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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.

Keywords

AKT; anaplastic; BRAF; follicular; NTRK1; papillary; PAX8-PPARG; PTEN; RAS; RET; thyroid carcinoma

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

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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 activity and increased MEK activation; those mutations which do not exhibit increased kinase activity can nonetheless produce higher ERK activation downstream (Wan et al., 2004).

A wide variety of BRAF mutations are found in a wide range of cancers, but more than 95% of all cases are of a single variety denoted BRAFV600E. A missense thymine to adenine transversion at the 1799 nucleotide position leads to a valine to glutamate substitution at the 600 amino acid position. The mutation results in a constitutively active BRAF, no longer dependent on RAS, and hence causes constitutive MEK/ERK activation (Cantwell-Dorris et al., 2011; Wan et al., 2004). In addition to PTCs, BRAFV600E is found in the majority of malignant melanomas and hairy cell leukemias, as well as in significant fractions of other cancers such as astrocytomas and carcinomas of the colon, lung and ovary (reviewed in Pakneshan et al., 2013).

Mutant BRAF expression contributes to the transformation of cell lines and thyroid tumor formation in mice. BRAFV600E induces genomic instability in the rat PCCL3 thyrocyte cell line and increases focus formation in NIH3T3 cells (Mitsutake et al., 2005; Moretti et al., 2006). Expression of rare BRAF mutants, including fusion chimera generated by chromosomal rearrangements and truncated proteins generated by alternative splicing, shows that uninhibited BRAF kinase activity generally has pro-oncogenic effects (Baitei et al., 2009; Ciampi et al., 2005; Liu et al., 2007b). Early or late expression of BRAFV600E in transgenic mice rapidly produces enlarged and abnormal thyroids followed by invasive PTC

within a year, confirming BRAF mutations as a causative event in PTCs (Charles et al., 2011; Knauf et al., 2005).

Due to differing techniques, cohorts, etc., the reported prevalence of BRAF mutations in PTC varies considerably, though it is clearly the most common mutation in PTC and therefore in thyroid carcinomas. The estimate for occurrences of BRAF mutations in general and BRAFV600E in particular range from 28% to 77% of all PTC cases; the average reported value is ~45% (Cohen et al., 2003; Fernandez et al., 2013; Frattini et al., 2004; Guerra et al., 2012; Lim et al., 2013; Namba et al., 2003; Nikiforova et al., 2003a; Nikiforov, 2011; Puxeddu et al., 2004). BRAF mutations are particularly common in TCV PTC, and are uncommon in FVPTC.

The presence of BRAF mutations correlates with more aggressive disease. Data from numerous groups and a meta-analysis associate BRAF mutations in PTC with large tumor size, extrathyroidal extension, higher stage at presentation, lymph node metastasis and increased risk of recurrence (Elisei et al., 2012; Fernandez et al., 2013; Jo et al., 2006; Kim et al., 2012; Lim et al., 2013; Namba et al., 2003; Nikiforova et al., 2003a; Xing et al., 2005). A recent retrospective analysis of 1849 PTC patients (Xing et al., 2013) found a mortality rate of 5.3% in BRAFV600E-positive patients versus 1.1% in mutation-negative patients. However, the association of BRAFV600E with mortality was lost after adjusting for standard clinical and histological prognostic features (e.g. the presence of extrathyroidal invasion or metastases). On the one hand, this suggests that BRAFV600E is a major driving force that underlies these traditional clinical and histological prognostic features. On the other hand, the data call into question the added value of determining the BRAF status of a given tumor, at least in terms of predicting mortality.

A clinically relevant feature of BRAF-mutated PTCs is their diminished responsiveness to radioactive iodine (RAI). Thyrocytes concentrate and organify iodine as part of their physiological function, making RAI useful to identify and ablate remnant and metastatic thyroid carcinoma. Loss of RAI avidity is a significant problem in progressive disease and severely limits the available treatment options. BRAF-mutated PTCs are associated with decreased expression of proteins involved in the uptake and organification of iodide, such as the sodium iodide symporter (NIS), resulting in an increased number of RAI courses required to achieve disease free status and increased incidence of RAI refractory recurrence (Barollo et al., 2010; Durante et al., 2007; Elisei et al., 2012; Gao et al., 2012; Riesco-Eizaguirre et al., 2006).

Therefore, re-establishment of RAI avidity is a major avenue of research in thyroid cancer. Small molecule inhibitors against BRAF or its downstream effector MEK are effective at increasing NIS expression in preclinical models (Durante et al., 2007; Liu et al., 2007a; Nucera et al., 2009). Selumentinib (AZD6244, ARRY-142886) is a MEK inhibitor that increases RAI uptake and effects partial responses in some BRAF or RAS -mutated, RAI-refractory patients (Ho et al., 2013).

