Role of thyroid hormones in the neoplastic process: an overview

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Abstract

Thyroid hormones (TH) are critical regulators of several physiological processes, which include development, differentiation and growth in virtually all tissues. In past decades, several studies have shown that changes in TH levels caused by thyroid dysfunction, disruption of deiodinases and/or thyroid hormone receptor (TR) expression in tumor cells, influence cell proliferation, differentiation, survival and invasion in a variety of neoplasms in a cell type-specific manner. The function of THs and TRs in neoplastic cell proliferation involves complex mechanisms that seem to be cell specific, exerting effects via genomic and nongenomic pathways, repressing or stimulating transcription factors, influencing angiogenesis and promoting invasiveness. Taken together, these observations indicate an important role of TH status in the pathogenesis and/or development of human neoplasia. Here, we aim to present an updated and comprehensive picture of the accumulated knowledge and the current understanding of the potential role of TH status on the different hallmarks of the neoplastic process.

Introduction

The association between thyroid hormone (TH) status and cancer was reported as early as 1896, when Beatson used thyroid extract as a potential treatment for breast cancer (Beatson 1896). Since then, an impressive expansion of knowledge has established THs as key regulators of several physiological processes, including the embryonic development, growth and metabolism of virtually all tissues (Yen 2001). Additionally, recent data have demonstrated critical roles of THs in cell proliferation, differentiation and survival (Dentice et al. 2007, Lin et al. 2009, Pascual & Aranda 2013, Romitti et al. 2013, Sterle et al. 2014, Miro et al. 2017).

The human thyroid gland mainly secretes thyroxine (T₄), but the active hormone, triiodothyronine (T₃), mediates most of the hormonal actions. The main pathway for the production of the bioactive form in peripheral tissues occurs via outer ring deiodination of T₄ through the action of iodothyronine deiodinase types 1 and 2 (DIO1; D1 and DIO2; D2). In contrast, type 3 iodothyronine deiodinase (DIO3; D3) is mainly responsible for TH inactivation via inner-ring deiodination of both T₄ and T₃ (Maia et al. 2011). Intracellular T₃ bioavailability is controlled in a tissue-specific manner, depending mainly on its activation by D2 and inactivation by D3. Notably, proper deiodinase function depends on the availability of a yet unidentified thiol cofactor that acts as a reducing agent during the catalysis (Visser et al. 1976). Conditions that result in dysregulation of the intracellular redox state...
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THs exert their effects through genomic (nuclear) and nongenomic (cytoplasmic or membrane TH receptor (TR)) pathways. The genomic mechanisms are mediated mostly by T3 through nuclear TRs. The TRα and TRβ genes encode the TH-binding TR isoforms TRα1 and TRβ1–β3 (Kim et al. 2012). T3 binds to nuclear TRs that activate the transcription of target genes by binding to TH response elements (TREs) located in the regulatory regions. Gene transcription is regulated by an exchange of co-repressor (CoR) and coactivator (CoA) complexes. Negative TREs (nTREs) can mediate ligand-dependent transcriptional repression. However, in this case, the roles of CoAs and CoRs are not well defined (Yen 2001). The nature of the transcriptional response is determined by cell type and hormone status (Hulbert 2000, Aranda & Pascual 2001). On the other hand, the nongenomic effects are initiated by TH binding to integrin αvβ3 receptor, which leads to the activation of different signaling pathways, including mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K), signal transducers and activators of transcription (STAT) pathways. These cascades result in distinct cellular events, such as cell division, proliferation and angiogenesis (Bergh et al. 2005, Lin et al. 2007, Davis et al. 2008, 2009, Cheng et al. 2010).

In past decades, several clinical studies have indicated that an altered TH status might be a risk factor for the development of tumors, such as liver, breast, colon, prostate and thyroid malignancies (Boelaert et al. 2006, Reddy et al. 2007, Polyzos et al. 2008, Fiore et al. 2009, Hassan et al. 2009, Hellevik et al. 2009, Tosovic et al. 2010, 2014). However, other studies have described TH alterations as clinically favorable, such as hypothyroidism for high-grade glioblastomas (Hercbergs et al. 2003). Several in vitro and in vivo studies have demonstrated that THs influence a myriad of oncological events and control the balance between proliferation and differentiation, which is one of the most important hallmarks of TH action in cancer cells (Kress et al. 2009b, Dentice et al. 2013, Pascual & Aranda 2013). Changes in TH levels caused by thyroid dysfunction or the disruption of deiodinases and/or TR expression in tumor cells influence cell proliferation, differentiation, survival and invasion in a variety of neoplasms in a cell type-specific manner (Lin et al. 2008, Dentice et al. 2009, Pinto et al. 2011). The function of THs and TRs in neoplastic cell proliferation involves complex mechanisms that seem to be cell type specific, exerting effects via distinct pathways, repressing or stimulating transcription factors, influencing angiogenesis and promoting invasiveness (Yen 2001, Kress et al. 2009b). Here, we aim to present an updated picture of recent advances in the current understanding of the potential effects of TH status on the different hallmarks of the neoplastic process.

Overview of the neoplastic process

The hallmarks of the neoplastic process include sustained proliferation signaling, resistance to growth suppressors, evasion of programmed cell death, replicative immortality, sustained angiogenesis and promotion of invasion and metastasis (Hanahan & Weinberg 2000). In the past decade, two emerging characteristics have extended our understanding of this process: reprogramming energy metabolism and evasion from immune destruction, both contributing to a favorable tumor microenvironment (Kroemer & Pouyssegur 2008, de Souza et al. 2011, Hanahan & Weinberg 2011).

The acquisition of multiple cancer hallmarks depends on a succession of alterations in the cellular genome (Hanahan & Weinberg 2011). Alterations affecting the DNA maintenance machinery, such as defects in genes involved in the detection and repair of DNA damage, or tumor suppressor genes, have been associated with the progression of the neoplastic process (Kastan 2008, Jackson & Bartek 2009, Ciccia & Elledge 2010, Negrini et al. 2010).

Solid tumors can also recruit new blood vessels through the secretion of angiogenic factors. Vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF; FGF2) and platelet-derived growth factor (PDGF) are examples of molecules that promote the proliferation and migration of vascular endothelial cells and can severely constrain angiogenesis and tumor growth (Kim et al. 1993, Mousa et al. 2014).

