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Differentiation Therapy in Thyroid Carcinoma

Eleonore Fröhlich[1,2] and Richard Wahl[1]
[1]*Eberhard-Karls University Tübingen, Internal Medicine, Department of Endocrinology, Metabolism, Nephrology and Clinical Chemistry,*
[2]*Medical University of Graz, Internal Medicine, Dept. of Endocrinology and Nuclear Medicine,*
[1]*Germany*
[2]*Austria*

1. Introduction

Thyroid cancer (TC) has a much lower incidence (0.74% in men, 2.3% in women worldwide) than cancers of breast, colon, prostate, lung and endometrium but is the seventh most frequent human malignancy and the most common neoplasm of the endocrine system. Thyroid cancer accounts for 1% of all newly diagnosed cancer cases. Over the past decades the incidence of thyroid cancer has increased significantly (50% in the last 25 years). It is suspected that the observed increase is mainly due to better detection methods because microcarcinoma are seen frequently (up to 35%) in autopsies (Harach et al., 1985). Most cancers of the thyroid originate from follicular thyrocytes, only a minority of cancers, namely medullary thyroid cancer, originate from calcitonin producing C-cells (C-cells). They belong to another entity of tumors and will not be addressed in this review.

Carcinomas of follicular cell origin include well-differentiated and poorly differentiated thyroid cancers (DTC) and anaplastic thyroid cancers. DTC comprises papillary thyroid carcinoma (PTC), which accounts for 80-90% of all thyroid cancer cases, follicular thyroid carcinoma (FTC) and Hürthle cell tumors. Undifferentiated/anaplastic thyroid cancer (ATC) is rare and accounts for only 1-2% of all TC.

The prognosis of DTC is good with a 10-year survival rate of 85% (Eustatia-Rutten et al., 2006). Recurrence, however, occurs in up to 30% of patients and only 30% of patients with distant metastases respond to radioiodine therapy with complete remission (Dohan et al., 2003). A total of 10-20% of patients develop distant metastases (Durante et al., 2006). In this group the 10-year survival rate drops to 40%. ATC usually has a fatal outcome.

2. Current treatment of thyroid carcinoma

The standard treatment of well-differentiated TC is surgery followed by radioiodine remnant ablation. As only thyrocytes are taking up iodide to a reasonable degree, radioiodine treatment is very specific and has a low rate of adverse effects. In case of insufficient iodine uptake options are few and survival is poor. External beam radiation is used as a palliative therapeutic option but these tumors usually are not responsive to this

therapy. Adriamycin is the only cytostatic drug approved by the FDA for treatment of radioiodine refractory thyroid carcinoma. ATC do not express thyrotropin receptors; they neither take up iodide nor produce thyroglobulin. Surgical resection is only recommended for localized disease, which is rarely the case. In the advanced stage patients do not profit from removal of the tumor mass. Palliation to improve survival includes tracheotomy, radiation and chemotherapy or a combination of the three treatments.

Tyrosine kinase inhibitors, PPAR-y activators, retinoids, bortezomib, galdanomycin, VEGF receptor antagonists, stimulation of antigen presenting dendritic cells and p53 gene therapy are not yet approved for treatment of metastatic thyroid cancer and reserved for patients with life-threatening disease.

This review focuses on re-differentiation as mode of therapeutic action. Tyrosine kinase inhibitors, which target general tumor features like proliferation and apoptosis, currently represent the most promising group of compounds for the treatment of radioiodine-refractive TC. Their mode of action and the most promising candidates will be shortly addressed.

3. Targeted therapy

3.1 Definition and types of targeted therapies

Targeted therapies interfere with a specific molecular target, which has a critical role in tumor growth and progression. For targeted therapies antisense drugs, monoclonal antibodies and small molecules may be used. Targeted therapies, which intend to remove a block in normal cell differentiation, are termed 'differentiation therapy'.

The following molecules are involved in transformation and progression of TC and are, therefore, used in drug development for targeted therapies (Table 1).

3.2 Tyrosine Kinase Inhibitors (TKI)

Receptors over-expressed in cancer cells stimulate cell growth and proliferation through a cascade of tyrosine kinases (TKs) (Figure 2). TKIs may either compete with the ligand by binding to the extracellular domain or they may bind to the ATP-binding site of the kinase. Examples for ligand analogues are monoclonal antibodies like the anti-human epidermal growth factor receptor 2 antibody **Herceptin®** (trastuzumab), which is very successful in the treatment of breast cancer. By contrast, anti-EGFR antibodies show no significant anti-tumor action in PTC cell lines (Gabler et al., 1997).

Small molecule inhibitors, also called ATP mimetics, hinder the binding of ATP to the ATP binding pocket of protein kinases. Other compounds bind to the substrate-binding domain. By this binding autophosphorylation and signal transduction is inhibited. TKIs can inhibit proliferation and induce cell differentiation and apoptosis. As the catalytic domain of the TKs is very similar, most TKIs are not specific for one growth factor.

The most promising TKIs are briefly mentioned in the following section. For more information, the reader is referred to one of the more recent reviews (e.g. Coelho et al., 2007; Ho & Sherman, 2011; Kapiteijn et al., 2011).

Molecular target	Function	Role in TC
VEGF	Neo-angiogenesis	Increased expression in TC (Soh et al., 1997)
RET oncogene	Receptor for ligands of the glial-derived neurotropic factor family Trigger for autophosphorylation and intracellular signalling with stimulation of Ras/ERK/and PI3kinase/V-Akt cascade	In PTC chromosomal inversions and recombinations cause chimeric RET/PTC sequences, which are found in around 30% of thyroid carcinoma (Rabes et al., 2000). RET/PTC is frequently seen in microcarcinoma suggesting a role in the early phase of tumorigenesis.
c-Met	Proto-oncogene and receptor for hepatic growth factor, important for cell migration, proliferation, differentiation and angiogenesis.	It is over-expressed in 70% of PTC (Di Renzo et al., 1992). EGFR, RAS and RET regulate its expression.
BRAF	Member of the RAF familiy of serine/threonine kinases and are components of the RAF-MAPK kinase-ERK (RAF-MEK-ERK) intracellular signalling pathway	Point mutations seen in about 44% of PTCs and mutations are associated with a more and more aggressive phenotype. BRAF mutations are associated with impairment of NIS causing resistance to radioiodine uptake (Riesco-Eizaguirre et al., 2006; Romei et al., 2008).
Hsp90	Multichaperone heat shock protein, which mediates maturation and stability of several proteins involved in oncogenesis like EGF-R, Her-2, Akt, BRAF, CRAF, p53	mRNA expression of Hsp90 correlated to aggressive biological behaviour in TC (Boltze et al., 2003)
RAS	GTP-binding protein involved in proliferation, differentiation and cell survival. Ras acts via phosphatidyl inositol-3–phosphate kinase (PI3K) and through mitogen-activated protein kinase (MEK) and extracellular signal regulated kinases (ERKs).	Ras mutations in H-,N- and K-Ras oncogenes are common in TC and appear to be an early event in FTC tumorigenesis and are reported in about 50% of FTCs (Lemoine et al., 1989).
Farnesyltrans-ferase	Anchor of RAS in the plasma membrane. This anchorage is necessary for activation of RAS.	Involved in the activation of p21 (ras) in thyrocytes (Laezza et al., 1998)
MEK (MAPK/Erk kinase)	Key mediator in growth-promoting signals.	This kinase plays an important role in the pathogenesis of TC (Fagin, 2004)
EGFR (Her1, ErbB1)	Member of the Erb family of receptors and abnormally regulated in many cancer types. In addition	Overexpression is correlated to the presence of metastases in TC (Rodriguez-Antona et al., 2010).

