Molecular Biology of Thyroid Cancer

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Introduction

Our medical discoveries often follow advancement in biologic techniques. The use of karyotypic analysis, fluorescent in situ hybridization, candidate gene sequencing, microarray expression analysis, and whole-genome associations has helped determine the molecular defects causing thyroid cancer. These and future discovered defects will allow clear classifications, precise prognosis, and targeted therapy. Genetic events involved in the development of well-differentiated papillary thyroid carcinoma (PTC) include rearrangement of the tyrosine receptor kinase RET and TRK and activating mutations of the intracellular signaling effectors BRAF (B-type Raf kinase) and RAS (see Fig. 2.1) [1]. Rearrangement of PAX8/PPARγ (peroxisome proliferator–activated receptor) and RAS mutations are frequent in well-differentiated follicular thyroid carcinoma (FTC). These mutations occasionally have been identified in benign follicular adenoma (FA). Also, loss of phosphate and tensin homolog (PTEN) and activation of PI3K/AKT are involved in FTC pathogenesis. Progression of PTC and FTC to anaplastic thyroid carcinoma (ATC) is associated with mutation of p53, β catenin, as well as members of PI3K/AKT pathway. Recent reports suggest that additional molecular mechanisms such as epigenetic modification and microRNA deregulation are involved in the development of thyroid tumorigenesis. This review summarizes the molecular characterization of thyroid cancer and the molecular mechanisms involved in thyroid carcinogenesis. Table 2.1 lists the nomenclature for the various abbreviations used throughout the text.

Gene Rearrangement

Translocation of chromosomes can fuse two genes together to produce a novel protein with oncogenic properties. About 36% of FTC, 11% of FA, and 13% PTCfv (follicular variant of PTC) have a chromosomal translocation t(2;3)(q13;p25) which fuses a thyroid-specific transcription factor PAX8 to PPARγ, a nuclear hormone receptor normally involved in the differentiation of cells of different tissues especially adipocytes (see Fig. 2.2) [2–4]. This gene rearrangement has

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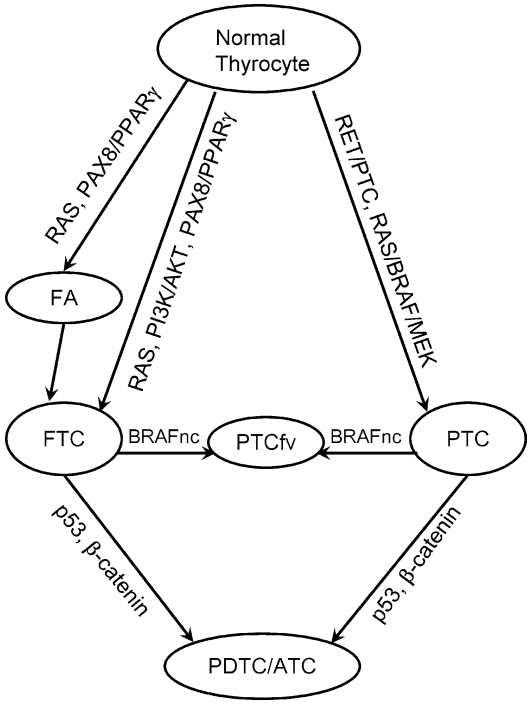

Fig. 2.1 Genetic events involved in thyroid tumorigenesis. *FA* follicular adenoma; *FTC* follicular thyroid carcinoma; *PTC* papillary thyroid carcinoma; *PTCfv* follicular variant of PTC; *PDTC* poorly differentiated thyroid carcinoma; *ATC* anaplastic thyroid cancer; *BRAFnc* nonconventional BRAF mutations (non-BRAF V600E). Adapted from Eberhardt et al. [1]