Small molecule inhibitors of BRAF are potentially useful drugs in BRAF-mutated PTCs. Sorafenib (BAY 43-9006) was identified as part of a drug discovery program targeting BRAF (Lyons et al., 2001). It also blocks the actions of VEGF receptors, PDGF receptors, Kit, and RET, making it among the first multikinase inhibitors to be in clinical trials (Caronia et al., 2011; Murphy et al., 2006). Sorafenib exhibits broad but modest and ultimately transient anti-tumor effects in clinical trials on patients with advanced, metastatic thyroid cancer, though a positive response does not appear to depend upon the BRAF status of the tumor (Capdevila et al., 2012; Gupta-Abramson et al., 2008; Hoftijzer et al., 2009; Kloos et al., 2009; Marotta et al., 2013; Schneider et al., 2012; Shen et al., 2012).

Vemurafenib is particularly interesting in that it is a specific inhibitor of BRAFV600E, not wild type BRAF. Vemurafenib is highly therapeutic in BRAFV600E melanomas, although resistance eventually develops. A phase I trial of vemurafenib in 3 BRAFV600E thyroid cancer patients resulted in one partial response (Kevin Kim et al., 2013).

2.2 RET

RET is a cell surface receptor tyrosine kinase that transmits environmental cues to RAS and the downstream MAPK pathway (Marotta et al., 2011). RET mutations in PTC are exclusively genetic rearrangements resulting in chimeric proteins denoted RET/PTC1, RET/PTC2, etc. RET/PTC is found in ~15% of PTCs. RET itself is not expressed in normal thyroid follicular cells, but the juxtaposition of the 3' kinase domain of RET to a 5' partner and its promoter leads to fusion oncoprotein expression and aberrant kinase activity, with downstream activation of the RAS/MAPK pathway and the phosphatidylinositide 3-kinase (PI3K)/AKT pathway (Bunone et al., 2000; Grieco et al., 1990; Melillo et al., 2005; Miyagi et al., 2004). Although many fusion partners of RET have been described, the most frequent are CCDC6 (resulting in RET/PTC1) and NCOA4 (resulting in RET/PTC3) (Bongarzone et al., 1994; Santoro et al., 1994). The common feature of the fusion partners is their ability to constitutively dimerize, which results in constitutive RET tyrosine kinase activity via autophosphorylation (Salvatore et al., 2000). There also is evidence that RET/PTC can heterodimerize with the EGFR, and that the EGFR kinase can then phosphorylate and activate the RET kinase domain (Croyle et al., 2008).

Exogenously induced expression of RET/PTC proteins results in PTC-like phenotypes in culture and mouse models. In non-malignant primary thyroid cells or cell lines, RET/PTC expression decreases thyroid specific gene expression, alters cell and colony morphology to resemble features of PTC, renders the cells insensitive to or independent of TSH signaling, and especially in the cases of RET/PTC3, markedly increases cell proliferation (Basolo et al., 2002; Bond et al., 1994; Santoro et al., 1993; Wang et al., 2003). Transgenic mice that express RET/PTC1 or RET/PTC3 in the thyroid acquire PTC-like thyroid carcinomas after long latency periods (Jhiang et al., 1996; Powell et al., 1998; Santoro et al., 1996).

Although RET/PTC rearrangements are substantially less common than BRAFV600E, there is a specific association of RET/PTC with radiation-induced thyroid cancer. For example, the Chernobyl accident which released nuclear materials including radioactive iodine was associated with increased numbers of RET/PTC thyroid cancers (Fugazzola et al., 1995; Rabes et al., 2000; Thomas et al., 1999). RET/PTC events also are prevalent in patients previously exposed to other forms of radiation, e.g. as part of medical treatment (Alipov et al., 1999; Bounacer et al., 1997; Collins et al., 2002; Nikiforov et al., 1997).

In contrast to the less common RET/PTC mutations, RET/PTC1 and RET/PTC3 involve fusion partners located on the same chromosome as RET. It is thought that chromosomal proximity of the fusion partners and fragile sites within those genes contribute to the high incidence of RET/PTC fusions in patients exposed to radiation (Gandhi et al., 2012, 2010a, 2010b; Nikiforova et al., 2000). In concordance with this hypothesis, irradiation of thyroid cell cultures generates RET/PTC fusions (Ito et al., 1993; Mizuno et al., 2000, 1997). Interestingly, several other thyroid cancer related mutations such as the AKAP9-BRAF, NTRK1-T1, and NTRK1-T2 fusions also involve intrachromosomal rearrangements (Santoro et al., 2006). AKAP9-BRAF in particular is overrepresented in PTCs attributable to radiation exposure, while BRAF point mutations are rare in the same population (Ciampi et al., 2005; Lima et al., 2004).

In general the prognosis for RET/PTC thyroid carcinomas is relatively good (Soares et al., 1998). Few correlations are found between RET/PTC mutations and clinical markers of

increased mortality or morbidity, though increased lymph node metastases are sometimes noted (Adeniran et al., 2006; Santoro et al., 2002; Tallini et al., 1998). RET/PTC1 tumors are associated with classical PTC histology while RET/PTC3 are associated with more aggressive solid and TCV PTC (Basolo et al., 2002; Nikiforov et al., 1997; Thomas et al., 1999).

