Thyroid hormone, thyroid hormone receptors, and cancer: a clinical perspective

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Abstract

Thyroid hormones (THs) may play a role in diseases other than hyper- and hypothyroidism. Several lines of evidence suggest tumor-promoting effects of TH and TH receptors. They are possibly mediated by phosphatidylinositol-3-kinase and MAPK and involve among others stimulation of angiogenesis via αvβ3. Thus, an increased risk for colon, lung, prostate, and breast cancer with lower TSH has been demonstrated in epidemiological studies, even suggesting a TH dose effect on cancer occurrence. Furthermore, higher TH levels were associated with an advanced clinical stage of breast and prostate cancer. In rodent models, TH stimulated growth and metastasis of tumor transplants, whereas hypothyroidism had opposite effects. In clinical studies of glioblastoma and head and neck cancer, hypothyroid patients showed longer survival than euthyroid patients. Also, patients with renal cell cancer that were treated with the tyrosine kinase inhibitor sunitinib and developed hypothyroidism in due course showed significantly longer survival than patients that remained euthyroid. Development of hypothyroidism was an independent predictor for survival in two studies. Yet, it is still possible that hypothyroidism is only a surrogate marker for treatment efficacy and does not positively influence treatment outcome by itself. Future cancer treatment studies, especially with substances that can induce hypothyroidism, should therefore be designed in a way that allows for an analysis of thyroid function status and its contribution on treatment outcome.

Key Words
- thyroxine
- PI3K
- αvβ3
- tyrosine kinase inhibitor

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Introduction

The thyroid hormones (THs) thyroxine (T_4) and triiodothyronine (T_3) are mostly recognized for their roles in normal growth, development, and metabolism, especially during fetal development and early childhood. In adults, the diseases usually associated with TH are excess and lack of TH and hyper- and hypothyroidism, with their distinct clinical symptoms. But TH may play a greater role in the development and course of diseases. This perspective focuses on evidence for tumor-promoting or suppressing effects of TH and their receptors and potential clinical consequences.

TH receptors and actions

TH action is mainly understood as modification of gene expression, mediated by the nuclear TH receptors (TRs). Two different genes, THRA on chromosome 17 and THRB on chromosome 3, encode TRα and TRβ respectively (Yen 2001). They share a highly homologous protein structure including a central DNA binding domain (DBD) and a C-terminal ligand binding domain (LBD). A short amino acid sequence within the DBD mediates TR binding to

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DNA and dictates sequence specificity. With the DBD, the TRs recognize TH response elements (TREs) in the promoter of their target genes that act as enhancers for genes positively regulated by TH. The LBD binds TH, T_3 with 10- to 15-fold higher affinity than T_4. Due to alternative splicing and promoter usage, various TR isoforms exist. The most studied isoforms are TRβ1 and TRβ2, which differ in the amino terminal domain, and TRα1 and TRα2, which differ in the C-terminal region in length and amino sequence. As a consequence, TRα2 lacks T_3 binding activity and acts as a weak antagonist *in vitro*. The TRα1, -β1, and -β2 isoforms bind DNA and T_3 and act as functional apo- and liganded TRs. In addition, truncated TR isoforms exist that lack amino terminal domains and DNA binding (Cheng *et al*. 2010).

Classical TH and TR action

In the classical model of gene induction by TH, the TRs bind to TREs in the promoter of target genes. Without T_3, corepressors with histone deacetylase activity are bound to the TR complex, preventing transcription. Upon T_3 binding, corepressors are released and replaced by coactivators, which ultimately engages the RNA polymerase II in transcription of the target gene. The TRs are therefore seen as ligand-dependent transcription factors. Studies from TR knockout mice and stably transformed HepG2 cells showed largely overlapping gene expression patterns of positively regulated genes for TRα and TRβ, suggesting that TR amount, rather than isoform type, is important (Yen *et al*. 2003). Yet, the TR isoforms show differential DNA binding affinity to promoters and the transcriptional response of a gene on a given tissue may depend on the predominant TR isoform (Chan & Privalsky 2009, Chiamolera *et al*. 2012). The clinical differences between patients with resistance to TH (RTH) due to TRβ and TRα mutations further demonstrate that distinct physiological roles for the TR isoforms exist (Refetoff & Dumitrescu 2007, Bochukova *et al*. 2012, Ferrara *et al*. 2012, van Mullem *et al*. 2012).