Table 2.1 Abbreviations used in this chapter

AKAP9	A-kinase anchor protein 9
AKT	Serine/thyreonine-specific protein kinase
APC	Adenomatosis polyposis coli
ATC	Anaplastic thyroid carcinoma
BRAF	V-raf murine sarcoma viral oncogene homolog B1
CK19	Cytokeratin 19
CS	Cowden syndrome
DAPK	Death-associated protein kinase
EGFR	Epidermal growth factor receptor
FA	Follicular adenoma
FAP	Familial adenomatous polyposis
FTC	Follicular thyroid carcinoma
GSK3	Glycogen synthase kinase-3 beta
HBME-1	Monoclonal antibody against a mesothelial cell antigen
HDAC	Histone deacetylase
Histone H4	Histone protein in nucleosome
HMGA2	High mobility group AT-hook 2
IRAK1	IL-receptor-associated kinase 1
LEF	lymphoid enhancing binding factor
MAPK	Mitogen-activated protein kinase
MEK	Mitogen-activated protein kinase 1
miRs	MicroRNAs
Myc	Transcription factor a portion of whose gene is similar to myelocytomatosis viral oncogene
NCOA4	Nuclear receptor coactivator 4
NFkB	Nuclear factor kappa B
NIS	Sodium iodide symporter
NTRK1	Neutropic thyrosine kinase receptor type 1
p53	Protein 53; a tumor suppressor protein
PAX8	Paired box gene 8
PDGFR	Platelet-derived growth factor receptor
PI3K	Phosphoinositide-3-kinase
PPARγ	Peroxisome proliferator-activated receptor (gamma)
PTC	Papillary thyroid carcinoma
PTCfv	Follicular variant of papillary thyroid carcinoma
PTEN	Phosphate and tensin homolog
RAS	Rat sarcoma oncogene; a transforming oncogene
RET	Rearranged during transfection; a proto-oncogene encoding a receptor tyrosine kinase
TCF	T-cell-specific transcription factor
TIMP3	Tissue inhibitor of metalloproteinase-3
TLR	Toll-like receptor
TMP3	Non-muscle tropomyosin
TRAF6	Tumor necrosis factor receptor-associated factor 6
TRK	Tyrosine receptor kinase
TSHR	Thyroid stimulation hormone receptor
TTF-1 -2	Transcription termination factor 1 and 2
3′ UTR	3′ untranslated region of mRNA
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
XRCC1	X-ray repair complementing defective repair in Chinese hamster cells 1

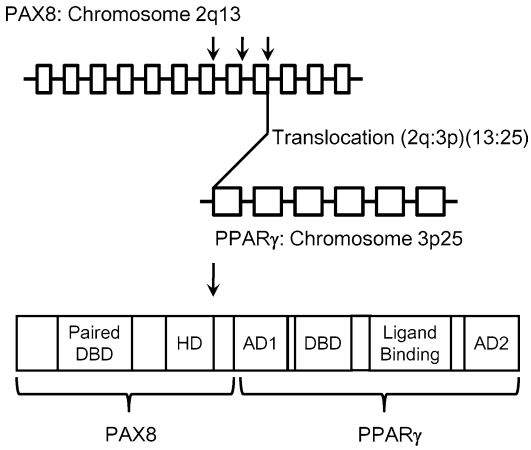

Fig. 2.2 Schematic diagram of translocation between PAX8 on chromosome 2q13 and PPARγ on chromosome 3p25. *DBD* DNA-binding domains; *HD* homeodomain; *AD* transactivation domain; ↓the different spliced isoforms of PAX8 which can fuse with PPARγ [4]

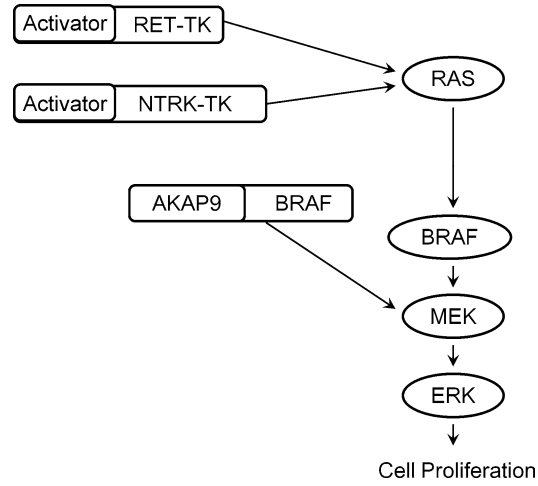

Fig. 2.3 Gene rearrangements in PTC. *TK* tyrosine kinase domain; *MEK* mitogen-activated protein kinase; *ERK* extracellular signal-regulated kinase

been identified as an early event in the development of FA and FTC. Opinions differ as to how the fusion product PAX8/PPARγ is oncogenic. Initial studies showed that the fusion protein can function as a dominant-negative suppressor of PPARγ-induced gene transcription [2] which confers anti-apoptotic properties [5]. Other studies showed that the fusion product can disrupt PAX8 transcriptional activity resulting in deregulation of expression of its target thyroid-specific genes such as thyroglobulin (Tg), thyroperoxidase (TPO), and sodium-iodide symporter (NIS) [6].

