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Review Article

Classification and General Considerations of Thyroid Cancer

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Abstract

Thyroid cancer is the most common malignancy in endocrine system, composed of four major types; papillary thyroid carcinoma, follicular thyroid carcinoma, anaplastic thyroid carcinoma, and medullary thyroid carcinoma. The incidence of thyroid cancer, especially differentiated thyroid cancer, is increasing in developed countries. Growing body of studies on molecular pathogenesis in thyroid cancer provide clues for further research and diagnostic/therapeutic targets. The general pathological classifications and clinical features of follicular cell derived thyroid carcinomas are overviewed, and recent advances of genetic alterations are discussed in this review.

ABBREVIATIONS

PTC: Papillary Thyroid Cancer; FTC: Follicular Thyroid Cancer; ATC: Anaplastic Thyroid Cancer; MTC: Medullary Thyroid Cancer; PDTC: Poorly Differentiated Thyroid Cancer; DTC: Differentiated Thyroid Cancer

INTRODUCTION

Thyroid cancer is the most common malignant disease in endocrine system and is rapidly increasing in incidence [1]. The increasing incidence partially reflects earlier detection of small asymptomatic cancers because of prevalence of screening (i.e., small papillary cancers). However, the incidence has also increased across all tumor sizes and stages [2]. Most of thyroid cancers show biologically indolent phenotype and have an excellent prognosis with survival rates of more than 95% at 20 years although the recurrence or persistent rate is still high [3]. The incidence of thyroid cancer is about three to four times higher among females than males worldwide, ranking the sixth most common malignancy diagnosed in women. Thyroid cancer can occur at any age but it is rare in childhood. Most tumors are diagnosed during third to sixth decade of life.

Most primary thyroid cancers are epithelial tumors that originate from thyroid follicular cells. These cancers develop three main pathological types of carcinomas: papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC) and anaplastic thyroid carcinoma (ATC). Medullary thyroid carcinoma (MTC) arises from thyroid parafollicular (C) cells. A histologic classification of thyroid tumors is shown in (Table 1) [4,5]. PTC and FTC are categorized as differentiated thyroid cancer (DTC) because of well differentiation and indolent tumor growth. PTC consists of 85-90% of all thyroid cancer cases, followed by FTC (5-10%) and MTC (about 2%). ATC accounts for less than 2% of thyroid cancers and typically arises in the elder patients. Its incidence continues to rise with age. The mechanism of MTC carcinogenesis is the activation of RET signaling caused by *RET* mutations [6], which are not observed in follicular thyroid cell derived cancers. Accordingly, this review mainly focuses on follicular thyroid cell derived cancers. The classic treatment for thyroid cancer is conventional thyroidectomy, in part of cases, with adjuvant radioiodine ablation, and most patients can be cured with these treatments. On the other hand, surgically inoperative recurrence, refractoriness to radioiodine in DTC, poorly differentiated thyroid carcinoma and ATC are still lethal diseases. The recent substantial developments in understanding molecular pathogenesis of thyroid cancer have shown promising treatment strategies. In this review, we discuss general pathological characteristics of follicular thyroid cell derived cancers and some recent advancement of molecular pathogenesis.

GENERAL AND PATHOLOGICAL FEATURES

Papillary carcinoma

PTC is a major differentiated adenocarcinoma which consists of 90% of thyroid cancers and shows papillary proliferation pathologically. Most cases have excellent prognosis but approximately 10% of PTC patients undergo recurrences such as lymph node recurrence and lung metastasis. Selecting such high risk patients is the most important challenge as well as treatment of radioiodine refractory PTC. Clinicopathologically, age>45 years, large tumor size, extra thyroidal invasion, distant

Table 1: Thyroid tumors by world health organization (2004).

