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Review

Thyroid hormones and their membrane receptors as therapeutic targets for T cell lymphomas

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ABSTRACT

Thyroid hormones (THs) are important regulators of metabolism, differentiation and cell proliferation. They can modify the physiology of human and murine T cell lymphomas (TCL). These effects involve genomic mechanisms, mediated by specific nuclear receptors (TR), as well as nongenomic mechanisms, that lead to the activation of different signaling pathways through the activation of a membrane receptor, the integrin αvβ3. Therefore, THs are able to induce the survival and growth of TCL. Specifically, the signaling induced by THs through the integrin αvβ3 activates proliferative and angiogenic programs, mediated by the regulation of the vascular endothelial growth factor (VEGF). The genomic or pharmacologic inhibition of integrin αvβ3 reduces the production of VEGF and induces cell death both *in vitro* and in xenograft models of human TCL.

Here we review the mechanisms involved in the modulation of the physiology of TCL induced by THs, the analysis of the interaction between genomic and nongenomic actions of THs and their contribution to T cell lymphomagenesis. These actions of THs suggest a novel mechanism for the endocrine modulation of the physiopathology of TCL and they provide a potential molecular target for its treatment.

Contents

1. Introduction

Thyroid hormones (THs), triiodothyronine (T3) and thyroxine (T4) modulate several physiologic processes and are critical for the growth, development, differentiation and the maintenance of metabolism and homeostasis [1]. The effects of THs are mainly mediated by classical signaling mechanisms initiated by T3 bind to their nuclear receptors (TR). These receptors interact with

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specific responding elements (TREs) within the promoters of target genes, thus regulating their transcription [2,3]. Two different genes encode these receptors: the *THRA,* that is located in the chromosome 17, and the *THRB* located in the chromosome 3, codifying for the TRα and TRβ proteins, respectively [4]. Different expression patterns of these isoforms have been found during the embryonic development or in adult tissues [1]. The TRα1 is mainly expressed in brain, heart and skeletal muscle, the TRβ2 is mostly expressed in brain, retina and inner ear, while TRβ3 is expressed in kidney, liver and lung [4]. There are also other truncated isoforms which are not active. Mutations of TRs have been detected in several cancers, such as erythroleukemia and liver, kidney and thyroid cancers [5,6].

THs actions on the cell physiology are also exerted through non-classical mechanisms, originally called nongenomic, as they do not implicate the direct transcription of genes by TRs. These mechanisms are quick and involve the activation of intracellular signaling cascades which finally lead to the activation of transcription factors, thus indirectly regulating gene transcription [3,7]. Many of these non-classical mechanisms have been demonstrated to be mediated by a plasmatic membrane receptor (mTR), although they can also begin at receptors in the mitochondria or cytoplasm [8]. Several studies have identified the integrin αvβ3 as the mTR [9] in different tissues, such as blood vessels and heart [7]. This integrin is the receptor for vitronectin, and is a member of the superfamily of glycoproteins of adhesion molecules that mediate the binding of cells to the extracellular matrix through the recognition of the conserved sequence RGD (Arginine– Glycine–Aspartate) of many plasmatic and matrix proteins. An interesting data is that this integrin is mainly expressed in cancer cells, proliferating endothelial and vascular smooth muscle cells and osteoclasts [10]. The tumor growth, its invasiveness and metastatic dissemination are highly associated with angiogenesis. Several evidences demonstrate that the THs stimulate the production of angiogenic factors in the T lymphoma cells through their interaction with the integrin αvβ3 [11]. Therefore, the presence of integrin αvβ3 in the vascular endothelium and in the tumor cells could explain the proangiogenic and proliferative effects of THs on some cancer cells, including gliomas [4].

Studies performed in several human cancer cell lines, such as breast adenocarcinoma [12], papillary and follicular thyroid carcinoma [13], glioma [14] and lung carcinoma [15], showed that the treatment with physiological concentrations of T3 and T4 induces the activation of intracellular signaling pathways that involve the extracellular signal-regulated kinases (ERK), leading to cell proliferation. These effects were blocked when the cells were pre-treated with the RGD peptide. Also an ERK-independent, PI3 K dependent mitogenic nongenomic effect of THs was demonstrated in pancreatic and ovarian cancer cell lines [16]. Therefore, THs bind to the integrin αvβ3 within the plasmatic membrane and initiate nongenomic actions that activate intracellular signaling cascades leading to the proliferation of tumor cells.