Programmed cell death is a natural mechanism that is as important for healthy tissue growth as controlled cell proliferation. In order to grow indefinitely, cancer cells must overlap apoptosis mechanisms, disabling the cellular apoptosis-inducing circuitry. The intracellular apoptotic machinery depends on a family of proteolytic enzymes called caspases, which participate in a process that can be initiated by either extracellular or intracellular death signals. Caspase activation is tightly regulated by members of the B-cell lymphoma 2 (BCL2) and inhibitors of apoptosis proteins families, proteins that can either be pro- or anti-apoptotic (Evan & Voussden 2001, Lowe et al. 2004).
Another distinct attribute of cancer cells, which is functionally important for tumor development involves major reprogramming of the cellular energy metabolism to support continuous cell growth and proliferation, replacing the metabolic program that operates in most normal tissues (Hsu & Sabatini 2008). Neoplastic cells typically generate more reactive oxygen species (ROS) than normal cells, a mechanism that can be partially explained by oncogenic signaling and downregulated mitochondrial function (Lee et al. 1999, Gogvadze et al. 2008). ROS promote DNA damage and signaling mediation, and their presence may contribute to the transformation of cells (Dewhirst et al. 2008).

More recently, disruption of the mechanisms involved in cellular autophagy has emerged as a new hallmark of cancer (White 2015). Controlled autophagy prevents intracellular components, such as proteins, lipids and organelles, from accumulating, which can be harmful to cells (White 2012).

As the effects of THs on these processes are variable and complex, we comprehensively organized our review according to the cancer hallmarks described above (Fig. 1). The emerging effects of TH analogs on tumorigenesis and the disruption of signaling caused by TR mutations have been discussed elsewhere (Cheng 2003, Gonzalez-Sancho et al. 2003, Aranda et al. 2009, Davis et al. 2014a,b, Mousa et al. 2014) and are not included in this review.

### The roles of THs on the cellular hallmarks of cancer

#### TH effects on sustained proliferative signaling pathways

A vital capacity acquired by cancer cells involves their ability to sustain chronic proliferation through different pathways (Di Cristofano & Pandolfi 2000, Shields et al. 2000, Brazil & Hemmings 2001, Evan & Vousden 2001, Zhang & Liu 2002). THs influence cell growth, acting either as growth factors or as cell growth inhibitors through several proliferation pathways.

Davis and coworkers (Davis et al. 1999) demonstrated for the first time the nongenomic actions of THs in the induction of the MAPK pathway in HeLa and CV-1 cells (Lin et al. 1999a). T₄ promotes the phosphorylation of MAPK and the co-immunoprecipitation of nuclear tyrosine phosphorylated MAPK with STAT-1a and STAT-3 (Lin et al. 1999b). This effect causes the MAPK-mediated serine phosphorylation of TRδ1, which dissociates the

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**Figure 1**

The effects of THs on the hallmarks of cancer involve several pathways and effectors. The THs (center) act via integrin αvβ3 or TRs (inner circle), modulating critical signaling pathways classically involved in carcinogenesis (middle circle). Note that for some nongenomically driven pathways, integrins have not been shown to be the membrane receptor mediators. Downstream targets of TH actions are represented in the outer circle.
TRβ1 and the co-repressor silencing mediator for retinoid receptors or TRs, thus affecting the nuclear receptor via a mechanism independent of the binding of T3 to TRβ1 (Davis et al. 2000). For this process to occur, a cell membrane T4 receptor is required. Later, the same group showed that a member of the plasma membrane heterodimeric integrin protein family, integrin αVβ3, binds T4 preferentially over T3 (Bergh et al. 2005). Presently, most of the nongenomic effects of THs are known to be mediated by activation of the integrin αVβ3 receptor, which sends several survival mechanism signals to the cell, including the stimulation of ERK- and AKT-dependent pathways (Cheng et al. 2010).

MAPK pathway The activation of MAPK (ERK1/2) by physiological levels of T4 influences tumor proliferation, as has been demonstrated in glioma (Davis et al. 2006), follicular thyroid carcinoma (FTC) and papillary thyroid carcinoma (PTC) (Lin et al. 2007), undifferentiated pheochromocytoma (Barbakadze et al. 2014) and myeloma (Cohen et al. 2015) (Fig. 2). In human breast cancer cells, T4 induces proliferation nongenomically, requiring ERK1/ERK2 and phosphorylating the estrogen receptor alpha (ERα). This observation highlights the crosstalk between THs and estrogen signaling pathways in certain cancer cells, culminating in specific intranuclear events.

Figure 2
Proposed mechanism of genomic and nongenomic actions of THs in the neoplastic process. The actions of THs occur at the plasma membrane, in the cytoplasm, and within the cell nucleus. To exert their genomic effects, T3 and T4 enter the cell through transporter proteins, such as monocarboxylate transporter (MCT) 8 and 10 or organic anion-transporting polypeptides. Inside the cells, D2 convert T3 to the active form T3, while D3 inactivates both THs, producing rT3 and T3 (1). T3 binds to nuclear TRs that activate transcription by binding TREs located in the regulatory regions of the target genes. Activity is regulated by an exchange of corepressor (CoR) and coactivator (CoA) complexes. Negative TREs (nTREs) can mediate ligand-dependent transcriptional repression; however, in this case, the roles of CoAs and CoRs are not well defined (2). THs can also regulate genes that do not contain a TRE by nongenomic effects. These ‘rapid effects’ are initiated by THs binding to integrin αVβ3 (3), leading to the activation of different signaling pathways and resulting in distinct cellular events, such as cell proliferation, migration, angiogenesis and apoptosis inhibition. One site of the integrin αVβ3 (4) binds T3 exclusively, activating PI3K via Src kinase (5), stimulating FAK, HIF-1α and mTOR, while also increasing the activity of the sodium pump (Na/K ATPase). The second site (4) binds T3 and T4, stimulating MAPK-dependent proliferation via phospholipase C (PLC) and protein kinase C (PKC), promoting the phosphorylation of several effectors (ERα, TRβ1, STAT1α, PS2 and STAT-3, among others) (6). THs can induce the expression of matrix metalloproteinases (MMPs) nongenomically via MAPK and PI3K, thereby enhancing invasiveness (7). Another action THs initiate at the cell surface is modulation of the activity of the Na+/H+-exchanger and Na/K ATPase (8). Furthermore, T3 also interacts with a TRα variant in the cytoplasm to cause a modification of intracellular actin that contributes to cell migration (9). T3 negatively regulates UHRF1 through Trx1, leading to inhibition of cancer growth, by promoting stability of a cyclin-dependent kinase inhibitor (p21) (10). While T3 negatively or positively regulates Wnt/β-catenin expression, depending on the TR that is active, Wnt/β-catenin regulates the intracellular levels of T3 by modulating Dio2 and Dio3 expression. The D2 level is downregulated by β-catenin while D3 is induced, illustrating the complex crosstalk between THs and the Wnt/β-catenin pathway (11). Note that for some nongenomically driven pathways, integrin αVβ3 has not been demonstrated as the membrane receptor mediator.
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(Tang et al. 2004). Another example of THs and estrogen crosstalk is the induction of proliferation in human lung cancer cells, which is initiated via the cell surface integrin αVβ3 (Meng et al. 2011).