I. Primary	
1. Epithelial	**2. Non-epithelial**
A. Follicular cell derived	- Primary lymphoma and plasmacytoma
1) Benign	- Angiosarcoma
- Follicular adenoma	- Teratoma
2) Uncertain malignant potential (UMP)	- Smooth muscle tumors
- Hyalinizing trabecular tumor	- Peripheral nerve sheath tumors
3) Malignant	- Paraganglioma
- Papillary carcinoma	- Solitary fibrous tumor
- Follicular carcinoma	- Follicular dendric cell tumor
- Poorly differentiated carcinoma	- Langerhans cell histiocytosis
- Undifferentiated (Anaplastic) carcinoma	- Rosai-Dorfman disease
B. C cell derived	- Granular cell tumor
- Medullary carcinoma	
C. Mixed follicular and C cell derived	
- Mixed medullary and follicular carcinoma	
- Mixed medullary and papillary carcinoma	
D. Epithelial tumors of different or uncertain cell derived	
- Mucoepidermoid carcinoma	
- Sclerosing mucoepidermoid carcinoma with eosinophilia	
- Squamous cell carcinoma	
- Mucinous carcinoma	
- Spindle cell tumor with thymus-like differentiation (SETTLE)	
- Carcinoma showing thymus-like differentiation (CASTLE)	
- Ectopic thymoma	
II. Secondary	

metastasis, vascular invasion and poor differentiated histology are well known detrimental prognostic factors [4].

PTC is usually gray-white color and shows a variety of gross appearance such as tumors with central scar and infiltrative borders, encapsulated tumor and lesional calcification (Figure 1A). Nearly half of PTCs have multifocal lesions and regional lymph node metastasis. These characteristics do not affect long-term survival [7-9].

Most of PTCs shows papillary growth pattern but nuclear features are more important diagnostic hallmark which are common in almost all cases than such growth pattern itself (Figure 1B) [4]. The nuclear appearances of PTC are clear, ground glass, or Orphan-Annie eyed [10,11]. These nuclei are larger than normal follicular nuclei and overlapping each other. The nuclei contain eosinophilic inclusions and have longitudinal grooves [12]. These nuclear features are important characteristics of PTC but not specific. Indeed, chronic thyroiditis frequently shows similar intranuclear inclusions or nuclear grooves as well as follicular adenoma [4].

Several subtypes are thought to be associated with either favorable or aggressive phenotype although it is still controversial. Here, we discuss about follicular variant, tall cell variant, diffuse sclerosis variant, and solid variant.

A certain part of follicular variant of papillary carcinoma (FVPTC) was classified as FTC or follicular adenoma in the past. The nuclei of this variant rarely have all of the features of PTC (eg. rare nuclear groove). Accordingly, FVPTCs are often diagnosed as indeterminate cytology in contrast to high diagnostic accuracy of usual PTC. FVPTC is recognized by its follicular structure with papillary cytology, and composed of 2 subtypes; diffuse/invasive (infiltrative) and encapsulated type. FVPTC is associated with favorable prognosis especially if tumor is encapsulated [13]. Diffuse/invasive subtype has similar clinical features to usual PTC. Diagnosis of encapsulated subtype is still under debate since this subtype shows no invasion or incomplete nuclear characteristics. This encapsulated subtype is slowly growing and conservative treatment may be warranted [14].

Tall cell variant composes 10% of PTC, and have a 10-year mortality rate of up to 25%, less favorable prognosis than usual PTC. This variant is often associated with poor prognostic characteristics such as elder age, extra thyroidal invasion, and high mitotic rate. The tall cells are twice as tall as its width, and should occupy >50% of papillary carcinoma cells [4].

The diffuse sclerosis variant is 3% of PTC, which infiltrates the entire thyroid gland and is associated with younger age [15]. Presence of many psammoma bodies is one of hallmarks of this variant. Extensive calcification causes exceedingly firm tumor. Background thyroid of this variant shows chronic lymphatic thyroiditis with lymphocytic infiltration, resembling Hashimoto disease [16]. This variant PTC often shows extra thyroidal extension and regional lymph node metastasis at diagnosis,

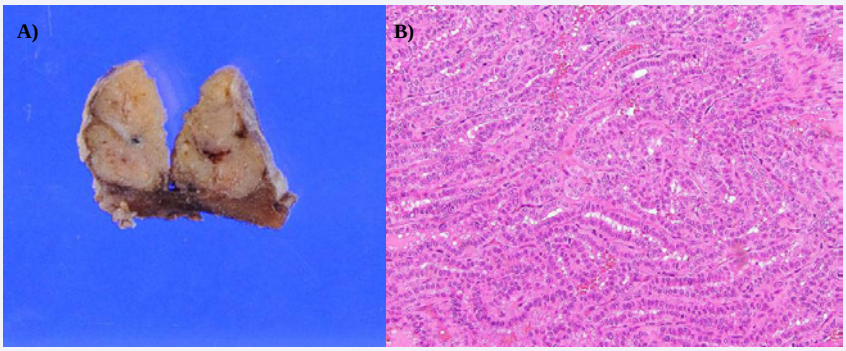

Figure 1 Typical images of papillary thyroid carcinoma
Macroscopic (A) (scale bar = 10 mm) and microscopic (B) (H&E, x200) features of PTC.

leading to decreased recurrence free survival although mortality is low [17].