We here review the actions that THs exert upon normal T lymphocytes and T lymphoma cells, as well as their impact in T lymphomagensis, with special focus in the potential targeting of the mTR for lymphoma treatment.

2. Thyroid hormone receptors and actions in T lymphocytes

All the cells of the immune system have receptor for THs indicating their important role in the physiology of the immune system. As an example, the existence of TRs in normal human lymphocytes [17] and in murine L1210 leukemia cells [18] was demonstrated. Also, the presence of TRβ1 mRNA in human lymphocytes at similar levels than those found in normal thyroid tissues, was described [19]. We found the presence of TRα1 in both murine [20] and human [21] normal and tumor T cells. This expression indicates that there is an important interaction between the thyroid axis and immune system. The existence of this relationship is strengthened by the alterations frequently observed in immunity during the physiological or pathological fluctuations of TH circulating levels [22–24]. Experimental hypothyroidism in rodents, induced by thyroidectomy or by anti-thyroid agent administration, lead to a decreased activity of the thymus, and to the involution of the spleen and lymph nodes, effects that were reversed by the treatment with THs [22,25]. According to these findings, the depression of humoral and cell-mediated immune responses was also observed [26–31]. The immunological disorders occurring during hypothyroidism contribute to the severity of the disease in mice infected with the respiratory syncytial virus [32]. In humans, hypothyroidism also leads to immunosuppression with clinical impact in different disease conditions. Schoenfeld et al. [33] described the suppression of cell mediated immunity in severe hypothyroidism, as well as restoration of lymphocyte function during the gradual return to the euthyroid state. A decrease in the number of circulating leukocytes, mononuclear cells and lymphocytes was described in hypothyroid patients [34]. In accordance, children with congenital hypothyroidism display a major deficiency of serum IgA and IgM levels [35]. Hypothyroidism may also aggravate the outcome of serious viral infections and sepsis [36–38].

Despite some controversial results, most studies demonstrate that hyperthyroid experimental conditions up regulate immune responses. An increase in the size and cellularity of the spleen, plasma cell differentiation, primary antibody responses, and T or B lymphocyte activation was observed in animals with high levels of circulating THs [22,27,29,39,40].

Immune competence declines with age, and this is generally associated with increased susceptibility to infections and malignancies [41]. Also, a relation between aging and altered pituitary-thyroid axis with high thyrotropin levels was shown [42]. A study in healthy elderly subject demonstrated that serum THs levels were positively correlated with several immune markers such as, markers of inflammation, proportion of NKT cells, IL-6 expression in activated monocytes, percentage of memory T lymphocytes, and IL-2 receptor density in T cells [43]. In contrast, the concentration of THs was inversely associated with early lymphocyte apoptosis and the relationship between naïve T cells and cytotoxic T lymphocytes [43]. Similar findings indicating that THs would be involved in reduced immunity due to aging was described in aged mice, in which immune function was restored by administration of T4 [31]. These results highlight the relationship between thyroid and immune function in healthy elderly individuals and the importance of their role under physiological conditions.

Despite the several evidences showing the influence of thyroid status on immune responses and inflammation [24,44], only few studies have reported the direct effects of THs on cells of the immune system and the participation of nongenomic mechanisms in this regulation [45]. In this way, integrin αvβ3 expressions was demonstrated in THP-1 human leukemic monocyte cells, where THs were shown to stimulate the production of reactive oxygen species (ROS) and cell migration, effects that were blocked by the RGD peptide and that involved ERK1/2 and PI3 K/Akt pathways [45]. THs were also shown to increase the production of ROS on human polymorphonuclear leukocytes, *via* a pertussis toxin-sensitive nongenomic mechanism that involves PKC and calcium intracellular pathways [46]. Also, both T3 and T4 enhance bactericidal activity of murine macrophages infected with *Neisseria meningitides* by nongenomic pathways involving the PI3 K and ERK1/2 kinases and initiated *via* the integrin αvβ3 [47].