T₃ also activates MAPK nongenomically but only at supraphysiological levels (Davis et al. 2000, Kozawa et al. 2001). Studies in glioma cell lines have shown that T₃ suppresses proliferation and induces redistribution in a mechanism independent of ERK 1/2 activation, suggesting a potential role of TRα1 (Liappas et al. 2011). In contrast, other studies have demonstrated that both T₄ and T₃ induce cell proliferation in glioblastoma and pheochromocytoma cells via ERK1/2 pathway activation (Lin et al. 2009, Barbakadze et al. 2014). In ovarian tumor cells, physiological concentrations of T₃ and T₄ induce MAPK-dependent cell proliferation and support cell survival in a process that requires an intact TH–integrin interaction for ERK activation (Shinderman-Maman et al. 2016).

The interaction between THs and the RAS signaling pathway also deserves attention due to its important role in carcinogenesis. RAS proteins act as key membrane signaling mediators by transferring information from this cellular compartment to the nucleus. RAS activates several pathways to regulate cell growth, survival, differentiation and angiogenesis; MAPK is a key downstream target of these pathways (Lowy & Willumsen 1993). Activating mutations in RAS genes and the consequent aberrations in the expression of the RAS–MAPK complex are implicated in several human cancers (Downward 2003, Rajalingam et al. 2007). Cyclin D1, which is critical for cell cycle progression, is one of the main mediators effecting the proliferative effects of RAS oncogenes (Filmus et al. 1994). T₃, acting through TRα1 and TRβ1, not only blocks the RAS-mediated proliferation of neuroblastoma cells via the regulation of cyclic AMP response elements but also represses their transcriptional activity, thus reducing the cyclin D1 levels and consequently the cell proliferation (Garcia-Silva & Aranda 2004).

Studies performed using hepatocarcinoma (HCC) cells and breast cancer cells originally lacking TRs have shown that the reexpression of TRβ1 abolishes tumor growth and migration (Martinez-Iglesias et al. 2009) while preventing tumor formation by RAS-transformed cells in nude mice, even under hypothyroid conditions (Aranda et al. 2009). In neuroblastoma (Neuro-2a) cells overexpressing TRβ1, T₃ treatment blocks cell proliferation through an arrest of cells in G0/G1 and induces morphological and functional cell differentiation through acetylcholinesterase activity (Lebel et al. 1994). Taken together, these data indicate that a loss of the expression and/or function of TRs could result in a selective advantage for malignant transformation in RAS-dependent tumors.

**PI3K/protein kinase B pathway** The PI3K/protein kinase B (AKT) pathway also plays a pivotal role in the regulation of cell growth and proliferation and its deregulation contributes to cellular transformation in a variety of neoplasms (Furuya et al. 2006, Franke 2008). Several nongenomic and genomic TH actions in tumors occur via the PI3K pathway. Incubation of endothelial cells with T₃ increases the association of TRα1 with the p85α subunit of PI3K by non-transcriptional mechanisms, leading to the phosphorylation and activation of AKT (Hiroi et al. 2006). Notably, in a mouse model of FTC, a TRβ mutant can activate the PI3K regulatory subunit p85α, affecting signaling in both the nuclear and extranuclear compartments (Furuya et al. 2006). Experimental data obtained using PTC and neuroblastoma cell lines show that T₃ promotes the activation of ERK, AKT and Src. T₃ can also induce AKT phosphorylation nongenomically through TRβ1 (Cao et al. 2009, Perri et al. 2014). In insulinoma cell lines (rIINm5F and hCM) that express TR isoforms TRα1, TRα2 and TRβ1, T₃ induces cell proliferation and is also able to promote survival due to a regulation of different cellular apoptotic proteins, specifically activating the PI3K pathway (Verga Falzacappa et al. 2006). In non-tumoral β-cells, T₃ action in the AKT pathway is also mediated by TRβ1, which contributes to the stimulation of proliferation and survival both in a rapid and long-term manner (Verga Falzacappa et al. 2009).

Interestingly, in contrast, T₃ treatment enhances PI3K activity in glioblastoma cells but leads to nonproliferative downstream functions (Lin et al. 2009). Taken together, these observations show the critical role of T₃ nongenomic effects on the rapid PI3K-AKT/PKB-mTOR activation in normal and neoplastic cells (Cao et al. 2005, Kenessey & Ojamaa 2006, Storey et al. 2006, Verga Falzacappa et al. 2009, Perri et al. 2014).

Unlike T₃, T₄ is unable to activate PI3K nongenomically, supporting the concept that the integrin αVβ3 receptor contains two specific sites in the hormone-binding domain. One site binds T₄ exclusively and activates PI3K via Src kinase. The second site binds both T₄ and T₃, which in turn, activates ERK1/2-dependent tumor cell proliferation (Fig. 2) (Lin et al. 2009).

Recently, alternative mechanisms for T₃- and T₄-dependent AKT activation have been proposed. In human umbilical vein endothelial cells (HUVECs), neither T₄ nor T₃-induced AKT phosphorylation was attenuated by the addition of tetrac (which blocks T₄ from binding to the...
integrin αVβ3 receptor) suggesting that integrin αVβ3 is not involved in the nongenomic actions of THs in these cells and raising the question whether membrane-localized TRs are involved in such rapid actions of THs. Of interest, the blockade of D2 activity abolished AKT phosphorylation, indicating that the conversion of D2-catalyzed T3 to T2 is required for TRα1/P3K-mediated nongenomic actions of T3 in HUVECs (Aoki et al. 2015).