Molecular target	Function	Role in TC
	to EGFR also ErbB2 (Her2/neu) is involved in the pathology of TC. EGFR tyrosine kinase activates Ras-Raf-MAPK cascade and the PI3K pathway.	
PI3K	Mediator of signals from many receptor tyrosine kinases.	Mutations and amplifications of PI3K have been described in differentiated and anaplastic primary tumors (Hou et al., 2007). Mutations in phosphoinositide-3-kinase alpha polypeptide and in Akt1 protein appear to be indicators for more aggressive, radioiodine refractory TC (Ricarte-Filho et al., 2009).
Mammalian target of rapamycin (**mTOR**)	Serine/threonine kinase, which serves as a downstream mediator of growth factors.	In thyrocytes, mTOR is also activated independent from Akt by direct stimulation through TSH (Brewer et al., 2007) and it may be suggested that mTOR is an especially useful target for the treatment of TC.
Akt/protein kinase B	Important mediator in apoptosis, proliferation and cell cycle progression.	Its expression is increased in sporadic FTC (Ringel et al., 2001).

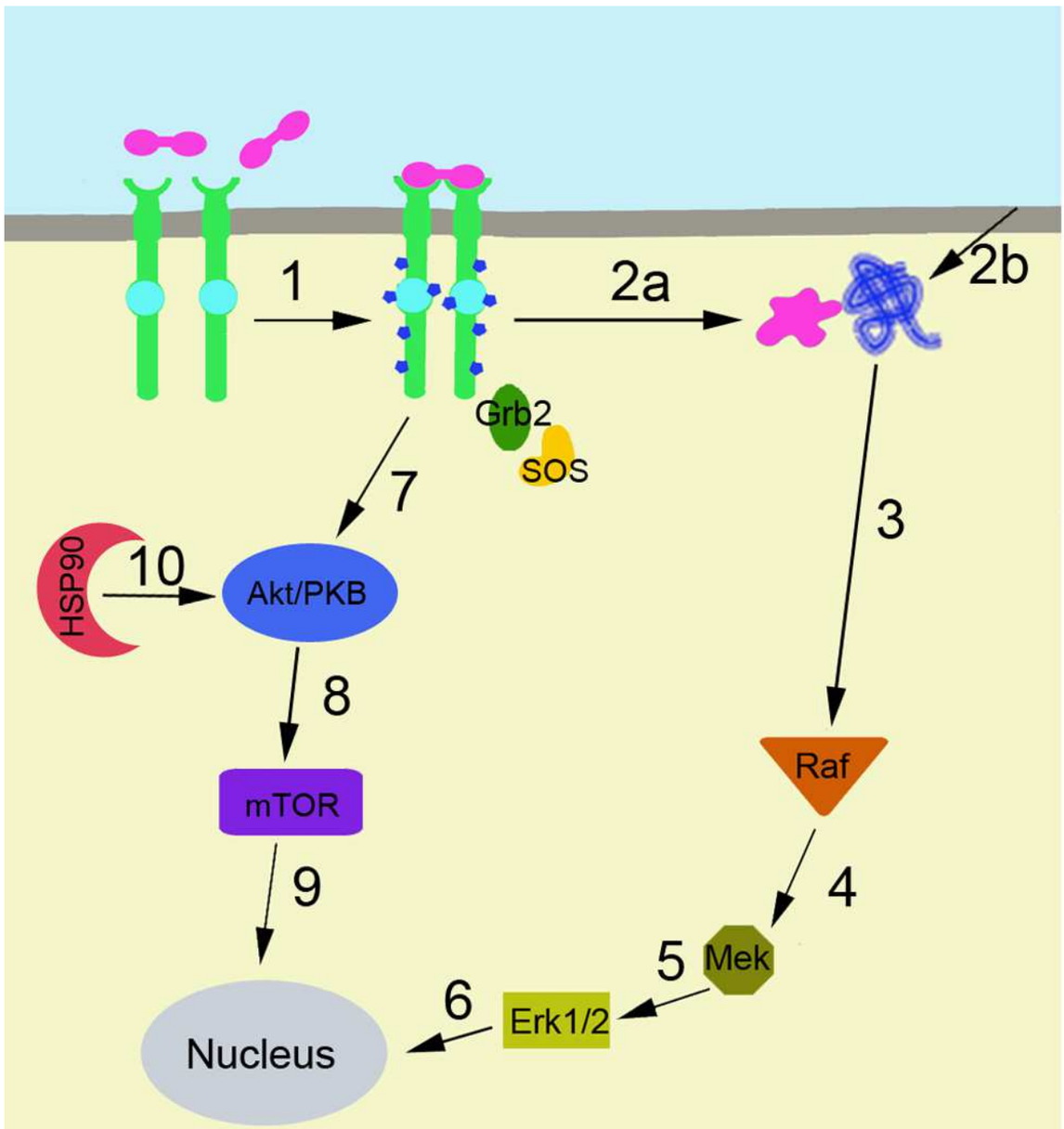
Table 1. Overview on established targets for targeted therapies

3.2.1 Non thyroid specific targets: Neoangiogenesis

Strategies to reduce/inhibit angiogenesis include inhibition of VEGF signalling, where several TKIs showed efficacy in thyroid cancer. Although **Sutinimib®** (SU11248), Motesanib diphosphate (AMG-706) and Pazopanib (**Votrient®**, GW-786034) also inhibit other TKs, it is postulated that the therapeutic effect is caused mainly by inhibition of VEGF signalling. These compounds and the selective VEGF-R inhibitor **Axitinib®** (AG-013736) induced stable disease as best response in 42%-67% of the patients. Inhibition of angiogenesis is also the target for other compounds like thalidomide **(Thalidomid®)** and lenalidomide **(Revlimid®,** CC-5013**)**, which achieved stable disease in clinical trials. The prodrug Combre(ta)statin A4 phosphate binds to tubulin and destabilizes tumor blood vessels. In trials with ATC the compound induced stable disease in 30% of the patients.

3.2.2 Non thyroid specific targets: Proliferation and apoptosis

The BRAF inhibitor **Nexavar®** (Sorafenib) (BAY 43-9006) has been tested in patients with radioiodine refractory TC. Although no iodine uptake was seen, partial responses and stable disease have been reported. XL281, a pan RAF inhibitor, induced stable disease in PTC patients. AZD6244 (ARRY142886, Selumetinib), a MEK1 and MEK2 inhibitor, showed



: growth factor like VEGF, EGF, HGF, : H-Ras; : GTP; : phosphate residue; : domain for kinase activity

Fig. 1. Activation of growth receptor TKs. 1: ligand binds to the receptor. Receptor dimerization and receptor binding to adapter protein, Grb2, coupled to the guanine nucleotide releasing factor, Son of Sevenless (SOS), occurs. Dimerization of the receptor leads to activation of Akt/PKB (7) and to activation of Ras (2a). Activation of Raf also needs anchorage of the Ras-GTP complex to the plasma membrane by farnesyltransferase (2b). Ras signalling acts through activation of Raf (3), MEK (4), ERK1/2 (5) that translocates into the nucleus (N) and acts (6) on transcription. Akt/PKB is activated by HSP90 (10) and stimulates through mTOR activation (8) transcription in the nucleus (9).

similar efficacy in the first studies but was ineffective in the most recent phase II trial on iodine refractory thyroid cancer. **Zelborat®** (PLX 4032 (RG7204, RO5185426, Vemurafenib) is an inhibitor of only mutated BRAF showing prolonged stable disease in a small phase I study. Stable disease was also obtained in a clinical trial with the EGFR inhibitor **Iressa®** (Gefitinib, ZD1939) in advanced thyroid cancers not amenable for surgery and/or RAI therapy. The authors explained the limited success of the drug by the fact that EGFR inhibitors, including Gefitinib, are ineffective in tumors with Raf mutations. Clinical trials on other TKIs like for instance the multi-kinase inhibitors **E7080 (Lenvatinib**[USAN]**)** and **AMG706 (Motesanib diphosphate)** are ongoing (www.clinicaltrials.gov).