In addition, T3 was shown to induce the maturation and activation of dendritic cells, through the activation of a cytoplasmic TRß1 receptor leading to the PI3K-independent phosphorylation

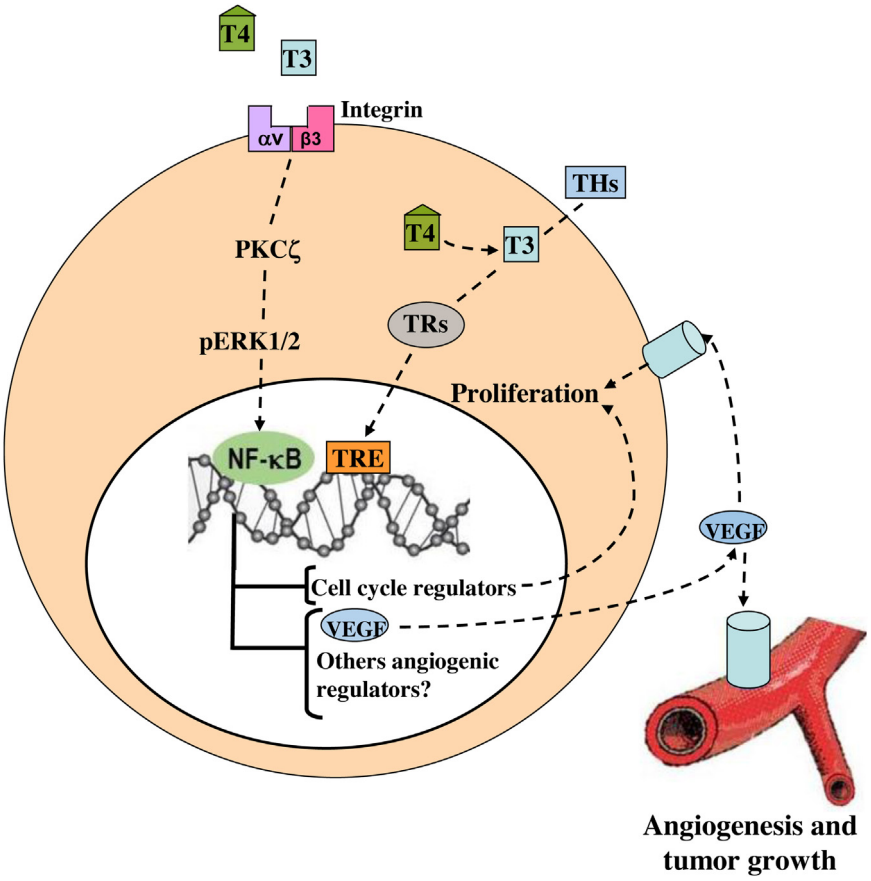

Fig. 1. Genomics and nongenomics actions of THs on TCL.
THs induce signaling pathways lead to the proliferation and survival of TCL through interaction with their nuclear receptors or the integrin αvβ3. Nongenomics pathways involve rapid activation of PKCζ, the ERK1/2 phosphorylation and NF-κB translocation to the nucleus. The genomic and nongenomic signals converge in the transcription of specifics genes required for cell proliferation, survival and angiogenesis, such as cell cycle regulators, VEGF, and probably other angiogenic regulators.

of Akt [48,49]. On cells from the adaptive immune response, we showed that normal T lymphocytes, displayed very low levels of the mTR, the integrin αvβ3 [21], and that THs were not able to exert the rapid activation of the intracellular signals involved in T cell proliferation [50]. Despite this, and as observed in other tumor cells, the mTR was found overexpressed in both murine [20] and human [21] T cell lymphomas (TCL), leading to the possibility of the participation of the integrin αvβ3 in T cell lymphomagenesis.

3. Direct action of THs on TCL lines. Genomic and nongenomic mechanisms

T cell lymphomas are a heterogeneous group of aggressive lymphoproliferative disorders of considerable clinical, morphologic, immunophenotypic and genetic variation, accounting for approximately the 10–15% of the total lymphoid malignancies [51,52]. With an approximate annual incidence of 1.77 per 100,000 population, its frequency varies geographically and its incidence increases 1–2% per year [53]. They usually affect adults and are more common in men than in women. The average age of diagnosis is 61 years, ranging from 17 to 90 years [53]. These lymphomas are a result of the exacerbated proliferation of mature post-thymic lymphocytes. Natural killer (NK) cell neoplasms are also included in this group. The last World Health Organization classification of hematopoietic malignancies has divided this group of disorders into those with predominantly leukemic (disseminated), nodal, extra-nodal or cutaneous presentation [51,54].

The most common types are those of nodal presentation, that include the peripheral T cell lymphoma not otherwise specified (PTCL-NOS), the anaplastic large cell lymphoma and the angioimmunoblastic TCL [54]. Although rare, cutaneous TCL deserved to be mentioned, as the skin is the second location in frequency of extranodal primary lymphomas [55]. The TCL can be exposed to a complex environment, formed by many growth factors, cytokines and hormones that are synthesized by neighbor or distal cells [56]. In our laboratory, we have demonstrated in the last years that one of the factors that regulate the biology of TCL are THs [20,21,50,57,58].