**Wnt/β-catenin pathway** The Wnt signaling pathway has a critical role in the embryonic development and regeneration of tissues. Mutations and/or deregulated expression of the Wnt pathway can induce cancer (Polakis 1999, Klaus & Birchmeier 2008). β-Catenin, a central mediator in the Wnt pathway, interacts with E-cadherin to control the cellular functions (Gottardi & Dentice 2001). The relationship between T3 and the Wnt pathway was demonstrated by an elegant study performed by Miller and coworkers (Miller et al. 2001), which showed that T3-induced cell proliferation is associated with the immediate silencing of Wnt signaling in rat pituitary cells. Later, studies in colon cancer cells demonstrated that T3/TRβ1 suppress the transcription of cyclin D1 by wild-type β-catenin (Natsume et al. 2003). Therefore, T3/TR signaling can negatively regulate the Wnt pathway by inhibiting transactivation by β-catenin/Tcf on the cyclin D1 promoter. The physical interaction of β-catenin and TRβ was also demonstrated in a mouse model of thyroid cancer. T3 binding to TRβ weakened the β-catenin/TRβ interaction, increasing the amount of β-catenin available to be degraded via the proteasomal pathway (Guigon et al. 2008).

β-Catenin also interacts with TRα1, but causes different effects when compared to β-catenin/TRβ interaction. TRα1 is primarily responsible for cell cycle regulation and proliferation in the normal intestinal epithelium (Kress et al. 2009a). In these cells, T3-activated-TRα1 receptor directly controls the transcription of the β-catenin in vitro, promoting cell proliferation (Pateroti et al. 2006). TRα overexpression also enhances the intestinal tumorigenic process in a predisposed genetic background. In human CaCo2 cells, TRα1 interacts with the β-catenin/Tcf4 complex, leading to a reduced TRα1 functionality. In this model, TRα1 is recruited to interact with Wnt-responsive element regions in pre-cancerous and cancerous intestinal lesions and stabilizes Wnt effectors on their target genes (Kress et al. 2010, Sirakov et al. 2012). Remarkably, the Wnt/β-catenin pathway modulates the colonic epithelium T3 concentration through the coordinated effects of D3 and D2 enzymes (Fig. 2). D3 is a downstream target upregulated by Wnt/β-catenin, while unknown mechanisms downregulate D2. In colon cancer cells, D3 depletion causes intracellular T3 levels to rise, promoting differentiation and reducing proliferation (Dentice et al. 2012). These observations demonstrate the complexity of the interactions among THs, deiodinases and the Wnt pathway in the balance of cell proliferation and differentiation. Notably, the effects of THs on colorectal cancer stem cells (CSCs) enhance the chemotherapy sensitivity and might be clinically important in the colon cancer therapy (Catalano et al. 2016).

TH and Wnt/β-catenin interactions are also involved in the hepatocellular physiopathology by regulating the cell cycle during development and regeneration in the liver (Francavilla et al. 1994, Bockhorn et al. 2007, Lade & Monga 2011). T3 enhances the activation of β-catenin in hepatocytes by increasing its phosphorylation through the activation of protein kinase A (PKA), indicating that T3-PKA-β-catenin crosstalk is essential for normal hepatocyte proliferation (Fanti et al. 2014). Wnt-β-catenin signaling is constitutively activated in HCC (Ihara et al. 1996) but a contributing role of THs in liver tumor proliferation through this pathway remains to be demonstrated.

**Sonic hedgehog (SHH) pathway** SHH signaling promotes cell differentiation and organ formation during embryogenesis (McMahon et al. 2003). SHH remains active in some organs through adulthood, and the deregulation of this pathway can result in uncontrolled cell proliferation (Pasca di Magliano & Hebrok 2003). Notably, SHH signaling is required not only for cancer initiation but also for growth and survival of several types of cancer (Fan et al. 1997, Oro et al. 1997, Ruiz i Altaba et al. 2002, Pasca di Magliano & Hebrok 2003, Dentice et al. 2007).

Basal cell carcinoma (BCC), the most prevalent cancer in light-skinned individuals, is associated with increased levels of D3, the main TH-inactivating enzyme. SHH, through Gli family zinc finger 2 (Gli2), directly induces D3 expression, which in turn reduces intracellular T3 levels and increases cell proliferation, indicating that D3 overexpression is a major player in BCC progression. Indeed, D3 depletion (or T3 treatment) significantly reduces proliferation and cyclin D1 levels in malignant keratinocytes (Dentice et al. 2007). T3 treatment or D3 depletion also downregulates mir21, a key miRNA involved in oncogenesis. In an opposite manner, mir21 positively regulates D3 expression in BCC through grainyhead-like
transcription factor 3 (GRHL3) (Di Girolamo et al. 2016). The crosstalk between the SHH and MAPK pathways for D3 upregulation has also been demonstrated in human PTC cell lines (Romitti et al. 2012, 2016). Similarly, D3 depletion reduces cell proliferation and decreases cyclin D1 levels (Romitti et al. 2016). Taken together, these data support the link between D3 overexpression and SHH/Gli2 pathway reactivation, suggesting that decreased intracellular levels of THs may be a critical factor for tumor growth, at least in some types of cancer.

**Other less characterized TH effects in neoplastic process** TH effects on other signaling pathways have also been described. In T-cell lymphomas (TCL), T3 activates αvβ3 integrin signaling inducing cell proliferation and angiogenesis, in part, via the upregulation of VEGF (Sterle et al. 2014, Cayrol et al. 2015). Interestingly, a paradoxical effect was found in mouse models inoculated with TCLs, in which high circulating levels of THs favored T lymphoma growth, while hypothyroidism promoted tumor dissemination (Sterle et al. 2016). Moreover, in vitro short-term TCL exposure to THs led to proliferation, while a longer treatment increased tumor cell apoptosis (Mihara et al. 1999, Sterle et al. 2016). In embryonic carcinoma cells, T3 treatment decreased the growth rate via the rapid downregulation of E2F1, a key regulator of proliferation. This effect is dependent on the presence of active TRs (Nygard et al. 2003).

Recently, an interaction was demonstrated between TRβ and nuclear corepressor 1 (NCoR), a coregulatory protein that mediates transcriptional repression via certain nuclear receptors. TRβ increases NCoR levels, thus suppressing the transcription of prometastatic genes, whereas decreased NCoR leads to increased tumor growth, invasion and metastasis, suggesting that NCoR is a critical mediator of the suppressive actions of TRβ in tumor growth and metastasis (Martinez-Iglesias et al. 2016a).