Out of the several inhibitors of Hsp90, the ligand of c-Met, which have been tested in-vitro only 17-allylamino-17-demethoxygeldanamycin (17-AAG) appeared to be potent enough to justify phase I/II clinical trial in TC. The farnesyltransferase inhibitors BMS-214662 and L744832 have been evaluated in clinical phase I trials including thyroid carcinoma patients and no improvement in survival was reported. Results of a phase II trial with a combination of Everolimus **Zortress®, Afinitor®** (RAD001), an inhibitor of mTOR and sorafenib are pending.

The antiproliferative therapy with the COX-inhibitor **Celebrex®** (celecoxib) was not successful in TC.

Meta-analysis in a phase II trial on **Velcade®** (bortezomib) achieved mainly stable disease in metastased DTC, but due to increased Tg levels, efficacy is not certain. The compound displays antitumor effects also in cell lines from ATC.

JNJ-26854165, which inhibits the ubiquitin protein ligase HDM2, prevents the degradation of the tumor suppressor p53, and showed moderate success rates in patients with progressive Hurthle cell carcinoma.

Some of these TKIs act also as differentiating agents: 17-AAG increases the accumulation of iodide by decreasing its efflux, whereas NIS localization and amount are not changed (Marsee et al., 2004; Elisei et al., 2006). The MEK inhibitor PD98059, a flavonoid, increases NIS protein, but not iodide uptake (Vadysirisack et al., 2007). As surface expression was not decreased, it is suspected that a lower Vmax decreased the turnover rate of iodide. The mTOR inhibitor **Rapamune®** (sirolimus) increased iodide uptake in rat thyrocytes (de Souza et al., 2010).

4. Re-differentiation therapy: Thyroid-specific targets

Re-differentiation intends to reverse changes, which occurred during transformation of the cells. Proteins involved in thyroid hormone synthesis include sodium-iodide symporter (NIS), thyroperoxidase (TPO), pendrin (PDS) and thyroglobulin (Tg).

For the synthesis of the thyroid hormones triiodothyronine (T_3) and thyroxine (T_4), iodide is taken up from the blood stream by NIS localized at the basal side of the thyrocyte (Figure 2). Iodide is concentrated 20-40 fold with respect to the plasma concentration by NIS, the uptake is active and iodide is translocated towards the colloid by iodide efflux mediated mainly by PDS. Thyroglobulin is produced in the endoplasmic reticulum and Golgi apparatus and secreted in the follicular lumen. At the cell-colloid interface iodide is coupled

to specific tyrosyl residues in thyroglobulin by the integral membrane protein TPO and monoiodotyrosine and diiodotyrosine is formed. Hydrogen peroxide for the oxidation of iodide by TPO is provided by the thyroid dual oxidase (DuOx). TPO also catalyzes the integration of hormone residues (coupling of iodotyrosines) in Tg. Excess hydrogen peroxide (H_2O_2) not involved in the oxidation of iodide may act mutagenic or carcinogenic. Selen-containing glutathione peroxidase is therefore typically upregulated to provide protection from oxidative damage. Some glutathione peroxidase gene polymorphisms are linked to an increased risk effect for TC presumably by lack of detoxification of hydrogen peroxide. Upon demand for thyroid hormones, endocytosis of iodinated Tg occurs. Iodinated Tg is hydrolysed in lysosomes and the hormones T_3 and T_4 secreted into the blood stream.

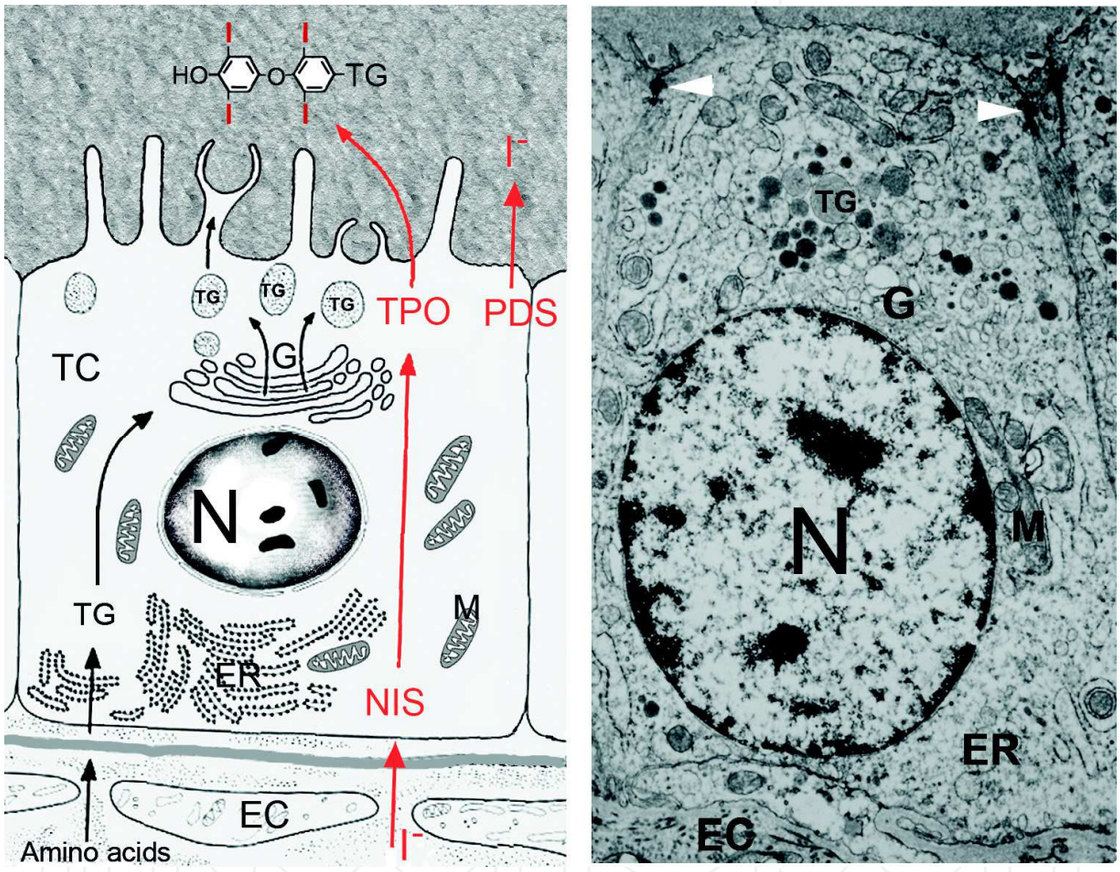


Fig. 2. Schematic drawing illustrating the synthesis of thyroid hormone in the thyroid gland and ultrastructure of a follicle cell. Iodide is taken up into the thyrocyte by NIS and Tg is synthetized from amino acids at the endoplasmic reticulum and the Golgi apparatus and transported in vesicles to the follicular lumen. PDS transports iodide into the lumen and TPO integrates iodide into Tg and couples iodotyrosines to hormone residues. The protein machinery for the synthesis of Tg, endoplasmic reticulum (ER), Golgi apparatus (G) as well as apical microvilli, tight junctions (arrowheads) and mitochondria (M) are clearly seen in the ultrastructure. N: nucleus, EC: endothelial cell.

In DTC NIS is expressed at different levels and pendrin expression is usually absent. TPO is expressed at low levels in FTC and follicular variants of PTC but below the detection limit in

PTC. The H_2O_2 generation system is present in DTC and levels increased in PTC. The TSH-R is present in most DTC. The capacity to synthesize iodinated and thyroxine rich Tg is lost in FTC due to defect in NIS and in PTC due to altered apical iodide transport and TPO activity (Gerard et al., 2003).