Nonclassical TH and TR action

A few years ago, it became evident that TH and TRβ could also act through a different mechanism: the ligand-bound TRβ could activate the phosphatidylinositol-3-kinase (PI3K) pathway via phosphorylation of Akt/PKB within minutes, which subsequently affected gene expression (Simoncini *et al*. 2000, Lei *et al*. 2004, Cao *et al*. 2005). This mechanism is independent of TRβ binding to DNA and TREs. Ultimately, this nonclassical action of TH results in induction of gene expression. For example, ZAKI-4α had previously been described as a TH-responsive gene. ZAKI-4α induction by T_3 is dependent on TRβ and could be blocked by PI3K inhibitors, such as LY294002 (Cao *et al*. 2005, Moeller *et al*. 2005*b*). Similar results as for TRβ were obtained for TRα. Cao *et al*. (2009) could demonstrate PI3K activation in TRα overexpressing neuronal cells and Hiroi *et al*. (2006) found TRα1 association with p85α followed by phosphorylation of Akt/PKB, a downstream target of PI3K, and activation of endothelial nitric oxide synthase.

αvβ3 as TR

Bergh *et al*. (2005) demonstrated that T_4 and T_3 could bind to a purified plasma membrane protein, the integrin αvβ3. αvβ3 contains two TH binding sites, denoted as S1 and S2, which translate the TH signal differently (Davis *et al*. 2011, Freindorf *et al*. 2012). S1 exclusively binds T_3 at physiological concentrations and leads to PI3K activation. S2 binds T_4, and to a lesser extent T_3, and ultimately activates the ERK1/2 pathway (Lin *et al*. 2009). As the integrin αvβ3 binds TH and transmits TH the signal into the cell, it clearly qualifies as a cell surface TR.

These various ways of action of TH and their receptors harbor potential to promote tumor growth. For example, the most highly induced genes in a microarray study of T_3-induced gene expression in human skin fibroblasts were the aldo-keto reductases 1–3 (AKR1C1–3; Moeller *et al*. 2005*b*), which are associated with aggressiveness of prostate cancer due to increased conversion of adrenal androgens to testosterone (Fung 2006, Penning & Byrns 2009). And the oncogenic PI3K pathway, activated by TH via TRα/β and the S1 site of αvβ3, facilitates cell growth and survival and inhibits apoptosis (Chalhoub & Baker 2009). Via PI3K, T_3 induces expression of the α subunit of the transcription factor hypoxia-inducible factor 1 (*HIF1*; Moeller *et al*. 2005*a*). *HIF1* target genes play key roles in cancer biology, from angiogenesis to adaptation to hypoxia, prevalent in rapidly growing tumors, and invasion and metastasis (Semenza 2009). *HIF1α* expression is a prognostic marker in renal cell carcinoma (RCC) and breast and prostate cancer, among others (Kimbro & Simons 2006). TH can, via αvβ3/S2, activate ERK1/2 and induce fibroblast growth factor 2 and promote angiogenesis, also crucial for rapid tumor growth (Davis 2004).

From a clinical perspective, the following important questions regarding TH and cancer arise: can TH influence tumor incidence, tumor progress and metastasis, and, ultimately, success of tumor treatment?

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Epidemiology suggests tumor-promoting effects of TH

A population-based case–control study of risk factors for ovarian cancer with 767 cancer patients and 1367 controls found a higher rate of patients with a history of hyperthyroidism in the cancer patients than in the controls. The odds ratio (OR) for ovarian cancer was almost doubled in participants with a history of hyperthyroidism (OR 1.8, adjusted for age, pregnancies, race, oral contraceptive use, hysterectomy, and familial history of ovarian cancer) (Ness *et al*. 2000). In a similar study on risks for pancreatic cancer, a history of hyperthyroidism was associated with a twofold increased risk (OR 2.1, adjusted for race, education, BMI, smoking, and history of diabetes) (Ko *et al*. 2007). While these retrospective studies indicated an increased cancer risk with higher TH levels, their results depended on self-reported thyroid disorders and thyroid function tests were not analyzed.