A number of small molecules targeting multiple tyrosine kinases inhibit RET and RET/PTC. Sunitinib targets RET among many other kinases and has modest efficacy in PTCs, although it has not been studied specifically in tumors expressing RET/PTC (Carr et al., 2010). Vandetanib and cabozantinib are inhibitors of multiple tyrosine kinases including RET and are approved for the treatment of medullary thyroid carcinoma (Thornton et al., 2012). Medullary thyroid carcinoma is a disease of calcitonin-producing thyroid C cells rather than thyroid follicular cells, and is frequently associated with activating point mutations in RET. Whether vandetanib and cabozantinib also may have specific efficacy in RET/PTC carcinomas is not known.

2.3. NTRK1

Chromosomal rearrangements involving the NTRK1 gene – another receptor tyrosine kinase - are found infrequently in PTC, probably in less than 5% of cases. Several fusion partners of NTRK1 have been described, and as with RET/PTC, the common feature is their ability to constitutively dimerize and thereby inappropriately activate the NTRK kinase (Bongarzone et al., 1989; Greco et al., 1995; Kaplan et al., 1991; Miozzo et al., 1990). Since NTRK1 rearrangements occur in a very small percentage of PTCs, data on their clinical significance is limited (Musholt et al., 2000; Rabes et al., 2000).

2.4. RAS and PAX8-PPARG

Activating RAS mutations and PAX8-PPARG translocations are the most common mutations found in FVPTCs. They also are the most common mutations in FTCs, and will be discussed under that heading.

3. Follicular thyroid carcinoma

FTCs account for the remaining differentiated thyroid carcinomas. Presently FTCs are identified by their thyroid follicular organization and by the lack of PTC nuclear features. The differences between FTCs and FVPTCs are not always clear. The diagnosis of FTC also depends on evidence of vascular or capsular invasion in the tissue sample, and therefore occasionally a minimally invasive FTC will mistakenly be classified as a benign follicular adenoma. Molecular markers that can reliably distinguish minimally invasive FTCs from adenomas have proved elusive but are continuously being sought.

3.1. RAS

The three RAS proteins H-RAS, N-RAS and K-RAS are small GTPases that regulate key cellular processes involved in growth, differentiation, survival, adhesion and migration. Downstream effectors of RAS include the RAF/MAPK pathway as noted above and the PI3K/AKT pathway. RAS exists in a GTP-bound active state or a GDP-bound inactive state, and RAS activation normally is induced by external signals such as from cell surface receptor tyrosine kinases. Constitutively activating RAS mutations probably are the most common mutations in all of cancer biology. In the thyroid, RAS mutations are present in ~40% of FTCs, 20–40% of benign adenomas, and 15–20% of PTCs – mostly FVPTC (Lemoine et al., 1988; Nikiforov, 2011; Suarez et al., 1990). Mutations in codon 61 of N-RAS are the most common, followed by mutations in codon 61 of H-RAS (Bamford et al., 2004; Namba et al., 1990; Volante et al., 2009).

Expression of mutated RAS oncoproteins transforms cells *in vitro* and *in vivo*. N-RASQ61 expression results in TSH independent proliferation and genomic instability in PCCL3 rat thyroid cell lines. Thyroid specific expression in mice results in the development of metastatic thyroid carcinoma with mixed follicular, papillary, and undifferentiated areas (Vitagliano et al., 2006). Expression of HRASV12 achieves similar results in cell lines and mice (Knauf et al., 2006; Rochefort et al., 1996; Saavedra et al., 2000).

The clinical significance of RAS mutations in thyroid carcinomas is unclear. A number of studies find correlation between RAS mutations and bone metastases, increased aggressiveness, or higher mortality across thyroid cancer types (Basolo et al., 2000; Garcia-Rostan et al., 2003; Hara et al., 1994; Karga et al., 1991; Manenti et al., 1994). On the other hand, RAS mutations also are prevalent in benign follicular adenomas, and are seen in unaggressive forms of FVPTC with few metastases (Gupta et al., 2013; Howitt et al., 2013; Zhu et al., 2003). A retrospective analysis found that RAS mutations are over-represented in differentiated thyroid carcinomas from patients with radioiodine-avid pulmonary metastases (Sabra et al., 2013), whereas BRAF mutations are over-represented in non radioiodine-avid metastatic disease. However, radioiodine-avid lung metastases were rarely cured by radioiodine therapy, and those with RAS mutations fared no better than radioiodine-avid metastases with BRAF mutations.