PTC is frequently (40–70%) associated with an RET gene rearrangement, in which the tyrosine kinase domain of the normally silent RET is fused with various constitutively expressed genes (see Fig. 2.3) [7]. The most common gene rearrangement products are RET/PTC1 (inv(10)(q11.2;q21)) and RET/PTC3 (inv(10)(q11.2;q10)). Both involve inversion of the long arm of chromosome 10, generating a fusion between RET and either histone H4 (histone protein in nucleosome) or nuclear receptor coactivator 4 (NCOA4) gene, respectively, for RET/PTC1 and RET/PTC3. Another gene rearrangement in PTC is an inversion of chromosome 7q generating fusion between BRAF and AKAP9 (A-kinase anchor protein 9 gene) containing BRAF kinase domain without the N-terminal auto-inhibitory domain. This fusion protein has elevated kinase activity. BRAF mutation is common in sporadic PTC, while this novel AKAP9/BRAF (inv(7)(q21–22q34)) rearrangement occurs in radiation-induced thyroid carcinomas [8]. The other less common (<12%) gene rearrangement in PTC involves the fusion between the 3′ terminal sequences encoding the kinase domain of NTRK1 (neutropic tyrosine kinase receptor type 1) on chromosome 1 and 5′ terminal sequences of various genes resulting in activated TRK oncogenes [9]. The most frequent fusion product is between NTRK1 and TMP3 (nonmuscle tropomyosin). In PTC, fusion proteins with constitutively activated kinase produced by gene rearrangements stimulate downstream mitogen-activated protein kinase (MAPK) signaling and finally promote thyroid carcinogenesis.

Somatic Mutation

PTC frequently (30–69%) has a missense somatic mutation of BRAF at nucleotide 1799 substituting an A for a T, which changes valine to glutamic acid at amino acid 600 [10]. It is the most frequently known genetic event in PTC; and this

mutation is associated with a block in differentiation of PTC. The change activates BRAF kinase leading to stimulation of the MAPK pathway, which blocks the normal differentiation of thyroid cells. The BRAF mutation occurs in about 40% of papillary and 25% of anaplastic thyroid tumors. Although this V600E BRAF mutation is highly prevalent in adult PTC, it is infrequent in childhood thyroid cancer as well as in radiation-induced thyroid tumors [11, 12]. RAS is a kinase that is upstream of BRAF. Three RAS (H-, N-, and K-) forms exist. RAS mutation occurs in 10–20% of PTC, 40–50% of FTC, and in more than 50% ATC. These mutations always localize to either codon 12, 13, or 61 [13, 14]. Mutations of either H-RAS or N-RAS at codon 61 are the most frequent RAS changes in thyroid cancer. This mutation inactivates the intrinsic GTPase activity, and, in turn, mutant RAS constitutively activates the MAPK and PI3K/AKT signaling pathways.

Signaling Pathways

Many of the genetic changes including RET/PTC gene rearrangements and RAS and BRAF mutations cause activation of the MAPK and PI3K/AKT signaling pathways (see Fig. 2.4) [15]. PTEN is a phosphatase that acts as a suppressor of PI3K/AKT pathway. Both allelic imbalance, including deletion of the PTEN locus at 10q23 (20–60% of thyroid malignancies), and silencing of PTEN by aberrant promoter methylation (>50% of FTC) enhance PI3K signaling