**Evading growth suppressors**

TH and TRs can act as tumor suppressors in specific types of tumors. These TH-mediated effects have been studied mostly in hepatic neoplastic and non-neoplastic cells, where T3 was shown to inhibit cell proliferation and to induce differentiation. T3 has a suppressive effect on the growth of specific liver tumors such as hepatoma, where the proliferative inhibitory effect of T3 is mediated by TGF-β upregulation (Yen et al. 2006). T3/TR signaling mediates Dickkopf 4 (DKK4) expression that inhibits the proliferation and migration of hepatoma cells via blockade of the Wnt signaling pathway (Liao et al. 2012). Similarly, THs inhibit cell proliferation by promoting p21 stability through endoglin upregulation (Lin et al. 2013a). Moreover, in TRα1-overexpressing hepatoma cells, T3/TR signaling promotes inhibition of liver cancer cell growth via downregulation of the ubiquitin-like with PHD and ring finger domains 1 (UHRF1) (Wu et al. 2015).

Interestingly, the treatment of preneoplastic hepatocytes with T3 or GC-1 (a TRβ antagonist) leads to a loss of markers associated with neoplastic processes, such as glutathione S-transferase and gamma glutamyl transpeptidase. Meanwhile, T3 promotes the reacquisition of the activity of glucose 6-phosphatase and adenosine triphosphatase, two enzymes expressed in normal hepatocytes. Notably, the reduction in the number of preneoplastic lesions occurs despite an increase in cell proliferation, indicating that active TRs negatively influence the carcinogenic process through the redifferentiation of preneoplastic hepatocytes (Perra et al. 2009). In a similar manner, T3 reduced the tumor development and metastasis rate in rats exposed to cycles of TH therapy. These data suggest that T3 could act as an anticarcinogenic molecule, most likely leading to hepatocyte redifferentiation (Ledda-Columbano et al. 2000).

Similarly, studies evaluating the effect of THs on glioma cell lines demonstrated T3-dependent cell redifferentiation at nearly physiological concentrations of the hormone. Remarkably, more aggressive tumors were more sensitive to the T3 inhibitory effects over cell proliferation, an effect that was mediated, at least in part, by TRα1 overexpression (Liappas et al. 2011). Consistent with these observations, it has been shown that several genes related to neuroblastoma cell differentiation are responsive to THs (Bedo et al. 2011).

On the other hand, TR action on tumor proliferation and metastasis might occur independently of the presence of T3 (Martinez-Iglesias et al. 2016b). Nevertheless, these effects have become increasingly difficult to study, in part due to the heterogeneous expression of TRs among different cancer types (and even within the same tumor type), the presence of TR mutations deregulating downstream pathways, and, as mentioned previously, due to parallel nongenomic effects of T3/T4 on the cellular metabolism (Cheng 2003, Chan & Privalsky 2006). Indeed, TRs, particularly the TRβ isoform, can act

**Evading cell death and enabling replicative immortality**

TH actions have also been demonstrated in the evasion of programmed cell death, an important feature of neoplastic transformation (Shih et al. 2001, Lin et al. 2007, 2008). In brief, apoptosis can be divided into two major circuits: the extrinsic and intrinsic apoptotic programs. The extrinsic apoptosis pathway involves the interaction of ligands, such as tumor necrosis factor (TNF)-α and Fas ligand, with specific receptors on the cell surface. THs decrease TNF-α, Fas receptor and Fas ligand expression and the activity of caspase-3, thus suppressing apoptosis in non-tumoral models (Laoag-Fernandez et al. 2004). An anti-apoptotic role of THs is also supported by the effect of T3 on apoptosis regulators. T3 decreases the cellular abundance of caspases and the proapoptotic Bcl-2-associated X protein (BAX) and increases the expression of the anti-apoptotic X-linked inhibitor of apoptosis protein (XIAP) (Zhang et al. 2011, Sterle et al. 2014). When considering the intrinsic apoptosis pathway, there is evidence that T3 administration protects hypothyroid rat liver cells from apoptosis induced by oxidative stress in a non-tumoral model (Mukherjee et al. 2014). TH also regulates proteins involved in the intrinsic apoptosis pathway. For example, T3 induces the expression of myeloid cell leukemia 1 (MCL-1), a Bcl-2-related protein located in the outer mitochondrial membrane (Pietrzak & Pużanowska-Kuznicka 2008), while T4 downregulates expression of the BAX gene, the gene product of which is proapoptotic mitochondria. These anti-apoptotic effects of THs are in accordance with the evidence that molecules inhibiting T4 action (tetrac/nanotetra) have proapoptotic effects on tumor growth (Yalcin et al. 2010a).

The nongenomic effects of T4 in the apoptotic pathway occur, at least in part, via induction of the MAPK pathway, initiated through the integrin αVβ3 receptor (Lin et al. 2007). The T4-induced MAPK activation results in the serine phosphorylation of the oncogene suppressor p53, STAT1α, STAT-3 and TRβ1, leading to proliferative and anti-apoptotic effects (Lin et al. 1999b, 2003, Davis et al. 2000, Shih et al. 2001). The T4 anti-apoptotic effect was demonstrated in human PTC and FTC cell lines incubated with resveratrol (RV), an apoptosis inducer that also initiates signaling via the plasma membrane integrin αVβ3 (Lin et al. 2007, 2008). In glioma cells, RV increases the nuclear content of cyclooxygenase-2 (COX2) via MAPK induction, while the incubation of RV-treated cells with T4 decreases the levels of the cytosolic proapoptotic protein B-cell lymphoma extra-large (Bcl-XL) and the formation of nuclear complexes between pERK and COX2. These effects lead to a blockage of p53 phosphorylation, thus inhibiting apoptosis (Lin et al. 2007). However, others have demonstrated that high concentrations of T3 induce breast cancer cell apoptosis via the TRβ-dependent downregulation of the anti-apoptotic senescence marker protein-30 gene (SMP30) (Sat et al. 2011). The involvement of TRβ in apoptotic pathways is further supported by studies showing that TRβ can act as a tumor suppressor, interfering with the recruitment of retinoblastoma protein and p53 via the SV40Tag oncoprotein through a protein–protein interaction (Kim et al. 2012). TNF-related apoptosis-inducing ligand (TRAIL/Apo2L) is a potent effector of tumorigenesis that not only promotes apoptosis but also triggers non-apoptotic pathways (Johnstone et al. 2008). T3 upregulates TRAIL expression at the transcriptional level in TR-overexpressing hepatoma cells, which in turn promotes cell migration and invasion (Chi et al. 2012).