A relationship also appears to exist between TH and prostate cancer: T_3 levels were measured and compared in 161 men with localized prostate cancer, 20 men with benign prostate hyperplasia (BPH), and 27 age-matched controls with no history of cancer, BPH, or thyroid disease (Lehrer *et al*. 2002). Patients with prostate cancer and BPH had significantly higher T_3 levels than controls. Furthermore, T_3 levels were associated with higher clinical stage and risk of recurrence of prostate cancer (Lehrer *et al*. 2001). At diagnosis, 68 prostate cancer patients were divided into three risk groups for recurrence, low risk (serum PSA <10, stage $\leq$T2a, or Gleason grade ≤ 6), moderate risk (serum PSA 10–15, stage $\leq$T2b, or Gleason grade 7), and high risk (serum PSA >15, stage T2c or T_3, or Gleason grade >7). While all patients had T_3 levels within the reference range, T_3 levels were highest in the high-risk group and significantly different from the low- and moderate-risk groups. More recently, a prospective, randomized, and control-matched study on THs and prostate cancer risk in smokers showed that hypothyroid men had a lower risk of prostate cancer than euthyroid men (OR=0.48, $P=0.006$) (Mondul *et al*. 2012).

Cristofanilli *et al*. (2005) retrospectively studied the prevalence of hypothyroidism in patients with breast cancer. They identified 74 hypothyroid women in 884 breast cancer patients. Compared with euthyroid patients, the hypothyroid patients were older at diagnosis (58.8 vs 51.1 years, $P<0.001$) and were more likely to be diagnosed at an earlier stage of breast cancer (pathologic stage I/II: 95 vs 85.9%, $P=0.025$), with a smaller tumor (T1 (≤ 2 cm): 72.5 vs 55%, $P=0.002$) and without pathologic lymph node involvement (63.9 vs 55.9%, not significant). These results seem to indicate that invasive breast cancer progression may be slower in hypothyroidism. In interpreting these results, it must be considered that hypothyroidism was determined by the use of thyroid supplements as TSH and free T_4 levels were not available. TH levels have probably been normal since start of T_4. Hypothyroidism in this study therefore refers to a period of assumedly low TH levels of unknown duration in the patients' past.

Also for breast cancer, a prospective study of 2696 women showed an association between T_3 levels at baseline and cancer risk during a mean follow-up of 19.3 years (Tosovic *et al*. 2010). The overall risk of breast cancer was statistically significantly higher for women with T_3 in the highest vs lowest quartile. This association was due to findings in the 1322 peri-/postmenopausal women because the association was even stronger in these participants, but absent in pre-menopausal women. There were three cases of breast cancer in the 196 women with a T_3 in the lowest quartile and 38 cases in the 408 women with a T_3 in the highest quartile. From lowest to highest T_3 quartile, the adjusted relative risk continuously increased from 1.00 to 3.26, 5.53, and 6.87 respectively. This increase was preserved when taking into account only tumors diagnosed 3 years after baseline. These results indicate a positive correlation and a dose response for T_3 and risk of breast cancer development in peri-/postmenopausal women.

Another prospective study assessed a connection of thyroid function with cancer risk: participants of the Nord-Trøndelag Health Study were studied for TH and TSH levels and cancer incidence (Hellevik *et al*. 2009). After exclusion of participants with a history of thyroid disease, a history of cancer or missing information, almost 30.000 participants, could be analyzed for cancer risk (29.691 people, 19.710 women, and 9.981 men) in a median follow-up of 9 years using the Cancer Registry of Norway. According to their TSH, the participants were placed in five categories: each one below and above the TSH reference ranges, indicating hyper- and hypothyroidism respectively and three groups within the TSH reference range. Participants with a TSH in the lower normal third were used as the reference group with a hazard ratio (HR) for cancer of 1.0 by definition. Total cancer risk for participants with a TSH below the reference range was higher than for people from any other category and 34% increased compared with the reference group (HR 1.34; adjusted for age, sex, and smoking status). This increased cancer risk was mainly due to an increased risk for colon

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cancer (HR 1.38), prostate cancer (HR 1.97), lung cancer (HR 2.34), and breast cancer (HR 1.20). When HRs were calculated only for cancers diagnosed 2 years and later after baseline, to exclude effects of yet undiscovered cancer on TH and TSH levels, these results were only strengthened. Interestingly, a subanalysis of the participants with a TSH below the reference range revealed that during follow-up starting 2 years after baseline, the HR for total cancer for participants with suppressed TSH and elevated free T_4 or total T_3 was higher (HR 2.35) than for those with either suppressed TSH and normal free T_4 and total T_3 levels or TSH between 0.2 and 0.49 mU/l (HR 1.42), again suggesting a dose effect for TH on cancer occurrence.

