Molecular pathogenesis of follicular cell derived thyroid cancers

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ABSTRACT

Thyroid cancers are the most common endocrine malignancy. Radiation exposure, family history of thyroid cancer and some inherited conditions are the most important predisposing factors for the development of thyroid cancer. Three mitogenic signalling pathways have been described in the thyroid cell, which are influenced by various stimulatory and inhibitory hormones, growth factors and neurotransmitters. Various proto-oncogenes and oncogenes like ras, braf, trk, met and RET also play a role in the signal transduction systems. Two theories have been described in thyroid cancer pathogenesis, the foetal cell carcinogenesis theory and the more common, multistep carcinogenesis theory.

The multistep carcinogenesis theory is now the accepted model in many human cancers, including thyroid cancer. The early events of tumour formation are the consequence of activation of either various growth factors or the proto-oncogenes like ras, met or ret. This results in the formation of differentiated thyroid cancers like the papillary, follicular or Hurthle cell cancers. The later stages of tumour formation involve further activation of proto-oncogenes and loss or inactivation of tumour suppressor genes like p53. Based on this theory, follicular carcinomas are generated from follicular adenomas and papillary carcinomas from precursor cells generated from thyrocytes. Anaplastic carcinoma may develop from papillary or follicular carcinoma by dedifferentiation. In this review article, we highlight the molecular pathogenesis of thyroid tumours.


1. Introduction

Thyroid cancer is the most common endocrine malignancy and usually originates from the follicular cell, except medullary cancer. In England and Wales, thyroid cancer accounts for less than 0.5 percent of all cancers and results in about 250 deaths per year. Studies have shown that the incidence of thyroid cancer is increasing worldwide, and this increase is predominantly in papillary thyroid cancer. Between 1973 and 2003, the incidence of papillary thyroid cancer rose by 189 percent in the USA. The apparently increased incidence is probably the result of better early detection of small cancers.

Various risk factors have been implicated in the pathogenesis of thyroid cancers and these include – radiation exposure, inherited conditions predisposing to thyroid neoplasia and, other factors like diet, pre-existing goitre, effect of hormones and occupation have also linked to thyroid cancer. Thyroid cancers develop as a result of a multistep process, consistent with the multistep carcinogenesis theory, which will be the focus of this review.

2. Mitogenic pathways in the regulation of thyroid growth and function

The thyroid gland is composed of follicular cells which constitute about 70 percent of the gland, endothelial cells which constitute about 20 percent of the gland and the rest formed by fibroblasts. In a normal adult, the weight and composition of the gland remain fairly constant, with cell turnover about 6–8 renewals in adult life. The growth of cells in the thyroid is closely regulated, with the thyrocyte controlling the functions of other cells through secretion of paracrine factors like fibroblast growth factor (FGF) and insulin-like growth factor 1 (IGF-1).

Abnormal proliferation leads to disease states like goitre, adenomas or carcinomas, whilst hypoplasia can lead to hypothyroidism. Thyroid follicular cells undergo differential growth patterns with different rates of growth within the same thyroid gland due to different patterns of growth factor responsiveness, thereby leading to the goitrous state. With further stimulation by growth factors over time, focal hyperplasia may result.

In the thyroid gland, three distinct mitogenic pathways (Fig. 1.) have been well defined namely: the hormone receptor–adenylate cyclase–cAMP protein kinase A system (AC/cAMP/PKA), the
hormone receptor–tyrosine protein kinase pathways, and the hormone receptor–phospholipase C cascade (PLC) pathway. TSH is the major stimulator of the AC/cAMP/PKA pathway by interacting with the TSH-receptor (TSH-R). Binding of TSH to TSH-R activates Gsα and adenylate cyclase, which results in the generation of cAMP, and further activates protein kinase A (PKA). This cascade accounts for TSH-mediated regulation of function, differentiation and proliferation of the thyroid gland.8,9

In the receptor tyrosine kinase (RTK) pathway, ligand binding of RTK by epidermal growth factor receptor (EGFR), a product of the erb B proto-oncogene.10 EGF stimulates the PLC–PKC–calcium systems,11 and mainly the ras pathway, which finally leads to an increased transcriptional activity. EGF also stimulates the increased expression of c-fos and c-myc oncogenes.12

The PLC cascade pathway is activated by TSH binding, neurotransmitters, circulating growth factors and phorbol ester, mediated via the TSH-R and PKC receptor. The activation of TSH-R leads to increased PLC activity, resulting in the formation of inositol 1,4,5-triphosphate (IP3) and diacylglycerol (DAG), which then subsequently increases the intracellular calcium and PKC activity. About a 1.2–2 fold increase in PLC activity has been shown in response to TSH in normal, benign and early thyroid cancers, with no increase detected in invasive or metastatic cancers.13

3. Models of thyroid carcinogenesis

Two models of thyroid carcinogenesis have been described, the foetal carcinogenesis theory and the common, multistep carcinogenesis theory.