Compilation of data supports the anti-apoptotic activity of THs in several tumor cells. TH action occurs mainly through physiological levels of T3 via genomic and nongenomic signaling modulating multiple components of the extrinsic and intrinsic apoptosis pathways.

The maintenance of telomere integrity and telomerase protect cells from apoptosis. Telomerase inhibition elicits an apoptotic response in cancer cells, while restoration of telomerase activity in somatic cells promotes resistance to apoptosis (Mondello & Scovassi 2004). Thus far, no studies on the effect of THs on telomerase activity in cancer models have been reported. However, hypothyroidism leads to decreased telomerase activity in stem cells (Simsek et al. 2014), an observation that should be further explored.

**Tissue invasion and metastasis**

The spread of cells from the primary lesion to distant organs is the most worrisome aspect of cancer. Alterations in cell shape and in their attachment to both other cells and the extracellular matrix (ECM) are essential for this process (Fidler 2003). Tumor cells must invade the basement membrane and migrate through the ECM surrounding the tumor epithelium to spread, which occurs...
mainly via interactions between integrin receptors and ECM components. Matrix metalloproteinase-9 (MMP-9) is a pivotal matrix metalloproteinase that contributes to ECM degradation, thereby enhancing invasiveness (Egeblad & Werb 2002). THs contribute to the regulation of cell adhesion and migration in several tumor models (Dietrich et al. 2000, Liao et al. 2010). For instance, THs induce MMP-9 via the αVβ3-MAPK pathway, promoting increased adhesion to fibronectin and enhancing cell migration in myeloma cells (Cohen et al. 2014).

THs status might influence the spread of liver cell cancer. However, as already mentioned, the effects of THs on liver tumorigenesis are complex and depend on TR expression status, cancer stage and other co-effectors present in the tumor microenvironment (Wu et al. 2013). Acting mostly through TRs, actions of TH on HCC development may lead to the suppression or promotion of metastatic mechanisms. T3 enhances HCC cell invasion in vitro and in vivo (Wu et al. 2013). T3 treatment increases the invasive capacity of HepG2 cells expressing TRs, possibly due to the upregulation of furin, a calcium-dependent serine endoprotease, which increases the processing of MMP-2 and MMP-9. Moreover, T3 administration to mice inoculated with HepG2-TRα1 cells caused furin overexpression. Notably, these animals displayed greater tumor sizes and metastasis rates than euthyroid animals, supporting the metastasis-promoting effect of T3 in HCC (Chen et al. 2008). Several members of the MMP family, including MMP-2, MMP-9 and MMP-7, are upregulated upon r-TRAIL stimulation in hepatoma cells, an effect confirmed by increased invasiveness in both in vitro and in vivo models (Chi et al. 2012). Cathepsin H, a protease involved in the degradation of ECM components, leading to cancer cell migration and metastasis, is induced by T3 in HCC cells, enhancing the invasion potential of hepatoma cells in vitro and in vivo (Wu et al. 2011). Likewise, T3 treatment in HCC cells also enhanced tumor cell migration and invasion by stimulating the overexpression of brain-specific serine protease 4 protein levels, which was associated with ERK1/2-C/EBPβ-VEGF cascade activation (Chen et al. 2014). Inversely, other studies have demonstrated that T3 treatment of the same cells leads to spondin 2 overexpression, which inhibits cell invasion and migration (Liao et al. 2010). T3 treatment also upregulates the expression of DKK4 protein, an antagonist of Wnt, in HepG2 TR-expressing cells (Chi et al. 2013), suggesting that the T3 upregulation of the TR/DKK4/Wnt/β-catenin cascade inhibits the metastasis of hepatoma cells (Liao et al. 2012).

T3-induced cell migration in HCC is mediated in part to a reduction in miR-17 and miR-130b expression (Lin et al. 2013b, 2015) and the overexpression of miR-21 (Huang et al. 2013). The overexpression of miR-17 markedly inhibits HCC cell migration and invasion in vitro and in vivo via the suppression of MMP-3 (Lin et al. 2013b), whereas the effect of miR-130b involves the regulation of genes critical for metastasis, such as MMP-9, mTOR, ERK1/2, AKT and STAT-3 (Lin et al. 2015).

Breast cancer cell migration is also influenced by the nongenomic action of T3. The focal adhesion kinase (FAK) protein is an essential regulator of the actin cytoskeleton, thus modulating the steps involved in cell migration and invasion. T3, acting through integrin αVβ3, promotes the phosphorylation of FAK by activating the Src/FAK/P13K pathway, thereby modulating cell adhesion and migration (Flamini et al. 2017).

### Induction of angiogenesis

Tumor growth, invasion and metastasis are strongly dependent on angiogenesis (Folkman 1995). The initiation and maintenance of a vascular supply involve the local release of angiogenic molecules, such as VEGF, FGF2, PDGF, TGFs and angiopoietins (Angs) (Risau 1997). The concept of TH-induced neovascularization was first described a decade ago in the chick chorioallantoic membrane assay of angiogenesis (Davis et al. 2004, Bergh et al. 2005). TH pro-angiogenic effects seem to be mainly promoted by T4 binding to integrin αVβ3, followed by MAPK signal transduction. The TH-αvβ3 complex causes the transcription of several factors, such as TRβ1, ERs, TP53 and STATs, leading to the increased expression of angiogenic modulators, such as FGF2, VEGF and Ang-2 (Mousa et al. 2005, 2014, Bockhorn et al. 2007, Davis et al. 2009). The addition of T3 to cultures of HCC, lung and kidney carcinoma cells leads to HIF-1α induction and increases in VEGF levels (Otto & Fandrey 2008). T3 upregulates HIF-1α through the PI3K pathway, which in turn stimulates the secretion of HIF-responsive genes, such as VEGF, FGF2, Interleukin-6, stromal cell-derived factor-1 and TGF-β1 (Davis et al. 2011). T3 and T4 also regulate the differentiation and migration of mesenchymal stem cells (MSCs) via integrin αVβ3. This regulation affects not only indicators of tissue remodeling and invasion, such as tenascin-C (TN-C) and thrombospondin-1 (TSP1), but also proteins associated with angiogenesis, such as α-smooth muscle actin (α-SMA), desmin and VEGF, thus contributing to tumor stroma dysregulation (Schmohl et al. 2015).
Of note, tetrac reduces VEGF-A mRNA levels while increases the transcripts of the THBS1 gene, an adhesive glycoprotein that mediates cell-to-cell and cell-to-matrix interactions, blocking the T4 proangiogenic effects (Glinskii et al. 2009, Yalcin et al. 2010b). Indeed, tetrac administration to nude mice inoculated with FTC or medullary thyroid carcinoma (MTC) cells reduces the vascularization and growth of grafted tumors (Yalcin et al. 2010a,b). The tetrac-associated inhibition of angiogenesis has been observed in a variety of tumor xenografts, indicating a therapeutic potential that merits exploration in clinical settings (Yalcin et al. 2009, 2013, Mousa et al. 2012).