Solid variant PTC is diagnosed when solid growth represents more than 50% of tumor. This variant is commonly seen in children and often associated with secondary PTC patients after the Chernobyl nuclear accident [18,19]. Both lymphatic and venous invasion are frequently observed in this variant [20]. Some studies reported that the solid variant is associated with poor prognosis whereas others considered the prognosis of this variant is almost as good as usual PTC [21,22].

Follicular carcinoma

FTC represents 5-15% of thyroid cancer with follicular differentiation but no papillary nuclear characteristics [4]. FTC is a solitary encapsulated tumor with gray-tan-pink color, usually focal hemorrhage. FTC is diagnosed by follicular cell invasion of the tumor capsule and/or blood vessels. Vascular invasion leads to worse prognosis than capsular infiltration alone [23]. Majority of FTCs are minimally invasive with slight tumor capsular invasion alone (Figure 2). These minimally invasive FTCs are similar appearance to follicular adenomas and rarely cause distant metastasis [24]. Accordingly, a minimally invasive FTC is difficult to distinguish from a follicular adenoma in cytology or frozen section, and can be diagnosed only after thyroidectomy. Widely invasive FTC is much less common but ~80% of these tumors cause distant metastasis, leading to high mortality rate at around 20% [4]. The poor prognostic factors are distant metastasis, age>45 years, large tumor size, extensive vascular invasion, extra thyroidal extension, and widely invasive tumors [25].

Hürthle cell carcinoma

Hürthle cell carcinoma (oxyphilic cell carcinoma) is presumed to be a variant of FTC but its prognosis is thought to be worse than usual FTC [26,27]. A variant of papillary carcinoma is rare and have similar prognosis as FTC [28]. More than 75% follicular cells with oncocytic characteristics are included in Hürthle cell tumor [29]. Oxyphilic or oncocytic cells are characterized by its polygonal shape, eosinophilic granular cytoplasm, hyper chromatic or vesicular nuclei with large nucleolus, and abundant mitochondria.

Anaplastic carcinoma

ATC is extremely aggressive undifferentiated tumor, with almost 100% disease-specific mortality [30], representing about 40% thyroid cancer deaths by only <2% of thyroid cancers. The median survival from diagnosis is around 6 months [31]. ATC extensively invades into surrounding structures, and distant metastases are observed at diagnosis in one-third of ATC patients. Peak age of patients is older than that of DTCs and >70% of patients are women [32]. Approximately 50% of ATC patients have prior or concurrent DTC. It is suggesting that ATC emerges as a result of de-differentiation of DTC. In contrast to DTC, ATC usually does not uptake iodine, leading to refractoriness against radioiodine treatment. Although clinically apparent ATCs are usually unresectable, intrathyroidal ATCs are surgically resectable and such radical resection offers better outcomes [33]. ATC shows extremely invasive large solid tumor with necrosis and hemorrhage (Figure 3). Large, pleomorphic giant cells resembling osteoclasts is one of hallmarks of ATC cells [34]. ATC is composed of spindle cells and squamoid cells.

Medullary carcinoma

MTC represents less than 5% of thyroid carcinomas, which is neuroendocrine tumor originated from C cells of ultimobranchial body of neural crest and secrets calcitonin. Seventy to eighty percent of MTCs are sporadic while 20-30% of MTCs are familial. Familial MTCs are all autosomal dominant inheritance of germ line *RET* mutations and classified to 3 categories; multiple endocrine neoplasia 2A (MEN2A), multiple endocrine neoplasia 2B (MEN2B), and familial medullary thyroid carcinoma (FMTC) [35]. Peak age of familial MTC is younger (approximately 35 years) that that of sporadic MTC (40-60 years). The overall 5-year survival of patients with MTC is 86%. Poor prognostic factors include older age, advanced stage, the presence of lymph node metastasis at diagnosis, and somatic *RET* mutation [36]. Sporadic MTC is usually solitary whereas most of familial MTC exhibit bilateral, multicentric foci.

