDP) and an active form that exhibits guanosine triphosphatase (GTPase) activity. Their function is to convey signals originating from tyrosine kinase membrane receptors to a cascade of mitogen-activated protein kinases (MAPKs). This activates the transcription of target genes involved in cell proliferation, survival, and apoptosis [54]. Oncogenic RAS activation results from point mutations, affecting the GTP-binding domain (codons 12 or 13) in exon 1 or the GTPase domain (codon 61) in exon 2, which fix the protein in the activated state and thus resulting in chronic stimulation of downstream targets, genomic instability, additional mutations, and malignant transformation [55]. The RAS mutations are among the most common mutations found in transformed cells. Mutations in all three cellular RAS genes have been identified in benign and malignant thyroid tumors. They seem to be common in follicular carcinoma, PDTC, and ATC and occur less frequently in PTC [56, 57]. The role of oncogenic RAS in thyroid tumor progression is unclear.

Some studies have shown a similar prevalence of RAS mutations in benign and malignant thyroid neoplasms, suggesting that RAS activation may represent an early event [58]. Other studies have shown that RAS mutations, specifically mutations at codon 61 of N-RAS, are involved with tumor progression and aggressive clinical behavior [59, 60]. Transgenic mice with thyroid-specific mutant RAS expression develop thyroid hyperplasia and carcinoma [61]. A recent study by Garcia-Rostan et al. [62] demonstrated that the presence of RAS mutations predicted a poor outcome for WDTC independent of tumor stage.

Furthermore, they found that PDTC and ATC often harbor multiple RAS mutations. These mutations probably represent an intermediate event in the progression of thyroid carcinoma.

4. BRAF Mutation and MAP Kinase Signaling Pathway in Thyroid Cancer

The evolutionarily conserved mitogen-activated protein kinase (MAPK) signaling pathway allows a cell to respond to external stimuli such as hormones and growth factors that interact with various receptors, including tyrosine kinase receptors like RET and G-protein-coupled receptors like the TSH receptor. In thyroid cancer, RET/PTC rearrangement is a common activator of the MAP kinase pathway [63]. Activating Ras mutations, which can activate the MAP kinase pathway, are also common in thyroid cancer [64].

BRAF mutation is a major cause of aberrant activation of the MAP kinase pathway in human cancers [65]. Among the three known Raf kinases, A-Raf, B-Raf (BRAF), and C-Raf, BRAF is the most potent activator of the MAP kinase pathway [66]. The T1799A point BRAF mutation accounts for more than 90% of the more than 40 mutations identified in the BRAF gene [63]. This mutation causes a V600E amino acid change in the BRAF protein, resulting in constitutive and oncogenic activation of the BRAF kinase [67, 68].

Discovery and characterization of the T1799A BRAF mutation in thyroid cancer represent one of the most exciting advances in the molecular biology of thyroid cancer in recent years [69, 70]. In fact, this mutation is the most common known genetic alteration in thyroid cancer. A few other activated BRAF mutants are only rarely found in thyroid cancer. These include the BRAF K601E [71], AKAP9-BRAF [66], BRAF V600E+K601del [72, 73], BRAF V599ins [74], and V600D+FGLAT601-605ins, which result from an insertion of 18 nucleotides at nucleotide T1799 [73]. Thus, the T1799A mutation is the most common and virtually the only BRAF mutation identified in thyroid cancer, commonly referred to as "BRAF mutation."

Previous studies have showed that BRAF mutation was not a germline mutation in familial nonmedullary thyroid cancers [75, 76] and, as a somatic genetic alteration, occurs exclusively in PTC and PTC-derived ATC, with an average prevalence of about 45% in the former and 25% in the latter; it does not occur in FTC or other types of thyroid tumors [66, 68]. Transgenic mouse model [73] with cell line and xenograft tumor studies [77, 78] demonstrated the tumorigenic ability of the BRAF mutation and its requirement to maintain cancer cell growth and proliferation.