Genomic instability and cellular senescence

Genomic instability is a hallmark of most cancer cells. Failure in maintaining DNA integrity impairs cell proliferation and survival, resulting in senescence, a phenomenon in which normal cells cease to divide. Cells can be induced to senesce via DNA damage due to increased ROS levels (Campisi 2013). T3, mediated by TRβ, induces senescence in mouse embryonic fibroblasts, promoting DNA damage secondary to oxidative stress. The effect is dependent on the activation of ataxia telangiectasia mutated (ATM)/adenosine monophosphate-activated protein kinase (PRKAA), proteins that play pivotal roles in detecting genomic damage (Zambrano et al. 2014). Of note, TRβ1 and TRβ2 are highly expressed in retinoblastoma cells, and participate in maintaining genomic stability (Pappas et al. 2017).

Dysregulation of cell bioenergetics/energy metabolism

The sustenance of cancer cells also depends on metabolic adaptations. Tumor cells are characterized by increased aerobic glycolysis and lactic acid production in normoxic conditions. This phenomenon, which has been a biochemical hallmark of cancer for decades, is known as the Warburg effect (Koppenol et al. 2011, Warburg 1956). Lately, some studies have established a connection between the mitochondrial and TH metabolisms in the context of modulating the Warburg phenomenon in breast cancer (Suhane & Ramanujan 2011, Silvestri et al. 2014). The authors evaluated the effects of T3 in modulating the bioenergetics profiles by monitoring glucose uptake, lactate generation and the mitochondrial oxygen consumption rate. Interestingly, they showed that T3 directly increases the mitochondrial metabolism in aggressive breast cancer cells and directly regulates one of the isoforms of pyruvate kinase that is vital for sustaining the Warburg effect (Suhane & Ramanujan 2011).

Oxidative stress is known to disrupt the function of deiodinases (Wajner et al. 2011), key enzymes for the regulation of the intracellular levels of active THs (St Germain et al. 2009, Maia et al. 2011). Neoplastic cells are known to be hypoxic, a condition that has been shown to upregulate D3 expression through HIF-1 in non-tumoral models (Simonides et al. 2008, Ciavardelli et al. 2014). D3 reactivation in the neoplastic cells of solid tumors increases TH inactivation and reduces the metabolic rate, which may favor cell proliferation. This phenomenon has been associated with a poor therapeutic response and an increased risk of recurrence (Keith & Simon 2007). In a non-tumoral model of rat brain, D3 participates in the hypoxia-induced reduction in TH signaling. Moreover, ischemia/hypoxia induces a heat-shock protein 40 (HSP40)-mediated translocation of D3 to the nucleus, facilitating TH inactivation proximal to the TH receptors (Jo et al. 2012, Huang et al. 2014). THs can directly protect or damage cells by modulating oxidative stress (Mancini et al. 2016). Thus, it is reasonable to consider that intracellular TH levels contribute to the disruption of tumoral bioenergetics. The effects of THs on glycolytic fueling require further exploration since common pathways appear to be activated in several tumors (DeBerardinis et al. 2008).

Intracellular microenvironment: deiodinase control over TH status

The intracellular TH status is highly dependent on the activation or inactivation of THs by deiodinases. Particularly, alterations in the balance between TH-activating and TH-inactivating deiodinases can be critical in modulating the balance between cell proliferation and differentiation (Kress et al. 2009b, Dentice et al. 2013). Indeed, changes in the expression levels of deiodinases are present in several malignant human neoplasias. DIO1 downregulation occurs in renal, lung, hepatic and prostate cancer tissues (Dutkiewicz et al. 1995, Sabatino et al. 2000, Pachucki et al. 2001, Wawrzynska et al. 2003). Studies performed using human PTC samples found a consistent decrease in DIO1 levels compared with the surrounding thyroid tissue, suggesting that diminished DIO1 expression might be an early event in thyroid cell dedifferentiation. In contrast, DIO1 and D1 activity levels are increased in follicular adenoma and FTC.
samples (de Souza Meyer et al. 2005). In renal clear cell cancer, miR-224 expression correlates negatively with the DIO1 mRNA level and T3 concentration, suggesting that miR-224 induces intracellular hypothyroidism via reduced D1 function (Boguslawska et al. 2011). Interestingly, D1 activity does not differ significantly between benign and malignant tumors as compared with healthy liver parenchyma cells (Kornasiewicz et al. 2014). In contrast, D1 activity in non-cancerous breast tissues is very low or non-measurable, whereas it is increased in breast cancer, indicating a tissue-specific regulation of D1 expression (Debski et al. 2007).

Changes in DIO2 expression have also been demonstrated in several human neoplasias. DIO2 expression is induced in most brain tumors, including those derived from glial cells (Mori et al. 1993, Murakami et al. 2000, Nauman et al. 2004), FTC cells and MTC cells (Kim et al. 2003, Meyer et al. 2008). In contrast, DIO2 mRNA and activity are decreased in PTC cells as compared with normal follicular thyroid cells (Arnaldi et al. 2005, de Souza Meyer et al. 2005).