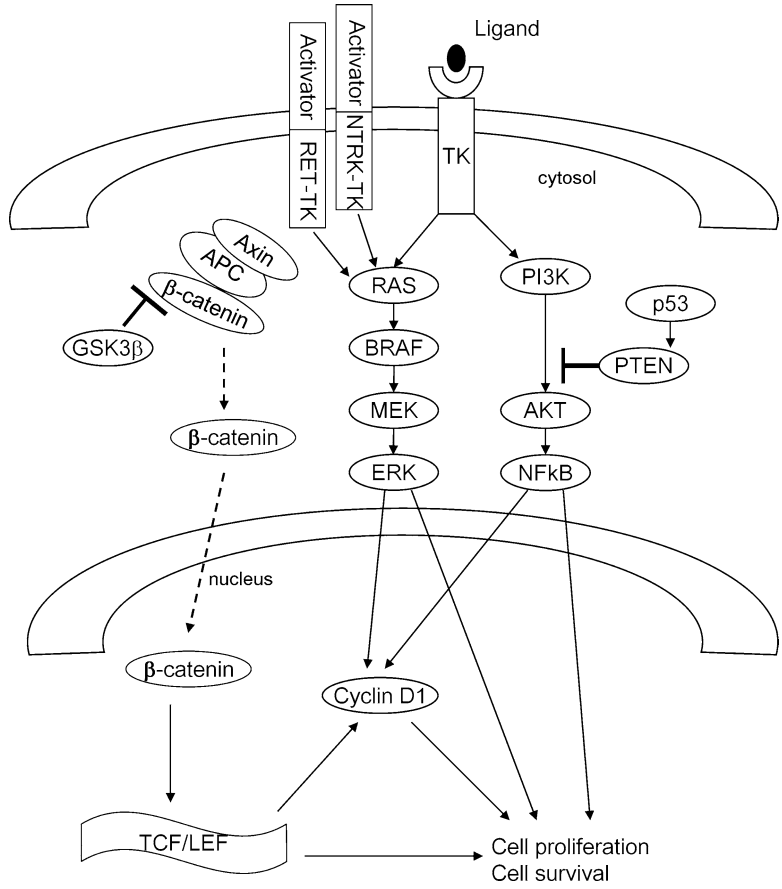

Fig. 2.4 Signaling pathways involved in thyroid tumorigenesis. *TK* tyrosine kianse; *NFkB* nuclear factor kappa B; *GSK3β* glycogen synthase kinase 3 beta; *TCF/LEF* T-cell specific transcription factor/lymphoid enhancer binding factor

and is associated with progression of thyroid tumors [16–18]. Beta-catenin signaling has emerged as another pathway of significance in thyroid cancer since proteins that regulate β-catenin (beta) activity are frequently activated, including AKT [19]. Beta-catenin is a part of a cytoplasmic complex also containing APC (adenomatosis polyposis coli) and axin, which is regulated by glycogen synthase kinase-3 (GSK3β). When the complex is phosphorylated by GSK3β, it undergoes ubiquitination and degradation. AKT phosphorylates and inactivates GSK3β releasing β-catenin from the complex, allowing it to be translocated to nucleus. In the nucleus, β-catenin activates T-cell-specific transcription factor/lymphoid enhancer binding factor (TCF/LEF) target genes such as cyclin D1 and myc, which promote cell proliferation. In some poorly differentiated PTC and undifferentiated ATC, β-catenin harbors a mutation in exon 3 where phosphorylation sites are involved in β-catenin degradation. Therefore, the mutation is associated with aberrant nuclear localization of the protein and stimulation of cell proliferation. These mutations of β-catenin are associated with a poor prognosis [20]. In PTC cell lines transfected with RET/PTC, β-catenin nuclear localization was dependent on RET/PTC kinase activity; and silencing of β-catenin by siRNA suppressed cell proliferation [21].

Epigenetic Regulation Of Genes

Two mechanisms are commonly involved in epigenetic regulation of genes: DNA methylation and histone modifications. Many thyroid-specific genes such as those for the sodium iodide symporter (NIS) and thyroid-stimulating hormone receptor (TSHR) are methylated in their promoter and their expression in thyroid cancer is frequently lost. Exposure of these cells to a histone deacetylase (HDAC) inhibitor in vitro can induce NIS expression in thyroid cancer cell lines, suggesting a role of deacetylation of histones in thyroid tumorigenesis [22]. Studies have shown that thyroid cancer cells with a BRAF mutation can be associated with methylation of iodide-metabolizing genes [23, 24]. Treatment of a human PTC-derived cell line that has a BRAF V600E mutation with a mitogen-activated protein kinase 1 (MEK) inhibitor restored the expression of TSHR and NIS [25]. Aberrant promoter methylation of the tumor suppressor gene PTEN occurs in more than 50% of FTC, which leads to gene silencing of PTEN resulting in activation of the PI3K/AKT signaling pathway [26]. In PTC, aberrant methylation of tumor suppressor genes such as TIMP3 (tissue inhibitor of metalloproteinase-3) and DAPK (death-associated protein kinase) has been associated with tumor aggressiveness [27].