Different results were obtained in a case–control study for hepatocellular carcinoma (HCC). Women, but not men, with a history of hypothyroidism had a 2.8-fold higher risk of HCC than participants without a history of hypothyroidism (after adjustment for age, race, diabetes, smoking, alcohol consumption, family history of cancer, and HBV/HCV status) (Hassan *et al.* 2009). This calculation was based on self-reported absence or presence of hypothyroidism because TH levels and data regarding substitution were not available. In this context, it is interesting that hypothyroidism was significantly more prevalent in patients with HCC of unknown etiology than in HCC patients with alcoholic liver disease or HCV in another case–control study (Reddy *et al.* 2007), suggesting that hypothyroidism may be a permissive factor in the development of HCC.

TH, TRs, and tumor progress in animal models

An experimental method for demonstrating that TH are involved in tumor growth has been the xenograft assay, which involves s.c. implantation of tumor cells into immunodeficient mice with subsequent treatment, e.g. TH treatment or induction of hypothyroidism, and measurements of tumor growth rates and extent of metastasis.

TH effects in rodent tumor implant models

Evidence for tumor-promoting effects of TH stems from mouse models of cancer cell lines (Table 1). Shoemaker *et al.* (1976) reported a connection between survival and induced hypothyroidism in mice after implantation of murine mammary adenocarcinoma cells. Half of the mice were treated with propylthiouracil (PTU) for 21 days, starting on day 14 postimplant through day 35. Tumors had grown in all mice until day 13 and from day 16 on the tumor size was different between the PTU-treated group and the untreated control group with 0.22 ± 0.2 and 0.63 ± 0.45 cm^3 respectively. This difference was maintained throughout the rest of the experiment with mean tumor sizes in the surviving animals of 8.3 ± 5.1 vs 17.6 ± 8.2 cm^3

Table 1 Influence of TH on tumor growth and metastasis formation in tumor implant rodent models.

	Tumor implant (cell line)	**Tumor origin**	**Comparison**	**Observation**	**Reference**
1	Mammary adenocarcinoma (C3HBA)	Murine	No treatment vs PTU	Reduced tumor size and prolonged survival in the PTU group	Shoemaker *et al.* (1976)
2	Sarcoma (S1), fibrosarcoma (T241)	Murine	No treatment vs T_4 treatment vs ^{131}I-induced hypothyroidism	Tumor weight and metastatic index increased in the T_4 group and reduced in the hypothyroid group	Kumar *et al.* (1979)
3	Morris hepatoma 44	Rat	No treatment vs hypothyroidism	Reduced tumor size, lung metastasis, and prolonged survival in the hypothyroid groups	Mishkin *et al.* (1981)
4	Prostate adenocarcinoma (PC3)	Human	No treatment vs PTU	Reduced tumor growth in the PTU group	Theodossiou & Schwarzenberger (2000)
5	Prostate adenocarcinoma (PC3), lung adenocarcinoma (201T)	Human	No treatment vs PTU-induced hypothyroidism	Reduced tumor growth in the PTU group	Theodossiou *et al.* (1999)
6	Hepatocarcinoma (SK-hep1), breast cancer (MDA)	Human	No treatment vs methimazole-induced hypothyroidism	Reduced tumor growth and proliferation, but enhanced invasiveness and metastasis in hypothyroid mice	Martinez-Iglesias *et al.* (2009)

PTU, propylthiouracil.

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(PTU treated vs control) on day 48. The delay in tumor growth seemed to be reflected in survival time with the PTU-treated animals surviving 58.9±24.7 vs 42.7 ±10.4 days of the control mice. However, the extent of hypothyroidism achieving this effect is unknown as hormone values are not available for this experiment.

In rats, hypothyroidism inhibited both local and metastatic growth of hepatomas and prolonged host survival. Rats, in which hypothyroidism was induced by either PTU or ^{131}I treatment or thyroidectomy 2 weeks after hepatoma implantation (Morris hepatoma 44) into the hind limbs, survived longer and developed smaller tumors than untreated controls (Mishkin *et al*. 1981). The time of induction of hypothyroidism by ^{131}I treatment influenced the outcome significantly: while early treatment 2 weeks after implantation led to 78% longer survival compared with untreated controls, the survival benefit was reduced to 35% at 6 weeks and 17% at 11 weeks postimplantation. Similarly, incidence of pulmonary metastasis was reduced from 80% in untreated controls to 30 and 40% with ^{131}I treatment after 2 and 6 weeks respectively and unchanged with 88% after 11 weeks.