Numerous clinical studies demonstrated an association of BRAF mutation with aggressive clinicopathological outcomes, including tumor invasion, metastasis, and recurrence of PTC [66, 68]. Moreover, it was demonstrated an interesting association of BRAF mutation with loss of radioiodine avidity in recurrent PTC and its failure to be cured [79]. This is consistent with research data of BRAF mutant-promoted silencing of thyroid iodide-handling genes and the reversal of this process by silencing the expression of BRAF mutant in thyroid cells. Additionally, several studies demonstrated a close association of BRAF mutation with dedifferentiation of PTC as reflected by decreased expression of thyroid-specific genes in PTC, including NIS [80, 81], TPO [77–84], pendrin [84], and Tg [80]. Therefore, BRAF mutation is a novel powerful molecular prognostic marker for poorer prognosis of thyroid cancer.

5. PI3K/Akt Signaling Pathway in Thyroid Cancer

Like the MAP kinase pathway, the phosphatidylinositol-3 kinase (PI3K)/Akt signaling pathway (PI3K pathway) plays a fundamental role in the regulation of cell growth,

proliferation, and survival, and in human tumorigenesis [85, 86]. Among the several classes of PI3Ks, class I is the best characterized and is composed of heterodimers of a regulatory subunit, particularly p85, and one of the several p110 catalytic subunits. The α-type (PIK3CA) and β-type (PIK3CB) p110 subunits are widely expressed in different tissues, whereas other types of p110 subunits are only expressed in limited tissues.

There are three types of Akts: Akt-1, Akt-2, and Akt-3. Activated Akt phosphorylates downstream protein effectors and amplifies the signaling cascade, promoting cell proliferation and inhibiting apoptosis. Signaling of the PI3K/Akt pathway is antagonized by the tumor suppressor gene PTEN product, PTEN, which is a phosphatase that dephosphorylates PIP3, hence terminating the signaling of the PI3K/Akt pathway [87].

Previous studies showed common activation of the PI3K signaling in thyroid cancers [88]. The three isoforms of Akt, Akt-1, and Akt-2 were the most abundant and important in thyroid cancer. It was reported that genomic copy gain and amplification of the PIK3CA occur in thyroid tumors, particularly FTC and ATC [89–91]. Moreover, PIK3CA mutation is particularly common in ATC and is relatively uncommon but can occur in differentiated thyroid cancer [88–91]. A number of genetic alterations in the PI3K pathway, including PIKCA mutation and amplification, Ras mutation, and PTEN mutation are found in a relatively high prevalence, particularly in FTC and ATC tumors [90, 91]. Coexistence of some of these genetic alterations and their coexistence with BRAF mutation were more frequently seen in aggressive thyroid cancers, particularly ATC [90]. Interestingly, genetic alterations that could activate both the MAP kinase and PI3K pathways were found in most (81%) ATCs.

These data provide the strongest genetic evidence for an extensive role of dual involvement of the MAP kinase and PI3K pathways in the pathogenesis of ATC, supporting a recent hypothesis that targeting multiple signaling pathways, particularly the MAP kinase and PI3K/Akt pathways, may be an effective and necessary therapeutic strategy for thyroid cancer.

6. PAX8-PPARγ Rearrangement

The PAX8 gene encodes a transcription factor essential for the genesis of thyroid follicular cell lineages and regulation of thyroid-specific gene expression. The peroxisome proliferator-activated receptor γ (PPARγ) is a member of the nuclear hormone receptor superfamily that includes thyroid hormone, retinoic acid, and androgen and estrogen receptors [92]. The PAX8-PPARγ rearrangement leads to in-frame fusion of exon 7, 8, or 9 of PAX8 on 2q13 with exon 1 of PPARγ on 3p25 [93].

The exact mechanism by which this rearrangement imparts a carcinogenic phenotype is not fully understood. It appears as though the PAX8-PPARγ chimeric protein inactivates the wild-type PPARγ, which is a putative tumor suppressor [93, 94].

As with RAS mutations, PAX8-PPARγ rearrangement has also been shown to be involved in the development of thyroid follicular carcinoma. The PAX8-PPARγ rearrangement is found in follicular thyroid carcinoma and in the follicular variant of PTC, where it occurs in approximately 33% of all tumors [95, 96]. The rearrangement has also been shown to occur in follicular adenomas and is not specific for carcinoma [95].