Micro RNA

MicroRNAs (miRs) are short noncoding RNAs involved in gene silencing by binding to complementary sequences in the 3′UTR (untranslated region) of target mRNAs. A multitude of genes are regulated by miRs, including those involved in cell proliferation, apoptosis, and differentiation. Aberrant expression of miRs occurs in human cancers. miR expression profile analysis by microarrays containing precursor and mature miR oligonucleotide probes have been examined in thyroid cancer and have identified a distinct set of miR transcripts including upregulation of miR-221, -222, -181b, and -146 in PTC compared to normal thyroid tissue [28–30].

Laboratory studies using human PTC-derived cell lines have shown that overexpression of miR-221 in these cells lead to their enhanced proliferation; in contrast, inhibition of miR-221 expression by an antisense oligonucleotide inhibited their cell growth [30]. One of the predicted target genes of miR-221 is Cyr61 which was shown to be downregulated in a study that examined both RNA levels and protein expression by tissue microarrays on 107 PTC samples compared to normal thyroid tissue [31]. Further studies are required to elucidate the role of Cyr61 in thyroid pathogenesis. Another miR of interest is miR-146a. A common (6%) polymorphism in the precursor of this miR causes decreased expression of the mature miR-146a, which reduces the inhibition of its target genes [32]. Two of these

are IL-1 receptor-associated kinase 1 (IRAK1) and TNF receptor-associated factor 6 (TRAF6), two key molecules in the toll-like receptor (TLR) signaling pathway. Activation of TLR signaling activates the NFκB pathway and promotes thyroid tumorigenesis [33, 34]. This suggests that patients carrying this common polymorphism in their germ line have a predisposition to PTC.

Genetic Signatures of Malignancy

Microarray technology has provided molecular characterization of thyroid pathologies. Up to 20% of thyroid nodules cannot be diagnosed by fine-needle aspiration biopsy. Microarrays and multigene assays can be used as adjuncts to morphology after obtaining a biopsy. Gene expression analysis demonstrated that cyclin D1 is overexpressed in PTC, which is not detectable in normal thyroid tissue [35]. This suggests that the levels of cyclin D1 can be used as a diagnostic marker. Changes in gene expression profiles provide insights into stages of tumor progression. For example, a study of 100 benign and 105 malignant thyroid tumors using a panel of 57 molecular markers found an association of tumor pathology with the expression of a subset of markers including cytokeratin 19 (CK19), galectin-3, HBME-1, vascular endothelial growth factor (VEGF), androgen receptor, p16, and aurora-A kinase [36]. They showed that this subset of markers can discriminate benign versus differentiated thyroid carcinoma. Among the markers, CK19, galectin-3, HBME-1, and VEGF have been successfully used as preoperative diagnostic markers from tissue obtained by fine-needle aspiration and biopsy [37–40]. In another microarray analysis of 54 benign and 44 malignant tumors, 12 genes were identified as differentially expressed. Nine genes were overexpressed [high mobility group AT-hook 2 (HMGA2), leucine-rich repeat kinase 2, pleiomorphic adenoma gene 1, dipeptidyl-peptidase 4, P-cadherin, CD66c, serine protease 3, testican-1, and phosphodiesterase 5 A] and three were underexpressed (recombination activating gene 2, angiotensin II receptor type 1, and thyroid peroxidase transcript variant 5) in malignant thyroid tumor compared with benign thyroid masses [41]. Expression of HMGA2 correlates with malignant phenotype of thyroid tumors and can be used as a tool to differentiate malignant from benign lesions [42, 43].

Genetic Susceptibility

Genome-wide association studies enable identification of genetic susceptibility loci for the development of tumors (Table 2.2) [15, 44–48]. In one study of a European population, common variants on 9q22.33 and 14q13.3 were associated with thyroid cancer [44]. Individuals who were homozygous for both variants were at a 5.7-fold greater risk of developing either PTC or FTC. Two transcription factors, TTF-1 and -2 (transcription termination factor 1 and 2), are located at these regions. Both transcription factors are involved in the regulation of thyroglobulin and TPO which are crucial for thyroid organogenesis and differentiation. Also, a putative noncoding RNA gene AK023948 on chromosome 8q24 has