4. Foetal cell carcinogenesis theory

The foetal cell carcinogenesis theory was proposed by Takano.14 The theory hypothesises that cancer cells are derived from the remnants of foetal thyroid cells. The foetal thyroid cells are rarely seen in normal thyroid development, whereas once the foetal cells are transformed into cancer cells, the cells are no longer under control. According to the foetal cell theory, genomic changes do not play any role in the foetal cell carcinogenesis, unless the genomic changes prevent the foetal cells from differentiation.15

The three proposed origins of the thyroid cancer cells are, prothyrocytes, thyroblasts and thyroid stem cells.10 The thyroblasts express thyroglobulin and oncofoetal fibronectin (onfFN), do not form follicles, and are the precursor cells for papillary cancer. The prothyrocytes are more differentiated than fibroblasts, express thyroglobulin (Tg) mRNA but not onfFN and form thyroid follicles. According to this theory, papillary thyroid cancers are formed from thyroblasts. Follicular thyroid cancers are formed from prothyrocytes and anaplastic cancers from thyroid stem cells.

5. Multistep carcinogenesis theory

According to the multistep carcinogenesis theory, most cancers are clonal in origin, arising from a single abnormal cell and progress as a result of number of inheritable alterations.17 This model has been supported by evidence from clinical and experimental models and is now the accepted model in many human cancers. The sequential event in cancer pathogenesis was originally shown convincingly in colorectal carcinoma by Vogelstein et al.18

Based on the multistep carcinogenesis theory, follicular carcinomas are generated from follicular adenomas and papillary carcinomas from precursor cells generated from thyrocytes. Anaplastic carcinoma may develop from papillary or follicular carcinoma by dedifferentiation. The ideas are illustrated in Fig. 2. The various factors involved in the development and progression of follicular cell derived thyroid cancers are discussed in the next few sections.

6. Molecular pathogenesis of papillary thyroid cancer

Papillary thyroid cancer accounts for up to 70–90 percent of the differentiated thyroid cancer types. They are commoner in women and peak in the second and third decade of life. The tumours are usually slow growing, unencapsulated and metastasize to the regional lymph nodes. They are multifocal in about 30 percent of cases and in about 30 percent of patients; palpable lymph nodes
may be found. Histologically the tumours typically show the presence of branching papillae with fibrovascular core, lined by a single layer of cells. The nuclear features include the presence of large pale staining cells, with an Orphan Anne eye nucleus and nuclear grooving. The predisposing factors for the development of sporadic papillary thyroid cancer are: history of irradiation to the head and neck region, Hashimoto’s thyroiditis, familial adenomatous polyposis and Cowden’s syndrome. There are three major genetic alterations in PTC, involving that of the RET, RAS and BRAF genes, which is discussed below. The frequency of the genetic alterations is shown in Table 1.

The most frequent genetic alteration in papillary thyroid cancer involves RET (rearranged during transfection), despite the absence of RET protein in thyroid follicular cells. The RET proto-oncogene is located on chromosome 10q11.2 and encodes a receptor tyrosine kinase. The frequency of RET/papillary thyroid cancer (RET/PTC) alteration in papillary thyroid cancer varies between 5 and 70 percent. The rearrangements lead to the fusion of the RET tyrosine kinase domain with the 5'-terminal regions of heterologous genes, generating chimeric oncogenes designated as RET/PTC. Twelve different chimeric protein arrangements have been described that have been isolated from sporadic and radiation-associated thyroid tumours and include RET/PTC 1–9, PCM1–RET, ELKS–RET, and RFP–RET. RET/PTC 1, 2 and 3 are the most common rearrangements in PTC, with the RET/PTC 3 variant associated with more aggressive histotypes in post-radiation PTCs.