4.1 Sodium-iodide symporter (NIS)

NIS is an integral plasma membrane glycoprotein, which transports two sodium ions along with one iodide ion. The transmembrane gradient of sodium serves as the driving force for iodide uptake. The mature NIS protein has 13 transmembrane regions, the N-terminus is facing the extracellular milieu and the C-terminus is directed towards the intracellular milieu. Glycosylation occurs at three sites in the protein, but does influence neither stability nor membrane targeting. Phosphorylation occurs at the C-terminus. Affinity of NIS is higher for perchlorate and rhenium oxide than for iodide.

NIS is not only expressed in the thyroid but also in salivary gland, choroid plexus, gastric mucosa, lactating mammary gland and ciliary body of the eye. Potential expression of the protein has also been shown in colon, kidney, pancreas, rectum, thymus, placenta and non-lactating mammary gland (Wapnir et al., 2003). mRNA has been detected in almost all tissues but RT-PCR yields a large number of false positive results because of its high sensitivity (Dohan et al., 2003).

4.1.1 Regulation of NIS in the normal thyroid

TSH acts both on NIS transcription and on targeting of NIS to the plasma membrane through increase of c-AMP levels. The NIS promoter contains two important regions: (a) the proximal NIS promotor, where thyroid transcription factor-1, NIS-TSH-responsive factor-1 and Specificity protein 1 (Sp-1) bind and (b) the NIS upstream enhancer with binding sites for the paired domain factor Pax-1, thyroid transcription factor-1 and c-AMP-responsive element like sequences. The interaction of c-AMP-responsive element like sequences with Pax-1 is necessary for transcription of NIS. The localization to the plasma membrane appears to be mainly caused by binding of protein-recognition PDZ target motif at the carboxyl-terminus of the protein to PDZ-binding proteins, not by phosphorylation. TSH also regulates half-life of NIS: in the presence of TSH it is 5 days, in the absence 3 days (Riedel et al., 2001).

Cytokines like tumor necrosis factor α, interferon-γ, interleukin (IL)-1α, IL-1β and IL-6 inhibit NIS mRNA expression and iodide uptake. This inhibition may be the cause of hypothyroidism in autoimmune processes.

Tumor necrosis factor β in addition to decreasing TSH-induced NIS expression also changes the morphology of thyroid cells from cuboidal to flattened phenotype.

Estradiol down-regulates NIS expression and thereby may contribute to the higher incidence of goiter in women.

High intracellular iodide concentration down-regulates NIS. Similarly, follicular Tg acts as a potent suppressor of all thyroid-specific genes. This inhibition may represent a negative feedback autoregulatory mechanism and corresponds to the morphological heterogeneity of

thyroid follicles: the active follicles display a cuboidal epithelium with high NIS expression and little Tg in the lumen, inactive follicles show a flattened epithelium, low or absent NIS expression and much Tg in the lumen.

High extracellular concentrations of iodide decrease the function of NIS, in addition to other effects. This phenomenon is called Wolff-Chaikoff effect (Wolff & Chaikoff, 1948). Although, the effect has been known for many years, its mechanism is still not well understood; transcriptional and post-transcriptional changes are involved.

4.1.2 NIS in thyroid cancer

NIS in thyroid cancer is not mutated (Russo et al., 2001), and various groups reported the amount of mRNA, compared to normal tissue, differently. As NIS protein is regulated at different levels (transcriptional, translational, posttranslational, targeting and intracellular distribution) the detection of mRNA is poorly predictive for normal function. NIS protein levels in thyroid cancer were reported to be higher than in normal tissue by some groups and lower than normal by others (Arturi et al., 1998; Saito et al., 1998; Lazar et al., 1999; Park et al., 2000). Impaired iodide uptake can be caused by absent or decreased NIS expression and by impaired targeting and insufficient retention at the plasma membrane. In the largest study on tissue, overexpression in combination with intracellular localization was seen in 70% of the TC samples (Dohan et al., 2001). Plasma membrane localization was rare and often not polarized but present at the apical and basal membrane. It is presumed that the altered trafficking of NIS causes NIS dysfunction. The pathological localization of NIS may also be induced by binding to the proto-oncogene pituitary tumor-transforming gene binding factor (PBF). Overexpression of this factor is associated with aggressive behaviour of TC. PBF binds to NIS, alters its subcellular localization and, thereby, inhibits its ability to take up iodide (Smith et al., 2009). Paired mRNA and protein analysis showed that decreased mRNA levels were associated with increased cytoplasmic staining of NIS (Wang et al., 2011). It was also suggested that NIS protein in cancer tissue is immature and has an abnormal turn-over rate (Saito et al., 1998, Dohan et al., 2001).

Intracellular NIS can cause negative feed-back on NIS mRNA synthesis. Reduced TSH-R may also cause low NIS mRNA levels and deficient NIS migration (Sodre et al., 2008). Activation of BRAF, Ras and RET decrease NIS mRNA. BRAF, in addition, also impairs targeting of NIS to the plasma membrane (Riesco-Eizaguirre et al., 2006).

4.2 Pendrin (PDS)

Pendrin is a transmembrane glycoprotein with three putative extracellular glycosylation sites on asparagine-residues. Both C- terminus and N-terminus are located inside the cytosol and contain a sulphate transporter/antisigma factor antagonist domain (Royaux et al., 2000). PDS was identified as the most important transporter for iodide export but its unique role is questioned because patients with biallelic mutation display only mild thyroid symptoms and PDS knock-out mice do not develop goiter (Wolff, 2005). On the other hand, TSH stimulates iodide transport across the apical membrane (Nilsson et al., 1990) and induces a rapid translocation of PDS from endosomes to the plasma membrane (Kopp et al., 2008) suggesting a causative link between translocation and iodide metabolism. Efflux by an

additional transporter is hypothesized: the formerly named apical iodide transporter (AIT), which has been re-named to sodium/monocarboxylate transporter (SMCT), has been removed from the list of potential candidates (Paroder et al., 2006).

Extrathyroidal expression of PDS is more restricted than that of NIS. Expression has been detected in kidney, Sertoli cells, inner ear, mammary gland and placenta (Lacroix et al., 2001; Wangemann et al., 2004)

PTCs without iodide uptake have slightly reduced NIS and significantly reduced Tg, TPO and PDS levels (Mian et al., 2008). This shows that loss in iodide uptake depends not only on NIS function but also on other molecules in the intracellular thyroid metabolism. Together with NIS, PDS and Tg, TPO expression is decreased in PTC with BRAF mutation (Durante et al., 2007).

4.3 Thyroperoxidase (TPO)

TPO is a glycosylated transmembrane hemoprotein, which uses H_2O_2 as cofactor and catalyses the oxidation of iodide to iodines and the attachment of oxidized iodines to certain tyrosine residues on the protein Tg, producing 3-iodotyrosine (MIT) and 3,5'- diiodotyrosine (DIT). Thirdly, TPO and H_2O_2 are further used to couple two DIT residues, or one MIT with one DIT residue, to produce T4 or T3 and rT3, respectively (Dunn & Dunn, 2001). Expression of TPO is regulated by the transcription factors TTF-1, TTF-2 and Pax-8. Estrogen stimulates TPO in addition to NIS in rats (Lima et al., 2006). The action of estradiol is variable and depends on the gonadal status and the age of the animal.

Cancers with no iodide uptake contain approx. 30-fold less TPO and 20 fold less PDS (Mian et al., 2008). These TCs have a high frequency of BRAF mutation and 5-fold Glut-1 expression. TPO in TC is suppressed on the mRNA and on the protein level (Tanaka et al., 1996).

