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Review

Genetics and epigenetics of sporadic thyroid cancer ☆

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ABSTRACT

Thyroid carcinoma is the most common endocrine malignancy, and although the disease generally has an excellent prognosis, therapeutic options are limited for patients not cured by surgery and radioiodine. Thyroid carcinomas commonly contain one of a small number of recurrent genetic mutations. The identification and study of these mutations has led to a deeper understanding of the pathophysiology of this disease and is providing new approaches to diagnosis and therapy. Papillary thyroid carcinomas usually contain an activating mutation in the RAS cascade, most commonly in BRAF and less commonly in RAS itself or through gene fusions that activate RET. A chromosomal translocation that results in production of a PAX8-PPARG fusion protein is found in follicular carcinomas. Anaplastic carcinomas may contain some of the above changes as well as additional mutations. Therapies that are targeted to these mutations are being used in patient care and clinical trials.

Contents

Abbreviations: ATC, anaplastic thyroid carcinoma; DTC, differentiated thyroid carcinomas; FTC, follicular thyroid carcinoma; FTS, farnesylthiosalicylic acid; FVPTC, follicular variant papillary thyroid carcinoma; HDAC, histone deacetylase; IDH, isocitrate dehydrogenase; lncRNA, long non-coding RNA; MAPK, mitogen activated protein kinase; MTHFR, methylenetetrahydrofolate reductase; NIS, sodium iodide symporter; PI3K, phosphatidylinositide 3-kinase; PPFP, PAX8-PPARG fusion protein; PTC, papillary thyroid carcinoma; RAI, radioactive iodine; TCV, tall cell variant.

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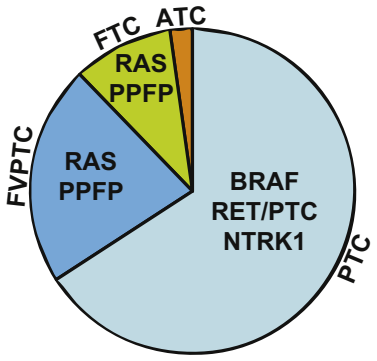

Fig. 1. Pie chart showing the most common histological types of thyroid carcinoma and the most common mutations and gene fusions within each type. ATC, anaplastic thyroid carcinoma; FTC, follicular thyroid carcinoma; FVPTC, follicular variant papillary thyroid carcinoma; PPFP, PAX8-PPARG fusion protein; PTC, papillary thyroid carcinoma. Recurring mutations in ATC are not shown.

1. Introduction

Cancer is a consequence of accumulated genetic alterations; understanding how these changes effect the disease state offers the hope of developing new and better treatments, and may provide improved prognostic information for the individual patient. Thyroid cancer is the most common endocrine malignancy and more than 1800 US deaths are estimated to result from thyroid carcinomas annually (Cancer of the Thyroid – SEER Stat Fact Sheets; Tuttle et al., 2010). We offer below a review of genetic abnormalities commonly encountered in sporadic thyroid carcinomas. This review will be focused on carcinomas of the major thyroid cell type, the thyroid hormone-producing follicular cell. It will not discuss medullary thyroid carcinomas, which are tumors of the calcitonin-producing parafollicular C cells.

Thyroid carcinomas are classified by their histological appearance in a schema largely affirmed by more recent molecular data. Differentiated thyroid carcinomas (DTC) are the most common and contain cells which retain many features of normal thyrocytes. DTCs are further divided into papillary and follicular thyroid carcinomas (PTC and FTC, respectively). Anaplastic thyroid carcinomas (ATC) are completely undifferentiated, aggressive, therapy resistant, and usually fatal cancers (Cooper et al., 2009). Recurrent mutations in thyroid carcinomas are predominantly associated with specific tumor histologies and are implicated in disease etiology (Fig. 1 and Table 1).

2. Papillary thyroid carcinoma

Papillary thyroid carcinomas account for more than 85% of DTCs. PTCs are etymologically derived from the replacement of normal thyroid follicular structures by papillae – several layers of neoplastic thyroid epithelial cells lining a fibrous core. Presently PTCs are identified by certain characteristic nuclear features such as larger, clearer nuclei with inclusion bodies of cytoplasm and nuclear grooves (Baloch and LiVolsi, 2005). There are several histological subtypes of PTC, including classic PTC, follicular variant PTC (FVPTC), tall cell variant (TCV) and others. FVPTCs lack papillary structures but contain follicles and retain nuclear features of PTC; it is this latter attribute that separates them from pure FTCs. However, as will be described subsequently, the mutational profile of FVPTCs closely resembles that of FTCs. TCV PTCs contain cells that are at least twice as tall as wide. These carcinomas tend to be more aggressive, and the tall cell phenotype has a specific mutational correlate. Mutations or translocations in BRAF, RET, RAS, and NTRK1 – all participants in the same signaling cascade – are known in PTC (Fig. 2). In addition, translocations between PAX8 and PPARG occur in FVPTC.

2.1. BRAF

BRAF is a member of a small family of RAF proteins that function as cytoplasmic serine/threonine protein kinases in the mitogen activated protein kinase (MAPK) signaling cascade. Members of the MAPK cascade modulate essential cellular processes such as proliferation, differentiation, and survival. BRAF is physiologically activated by RAS (Avruch et al., 2001). Once activated, BRAF can activate MEK by phosphorylating it and thereby transduce the mitogenic signals to downstream elements such as ERK. BRAF mutations found in cancer generally result in unregulated kinase

Table 1
Detailed listing of gene mutations associated with sporadic thyroid carcinomas.

Gene	Mutations	Activating or Inactivating	Common associations
AKT1	G49A	Activating	Poorly differentiated carcinomas
ALK	Exon 23	Activating	Poorly differentiated and anaplastic carcinomas
BRAF	V600E, K601E, AKAP9 gene fusion	Activating	Papillary and anaplastic carcinomas. V600E is by far most common and is over-represented in tall cell variant, uncommon in follicular variant. AKAP9-BRAF is over-represented in radiation induced papillary carcinomas
CTNNB1	Exon 3	Activating	Poorly differentiated and anaplastic carcinomas
IDH1	Exon 4	Abnormal activity	Identified in a minor fraction of most types of thyroid carcinoma
NDUFA13 (GRIM19)	Various	Inactivating	Hurthle cell carcinoma
NTRK1	Gene fusions with TPM3, TPR, and TFG	Activating	Infrequently found in papillary carcinoma
PIK3CA	Exons 9, 20	Activating	Follicular, poorly differentiated, and anaplastic carcinomas.
PPARG	Gene fusion with PAX8, rarely with CREB3L2	Context dependent	Follicular carcinomas and follicular variant of papillary carcinomas
PTEN	Deletion or inactivating mutation	Inactivating	Follicular, poorly differrentiated and anaplastic carcinomas
RAS	NRAS Q61, HRAS Q61, KRAS G12, G13	Activating	Follicular, follicular variant of papillary, poorly differentiated and anaplastic carcinomas. NRAS mutations are most common, KRAS are least common
RET	Gene fusions with CCDC6 (RET/PTC1), NCOA4 (RET/PTC3), and others	Activating	Papillary carcinomas. Gene fusions result in constitutively active RET kinase domain. RET/PTC1 and RET/PTC3 are over-represented in radiation induced thyroid cancer
TP53	Exons 5–8	Inactivating	Poorly differentiated and anaplastic carcinomas

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