Increased DIO3 expression is observed in several human tumor types, including astrocytoma, oligodendroglioma, glioblastoma multiforme and BCC (Gereben et al. 2008). Tumoral D3 activity is markedly elevated in vascular tumors, including infantile hemangiomia and hemangioendothelioma in adults (Huang et al. 2000, 2002, Luongo et al. 2013), even to the extent of inducing clinical hypothyroidism (consumptive hypothyroidism). Opposing regulation of DIO3 or DIO1/DIO2 expression has been reported in various human neoplasias, such as PTC, TSH tumors, BCC and colon cancer (de Souza Meyer et al. 2005, Dentice et al. 2007, 2012, Luongo et al. 2013, Romitti et al. 2016). Studies performed using 105 pituitary tumors demonstrated that D2 and D3 mRNA levels were significantly augmented in pituitary tumors compared with normal pituitary tissue. In the rare TSH-secreting pituitary tumor subtype, increased D3 expression and D2 mRNA downregulation were observed, which may explain the ‘resistance’ of these tumors to TH feedback (Tannahill et al. 2002). In human BCC samples, upregulated DIO3 expression correlated with the functional status of the SHH pathway described above, which is a critical oncogenic pathway (Dentice et al. 2007). Interestingly, co-expression of D3 and D2 was found in BCC, and manipulation of the expression of each enzyme, with consequent alteration of intracellular TH levels, dramatically modifies the proliferative potential of BCC (Miro et al. 2017). This illustrates the critical regulatory role of THs on proliferation of certain tumors.

The induction of DIO3 expression was also recently demonstrated in human PTC samples. Remarkably, D3 levels were positively associated with increased tumor size and increased rates of local and distant metastasis at diagnosis (Romitti et al. 2012). Most interesting, D3 upregulation in PTC samples is modulated by crosstalk between the MAPK and SHH pathways and varies according to the genetic alterations in this tumor type (Romitti et al. 2016). Increased DIO3 expression was also observed in FTC but not in medullary or anaplastic thyroid carcinoma samples (Romitti et al. 2012). Higher levels of D3 were also detected in human intestinal adenoma and carcinoma compared with healthy intestinal tissue. However, DIO3 expression was reduced in lesions with higher histological grades (Dentice et al. 2012).

**Tumor microenvironment**

Increasing evidence indicates that what is occurring inside tumor cells depends on exogenous stimuli originating around the tumor cells (Joyce & Pollard 2009, Goubra et al. 2014). Specifically, surrounding tumor stroma and immune cells can be ‘activated,’ thus influencing tumor behavior.

**Evading immune destruction and promoting inflammation**

The immune system antagonizes and enhances tumor development and progression. The tumor-associated inflammatory response has the paradoxical effects of promoting tumorigenesis and helping neoplastic cells acquire hallmark capabilities (Colotta et al. 2009, Grivennikov et al. 2010). The endocrine and immune systems are complexly interconnected, and THs affect immune cells, modulating their responses (De Vito et al. 2011).

THS seem to enhance the antiviral action of interferon-γ via the MAPK pathway (Lin et al. 1996). Moreover, T3 activates PI3K/AKT signaling, thus activating myeloid cell leukemia-I (MCL1) (Pietrzak & Pazuniowska-Kuznicka 2008) and the HIF1A gene (Lin et al. 2009), which are critical molecules that elicit the immune response.

*In vitro* models have shown that T3 promotes tumor growth through the modulation of soluble factors released by surrounding microglial cells (Perrotta et al. 2015). In contrast, the T3–TRβ complex influences the antitumor responses of dendritic cells (DCs), the main antigen-presenting cells during tumor growth when activated by T cells (Alamino et al. 2015). This TH effect seems to depend on AKT activation (Mascarenhot et al. 2010), while AKT
phosphorylation enhances DC survival (Park et al. 2006). In addition to the complex effects of THs on T lymphoma cell proliferation and death, Sterle’s group has investigated thyroid status in the tumor microenvironment (Sterle et al. 2016). They found that THs have a substantial effect on the distribution of different immune cell populations and on lymphocyte infiltration, particularly on the prevalence of cytotoxic T cells. Together, these results highlight the importance of THs in modulating the immune response and related signaling in the tumor milieu through different pathways.

Cancer stem cells (CSCs)

CSCs may be involved in tumor initiation and may drive tumor progression. They carry oncogenic and tumor suppressor mutations that genetically define the disease. Both T₃ and T₄ increase the migration of MSCs toward tumor signals and increase the invasion of MSCs into tumor cell spheroids, thus impacting crucial steps of tumor stroma formation (Schmoehl et al. 2015). In a model of HCC CSCs, T₃ was a potent promoter of CSC self-renewal. TH signaling in HCC occurs through the nuclear receptor TRα with the cooperation of NF-κB, inducing the expression of stem cell genes, such as CD44, BMI1, NOTCH1 and HIF1A, thus enhancing the self-renewal of HCC CSCs (Wang et al. 2016). However, evidence of impact of TH on CSCs remains scarce.

Conclusion and future directions

In conclusion, an extensive set of data has indicated that the status of THs plays a significant role in the carcinogenesis process. Changes in TH levels seem to occur due to a disruption in TR and/or deiodinase expression and via nongenomic signaling pathways that broadly contribute to the acquisition of steps necessary for cancer development. TH status alterations are known to contribute to cancer development and/or progression via direct effects on virtually all the hallmarks of cancer. Therefore, adjuvant therapies targeting TH actions might be considered alternative treatments for cancer cell proliferation, metastasis and angiogenesis.

The genomic and nongenomic actions of THs overlap in the regulation of pro- and anti-tumoral cascades that lead to cancer growth. THs have a wide effect on tumoral progression, contributing to the acquisition of all hallmarks of cancer by predisposed cells. Moreover, intracellular TH changes due to a disruption in deiodinase status seem to be critical for modulating cell proliferation and differentiation. Accordingly, experimental and observational studies indicate TH status imbalance as a risk factor for several neoplasias. Furthermore, clinical trials have demonstrated that induced hypothyroidism leads to extended survival in different types of cancer (Hercbergs et al. 2003, 2015). Targeting cancer pathways to control tumor dissemination has been studied through integrin αVβ3 blockade, in an effort to inhibit angiogenesis. Pharmacologically targeting the membrane receptor with tetrac and other derivatives inhibits the trophic effects of the hormone in some cancer cells (Rebbaa et al. 2008, Yalcin et al. 2010b). Moreover, targeting the SHH pathway in BCC inhibited proliferation in clinical settings (Sekulic et al. 2012, Tang et al. 2012), although the direct effect on D3 activity was not analyzed. Theoretically, the pharmacological modulation of intracellular TH levels in a cell-specific manner could contribute to cancer treatments. In the same way, blocking pathways abnormally activated by THs, without interfering with the systemic balance of the TH metabolism, could lead to proapoptotic and anti-proliferative actions to control tumor growth or enhance the effectiveness of existing chemotherapeutic cancer drugs.

Declaration of interest

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

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