RET rearrangements probably represent early events in thyroid tumour pathogenesis, based on the fact that there is a high prevalence of RET/PTC transformation in papillary microcarcinomas and lack of association with markers of clinical aggression.

The ras oncogenes play an important role in the regulation of cell growth and differentiation. Activating mutations in codons 12, 13 and 61 of the three ras genes, namely H-ras, K-ras and N-ras, converts them into active oncogenes, which play an important role in the pathogenesis of many tumours. The prevalence of ras mutations is 10–15 percent in papillary cancers, particularly in follicular-variant papillary thyroid cancer (FVPTC). Di Cristofaro et al. found no mutation of N-ras in classical PTC in comparison to 25 percent seen in FVPTC. Tumours that express ras mutations are associated with low rates of lymph node metastasis. The tumours that harbour the ras mutations are prone to dedifferentiation of the PTC into the anaplastic cancer type, in the presence of additional mutations.

The braf gene encodes for a protein belonging to the family of protein kinases and is the most potent activator of the MAK kinase pathway. More than 80% of all the BRAF mutations are the T1799A transversion mutation and have been reported in many human cancers, including that of thyroid cancer, ranging from 29 to 83%.

### Table 1

<table>
<thead>
<tr>
<th>Thyroid tumour</th>
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<tr>
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<tr>
<td>RET/PTC</td>
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<tr>
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<td>Aneuploidy</td>
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<td><strong>Hurthle cell cancer</strong></td>
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<td><strong>Anaplastic thyroid cancer</strong></td>
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<td>40–70</td>
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<tr>
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<td>RAS</td>
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</tr>
<tr>
<td>BETA CATENIN</td>
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**Fig. 2.** Multistep carcinogenesis model of thyroid cancer formation. Formation of benign thyroid tumours occurs as a result of alteration of various growth factors. The follicular neoplasms are formed from thyrocytes by mutations of ras and other factors as shown in the figure. Papillary cancers are formed by alterations in RET/PTC and other oncogenes. The undifferentiated tumours are formed from the differentiated tumours by mutations of tumour suppressor genes.
PTC-derived anaplastic cancers, but not in follicular cancer, medullary cancers, or benign thyroid neoplasms. Pooled data from various studies have shown the prevalence of BRAF mutation of to be 44 percent (810/1856) in PTC. The prevalence of BRAF mutation is highest in tall-cell variant of papillary cancer (77%), 60% in conventional PTC, and lowest in follicular-variant PTC (12%). Several studies have shown the association of BRAF mutation and advanced stage, lymph node metastasis, and poor patient survival. Mutation in BRAF may also be responsible for dedifferentiation of PTC into anaplastic thyroid cancer.

Another oncogene that play a role in thyroid carcinogenesis is the receptor tyrosine kinase (RTK), PI3K/Akt and MAPK pathways are prevalent in FTC, suggesting the role of these signalling pathways mediated by growth factors and oncogenes like ras in these tumours. Unlike PTC, RET and BRAF do not play any role in the pathogenesis of follicular thyroid cancers. Follicular cancers show a predominance of ras mutations, PAX8–PPARγ rearrangements and aneuploidy.

Point mutations of ras oncogenes are seen in about 40 percent of thyroid tumours, with a predominance of N-ras over K-ras and H-ras; however a high rate of K-ras mutation in follicular thyroid cancers, with a predominance of N-ras over H-ras and K-ras. Amplification is seen in 75 percent of papillary thyroid cancers and has been shown to be a marker for the tall-cell variant of papillary carcinoma, which has an aggressive clinical course. Aneuploidy or aberrant chromosome number has been recognized as a common characteristic of cancer cells for many years and has been implicated in tumourigenesis. Aneuploidy can either act as an oncogene or as a tumour suppressor gene based on the cell type and the presence or absence of additional genetic damage. Aneuploidy is observed in about 12–24 percent of adenomas and 30–64 percent of carcinomas. There is a higher incidence of aneuploidy in widely invasive carcinomas in comparison to the minimally invasive carcinomas. Using fluorescence in situ hybridization analysis (FISH), Roque et al. showed an increase in percentage of gain of chromosome 7 and 12 in the different phenotypes analysed. The percentage was low for goiters, slightly higher in adenomas and highest in carcinomas (18, 52 & 66 for chromosome 7; 9, 43 and 66 for chromosome 12). This suggests a role of the increasing frequency of polynomials of chromosomes 7 and 12 in the multistep pathogenesis of thyroid neoplasms.