Table 2.2 Genetic susceptibility loci for thyroid cancer

Chromosome	Gene	Function	Specific type of thyroid cancer
1q41–42	ADPRT	ADP-ribosyltransferase	PTC and FTC [47]
2q12–14	VDR	Vitamin D receptor	FTC [46]
5q33	Pre-MiR-146a	Gene regulation	PTC [32]
8q24	AK023948	Noncoding RNA	PTC [45]
9q22.33	FOXE1	Thyroid differentiation	PTC and FTC [44]
12q24	P2X7R	Purinergic receptor	PTCfv [48]
14q13.3	TTF-1	Thyroid differentiation	PTC and FTC [44]
19q13.2–13.3	XRCC1	DNA repair	PTC and FTC [47]

Adapted from Kouniavsky and Zeiger [15]

been identified as a susceptibility gene for PTC [45]. Expression analysis showed that AK023948 is downregulated in PTC. In another study, a vitamin D receptor polymorphism was associated with an increased risk of FTC [46]. In addition, polymorphism of a DNA repair gene XRCC1 (X-ray repair complementing defective repair in Chinese hamster cells 1) is associated with either radiation-induced or sporadic PTC [47]. Approximately 5% of thyroid cancers are associated with hereditary germline genetic changes (see Fig. 2.5) [49]. Identification of the susceptibility genes for these familial cancer syndromes can aid in early diagnosis (see Table 2.3) [49]. Inactivating mutation of APC tumor suppressor gene results in familial adenomatous polyposis (FAP) and some of these patients will develop PTC which is associated with acquiring an additional RET/PTC somatic mutation. Cowden syndrome (CS) is an autosomal-dominant disorder resulting from a PTEN germline mutation. Approximately two-thirds of the CS patients will develop benign thyroid lesions and 10% have an increased risk for developing thyroid cancer [50].

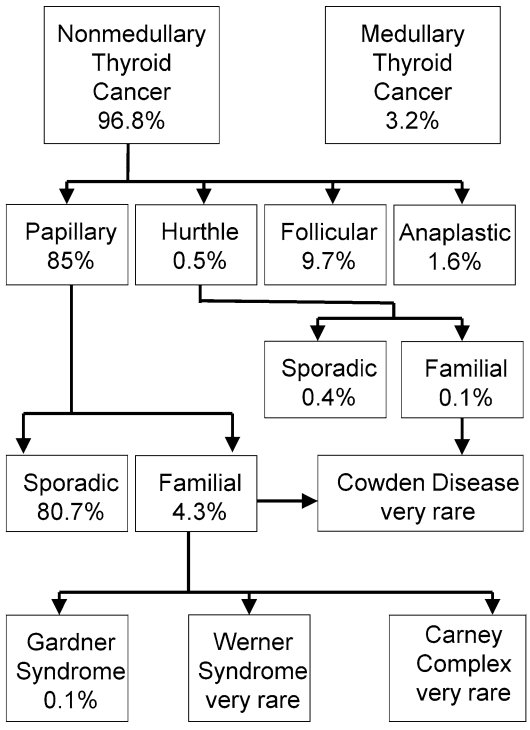

Fig. 2.5 Relative frequency of different types of familial/thyroid cancer

Table 2.3 Familial thyroid cancer syndromes

Name	Gene mutation	Histological features
FAP	APC	Cribriform variant of PTC
Gardner's syndrome	APC	Cribriform variant of PTC
Cowden's disease	PTEN	FTC
Werner's syndrome	WRN	PTC,FTC,ATC
Carney's complex	PRKAR1alpha	PTC,FTC

FAP familial adenomatous polyposis. Adapted from Vriens et al. [49]

Conclusions

Advancement of molecular biology technique provides insights into cause, classification, and prognosis of thyroid cancer. The early genetic events such as mutation of BRAF and rearrangement of PAX8/PPARγ leading to PTC and FTC are mutually exclusive events, suggesting their downstream pathways may intersect. These, as well as RAS mutations, can provide accurate diagnostic markers for initial fine-needle aspiration. Gene expression analysis has begun to elucidate a diagnostic signature of thyroid cancer versus non-neoplastic masses. Further enhancement of accurate diagnosis will be attained when more biological markers have been identified and validated.

During the progression of thyroid tumors, overexpression of EGFR (epidermal growth factor receptor), PDGFR (platelet-derived growth factor receptor), and VEGFR (vascular endothelial growth factor receptor) often occurs. Clinical studies with inhibitors of several tyrosine kinase receptors have shown that these activated growth factor receptors can be suppressed resulting in stabilization or partial remissions of the thyroid cancer [51–54]. Identification of additional molecular targets will enhance the identification of more effective approaches to advanced thyroid cancer.

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