The effect of T_4 treatment and ^{131}I-induced hypothyroidism on tumor growth and metastasis formation was compared to that in control mice for two murine cancer models, sarcoma (S1) and fibrosarcoma (T241) (Kumar *et al*. 1979). T_4 treatment led to increased growth rate of tumor implants and rate of metastasis to the popliteal lymph nodes and thymus or lung. Strikingly, hypothyroidism appeared to reverse the effect of T_4 with reduced tumor weight as well as reduced metastasis. For these experiments, hypo- and hyperthyroidism were documented by increased or undetectable serum T_4 levels. These results were obtained in syngenic murine tumor systems. Similar effects could be observed in xenografts with human cancer cell lines. A prostate cancer cell line, PC-3, grew to significantly larger tumors in untreated mice compared to PTU-treated mice with roughly doubled size after 30 days (Theodossiou & Schwarzenberger 2000). In a similar experiment, mice were inoculated with PC-3 cells or the poorly differentiated lung carcinoma cell line 201T (Theodossiou *et al*. 1999). The mice were treated with PTU 3 weeks before inoculation and through the 42 days of the experiment or not treated with PTU. All animals developed tumors, but for both carcinoma cell lines, the tumors in PTU-treated mice were significantly smaller than in untreated mice, demonstrating again that tumor growth is diminished in hypothyroidism.

Experiments with hepatocarcinoma and breast cancer cell lines that lost TR expression and the same cells with TRβ1 re-expression (SK/SK-TRβ and MDA/MDA-TRβ respectively) injected into nude mice produced similar results regarding tumor growth but different results with regard to metastasis (Martinez-Iglesias *et al*. 2009). Hypothyroidism reduced tumor volume, tumor proliferation, measured by KI67 index, and increased tumor necrosis in both parental cell lines and the TRβ expressing cells. Yet, SK cells inoculated into hypothyroid mice always led to tumors that infiltrated adjacent muscle, skin, and vessels, whereas this occurred only in 60–80% of euthyroid control mice. In 25% of hypothyroid mice, SK cells metastasized into lung and liver, while in euthyroid mice, no distant metastases were observed.

In vivo effects of αvβ3 inhibition on tumor growth

The effect of TH-stimulating cell proliferation and angiogenesis via integrin αvβ3 has been demonstrated *in vitro* for several cell lines. For example, T_4 and T_3 stimulated proliferation of human non-small cell lung cancer cells (NSCLC, NCI-H1299) in a concentration-dependent manner as measured by PCNA accumulation (Mousa *et al*. 2012). This effect was inhibited by co-treatment with antibodies against αvβ3 as well as Tetrac, which confirms that the TH effect is indeed dependent on αvβ3. Xenografts of the same cell line were implanted in nude mice and treatment with Tetrac resulted in significantly smaller tumor volumes and lower tumor weights as well as lower hemoglobin content as a measure of tumor vascularity (Mousa *et al*. 2012). The antitumor effect of Tetrac has also been shown in other xenograft models, e.g. medullary thyroid carcinoma, follicular thyroid carcinoma, and RCC (Yalcin *et al*. 2009, 2010*a*,*b*). These observations are very promising because they go beyond merely describing an effect of TH and provide a potential treatment. As the stimulatory effect of TH on cell proliferation and angiogenesis could clearly be inhibited by Tetrac *in vitro*, it seems logical to assume that the same mechanisms apply *in vivo*. But a demonstration that a tumor-stimulating effect of TH effect observed *in vivo*, as described earlier, can be blocked by Tetrac treatment has yet to be provided. In a live tumor environment, more signals other than TH (e.g. various growth factors, hypoxia) influence tumor progress, which may in part also be mediated by αvβ3 and consequently blocked by Tetrac.