7. Follicular thyroid carcinoma (FTC)

Follicular thyroid cancer is the second commonest cause of differentiated thyroid cancer, accounting for 15 percent of all thyroid cancers. They are common in women and is usually seen in middle age to elderly individuals. Population based studies have shown the incidence of FTC to be higher in iodine deficient areas, however, since the dietary iodine supplementation programme introduced by the WHO, the frequency of FTC has declined. Rarely, follicular carcinoma may arise from a follicular adenoma. Dys hormonogenesis, a history of irradiation and Cowden's syndrome are predisposing factors for the formation of follicular cancer. Unlike PTC, the cancers usually metastasize through the blood stream into the bones, and lymph nodal disease is rare.

The receptor tyrosine kinase (RTK), PI3K/Akt and MAPK pathways are prevalent in FTC, suggesting the role of these signalling pathways mediated by growth factors and oncogenes like ras in these tumours. Unlike PTC, RET and BRAF do not play any role in the pathogenesis of follicular thyroid cancers. Follicular cancers show a predominance of ras mutations, PAX8–PPARγ rearrangements and aneuploidy. Point mutations of ras oncogenes are seen in about 40 percent of thyroid tumours, with a predominance of N-ras over H-ras and K-ras; however a high rate of K-ras activation is seen in radiation induced follicular cancers in comparison to the spontaneous type.

In a recent study by Rivera et al. N-ras mutations were the most frequent oncogenic activation in 45 percent of the follicular thyroid tumours with features of high grade. The presence of ras mutation in both follicular adenomas and carcinomas may suggest their role in early steps of thyroid carcinogenesis. Using in vivo models Miller et al. showed that simultaneous activation of K-ras with P13K signalling was necessary for oncogenic transformation into invasive and metastatic cancers. Follicular cancers that harbour ras mutations may be at a risk of dedifferentiating into anaplastic thyroid cancers. Mutations of ras gene are associated with poor histological features and poor patient survival.

Pax8 encodes a transcription factor essential for the genesis of the follicular thyroid cell lineage and thyroid-specific gene expression. Kroll et al. in 2000 identified PAX8–PPARγ gene fusion in a significant portion of follicular carcinomas, some with a cytogenetically detectable translocation t(2;3)(q13;p25) (Kroll et al. 2000). This was initially thought to be a specific molecular marker of FTC, however, further studies showed the prevalence to be about 26–56% in follicular carcinomas and in 0–13% of follicular adenomas, 0–3% of Hurthle cell carcinomas, and 0–1% papillary carcinomas. No point mutations of PPARγ gene have been shown in thyroid carcinomas and the mechanism of PPARγ activation is believed to be chromosomal rearrangement. PPARγ activation may be involved with vascular invasion, and this may be due to up-regulation of target genes like angiopoietin-like 4 and aquaporin 7. Underexpression of p105/p130 Bcl-2, BRCA1, and p53 have been reported in FTC. The frequency of mutations of ras oncogenes is lower in FTC in comparison to the PTC. PAX8–PPARγ gene fusion has been shown to increase in radiation induced follicular cancers in comparison to the spontaneous type.

8. PTEN

Phosphate and tensin homolog (PTEN) gene is a tumour suppressor gene by negatively regulating the PI3K signalling pathway, and is activated in many human cancers. In Cowden's syndrome, inactivating mutation of PTEN has been shown to be the cause of the disease. In sporadic follicular thyroid cancer, somatic intragenic mutations of PTEN are rare. However loss of heterozygosity at 10q23 of the PTEN gene has been associated with follicular thyroid carcinomas. The frequency of PTEN mutations have been reported to be a higher frequency in comparison to follicular cancer, implying the role of the gene in dedifferentiation from differentiated cancer.

9. PI3KCA

The phosphatidylinositol 3-kinase (PI3K) pathway involves signal transduction by tyrosine kinase receptors and promotes cancer cell proliferation and survival. The gene encoding for PI3KCA is either amplified, or undergo homozygous point mutations in cancers. The frequency of point mutations in follicular cancer has been reported between 6 and 13 percent. PTEN gene when silenced with genetic alterations in PI3KCA pathway may contribute to progression of thyroid cancers.