MTCs typically exhibit gray-tan color, firm, solid tumors and do not have a well-formed capsule. Tumor includes high concentration of C cells. MTC cells are round to oval, spindle, or polyhedral. Broad fibro vascular bands separate tumors into nodules (Figure 4). The nuclei are round to oval with salt-and-pepper nuclear chromatin. Amyloid deposits from calcitonin are

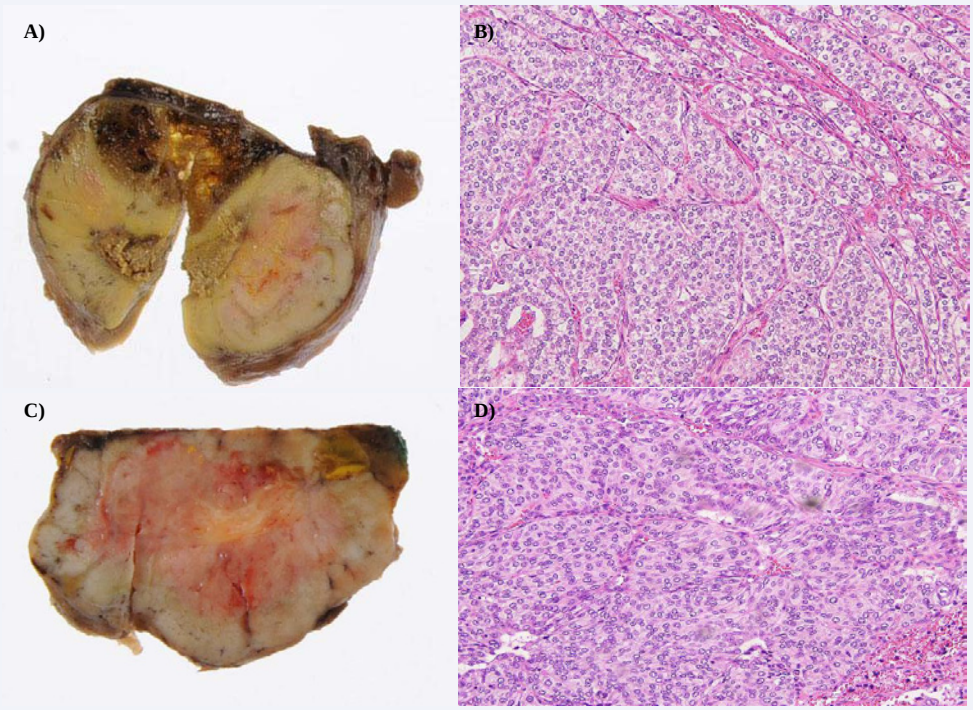

Figure 2 Typical images of follicular thyroid carcinoma
Gross (scale bar = 10 mm) and microscopic (H&E, x200) images of minimally invasive (A and B) or widely invasive (C and D) FTC

Table 2: Genes involved in thyroid follicular cell derived tumors.

Genes	Type of tumors		Associated signaling pathways
BRAF^{V600E} (mutation)	PTC (usual)	45	MAPK
	FVPTC	15	
	TCPTC	80-100	
	ATC	25	
RET/PTC (translocation)	PTC (usual)	15-45	MAPK and PI3K-AKT
	FTC	0	
	PDTC	0-10	
	ATC	0	
HRAS, KRAS, NRAS (mutation)	FA	20-25	MAPK and PI3K-AKT
	FTC	30-50	
	PTC (usual)	0-20	
	FVPTC	30-50	
	PDTC	20-40	
	ATC	20-30	
PAX8/PPARγ (translocation)	PTC (usual)	0	PAX8-associated nuclear transcription
	FVPTC	0-30	
	FTC	25-65	
	PDTC	0	
	ATC	0	
PTEN (mutation)	FA	0	PI3K-AKT
	PTC (usual)	<2	
	FTC	10-15	
	ATC	10-20	

PTEN (deletion)	FTC	30	PI3K-AKT
CTNNB1 (mutation)	PDTC	25	WNT-β-catenin
	ATC	60-70	
TP53 (mutation)	PDTC	25	p53-coupled pathways
	ATC	70-80	
IDH1 (mutation)	PTC (usual)	10	IDH1-associated metabolic pathways
	FVPTC	20	
	FTC	2-25	
	ATC	10-30	
NDUFA13 (*GRIM19*) (mutation)	HCTC	15	Mitochondrial function

Abbreviations: FVPTC: Follicular Variant PTC; TCPTC: Tall Cell Variant PTC; FA: Follicular Adenoma; PDTC: Poorly Differentiated Thyroid Cancer; HCTC: Hürthle Cell Thyroid Cancer; IDH1: Isocitrate Dehydrogenase 1; NDUFA13: NADH Dehydrogenase (Ubiquinone) 1α Subcomplex 13

frequently present in stroma. A background of C cell hyperplasia is observed in familial but not in sporadic MTCs [37].