4.4 Thyroglobulin (Tg)

Tg is a large (660kD) dimeric protein, forming the main protein compound of the follicular colloid. Despite variable correlation of Tg levels and metastatic status, Tg mRNA in blood serves as a marker for TC and as follow-up of removed DTC. mRNA of Tg is significantly lower in TC and in adenoma and the decreases correlate to those in TSH-R mRNA. By contrast, mRNA of TPO showed no marked differences between normal and transformed thyroid tissues (Ohta et al., 1991). By other authors, levels of Tg mRNA varying from normal to complete loss in TC were reported (Brabant et al., 1991; Hoang-Vu et al., 1992)

4.5 TSH-receptor (TSH-R)

TSH and TSH-R are required for proliferation of thyrocytes and expression of differentiation markers like NIS (Garcia-Jimenez & Santisteban, 2007). The TSH-R is a 7-transmembrane spanning glycoprotein, also expressed in bone, brain, kidney, testes and cells of the immune system. In the extrathyroidal tissues its role is not clear (Matsumoto et al., 2008). TSH-R molecules are quite stable in the membrane and signalling occurs through TSH-binding. TSH activates the TSH-R and G-proteins such as G_S-alpha at the surface of thyrocytes. Intracellular production of cyclic AMP by adenylyl cyclase stimulates the cAMP-dependent

protein kinase A, which in turn phosphorylates cytoplasmic and nuclear target proteins. One substrate is the nuclear transcription factor CREB, which activates the transcription of cAMP-responsive genes after being phosphorylated by PKA. TSH, at much higher levels, acts via phospholipase C and the phosphatidyl-inositol/Ca^{2+} signalling cascade with activation of protein kinase C (Hard, 1998). The cAMP pathway is functionally responsible for cell proliferation, iodide uptake, Tg and TPO expression, whereas the phosphatidyl-inositol/Ca^{2+} signalling pathway stimulates generation of hydrogen peroxide and iodide efflux. Insulin and IGF-1 control TSH-R and Tg gene expression in rats and are necessary co-factors for TSH in most species. Iodide, or the organic intermediate 2-iodohexadecanal, inhibits adenylate cyclase, TPO and NADPH oxidase. Another intermediate, the δ iodolactone 6-iodo-5-hydroxy-8,11,14- eicosatrienoic acid inhibits specifically IP3 formation induced by growth factors. The receptor is hyperactivated in adenoma, less expressed in DTC and silenced in ATC. Inactivating mutations of the TSH-R have been reported in TC but appear not to be related to tumor onset but to be a marker of the ongoing de-differentiation. Activating mutations have been reported in some TC (Cetani et al., 1999,Esapa et al., 1997). Expression of TSH-R is similar in cancer and in thyroid adenoma tissues and the mRNA levels are only slightly decreased compared to normal thyroid tissue (Lazar et al., 1999). Reduced expression of TSH-R protein was seen only in high risk PTC (Tanaka et al., 1997) and low protein levels of TSH-R correlate with high proliferation (high Mib-1 index) in poorly differentiated TC (Matsumoto et al., 2008). TSH-R expression decreases to a lesser extent in cancer tissues than other thyroid-specific proteins like NIS, TPO and Tg. Defective TSH-R cAMP signalling in FTC thyroid cancer cell lines (Demeure et al., 1997) and impairment in signal transduction have been demonstrated in TC (Kimura et al., 1992)

4.6 Molecular candidates for re-expression of thyroid-specific proteins

Re-expression of thyroid-specific proteins in thyroid cancer is expected to increase iodide uptake and thereby increase the efficacy of radioiodine treatment. For the re-induction of thyroid-specific genes, the following nuclear targets are the most promising candidates:

Retinoic acid receptors are crucial for the differentiation of tissues. Retinoids act as chemopreventive agents and increase differentiation in a variety of cancers.

Peroxisome proliferator-activated receptor gamma (PPAR-γ) activation leads to activation of PTEN, which inhibits PI3K. DTCs show a decreased expression of this receptor, therefore PPAR-γ agonists may have a beneficial effect.

Histone deacetylases and **DNA methylases** prevent transcription of genes linked to differentiation. Inhibitors of these enzymes may lead to re-differentiation.

5. Compounds for re-differentiation

5.1 Retinoids (RT)

Retinoids, retinol and its derivatives, act on the nuclear receptors retinoic acid receptor (RAR) and retinoid X receptor (RXR). Retinoids are related to vitamin A and three generations of retinoids have been developed so far. First generation retinoids include retinol, retinal, retinoic acid (all-trans RA, 9-cis RA and 13-cis RA) and isoretinon, second generation retinoids were etretinate and acitretin and third generation retinoids comprise

tazarotene and bexarotene. The naturally occurring retinoids all-trans RA, 9-cis RA and 13-cis RA are interconverted in vivo. Thyrocytes mainly express receptors for RAR-α and RXR-γ. RXR-β expression was reduced in the majority of poorly differentiated and anaplastic cell lines and tumor samples (Schmutzler et al., 1998). Retinoids can act through homodimers of retinoid receptors or as heterodimers of the RXR receptor with the PPAR-γ receptor (Figure 3). It is hypothesized that retinoids upregulate NIS expression mainly by activation of RAR (Kogai et al., 2004).

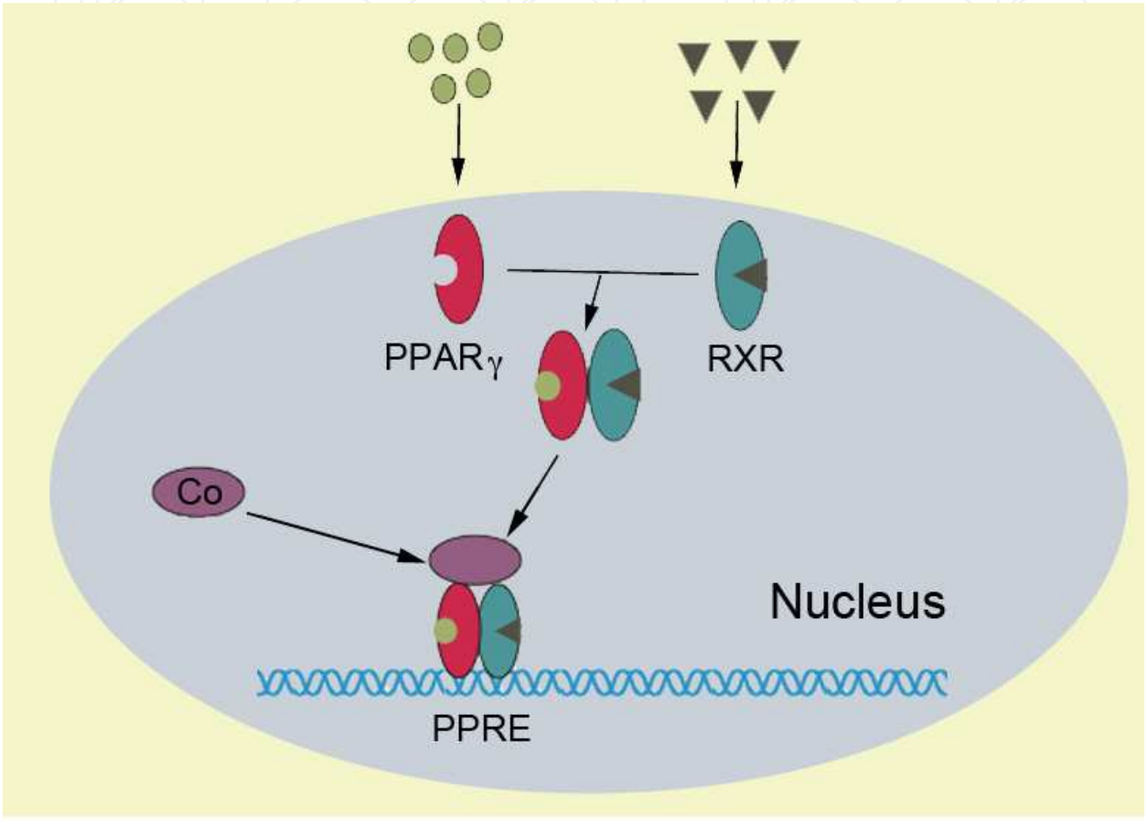


Fig. 3. Retinoids bind to the RXR/PPAR-γ receptor dimer and this heterodimer binds to peroxisome proliferator response elements (PPRE). Subsequently, a co-activator, possessing histone acetylase activity, attaches to the complex (Co) and induces gene transcription.