The role of this rearrangement in the progression and dedifferentiation of follicular thyroid cancer to PDTC and ATC has not been well defined.

7. p53 Inactivation

The p53 gene encodes a nuclear transcription factor that plays a central role in the regulation of cell cycle, DNA repair, and apoptosis [97]. As the guardian of the genome, p53 is overexpressed after cellular exposure to DNA-damaging agents and causes transient cell cycle arrest, presumably to allow for DNA repair [98].

However, if the damage is severe, it initiates apoptosis to prevent replication of the flawed cell. Cells with impaired p53 function are likely to accumulate genetic damage and are at a selective advantage for clonal expansion. Alterations in the p53 tumor suppressor gene by inactivating point mutations, usually involving exons 5–8, or by deletion result in progressive genome destabilization, additional mutations, and propagation of malignant clones. This represents the most frequent genetic damage in human cancer, usually occurring as a late tumorigenic event.

Among thyroid tumors, p53 mutations are generally restricted to PDTC and ATC [99, 100]. Point mutations of p53 occur in approximately 60% of ATC and in 25% of PDTC [99–101]. Moreover, in tumors with both well-differentiated and anaplastic components, p53 mutations were present only in the anaplastic component [102–104]. These findings are consistent with the hypothesis that p53 inactivation likely serves as a second hit, triggering tumor dedifferentiation and progression to PDTC and ATC.

Experimental studies have shown that loss of p53 results in progressive dedifferentiation of thyroid tumors. Transgenic mice with thyroid-specific RET/PTC rearrangements developed PTC, but when crossed with $p53^{-/-}$ mice, the progeny succumbed to rapidly growing PDTC and ATC [105, 106]. Conversely, the recovery of wild-type p53 in cultured ATC cells resulted in the re-expression of thyroid-specific genes and the reability to respond to thyroid-stimulating hormone [107, 108].

It is unlikely that p53 mutation is an initiating event in PDTC or ATC; it is likely a late event that contributes to the evolution of the transformed phenotype.

8. Epigenetic Regulation in Thyroid Cancer

Recognizing that DNA is associated with histone proteins to form a condensed structure known as chromatin, research is now investigating how modifications in chromatin structure may contribute to carcinogenesis. Epigenetic modifications refer to heritable alterations of the DNA structure, histones, and/or in nucleosome remodeling, resulting in altered gene

expression [109]. Epigenetic changes have been described in thyroid cancer, most notably the altered DNA methylation patterns in the CpG islands of promoters of genes important in normal thyrocyte function such as the sodium-iodide symporter and the TSH receptor [110, 111]. Increased promoter methylation by DNA methyltransferases (DNMTs) leads to gene silencing and further dedifferentiation of the thyroid tumor. DNMT inhibitors such as 5′-aza-deoxycytidine are being evaluated as "redifferentiation" agents, thereby allowing tumors to again become more responsive to conventional therapy such as radioactive iodine [112]. Identification of specific methylation patterns may also allow stratifying tumors that may no longer be responsive to thyroid hormone suppressive therapy and I-131.

Research on how posttranslational modification of histones may influence cancer has recently seen tremendous growth. The nucleosome, or basic structural unit of chromatin, consists of 147 bp of DNA wrapped around an octamer of four core histone proteins (H2A, H2B, H3, and H4) [113]. Histone modifications include methylation, acetylation, phosphorylation, and ubiquitination and may act in concert with DNA promoter methylation to modulate gene silencing [114]. Epigenetic drug targets may play a more central role in cancer treatment in the future.

9. Conclusions

Remarkable advances have occurred in recent years in understanding the molecular biology of thyroid cancer.

This is reflected in several major biological areas of thyroid cancer, including the molecular alterations for the loss of radioiodine avidity of thyroid cancer, the pathogenic role of the MAP kinase and PI3K/Akt pathways and their related genetic alterations, and the aberrant methylation of functionally important genes in thyroid tumorigenesis and pathogenesis. These exciting advances in molecular biology shine great promises on the development of novel molecular-based strategies to effectively tackle these diagnostic, prognostic, and therapeutic obstacles of thyroid cancer.

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