The broad scope of RAS actions presents many potential therapeutic targets. Farnesylthiosalicylic acid (FTS) blocks the association of RAS with the cell membrane, resulting in RAS degradation. FTS has efficacy against thyroid cancer cells in pre-clinical models (Biran et al., 2011; Levy et al., 2010; Marciano et al., 1995). FTS in combination with the multikinase inhibitor sorafenib may have some activity in patients with metastatic thyroid carcinoma (Hong et al., 2011). Other drugs may disrupt RAS actions by inhibiting downstream targets in the MAPK and/or PI3K pathways (Chan et al., 2012; Jin et al., 2011; Liu et al., 2012). As noted previously, the MEK inhibitor selumentinib increased RAI uptake in iodide-refractory patients, particularly those with RAS mutations (Ho et al., 2013).

3.2. PAX8-PPARG

PAX8-PPARG is the other major mutation found in FTC, accounting for ~35% of cases. It also is found in FVPTC and occasionally in benign follicular adenomas (Eberhardt et al., 2010). A t(2;3)(q13;p25) chromosomal translocation fuses the promoter and most of the PAX8 gene to the coding exons of the PPARG gene. Thus the PAX8-PPARG fusion protein (PPFP) is expressed under control of the PAX8 promoter, which is highly active in the thyroid (Kroll et al., 2000). PAX8 is a transcription factor that is important for thyroid development, and in the mature gland it drives the expression of many thyroid-specific genes such as those encoding thyroglobulin, thyroid peroxidase and the sodium iodide symporter. PPARG is a nuclear receptor transcription factor that is essential for adipogenesis, but is expressed at very low levels in the normal thyroid and has no known function in that organ. A separate fusion protein between CREB3L2 and PPARG has been reported in two cases of FTC (Lui et al., 2008). That two distinct fusion proteins involving PPARG have been associated with FTC suggests that modulation of PPARG-regulated pathways is important for PPFP-mediated carcinogenesis. However, the oncogenic mechanism of PPFP is poorly understood and its functional relationship to PPARG is complex.

PPFP has been shown to be a dominant negative inhibitor of PPARG-mediated gene activation in numerous transfection systems (Kroll et al., 2000; Powell et al., 2004; Yin et al., 2009, 2006). Additionally PPARG often is downregulated in other types of thyroid carcinomas, PPARG agonists have therapeutic effects in cell and mouse models of various cancers, and heterozygous PPARG deletion enhances tumorigenesis in a mouse model of

non-PPFP thyroid carcinoma (Aldred et al., 2003; Kato et al., 2006; Marques et al., 2004; Park et al., 2005). Overall these studies suggest that PPARG can have tumor suppressive function, and that PPFP may contribute to thyroid carcinogenesis by impeding this activity of PPARG.

On the other hand, there also is evidence that PPFP can transactivate at least some PPARG target genes. Significant numbers of PPARG target genes are upregulated in PPFP tumor samples compared to non-PPFP FTC or normal thyroid (Giordano et al., 2006; Lacroix et al., 2005). *In vitro*, exogenously induced PPFP expression stimulates the promoters of some PPARG genes while repressing others or sometimes both depending on the cellular context (Au et al., 2006; Giordano et al., 2006; Powell et al., 2004). Similarly, some PPARG target genes are induced and others are repressed in a transgenic mouse model of PPFP FTC (Dobson et al., 2011). However, treatment of these mice with the PPARG agonist pioglitazone caused broad upregulation of PPARG target genes and induced adipocyte transdifferentiation in the PPFP thyroid cancer cells. PPFP functional domains therefore necessarily retain their capacity to act in a strongly PPARG-like manner.

Stable transfection of PPFP in thyroid cell lines results in increased cell division, decreased apoptosis, and increased colony growth in soft agar (Au et al., 2006; Espadinha et al., 2007; Powell et al., 2004). Thyroid specific expression of PPFP in transgenic mice results in mild thyroid hyperplasia, but PPFP expression and thyroid-specific deletion of the tumor suppressor PTEN synergize to induce metastatic FTC (Diallo-Krou et al., 2009; Dobson et al., 2011). The mouse data are consistent with the biology of human PPFP FTCs, since these cancers have increased activated AKT (Diallo-Krou et al., 2009) and PTEN is a negative regulator of AKT. However, the role of PPFP in thyroid carcinogenesis may be complex because data suggest that PPFP also may inhibit tumor growth by suppressing neovascularization (Reddi et al., 2011, 2010).

The prognostic significance of PPFP expression in FTC or FVPTC has not been extensively studied. PPFP is associated with a younger age at presentation and increased vascular invasion (French et al., 2003; Marques et al., 2004; Nikiforova et al., 2003b). However, others report that PPFP is associated with indicators of good prognosis including markers of differentiation and few metastases (Sahin et al., 2005).