5.1.1 Compounds in clinical trials

Retinoids increased expression of thyroid-specific proteins (Schreck et al., 1994; Schmutzler et al., 1997; Kurebayashi et al., 2000; Jeong et al., 2006) and increased iodide uptake (van Herle et al., 1990). As retinoids were already approved for other indications, clinical trials were initiated. Varying results were obtained with isotretinoin **Accutane®, Roaccutane®** (13-cis-RA): iodide uptake was restored in 40% in the study by Simon et al. (Simon et al., 2002) but most other studies achieved much lower rates in the increase (Grunwald et al., 1998; Gruning et al., 2003; Kim et al., 2009). Similar inconsistent increases in iodide uptake were obtained by the use of tretinoin **Vesanoid®** (all-trans retinoic acid) and of **Targretine®** (bexarotene, Simon et al., 1996; Simon et al., 1998; Schmutzler & Kohrle, 2000; Simon et al., 2002; Coelho et al., 2004;

Short et al., 2004; Liu et al., 2006; Zhang et al., 2007). The expression of RAR-β and RXR-γ could serve as an indicator for the response to RA treatment but based on existing studies, retinoids alone appear not to be an effective therapy for radioiodine-refractory thyroid cancer.

5.1.2 Pre-clinical compounds

9-cis RA and retinol were both less well studied for application in TC. 9-cis RA was shown to induce cell cycle arrest and re-expression of RAR-β in TC cells (Fan et al., 2009) and retinol induced iodide uptake in differentiated cancer cell lines but had a low anti-proliferative effect (Fröhlich et al., 2009). Although retinol, compared to RA, shows a lower rate of adverse effects (e.g. Fluhr et al., 1999), the different intracellular concentrations of the active metabolite due to variations in serum retinol binding protein, in cellular transport proteins and in the activity of intracellular dehydrogenases diminishes its suitability as drug candidate in the treatment of TC.

5.2 Thiazolidinediones (TZDs)

Peroxisome proliferator-activated receptors (PPARs) are transcription factors belonging to the superfamily of nuclear receptors and related to the receptors for retinoic acid, estrogen, thyroid hormone, vitamin D and glucocorticoids. The three members of the PPAR family are PPAR-α, PPAR-β/δ and PPAR-γ. All members regulate energy metabolism. PPAR-γ promotes differentiation of mesenchymal stem cells into adipocytes and osteoclasts and plays a role in tumorigenesis (Wan, 2010). Rearrangements of PPAR-γ/PAX-8 occur in 36% to 45.5% of FTC and in 37.5% of follicular variants of PTC (Nikiforova et al., 2003; Castro et al., 2006). The rearrangement induces inactivation of PPAR-γ function. PPAR agonists bind to PPAR-γ and form a heterodimer with the RXR receptor at the response elements, activating the transcription of target genes (Figure 4). PPAR-γ is involved in the differentiation of pre-adipocytes. Ligands of PPAR-γ inhibit growth in PTC cell lines (Ohta et al., 2001). The growth inhibiting effect is not correlated to the degree of expression of PPAR-γ suggesting that mechanisms independent from signalling through this receptor are involved in the differentiating action of PPAR-γ agonists (Klopper et al., 2004).

5.2.1 Compounds in clinical trials

Clinical studies with **Avandia®** (rosiglitazone) showed increased radioiodide uptake in therapeutic ^{131}I scans (Kebebew et al., 2006; Tepmongkol et al., 2008). A current trial with rosiglitazone is ongoing and results are expected in the near future (www.clinicaltrial.gov). As PPAR-γ and RXRs form heterodimers there is the hope that, similar to results in other cancer types (Mehta et al., 2000), combinations of retinoids with TZDs may act synergistically. Based on data of an increased risk for cardiovascular events, however, the European Medicine Agency (EMA) has recommended in 9/2010 the withdrawl of all rosiglitazone-containing medications from the market.

5.2.2 Pre-clinical compounds

In vitro studies with troglitazone and rosiglitazone show that TZDs decrease proliferation and increase apoptosis and iodide uptake (Fröhlich et al., 2005). The anti-tumor effect of pioglitazone was much weaker than that of troglitazone and rosiglitazone. Also in primary

cultured ATC cells **Actos®** (pioglitazone) reduced proliferation to a lesser extent than rosiglitazone (Antonelli et al., 2009). **Rezulin®** (troglitazone) was the most effective compound regarding re-differentiation (Fröhlich et al., 2005) but its use in the treatment of TC is prevented by the withdrawal of the drug from the market due to severe liver toxicity. Another new agent, Ciglitazone induced decreased proliferation and increased apoptosis in a panel of TC cell lines with PPAR-γ expression (Martelli et al., 2002).

5.3 Epigenetic alterations

Epigenetic alterations are changes around the gene that alter gene expression. These changes include histone modifications and DNA methylation (Figure 4). Transcriptionally active chromatin regions are hyperacetylated and hypomethylated. Epigenetic alterations in tumor cells often result in silencing of genes involved in cell differentiation. Transcription factors generally act on un-methylated promoters at local sites where histones are acetylated. The silencing of a gene may result from the binding of methyl-binding proteins (e.g. MeCP2) to methylated cytosines, which recruits histone deacetylases (HDAC). Hyperacetylated histones activate a pre-programmed set of genes that leads to cell cycle arrest, differentiation and apoptosis (inhibition of tumor growth). HDAC inhibitors may contribute to the removal of MeCP2 from methylated cytosines and allow histone acetylase to re-acetylate histones at gene promoter. Hyperacetylated histones may recruit DNA demethylase and further provide

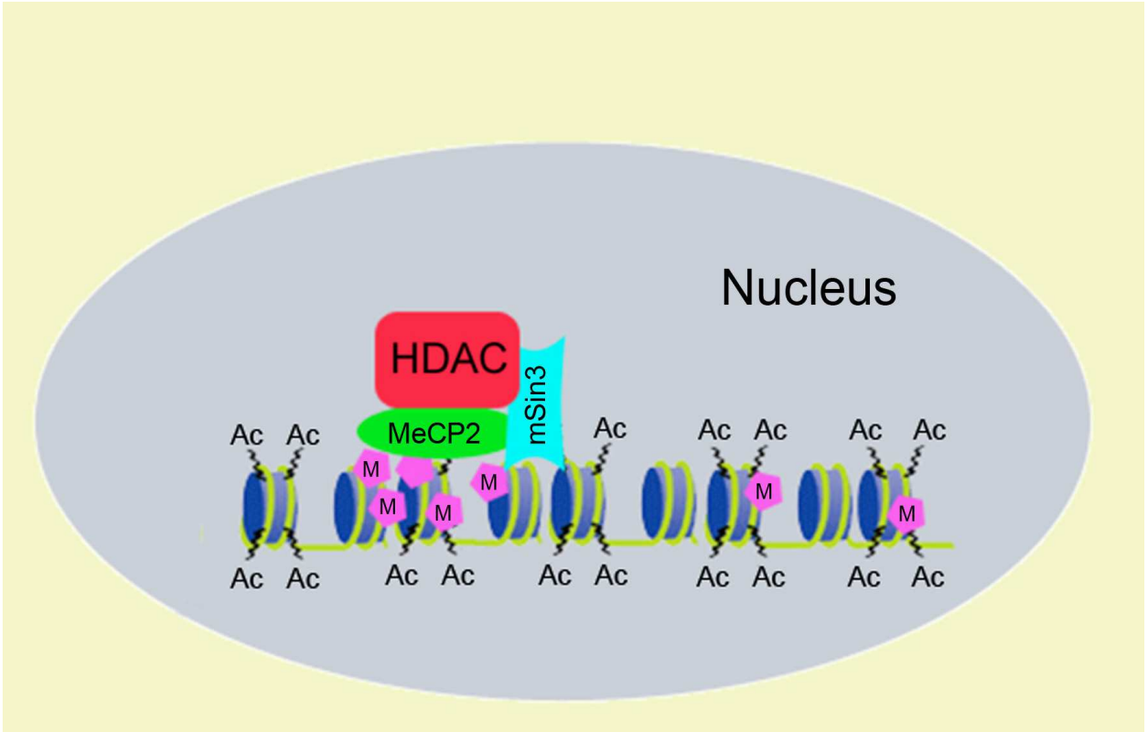


Fig. 4. Epigenetic changes include addition of acetyl-groups (Ac) by the action of histone acetylase and methylation of DNA (M) by DNA methyltransferase. The multiprotein repressor complex binds predominantly at cytosine- and guanine- rich DNA regions and consists of methyl-CpG-binding protein 2 and mammalian transcriptional repressor mSin3 and histone deacetylase (HDAC).