Molecular pathogenesis

Similarly to other solid cancers, thyroid cancer is initiated by genetic alterations and epigenetic changes in driver oncogenes or tumor suppressor genes [38,39]. Recent advancement of molecular diagnosis in thyroid cancer provides more effective treatment strategies for individual cases. The well known genetic mutation underlying tumorigenesis in thyroid is the activating mutation of *RET* oncogene in MTC [6]. This *RET* mutation is not present in thyroid follicular cell derived tumors which represent the most common types of thyroid neoplasms, that is, follicular adenoma and well differentiated papillary and follicular carcinomas. Poorly differentiated and anaplastic carcinomas are considered to develop as a consequence of dedifferentiation of a well differentiated PTC or FTC (Figure 5). In these follicular cell derived cancers, other molecular alterations such as the RAS pathway and the PI3K-AKT pathway are identified. Here, we focus on the molecular pathogenesis of follicular cell derived carcinoma. Table 2 demonstrates genetic alterations which have been identified to be involved in thyroid cancer development.

Gene mutations

BRAF point mutation (T1799A) in exon 15 leads to the expression of BRAF-V600E mutant protein and results in constitutive serine/threonine kinase activation [40,41]. $BRAF^{V600E}$ mutation is one of the most common genetic alteration in thyroid cancer, occurring in approximately 45% (30 to 70%) of sporadic PTC whereas about 15% in follicular variant PTC [42]. Particularly, 80 to 100% of tall cell variant PTC harbor $BRAF^{V600E}$ mutation. $BRAF^{V600E}$ mutation predicts poorer clinical outcomes in PTC, including aggressive pathological features, and higher recurrence rate [43,44]. $BRAF^{V600E}$ mutation is considered to cause loss of radioiodine avidity and consequently refractoriness to radioiodine treatment.

RAS point mutation is frequently found in thyroid cancer as well as other solid cancers. Among genes of three RAS isoforms (HRAS, KRAS, and NRAS), *NRAS* is predominantly mutated in thyroid tumors. *RAS* mutation is relatively rare (0-20%) in usual PTC whereas almost half of FTC and follicular variant PTC harbor *RAS* mutation [45,46]. *RAS* mutation is observed in approximately 20% of follicular adenoma, suggesting that *RAS* mutation is early event in tumorigenesis. *RAS* mutation dampens GTPase activity, leading to constitutive active state. *RAS* mutation activates PI3K-AKT pathway in thyroid tumorigenesis.

Tumor suppressor gene *PTEN* is a negative regulator of PI3K-AKT signaling pathway by opposing function of PI3K. Mutation or deletion of *PTEN* causes follicular thyroid cell tumorigenesis as well known in Cowden's disease (syndrome). Cowden's syndrome is an autosomally inherited disease caused by germ line mutations of the *PTEN* [47]. Cowden's disease is a cancer predisposition syndrome closely related to an increased risk of thyroid, breast and endometrial cancers as well as benign hamartomas. Alteration of *PTEN* is often observed in 40% of FTC overall. Silencing of *PTEN* by promoter hypermethylation is also found in FTC and ATC [48-50].

Other genes are also mutated in thyroid cancers such as *CTNNB1*, *TP53*, *IDH1* [51], and *NDUFA13* (*GRIM19*). *CTNNB1* is involved in WNT-β-catenin pathway and often mutated in ATC [52]. *TP53* encodes tumor suppressor p53 and is involved in a variety of solid cancers. *TP53* mutation is frequently observed in ATC (70-80%) [53,54]. Mutations *CTNNB1* and *TP53* are preferentially observed in ATC or poorly differentiated thyroid carcinoma, suggesting that these genetic alterations may be associated with dedifferentiation or late event in follicular cell derived cancer progression (Figure 5). Although Hürthle cell thyroid cancer does not carry common genetic alterations such as $BRAF^{V600E}$, *RAS* or *RET/PTC* [55], 15% of Hürthle cell thyroid cancer harbor mutations of *NDUFA13* (*GRIM19*) instead [56].