PPARG agonists have been disappointing as therapeutic agents in human cancers, despite the evidence that PPARG may be a tumor suppressor. However, in the above-mentioned mouse model of PPFP FTC, pioglitazone was strongly therapeutic, eliminating metastatic disease and greatly shrinking the size of the primary tumors. In addition, the remaining thyroid cells became adipocyte-like cells, accumulating large amounts of lipid (Dobson et al., 2011). It is hypothesized that this unique transdifferentiation event underlies the anti-tumor efficacy, which reflects the fact that the drug target is PPFP, not PPARG. The results suggest pioglitazone may be an effective treatment for PPFP thyroid carcinomas in patients.

3.3. PTEN/PI3K/AKT

PTEN is a phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase that functions as a negative regulator of PI3K (Fig. 2). Activated PI3K phosphorylates AKT, which then regulates a variety of cellular processes such as protein synthesis, survival and proliferation via the phosphorylation of many intermediates such as mTOR and FOXO. AKT is inappropriately active in many cancers, and as a negative regulator of AKT signaling, PTEN is an important tumor suppressor. Germline PTEN mutations cause Cowden syndrome, which is associated with increased risk of thyroid cancer, but which will not be discussed here since the focus of this review is sporadic thyroid cancers.

However, increased AKT activation also can be seen in sporadic thyroid cancers due to mutations or epigenetic changes (discussed subsequently) in PTEN or downstream components of this pathway (Orloff et al., 2013; Paes and Ringel, 2008). The overall incidence of PTEN mutation in sporadic thyroid carcinoma is ~8% in FTC, 2% in PTC, and 11% in anaplastic thyroid carcinoma (ATC) (Bamford et al., 2004; Dahia et al., 1997; Halachmi et al., 1998). Activating mutations of PIK3CA, the catalytic subunit of PI3K, are roughly as prevalent as PTEN mutations, although they occur in a mutually exclusive manner. In addition, PIK3CA gene copy number gain is found in 28% of FTCs and ~40% of ATCs, and this also might lead to increased AKT activation (Hou et al., 2007; Liu et al., 2008; Wang et al., 2007). Although inhibitors of the PI3K/AKT/mTOR pathway have shown efficacy against thyroid cancer in pre-clinical models, their success in clinical trials remains to be seen (Lin et al., 2012; Liu et al., 2011; Mandal et al., 2005; Papewalis et al., 2009).

3.4 IDH1

Isocitrate dehydrogenases 1 and 2 are enzymes of intermediary metabolism that interconvert isocitrate and 2-oxoglutarate (alpha ketoglutarate). IDH1 is cytoplasmic, whereas IDH2 is mitochondrial. Mutations in both enzymes have been described in a number of cancers, most prominently in glioblastoma multiforme and chondrosarcoma (reviewed in Losman and Kaelin, Jr., 2013). The cancer-associated mutations result in altered enzymatic activity such that 2-oxoglutarate is converted to 2-hydroxyglutarate rather than isocitrate. Evidence indicates that accumulation of 2-hydroxyglutarate is important to the role of IDH mutations in cancer, but the mechanisms by which this happens are poorly understood. Recently, IDH1 mutations have been identified in thyroid carcinomas (Hemerly et al., 2010; Murugan et al., 2010). In the study by Hemerly and colleagues, IDH1 mutations were found in 24% of follicular carcinomas, 18% of follicular variant of papillary carcinomas, and 8% of papillary carcinomas, but these differences in frequency were not significant due to small numbers of cases. IDH1 mutations also have been found in anaplastic and Hurthle cell carcinomas. The clinical significance of these mutations is not known. IDH2 mutations have yet to be identified in thyroid carcinomas.

3.5. THRB

The thyroid hormone receptor beta (THRB) mutation PV was initially knocked into mice to create a mouse model of resistance to thyroid hormone (Kaneshige et al., 2000). Homozygous or heterozygous THRB(PV) mice (in conjunction with markedly increased TSH stimulation) develop metastatic FTC, which was unforeseen (Kato et al., 2004; Suzuki et al., 2002). Mutations in THRB are generally thought to be very rare to non-existent in human PTC and FTC (Rocha et al., 2007; Takano et al., 2003), although one publication reported that nearly all PTCs contain THRB mutations (Puzianowska-Kuznicka et al., 2002).

However the mouse model remains useful to tease out how other clinically relevant pathways interact to cause human FTC (Guigon and Cheng, 2009). The important role of the PI3K/AKT pathway in human FTC is recapitulated in these mice, along with the discovery of a novel interaction between THRB and PI3K regulatory subunit p85 (Furuya et al., 2007, 2006; Guigon et al., 2009; Kim et al., 2005; Saji et al., 2011). Downstream of AKT, beta-catenin is protected from degradation by THRB(PV) and unliganded wildtype THRB, but not liganded THRB, suggesting a role for thyroid hormone in beta-catenin regulation (Guigon et al., 2008).