protection from DNA methylation. Inversely, demethylating agents can re-establish an active state by inducing the acetylation of histone. Via this mechanism inhibitiors of HDAC and of DNA methyltransferase could induce re-differentiation in thyroid cancer cells.

5.3.1 Histone deacetylase inhibitors (HDI)

In a nucleosome a DNA fragment is wrapped around a complex of histones (pair of H2A, H2B, H3 and H4). Acetylation occurs at lysine residues of the proteins. Deacetylation generates positively charged residues, which facilitate binding of histones to DNA leading to tightly packed chromatin. Thereby, binding to the promotor is prevented and gene transcription repressed (Xing, 2007). Genes silenced in TC include RAS, SF1A (signalling protein involved in RAS), tissue inhibitors of metalloproteinases, SLC5A8 (sodium coupled monocarboxylate transporter 1) as putative iodide transporter at the apical membrane), DARK (death associated protein kinase) and RAR-β2.

5.3.1.1 Compounds of HDI in clinical trials

Suberoyl anile hydroxamic acid (SAHA, vorinostat [rINN]) is the most advanced compound of this group for treatment of TC. In ATC and DTC cell lines significant increases in NIS expression and decreased growth rates were recorded (Fortunati et al., 2004). In one clinical study evaluating SAHA, patients with metastatic TC were included. One out of five patients showed an improved iodide uptake (Kelly et al., 2005). Based on these promising results a phase II trial with SAHA, approved by the FDA as **Zolinza®**, was initiated. Medication resulted in slightly more patients with stable disease than with progressive disease (Woyach et al., 2008). In a phase II study romidepsin, a depsipeptide with the trade name **Istodax®** (FK 228, FR 901228), restored radioiodine avidity in 2 of the 20 patients treated, but there were no objective responses even after ^{131}I treatment (Sherman et al., 2009). A phase II study on the new hydroxamic acid derived histone deacetylase inhibitor **panobinostat/panbinostat®** (LBH589) is currently recruiting participants. The recruitment status of a phase II study on **Depakene®** (valproic acid) initiated in 2007, is unknown (http://www.clinicaltrials.gov).

5.3.1.2 Pre-clinical compounds

Encouraging results on differentiated and poorly differentiated thyroid carcinoma cell lines were also obtained with other HDIs.

Trichostatin A® acted pro-apoptotic and increased NIS mRNA expression in TC cell lines (Puppin et al., 2005; Shen & Chung, 2005; Kondo et al., 2009). mRNA expression of PDS was reduced by trichostatin A treatment (Zarnegar et al., 2002).

Entinostat® (SNDX275, MS 275) restored functional NIS activity in FTC and ATO cell lines 20- 45 fold (Altmann et al., 2010).

Phenylacetate (Ammonul®) increased iodide uptake and decreased secretion of Tg in two of the five evaluated TC cell lines (Kebebew et al., 1999). The inhibition of Tg secretion was interpreted as increase in intracellular accumulation of this protein.

Apicidine and APHA compound 8 demonstrated a similar mode of action as valproic acid: all compounds strongly increased iodide-uptake with only a weak effect on proliferation (Fröhlich et al., 2009).

5.3.1.3 Combinations of HDIs with other compounds

SAHA in combination with the mTOR inhibitor temsirolimus and the Akt and PI3K inhibitor perifosine showed a strong synergistic effect on NIS expression and on TSH receptor expression (Hou et al., 2010). The expression of the latter raised hope that the tumors would become responsive to TSH, which together with a functional NIS could enhance iodide uptake markedly. Other studies also suggested strong synergistic effects between HDIs and other compounds: ATRA in combination with tributyrin strongly enhanced NIS mRNA and protein expression and radioiodine uptake in FTC133 cells (Zhang et al., 2011). Although no increases were obtained in TSH-R and TPO mRNA expression upon combined treatment of vitamin D3 and SAHA, growth arrest was achieved in several poorly differentiated cells (Clinckspoor et al., 2011).

5.3.2 Inhibitors of DNA methyltransferase (DMI)

Upon DNA methylation CH_3 groups are added to the fifth carbon position of the pyrimidine ring of cytosine residue in a CpG dinucleotide. CpG islands (regions rich in CpG dinucleotides) are usually located in the 5′ flanking promotor areas of genes. Gene promotor methylation near the transcription start site is usually associated with gene silencing (Xing, 2007). Methylated cytosine residues are bound by methyl-binding proteins that subsequently recruit HDACs and histone methytransferases, forming a complex with mSin3, a mammalian transcriptional co-repressor. In thyroid carcinoma cells TTF-1, the key transcription factor for thyroid-specific genes (Tg, TPO, TSH-R, PDS and NIS), is silenced by hypermethylation.

5.3.2.1 Compounds in clinical trials

A phase II trial on **Vidaza®** (5-azacytidine) in metastatic TC has been completed and results will be published soon. A phase II study on **Decitabine®** (5-Aza-2′-deoxycytidine) is listed as ongoing clinical trial evaluating re-differentiation for TC (http://www.clinicaltrials.gov).

5-Azacytidine was able to restore Tg expression in Ras-transfected TC lines (Avvedimento et al., 1989). In a study on mRNA expression of NIS, Tg, TPO and TSH-R and on iodide uptake in the PTC cell line B-CPAP, 5-Azacytidine compared to ATRA and trichostatin was very effective: it was the only compound, which increased iodide uptake (Tuncel et al., 2007). Also 5-Aza-2′-deoxycytidine increased differentiation and restored NIS expression in FTC, PTC and ATC cell lines (Kondo et al., 2009). 5-Aza-2′-deoxycytidine also induced mRNA expression of type I iodothyronine-5′-deiodinase, another thyroid-specific protein (Mentrup et al., 2002).

5.3.2.2 Combinations with other agents

Combination with retinoids may increase the efficacy of the treatment because 5-Aza-2′-deoxycytidine induced re-expression of the RAR-β receptor (Miasaki et al., 2008). 5-Azacytidine and RA together induced re-expression of differentiation-related proteins. In the human TC cell line FRO, TTF-1 and thyroglobulin were increased; in TT and WRO cell lines Pax-8 was increased; and in FRO and TT cell lines RAR-β and NIS mRNA were increased. Iodide uptake, however, was not increased and NIS localized in the cytoplasm

(Vivaldi et al., 2009). 5-Azacytidine and sodium butyrate increase NIS mRNA and iodide uptake in DRO cells. The NIS promotor region is often methylated and iodide-uptake apparently can be restored by the reversal of epigenetic changes (Venkataraman et al., 1999).

5.4 Other strategies for re-differentiation

Several compounds have been investigated in a less systematic way for their action in TC. In this section, compounds, belonging to other classes but displaying positive effects on TC cell lines and in patients, are discussed. Since mRNA expression of NIS alone may not reflect protein levels and, even if the protein is expressed, it may not be correctly localized and not be functional, it is difficult to predict whether these compounds will have beneficial effects in clinical trials.