The TRβPV mouse model

TRβ mutations that prevent T_3 binding or disturb interaction with corepressors and coactivators lead to

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RTH. In RTH, patients have raised serum TH and raised or inappropriately normal TSH levels. Common clinical features of RTH include goiter, tachycardia, and delayed bone growth with a variable phenotype (Weiss & Refetoff 2000). The TRβPV mouse, a TRβ knock-in mouse model initially generated as a mouse model of RTH, surprisingly provided more evidence for the involvement of the TRs in carcinogenesis and tumor progression. The TRβPV mutation, introduced by homologous recombination, was derived from a patient with severe RTH. A C-insertion at codon 448 (exon 10) produces a frameshift of the carboxyterminal 14 amino acids of TRβ1. This mutant completely lost T_3 binding ability, showed no transactivation activity, and exerted a strong dominant negative effect (Kaneshige *et al.* 2000). But, interestingly, not all modes of action of TRβ WT were lost in the TRβPV mutant. The TRβPV mutant bound significantly stronger to the regulating subunit of PI3K than WT TRβ, leading to stronger activation of PI3K and downstream kinases (mTOR, AKT, and $p70^{S6K}$) (Furuya *et al.* 2006). Other than the WT TRβ, the TRβPV was not able to bind T_3. The degree of PI3K activation therefore cannot be modified by T_3 levels. Rather, PI3K is constitutively activated by TRβPV.

The heterozygous mice, $TR\beta^{PV/+}$, reproduced the classical phenotype of RTH with elevated T_4 and TSH levels, enlargement of the thyroid gland, and delayed bone development (Kaneshige *et al.* 2000). The homozygous $TR\beta^{PV/PV}$ mice showed more severe RTH and the size of their thyroid gland was several fold increased. The enlargement of the thyroid in the homozygous $TR\beta^{PV/PV}$ mice began at 3 weeks and reached 19- and 36-fold the weight of WT mice at ages 5–7 and >12 months respectively (Suzuki *et al.* 2002). Furthermore, the homozygous mice showed poor survival compared with WT and heterozygous $TR\beta^{PV/+}$ mice: median survival was only 12.9 months and at age 14 months only 20% of the $TR\beta^{PV/PV}$ mice were alive, whereas almost all WT and heterozygous mice survived. Histopathological examination of the thyroid glands showed a neoplastic progression in these $TR\beta^{PV/PV}$ mice, from invasion of the thyroid capsule to development of focal anaplasia and distant metastasis, predominantly to the lung. The $TR\beta^{PV/PV}$ mouse spontaneously developed follicular thyroid cancer. Because the TRβPV mutant constitutively activates PI3K and subsequently Akt, phosphorylation status of these kinases was tested in the $TR\beta^{PV/PV}$ mice (Kim *et al.* 2005). pAKT was markedly increased in both the thyroid tumors and metastases. The importance of PI3K-Akt overactivation in the $TR\beta^{PV/PV}$ mice is highlighted by the fact that treatment with LY294002, a potent PI3K inhibitor, significantly decreased vascular invasion and prevented lung metastases. This led to significantly longer median survival of the LY-treated compared with untreated $TR\beta^{PV/PV}$ mice with 329±65 vs 244±63 days respectively (Furuya *et al.* 2007). PI3K is counteracted against by PTEN, which dephosphorylates PIP_3. To test whether reducing PTEN further increased tumor growth, mice haplodeficient for PTEN were crossed with the PV mice ($TR\beta^{PV/PV}Pten^{+/-}$ mice) (Guigon *et al.* 2009). Indeed, the $TR\beta^{PV/PV}Pten^{+/-}$ mice had a significantly shorter median survival time with 5.5 months than either $TR\beta^{PV/PV}Pten^{+/+}$ mice (10.0 months) or $TR\beta^{+/+}Pten^{+/-}$ mice (14.1 months). Capsular invasion was detectable at earlier age in the $TR\beta^{PV/PV}Pten^{+/-}$ mice compared with $TR\beta^{PV/PV}Pten^{+/+}$ mice and anaplasia, vascular invasion and lung metastasis occurred earlier and more frequently in the $TR\beta^{PV/PV}Pten^{+/-}$ mice, which was associated with an increased activation of PI3K.

TR mutants in human cancers

TRα and β mutants have been described in HCC, RCC, and papillary thyroid carcinoma (Lin *et al.* 1999, Kamiya *et al.* 2002, Puzianowska-Kuznicka *et al.* 2002). These mutants arise *de novo* in carcinomas and often harbor more than one mutation. The main consequences appear to be impaired T_3 binding and altered recognition of promoter sequences, leading to regulation of a set of genes distinct from that regulated by the wild-type receptors (Rosen & Privalsky 2011). This mechanism may contribute to tumor progress, but the clinical relevance is still unclear.

TH and success of tumor therapy

As TH appear to promote tumor growth, metastasis, and survival in animal models, it seems possible that thyroid function could influence the outcome of tumor therapy, which is defined by exactly these parameters.