4. Anaplastic thyroid carcinoma

Anaplastic thyroid carcinoma is the deadliest subtype of thyroid cancer. It is rare, accounting for at most 2% of cases but causes up to 50% of thyroid cancer deaths (Nagaiah et al., 2011). Mean survival time is ~5 months from diagnosis. ATCs are completely undifferentiated, aggressive, and therapy resistant. Treatment strategies are mostly palliative or designed to prevent airway compromise. Many patients present with widespread metastases but there are no effective systemic therapies (Smallridge et al., 2012). Targeted therapies may provide much needed options.

4.1. RAS, BRAF, PTEN, PI3K

A number of mutations described previously in differentiated thyroid carcinomas also are found in ATC. RAS mutations are found in 27% of cases, BRAF in 25%, PTEN in 11%, and PI3K catalytic subunit PIK3CA in 12% (Bamford et al., 2004; Smallridge et al., 2009). RET gene amplifications are reported, but not RET/PTC (Nakashima et al., 2007). The presence of these genetic changes alongside those more exclusively associated with ATC suggests a stepwise accumulation of mutations and dedifferentiated phenotypes (Nikiforov, 2004). Promising preclinical data indicate that these mutations remain relevant and are viable targets of therapy (Jin et al., 2011; Kim et al., 2007; Lin et al., 2012; Nehs et al., 2012; Yeung et al., 2007)..

4.2. TP53

TP53 is a tumor suppressor known to be mutated in a large variety of cancers. TP53 mutations are associated with 55% of ATCs but not differentiated thyroid cancers (Donghi et al., 1993; Fagin et al., 1993; Nakamura et al., 1992). Acquisition of TP53 mutations is thought to drive disease progression towards anaplasia (La Perle et al., 2000; Matias-Guiu et al., 1994). TP53 is a transcription factor that modulates the expression of a large number of genes in response to cellular stresses. TP53 regulates apoptosis, cell cycle progression, DNA repair, senescence, and stem cell homeostastasis, among many other processes. Loss of TP53 function abrogates the cell's ability to enter senescence or cell death appropriately (Stegh, 2012).

Loss of TP53 in transgenic mice leads to tumor formation. TP53 null mice crossed with RET/PTC1 transgenic mice generate larger, more anaplastic and invasive thyroid tumors (La Perle et al., 2000). Thyroid-specific loss of TP53 and PTEN results in the development of undifferentiated, aggressive thyroid carcinomas with substantial gene expression overlap with human ATC (Antico Arciuch et al., 2011).

Unfortunately, TP53 loss of function through mutation or deletion is difficult to restore. A number of small molecules exist which inhibit Mdm2, a negative regulator of TP53. However, a wild-type TP53 still needs to exist in the tumor population for this strategy to be useful (Shangary et al., 2008; Vassilev et al., 2004). Those patients with genomic loss of TP53 need another option. Re-introduction of the gene via an adenovirus vector achieved expression of TP53, but only near the injection site (Lang et al., 2003).

5. Epigenetic changes in thyroid cancer

Epigenetics refers to chromosomal changes that do not involve the nucleotide sequence and that have the potential to alter gene expression and to be heritable. DNA methylation and histone modification are common examples of epigenetic changes. The effects of epigenetic modifications are powerful, yet theoretically reversible by small molecules and endogenous enzymes, making them attractive targets to turn the course of malignant transformation.

5.1. DNA methylation

DNA methylation – the addition of a methyl group to the 5 position of cytosine – can lead to transcriptional silencing of a gene. The mechanism was first proposed for X chromosome silencing, and later shown to be at work much more widely (Li et al., 1993; Riggs, 1975). DNA methylation can be permanent and heritable, a mechanism to prevent reversion to less differentiated states. However, methylation patterns in many cancers including thyroid cancer are unstable, which may contribute to dedifferentiation as well as to the generation tumor heterogeneity (Hansen et al., 2011).

Methylation of tumor suppressor genes and markers of differentiation is common during oncogenesis. P16INK4A, RASSF members 1A, 2, and 10, and PTEN are downregulated in thyroid cancer by promoter methylation (Elisei et al., 1998; Hou et al., 2008; Schagdarsurengin et al., 2010, 2009, 2002). PTEN often is methylated in FTC and exhibits a pattern of increasing methylation with decreasing differentiation. Genes associated with differentiated function such as SLC5A5 (NIS) and NKX2-1 also are hypermethylated in undifferentiated thyroid cancer (Kondo et al., 2009; Venkataraman et al., 1999).

While methylation pattern changes are likely part of the transcriptional programs driving oncogenesis, specific mutations in the methylation pathway also can contribute to the disease state. Mutations in methylenetetrahydrofolate reductase (MTHFR), an enzyme in the folic acid metabolism pathway, can lead to defects in DNA methylation (Goyette et al., 1994; Paz et al., 2002). MTHFR mutations are associated with increased risk of thyroid carcinoma (Fard-Esfahani et al., 2011; Ozdemir et al., 2012; Prasad and Wilkhoo, 2011).