5.4.1 Pre-clinical compounds

5.4.1.1 Lovastatin '(e.g. Mevacor®)

This inhibitor of 3-hydroxy-3-methyl-glutaryl-CoA reductase is used for lowering cholesterol in hypercholesterolemia to prevent cardiovascular disease. Inhibition of protein prenylation by lovastatin has anti-proliferative effects in normal and transformed thyrocytes (Bifulco et al., 1999) and reduced growth and invasion and caused re-differentiation in ATC cell lines by increasing Tg expression (Wang et al., 2003; Zhong et al., 2005). Lovastatin reduced proliferation but did not increase iodide uptake in cell lines derived from DTC (Fröhlich et al., 2009) and reduced the growth of ATCs in mouse xenografts (Wang et al., 2010).

5.4.1.2 1,25-dihydroxyvitamin D(3) (VitD3) '(e.g. Rocaltrol®)

VitD3 acts through nuclear receptors expressed in most cell types. In addition to its main function on calcium and bone metabolism, the hormone also acts on proliferation, apoptosis and differentiation of cells. VitD3 appears to be a good target for cancer therapy because decreased levels have been demonstrated in breast, prostate and colon cancer. The situation in TC is not clear: whereas one study reported normal VitD3 levels in TC patients, another study reported decreased VitD3 levels in TC, though not in goiter patients (Laney et al., 2010; Stepien et al., 2010). In cancers with proven deficiency VitD3 shows cytostatic effects and was tested successfully in a phase II clinical trial on prostate cancer (Srinivas & Feldman, 2009). VitD3 reduced tumor growth and increased differentiation (NIS and Tg mRNA) in vitro and in tumor xenografts (Drackiw et al. 2004; Okano et al. 1994; Akagi et al., 2008). In combination with SAHA, VitD3 showed growth arrest but no effects on mRNA expression of TSH-R and of TPO in ATC cell lines (Clinckspoor et al., 2007).

5.4.1.3 Arsenic trioxide (ATO)

Clinical-grade ATO, **Trisenox®**, is used as second-line therapy in retinoic acid refractive acute promyelocytic leukemia (Shen et al., 1997). In the treatment of solid cancers, however ATO is not routinely used and only few clinical trials, like a phase II trial on hormone-refractory prostate cancer, have been successfully performed (Gallagher et al., 2004). ATO acts by multiple mechanisms: depletion of glutathione, increase of reactive oxygen species,

loss of mitochondrial potential and activation of caspase (Miller, 2002). Akt/protein kinase B pathway is also involved in the action. In several cell lines of differentiated TC the compounds reduced proliferation and increased apoptosis and iodide uptake (Fröhlich et al., 2008). Protein levels of NIS and PDS were not changed but in ATO-treated cells PDS displayed a polarized expression pattern. Depletion of glutathione increased the differentiating effect of ATO while Akt-inhibitors did not. Independent of the proliferation rate, ATO significantly decreased glucose uptake in TC cells as one additional mechanism of its multi-modal action.

5.4.1.4 Gene therapy

Transfection of TTF-1 and NIS together by an adenoviral vector into ATC cells achieved significant retention of iodide, whereas transfection with TTF-1 alone induced re-expression of TPO and Tg but not of NIS (Furuya et al., 2004). In extrathyroidal tissues, where no organification of iodide can occur, promising results were obtained. Re-circulation of iodide in the blood circulation of the liver results in high iodide-uptake rates and retention despite high efflux of iodide from the cells (Faivre et al., 2004). The successful introduction of functional and localized NIS was also demonstrated in dog prostate glands (Dwyer et al., 2005). Stable transfection of thyroid cancer cells with Pax8 leads to recovery of iodide uptake (Presta et al., 2005) but transfection with TPO is not sufficient to restore iodide trapping in ATC cell lines (Haberkorn et al., 2001).

5.4.1.5 Phosphatidylinositol-3-kinase inhibitors (PI3K inhibitors)/Akt-inhibitors

These agents are used in the treatment of several solid cancers but efficacy has not been shown in in-vivo studies for TC. PI3K-inhibition increased functional expression of NIS in FRTL-5 and PTC cell lines (de Souza et al., 2010) and the PI3K inhibitor LY294002 increased iodide accumulation in TC lines (Furuya et al., 2007). In parallel to increased iodide uptake, this inhibitor increased the expression of PAX-8, suggesting a posttranslational stimulation effect on NIS (Kogai et al., 2008). In the same study the Akt1/Akt2 selective inhibitor Akti-1/2 increased the expression of NIS-transfected TC cells not significantly. In non-transfected TC cell lines the re-differentiating effects of Akt inhibitor I (hydroxymethyl-chiro-inositol 2-(R)-2-O- methyl-3-O-octadecylcarbonate) and Akt inhibitor V (triciribine) were small (Fröhlich et al., 2008): the inhibitors showed an anti-proliferative effect but no increase in iodide uptake was seen. It appears that other Akt-inhibitors (e.g. KP372-1 and MK2206) also markedly reduce cell growth in various TC cell lines but have little effect on the expression of thyroid specific proteins (Mandal et al., 2005; Liu et al., 2011). Only in combination with MAPK inhibition Akt-inhibitors significantly induced NIS mRNA expression in several TC cell lines (Hou et al., 2007).

5.4.2 Compounds in clinical trials

5.4.2.1 Lithium

Eskalith®, Lithobid (lithium carbonate) is used in the treatment of manic depression and depressive disorders. It also causes an increased retention of iodide due to inhibition of the efflux of iodide leaving uptake of iodide unaffected (Temple et al., 1972). Despite causing an increase in radioiodine uptake, no beneficial effect was recorded in several studies on patients with metastatic DTC (Gershengorn et al., 1976; Pons et al., 1987; Koong et al., 1999; Liu et al., 2006).

5.4.2.2 Reverse transcriptase inhibitors

Reverse transcriptase inhibitors like **Sustiva®** (efavirenz) and **Viramune®** (nevirapine) are part of the antiretroviral therapy for the treatment of human immunodeficiency virus type 1 infection and AIDS. In addition, these compounds increase gene expression of TSH-R, thyroglobulin, TPO and NIS in the ATC lines (Landriscina et al., 2005). In a case report, up-regulation of Tg and NIS was shown in a patient treated with nevirapine resulting in improved survival of the patient with PTC. (Modoni et al., 2007).

6. Conclusion

Although DTC is generally regarded as a less problematic tumor, metastatic DTC has a poor prognosis and is unresponsive to conventional treatments. Novel therapies include inhibitors of various growth factor tyrosine kinases and of kinases involved in dys-regulated intracellular signalling. In addition, re-expression of thyroid specific proteins, mainly NIS, by retinoids, PPAR-γ agonists as well as DNA methyltransferase and histone deacetylase inhibitors have potential as novel therapies.

The TKIs sorafenib and sunitinib have entered clinical trials and appear to induce disease stabilization in treated patients. Differentiation therapy with retinoids did not live up to expected outcomes. The results of clinical trials with TZDs and HDIs are not yet known, though combination therapy with HDIs and conventional chemotherapy has shown promising early results. The final evaluation of these compounds is complicated by the fact that the achievement of stable disease cannot be regarded as a great success as many DTC do not progress rapidly any way. The inclusion of patients who only have progressive disease into clinical trials could enhance the clinical value of the induction of stable disease.

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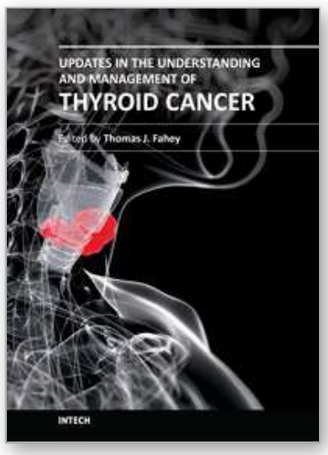

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51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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