Gene translocations

Chromosomal rearrangements of the tyrosine kinase proto-oncogene *RET*, specifically *RET/PTC* rearrangements, are found in 15-45% of usual PTC and 80% of radiation-induced PTC [57,58]. *RET* is a proto-oncogene encoding receptor tyrosine kinase (RTK). Accordingly, these rearrangements constitutively activate tyrosine kinase, resulting in activation of the MAPK and PI3K-AKT pathways. Among numerous types of *RET/PTC* translocation, *RET/PTC1* (fusion with CCDC6) and *RET/PTC3* (fusion with NCOA4) are most common [59,60]. In cases of the Chernobyl accident, *RET/PTC3* translocation was commonly observed, then followed by *RET/PTC1* translocation with delay [61].

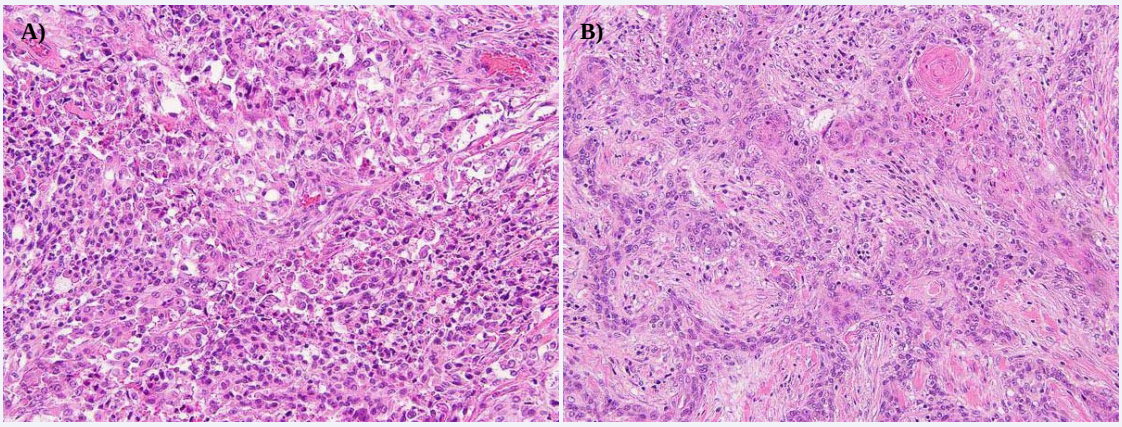

Figure 3 Anaplastic thyroid carcinoma
Microscopic images of 2 cases of ATC (H&E, x200).

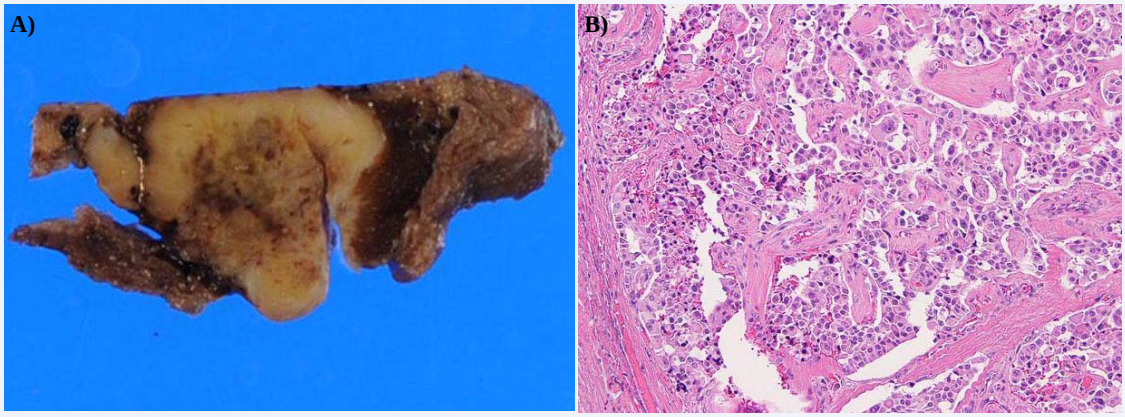

Figure 4 Medullary thyroid carcinoma
Macroscopic (A) (scale bar = 10 mm) and microscopic (B) (H&E, x200) features of MTC.