10. Hurthle cell carcinoma

Hurthle cell carcinoma accounts for 2–8 percent of differentiated thyroid cancers and are characterised by the presence of Hurthle cells, which are large eosinophilic thyroid cells that contain a large number of mitochondria. These tumours tend to be more aggressive than follicular thyroid cancers, metastasize often to lymph nodes and usually do not take up radiiodine. Previous exposure to radiation and somatic gene mutations are risk factors for the development of Hurthle cell cancer. These tumours tend to be seen in the fifth and sixth decade of life, with an increased female preponderance. Most common presentation is with a solitary nodule, however some patients present with nodal disease, and a few with compressive symptoms.
Hurthle cell carcinomas have a distinct oncogenic expression profile in comparison to the follicular thyroid cancers. Hurthle cells are characterised by the presence of abnormal mitochondria, usually associated with defective mitochondrial DNA (mtDNA) and intranuclear genes. Alterations in RET/PTC and chromosomal aberrations have also been described in Hurthle cell tumours.

11. Mitochondrial DNA

Mitochondrial DNA contains 37 genes that are responsible for normal mitochondrial function and are prone to somatic mutations that may result in cancer. Somatic mutations of mtDNA have been described in Hurthle cell tumours. Maximo et al. showed the presence of mtDNA in both adenomas and carcinomas, with a higher proportion of deleted DNA in carcinomas. More than 80 percent of mutations seen tend to be somatic transition mutations. The mutations are probably associated with disruption of oxidative phosphorylation, linked to increase in the 2 mitochondrial genes ND2 and ND5.

12. GRIM-19

GRIM-19 (Gene associated with retinoid-interferon-β-induced mortality) is an important protein that regulates interferon-β-mediated signal transduction in the endoplasmic reticulum. GRIM-19 is an important gene necessary for the function of the mitochondrial respiratory chain complex I assembly and activity. Mutations in genes directly or indirectly affecting mitochondrial function could be the cause of the increase in mitochondrial number in Hurthle cell tumours. The presence of GRIM-19 mutations have been reported only in Hurthle cell lesions, with none reported in non Hurthle cell lesions and this may explain their role in the pathogenesis of these tumours. Mutations identified in HCC by Maximo et al. were located at codons 26, 83, 88 (exon 1) and 198 (exon 5) of GRIM-19.

13. Chromosomal aberrations

Chromosomal aberrations by comparative genomic hybridization (CGH) are common in Hurthle cell neoplasms. In a study of 28 Hurthle cell tumours the most common chromosomal gain was that of 5p (29 percent) and loss was that of 2q and 9q. Widely invasive carcinomas and poorly differentiated carcinomas was associated with more chromosomal gains than that of well differentiated type, and this correlated with the stage of the disease. With the progression from benign to malignant phenotype, the incidence of trisomy 7 and 12 increases, thus implying the role in multistep tumourigenesis. Gains on chromosome 12 are more common in Hurthle cell carcinomas than in Hurthle cell adenomas, especially in patients with recurrent disease, again highlighting their association with phenotypical progression to malignant state.

14. ret/PTC

Alterations of ret/PTC is commonly associated with papillary thyroid cancer and not usually seen in classical Hurthle cell cancers. However, Hurthle cell carcinomas with papillary features shows ret/PTC alterations, with RET/PTC 1 the most common rearrangement.

15. Anaplastic thyroid cancer

Anaplastic thyroid cancer is the least common and most lethal of all thyroid cancers, with only a mean survival of 6 months after diagnosis. They commonly present with a rapidly enlarging mass, and commonly infiltrate the local structures, namely the trachea, oesophagus and the neck vessels. Lymph node involvement is commonly seen early in the disease. The cancer may arise either de novo, in long standing goitre or in patients with previous well differentiated thyroid carcinoma. Anaplastic cancers do not concentrate iodine and thyroglobulin. Histologically the most common type is the giant cell type, composed of large cells with cytological pleomorphism.

16. p53

The p53 suppressor gene, located on chromosome 17p13, plays an important role in the development of cancer. Studies have shown that p53 belongs to a multigene family of that also includes p63 and p73. The p53 gene encodes a nuclear phosphoprotein that acts as a transcription factor, and plays an important role as mediator of cell cycle arrest in G1 and G2 phase. Inactivating mutations of p53 have been described in 50% of human malignancies, and the majority of the mutations are in the exons 5–8. However in the thyroid gland, p53 mutations have been shown in 40–62% of undifferentiated carcinomas and only 5–10% in other carcinomas. The mutations of p53 or increased expression of p53 protein is associated with the progression from differentiated to anaplastic carcinoma. Thus, presence of p53 mutations is a late event in thyroid cancer progression. In addition to thyroid cancer progression, p53 inactivation has also been implicated in chemoresistance. Gene therapy using the E1B gene-defective adenovirus (ONYX-15), which only replicates in cells deficient in p53, have been used to kill anaplastic cancer cells, both in vitro and in vivo.