Treatment with 5-azacytidine or other DNA methyltransferase inhibitors can reverse the transcriptional repression of DNA methylation. THRB and RAP1GAP are frequently hypermethylated; 5 azacytidine restored their expression (W. G. Kim et al., 2013; Zuo et al., 2010). However, the efficacy of 5 azacytidine or similar drugs as tools for redifferentiation is not well established (Dom et al., 2013; Vivaldi et al., 2009), and these agents would likely seem to be too non-specific in their effects.

5.2. Histone modifications

Histones are the main protein component of chromosome structure, being the spool around which short segments of DNA are bound. Post-translational modifications of histones are numerous and include ADP ribosylation, acetylation, methylation, phosphorylation, ubiquitination and SUMOylation. These modifications affect transcriptional access to genes by changing DNA conformation. For example, histone acetylation can cause activation of gene transcription, deacetylation its arrest.

Global dysregulation of histone modifications is a feature and contributing factor of cancer (Chi et al., 2010). Acetylation at lysines 9–14 of histone H3 is higher in thyroid cancers compared to normal, and also higher in response to oncogene expression (Puppin et al., 2011).

It is not well known how histone modifications at specific sites in the genome contribute to thyroid carcinoma. However, treatment of thyroid cancer cell lines with histone deacetylase (HDAC) inhibitors changes the expression levels of key genes. HDAC inhibitors increase the transcript levels of markers of thyroid differentiation such as NIS, TPO, thyroglobulin and PAX8, making these possible reagents for restoring RAI avidity or effecting re-differentiation (Furuya et al., 2004; Kitazono et al., 2001; Pugliese et al., 2013; Puppin et al., 2005; Zarnegar et al., 2002). The HDAC inhibitor romidepsin restored some degree of RAI uptake in 2 of 16 patients in a clinical trial, although subsequent therapy with RAI did not

result in improvement in the overall disease status of these two patients (Sherman et al., 2012).

The broad actions of HDAC inhibitors also can increase tumor sensitivity to other treatments or be cytotoxic themselves. Valproic acid increases ATC sensitivity to doxorubicin and imatinib (Catalano et al., 2009, 2006). HDAC inhibitors alone induce ATC cell death in cell culture and xenograft models (Borbone et al., 2010; Catalano et al., 2012). A patient was apparently cured of ATC with multimodality therapy consisting of valproic acid, cisplatin, doxorubicin, radiation therapy and surgery (Noguchi et al., 2009).

Though not a direct epigenetic effect, inhibition of aurora kinases is another promising approach. Aurora kinases phosphorylate histones during mitosis to ensure correct chromosome segregation. Aurora kinases are overexpressed in thyroid carcinomas (Sorrentino et al., 2005). Multiple aurora kinase inhibitors show antitumor activity in ATC cell lines and mouse models by inducing mitotic catastrophe (Arlot-Bonnemains et al., 2008; Baldini et al., 2012; Libertini et al., 2011; Wunderlich et al., 2011).

5.3. Non-coding RNA

The mammalian transcriptome includes many RNA molecules that do not encode proteins. In fact, it is estimated that non-coding RNA transcripts outnumber mRNAs 10:1. A number of these play a role in epigenetic processes (Lee, 2012).

Long non-coding RNAs (lncRNAs) can bind to specific genomic DNA regions and direct epigenetic changes to chromosome structure. For example, HOTAIR is a lncRNA that binds to Polycomb Repressive Complex 2 and mislocalizes it on the genome, resulting in inappropriate gene silencing via histone H3 lysine 27 methylation. HOTAIR is overexpressed in a number of cancers and is predictive of aggressive disease and death. Loss of HOTAIR conversely inhibits metastatic potential (Gupta et al., 2010; K Kim et al., 2013; Kogo et al., 2011; Niinuma et al., 2012; Yang et al., 2011). PTEN is reportedly a target of HOTAIR (Li et al., 2013). However, HOTAIR expression has not been studied in thyroid carcinoma.

PTC susceptibility candidate 3 (PTCSC3) is a thyroid-specific lncRNA that is dramatically downregulated in PTC and appears to function as a tumor suppressor, possibly by regulating the activities of miRNAs (Fan et al., 2013; Jendrzejewski et al., 2012). NAMA is a lncRNA whose genomic locus exhibits loss of heterozygosity in thyroid carcinoma and whose expression is downregulated by BRAF activation (BRAFV600E) (Yoon et al., 2007). However, the function of NAMA has not been characterized.

6. Conclusion

Cancer is a disease of accumulated DNA damage whose progression is thought to be driven by the acquisition of additional genetic abnormalities. Understanding how these changes contribute to the disease process is essential to the development of novel prognostic and therapeutic strategies. The association of recurrent mutations with specific histological subtypes of thyroid carcinoma corroborates the visual acumen of past pathologists while offering new ways to confront ambiguous subtypes such as FVPTC. Targeting recurrent mutations singly can result in transient relief from disease progression. Combination therapy addressing a more comprehensive catalogue of driving mutations may achieve more durable responses and perhaps cures. Finally, epigenetic control of the tumor genome also is an attractive target to reverse disease progression.