For example, an association between TH levels and survival was found for patients with astrocytoma grades III and IV. Twenty-two patients with recurrence after initial surgery and chemo- and/or radiation therapy were treated with tamoxifen (Hercbergs *et al.* 2003). With the idea that IGF1 inhibits the efficiency of tamoxifen and IGF1 levels are reduced in hypothyroidism, the patients were co-treated with a fixed PTU dose to induce hypothyroidism. Eleven of the 22 patients became hypothyroid. Surprisingly, median survival was significantly longer in

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the hypothyroid patients (10.1 months) than in the euthyroid patients (3.6 months).

Nelson *et al*. (2006) analyzed retrospectively whether thyroid function is associated with treatment outcome in head and neck squamous cell cancer. One hundred and fifty-five patients with head and neck cancer were treated with radiation therapy alone or in combination with chemotherapy and/or surgery. Fifty-nine patients developed hypothyroidism with increased TSH levels. Hypothyroidism was most likely a consequence of radiation, but the radiation dose was not different for hypothyroid and euthyroid patients (70 vs 69 Gy, NS). Of the 59 patients who became hypothyroid during the course of treatment and follow-up, 16 had a recurrence (ten before or with diagnosis of hypothyroidism and six after), whereas recurrence was detected in 41 of 96 euthyroid patients. The risk for death or recurrence was significantly lower in hypothyroid patients (HR 0.37, $P<0.001$). In contrast to the intended induction of hypothyroidism in the glioblastoma patients, the hypothyroid head and neck cancer patients were started on T_4, but data on efficacy of T_4 supplementation were not available.

Hypothyroidism as a side effect of treatment and treatment outcome

Development of autoimmune thyroid disease, mostly thyroiditis with hypothyroidism and more seldom autoimmune hyperthyroidism, is a known side effect of interleukin-2 (IL2) treatment. A potential correlation between treatment outcome and thyroid function was noted in the 1990s, when in a small series of 13 patients with RCC or malignant melanoma 6 of 7 eu- or hyperthyroid patients died from progressive disease, but only one of five patients who developed hypothyroidism. Four hypothyroid patients were placed on T_4 supplementation (Reid *et al*. 1991). Similarly, of 15 cancer patients (RCC, malignant melanoma) treated with IL2 and lymphokine-activated killer cells, five of seven hypothyroid patients responded with partial or complete remission, but none of the euthyroid patients (Weijl *et al*. 1993). Three of the seven hypothyroid patients received T_4 substitution.

In the context of thyroid function and cancer treatment outcome, studies with tyrosine kinase inhibitors (TKIs) such as sunitinib are extremely interesting because hypothyroidism is a common side effect of TKIs. Sunitinib is an oral multitargeted TKI with activity against vascular endothelial growth factor receptor, platelet-derived growth factor receptor, KIT, and RET. Sunitinib is also the TKI most frequently associated with hypothyroidism with roughly one-third (range 14–85%) of patients on sunitinib treatment developing hypothyroidism (Lodish & Stratakis 2010, Brown 2011). In a recent study using a German pharmacy prescription claims database, 178 of 1295 patients (13.7%) on sunitinib treatment later received a first prescription for T_4 (Feldt *et al*. 2012). How TKI induce hypothyroidism is not fully understood and several mechanisms have been proposed, for example, reduction of thyroid volume due to atrophy of follicles, degeneration of follicular epithelial cells (Shinohara *et al*. 2011), and capillary rarefication (Kappers *et al*. 2011) or inhibition of iodine uptake (Mannavola *et al*. 2007). Extrathyroidal mechanisms affecting TH metabolism must also be involved because patients with medullary thyroid cancer treated with imatinib, who underwent thyroidectomy and were on T_4 replacement therapy, also developed hypothyroidism (de Groot *et al*. 2007). As one possible explanation, sunitinib appears to increase deiodinase 3 activity (Kappers *et al*. 2011).

A positive correlation between sunitinib-induced hypothyroidism and progression-free (PFS) or overall survival (OS) of RCC patients was first reported in 2008 (Wolter *et al*. 2008). Twenty-eight of 40 sunitinib-treated RCC patients became hypothyroid (70%) and their median PFS was significantly longer than that of euthyroid patients (10.3 vs 3.6 months) as was their OS (18.2 vs 6.6 months). Thirteen hypothyroid patients were supplemented with T_4.