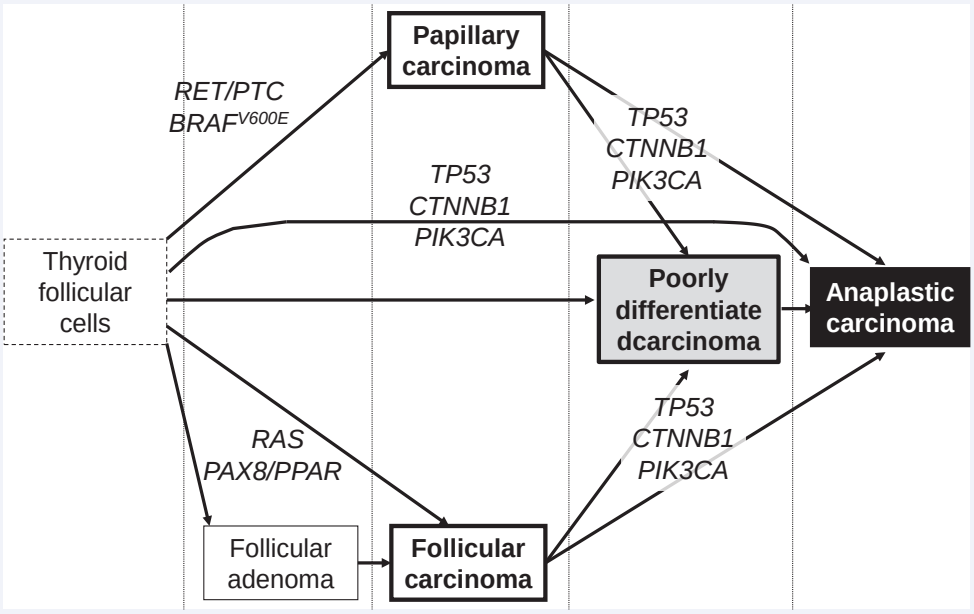

Figure 5 Putative progression steps of thyroid follicular cell derived tumors and associated genetic mutations.

The paired box 8 (*PAX8*)/ peroxisome proliferator-activated receptor γ (*PPARG*) gene translocation is another common recombinant oncogene in thyroid cancer. *PAX8/PPARG* translocation is often observed in FTC (25-60%) and follicular variant PTC (~30%). The PAX8/PPARG fusion protein acts as a dominant-negative inhibitor of wild-type tumor suppressor mechanism of *PPARγ* [62]. In contrast, the effects of *PAX8/PPARG* translocation on PAX8 function are still elusive.

DNA polymorphisms

According to recent advancement in genome-wide analysis, gene variants have been shown to affect on susceptibility to differentiated thyroid cancer (DTC) although it is likely to be low impact on tumorigenesis [63]. DNA polymorphism is a DNA sequence variation occurring commonly with the same population, where the minimum frequency is typically taken as 1%. Associations of DNA polymorphism with DTC are needed to be confirmed. Combined *GSTN1*-null/*GSTT1*-null (cytosolic phase II enzyme related genes) genotypes and homozygous carries of the *P53* 72Pro allele are reported to be associated with a high risk of DTC [64-66]. In the large-scale study in Iceland, two common variants on 9q22.33 and 14q13.3 are associated with DTC [67]. The gene nearest to the 9q22.33 locus is FOXE1 (TTF2) and NKX2-1 (TTF1) is among the genes located at the 14q13.3 locus. These genes encode important transcription factors associated with thyroid functions. Individuals who are homozygous for both variants showed 5.7 fold higher risk of DTC than non-carriers.

MicroRNAs

MicroRNA (miR) is a small (19-25 nucleotides) non-coding RNA that negatively regulates the expression of coding genes [68]. miRs are considered regulating around 30% of the human genome and may act as tumor suppressor genes or oncogenes [69]. A polymorphism in one miR (miR-146a) and other numerous miRs involved in major signaling pathways (mainly PTEN-PI3K-AKT pathway) are suggested to be important in DTC carcinogenesis [70].

CONCLUSION

This review overviews the general pathological features and molecular pathogenesis in follicular cell derived thyroid carcinomas. Recent advances in understanding molecular pathogenesis of thyroid carcinoma give clues to develop novel clinical strategies. However, the mechanisms of tumorigenesis in thyroid remain to be elusive including penetrance of genetic alteration or environmental factors.

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