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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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Highlights

- Most thyroid carcinomas contain one of a small number of recurring gene mutations.
- Specific mutations correlate with histological subtypes of thyroid carcinoma.
- Gene mutations provide insight into thyroid carcinoma pathogenesis.
- Thyroid carcinoma gene mutations are potential drug targets.

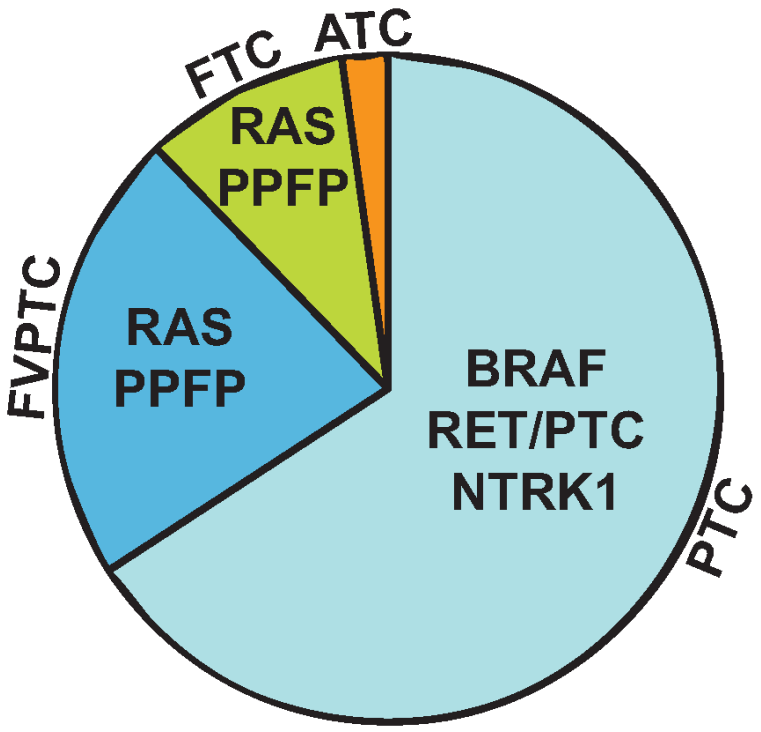

Fig. 1.

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.

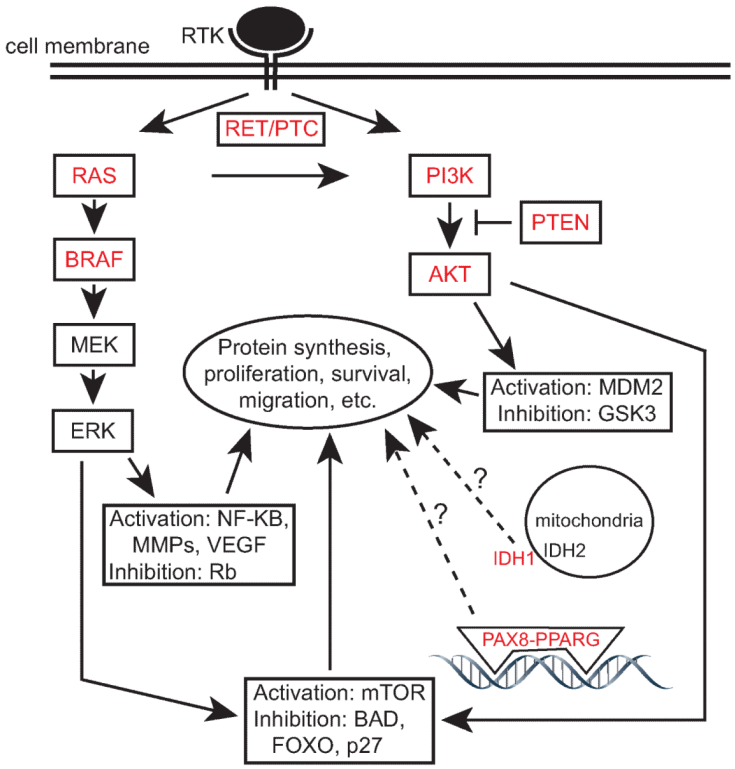

Fig. 2.

Gene mutations and signaling pathways in thyroid carcinomas. Simplified schematic diagrams are shown of the RAS/MAPK and PI3K/AKT pathways. Proteins with reported mutations in thyroid carcinomas are in red. There are many protein targets of these pathways that contribute to oncogenesis, some of which are common to both pathways. A subset of these targets is shown. A question mark appears with the arrow from PAX8-PPARG because the mechanisms by which this fusion protein contributes to oncogenesis are not well understood. Similarly, the arrow from IDH1 has a question mark since the mechanisms by which IDH1 mutations contribute to thyroid cancer are poorly understood. RTK, receptor tyrosine 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.