In a prospective Italian study, 13 of 22 sunitinib-treated RCC patients (59.1%) developed hypothyroidism as defined by at least one elevated TSH level (Baldazzi *et al*. 2012). Two patients required T_4 substitution. Again, the hypothyroid patients experienced a longer median PFS (8.55 months) compared with euthyroid patients (7.03 months, $P<0.05$). In an Austrian study, RCC patients were treated with either sunitinib or sorafenib and subclinical hypothyroidism occurred in 30 patients (36.1%) (Schmidinger *et al*. 2011). The rate of objective remission (RECIST criteria) was significantly higher in the hypothyroid patients than in euthyroid patients (28.3 vs 3.3%) and median survival was longer (not reached vs 13.9 months). T_4 replacement was started in 16 patients but normalized TSH in only four, while the other 12 remained hypothyroid. On multivariate analysis, only elevated TSH was an independent predictor of survival.

Development of hypothyroidism was again an independent prognostic parameter in another study of 66 patients with metastatic RCC and sunitinib or sorafenib

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treatment. Twenty-one patients developed hypothyroidism (31.8%), which was associated with a longer median PFS (16.0 vs 6.0 months) (Riesenbeck *et al.* 2011). Patients with overt hypothyroidism were placed on T_4 and the association of hypothyroidism with PFS was not diminished by T_4 replacement. Interestingly, a prospective study, for which the investigators chose to supplement all hypothyroid patients, overt and subclinical, found no association between survival and thyroid dysfunction (Sabatier *et al.* 2012): of 69 patients with RCC, euthyroid at initiation of standard treatment with sunitinib and without disease progression at a 6-month landmark, 45 (65%) developed hypothyroidism. Patients with elevated TSH were placed on T_4 replacement. Mean PFS was not significantly different with 15.9 months for euthyroid patients and 18.9 months for patients with thyroid dysfunction ($P=0.94$).

Similar effects as for sunitinib were observed for another TKI, cediranib: Speranza *et al.* (2011) reviewed NCI-sponsored single-agent clinical trials of cediranib and analyzed the response rate for patients with and without hypothyroidism. Hypothyroidism was reported in 168 of 504 (33.3%) cediranib-treated patients and these had a response rate of 25%, while only 8.6% of the patients without hypothyroidism showed a response to treatment ($P<0.001$).

Conclusion and outlook

Epidemiological data suggest a tumor-promoting effect of TH as the incidence of some tumors (colon, breast, prostate, and lung cancer) was found to be increased with increasing TH whereas other tumors, e.g. breast cancer, occur later and are diagnosed in a less advanced stage in patients with hypothyroidism. In tumor transplant rodent models, TH appear to stimulate tumor growth and metastasis, whereas hypothyroidism has opposite effects. Therefore, the results of clinical studies showing that treatment-induced hypothyroidism is associated with a favorable outcome in several cancer types, most prominently in RCC, are immediately comprehensible. In two prospective studies of RCC treated with sunitinib, development of hypothyroidism was an independent predictor of treatment success. Furthermore, in the only study replacing T_4 in every RCC patient with elevated TSH and including only patients with normal TSH in the final analysis, no difference in treatment outcome between the patients that developed hypothyroidism and those that remained euthyroid was observed (Sabatier *et al.* 2012). It is tempting to assume that induction of hypothyroidism is one of the mechanisms through which TKIs slow tumor growth and that correction of hypothyroidism eliminates the survival advantage. There is reasonable concern that substituting these cancer patients with T_4 could deprive them of the potential beneficial effects of hypothyroidism (Garfield *et al.* 2007, 2008).

Yet, one must be cautious because it cannot be ruled out that hypothyroidism is only a surrogate marker of antitumor treatment efficacy due to higher drug levels or different drug metabolism or susceptibility of the immune system in a subset of patients and does not influence tumor growth on its own. There may also be a bias because cancer patients on successful, and therefore continued, treatment are exposed to higher cumulative doses and have more time to develop hypothyroidism than rapidly deteriorating patients. Additionally, a tumor-promoting effect of TH may only be found in certain types of cancer, such as glioblastoma and RCC, but not for others, e.g. HCC.

Given the results of the tumor implant animal models and the TKI trials in cancer patients, it is of great clinical importance to determine whether and in which types of cancer hypothyroidism can contribute to prolonged survival and should be tolerated or, more provocative, should even be induced. To address these questions, future cancer treatment studies, especially with substances that can induce hypothyroidism, should be designed in a way that allows for an analysis of thyroid function status and its contribution on treatment outcome.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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