17. PI3KCA

P13K pathway is a main regulator of cell growth, metabolism and survival. PI3KCA encodes for a catalytic subunit of P13K and is located on the chromosome 3q26.3. Mutation of PIK3CA have been shown in 12–23 percent of anaplastic thyroid cancer. In 18 out of 20 cases of anaplastic cancer studied, coexisting areas of differentiated cancer showed no expression of PIK3CA unlike the anaplastic areas. Akt, a downstream effector of the P13K gene, has been shown to be activated in up to 93 percent of cases. PTEN a negative regulator of P13K is down-regulated in 37 percent of differentiated thyroid cancers, with no expression in anaplastic cancer.

18. MAPK effector genes

Ras and BRAF are oncoproteins that activate the MAPK kinase and ERK pathway, and aberrations of signalling in this pathway leads to tumour formation, transformation and maintenance. Ras mutations are seen in both differentiated and undifferentiated cancer types, with a frequency of 6–50 percent in anaplastic cancer. The frequency of BRAF mutations in anaplastic cancer ranges from 0 to 50 percent. In tumours that harbour both papillary and anaplastic thyroid cancer, the profile of BRAF alterations tends to be similar, thereby supporting the hypothesis that anaplastic cancers arise from well differentiated cancer.

19. Wnt pathway genes

Beta catenin is a gene that is involved with Wnt signalling and cell adhesion and deregulation is associated with the development and progression of cancer. Well differentiated cancers do not show any abnormalities in the signalling pathways involving
Wnt. However, mutation in the pathways has been shown in 61 percent of cases and 32 percent of poorly differentiated cancers. Galectin-3, a β-galactoside-binding protein is a binding partner of beta catenin of the Wnt pathway. Cytoplasmic expression of galectin-3 has been to be absent in anaplastic cancers in comparison to well differentiated thyroid cancers, implying the role of these pathways in thyroid cancer progression. In a study of 5 cases of anaplastic thyroid cancer with areas of well differentiated tumours type, areas of dedifferentiated tissues showed no immunolabelling for galectin-3, with strongly reactive labelling in differentiated areas.

20. Molecular profiling as a preoperative tool for diagnosis

Currently FNAC is the most important tool to diagnose a nodule as benign or malignant to aid the surgeon in the definitive treatment. There is clearly evidence of differential expression of various molecular genetic markers between benign and malignant thyroid nodules, and between various thyroid cancer subtypes, discussed in the previous sections. Recently molecular profiling has been used in combination with FNAC, and it has shown improved prediction of malignancy and diagnostic accuracy.

21. Molecular pathways as therapeutic targets

There is no doubt about the role of signalling pathways, oncogenes and tumour suppressor genes in the molecular pathogenesis and progression of thyroid cancer. They also have been used as markers of prognosis. Recent advances have targeted these signalling pathways, predominantly the MAPK pathways. The patients with well differentiated cancers respond well to conventional treatment of thyroidectomy and radiiodine ablation. However the poorly differentiated or anaplastic cancers do not respond to radiiodine and may be the potential targets for such treatments. Various compounds have been used to target different key molecular pathways, and includes those of RET, BRAF and growth factors. Most of the studies are limited to Phase I or II trials or in vitro models. Some of the compounds currently in targeted therapies are illustrated in Table 2.

22. Conclusions

To summarize, thyroid tumours develop as a result of sequential accumulation of alterations in the genes involved in the control of cell proliferation, differentiation or death according to the multistep carcinogenesis theory. The early steps of thyroid cancer formation are the result of activation of proto-oncogenes, oncogenes and growth factors. With further mutations involving tumours suppressor genes differentiated cancers progress into the dedifferentiated state. Some of the molecular changes are specific to certain cancer types, which makes it possible to ascertain both diagnostic and prognostic information. The understanding of the molecular aspects of the disease including the various signalling pathways has the potential to offer target based therapies.

Table 2

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<tr>
<th>Agent</th>
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Conflict of interest
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Ethical approval
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References