Studies performed with free THs or agarose-coupled THs (TH-AG, which are incapable of crossing the cell membrane) have demonstrated that the genomic and nongenomic actions of THs contribute to the proliferation of human and murine TCL lines. Additionally, these studies indicated the participation of a mTR in the rapid effects of THs in these cells [20,21,50]. The nongenomic signaling triggered by THs through the mTR in murine TLC involves the rapid translocation of the ζ isoform of protein kinase C (PKCζ) to the cell membrane, essential for the proliferation and survival of TCL [50,57], the nongenomic phosphorylation of ERK 1/2 kinases and the activation of the transcription factor NF-κB [20,57].

We have recently demonstrated that the integrin αvβ3 is the mTR in human TCL lines. Thus, in a panel of 9 TCL lines of the different subtypes of human TCL, we have demonstrated the proliferative

action of THs. This effect was blocked by the RGD peptide and was not observed when the expression of the integrin αvβ3 was inhibited using small interfering RNA (siRNA) for the integrin αv or β3 [21]. Additionally, we have evidenced in immature and mature TCL that these effects were accompanied by the regulation of the cell cycle. According to this, in breast cancer cells the tetraiodothyroacetic acid (TETRAC), that inhibits the effects of THs on the mTR, led to an increase in the expression levels of proapoptotic genes, which demonstrates that THs are necessary for cell survival [7,59].

Using RNA sequencing techniques and bioinformatics, we identified in TCL the transcriptional programs activated by THs through their membrane receptor. Among these genes, we found some related to protein translation, lymphocyte proliferation/differentiation, DNA replication and angiogenesis. Interestingly, we verified an increment in the mRNA levels of the vascular endothelial growth factors (VEGF), VEGFA and VEGFB. Besides being mediated *via* the mTR activation, this effect was dependent on the activation of the transcription factor NF-κB, as no increase of VEGF levels was detected in cells pre-treated with a NF-κB inhibitor [21]. This association between integrin αvβ3 and VEGF was also evidenced in PTCL patient samples, as a positive correlation between the mRNA levels of the integrins αv or β3 and the VEGFA or VEGFB gene. We also demonstrate that THs induce the production of VEGF functional angiogenic factors in TCL, functioning in a paracrine or autocrine manner. In fact, THs were able to increase the migration of human endothelial cells, as well as to induce tumor cell proliferation mediated by THs. Bevacizumab, a blocking antibody against VEGF, abrogated both effects. Also, the proliferative action of THs on TCL was impaired by Axitinib, a pharmacologic inhibitor of the VEGF receptor [21]. These results are summarized in Fig. 1.

The ability of THs to induce the expression of VEGF receptors and their ligands, the fibroblast growth factor (FGF), the platelet-derived growth factor (PDGF) and the epidermal growth factor (EGF), as well as some angiogenic chemokines, has also been demonstrated in other tumor cell types [60]. THs can also increase the activity of bradykinin and angiotensin II, which contribute to vascularization [60]. In human breast cancer cells treated with TETRAC the proliferative and proangiogenic action of THs was blocked through the inhibition of the angiogenic effects of VEGF and FGF [7,59].

In summary, both proliferation programs, initiated by THs through their nuclear and membrane receptors, favor the survival and proliferation of TCL, contributing to their malignant phenotype.

4. Possible use of the mTR as a therapeutic target for the treatment of TCL

Based on the above, it could be expected that the circulating levels of THs, would influence the tumor microenvironment in patients with TCL and determine their development and/or progression. Therefore, decrease of circulating levels of THs, leading the hypothyroid state, would be an attractive alternative adjuvant therapy for impairing cancer cell growth and angiogenesis. However, there are no concluding evidences about the effect of thyroid status on tumor processes. The greatest controversial results come out from the analysis of the relation between thyroid disease and cancer risk or incidence in human epidemiological studies. Experimental evidences also show that the thyroid status may influence cell components of the anti-tumor immunity, which would explain in part some controversial results also found at this level on the effect exerted by hypothyroidism and hyperthyroidism in tumor growth *in vivo*. A brief summary of these findings is highlighted below.

4.1. Thyroid status and tumor progression

Several epidemiological studies have evaluated if cancer is associated with alteration in thyroid status. Both hyperthyroidism and hypothyroidism were shown to influence cancer development. However the final consequence of this influence depends on the sampled population and the tumor type. Excellent reviews have been published in the last years on this respect [61–65]. Some examples of these studies are shown in Table 1 for hyperthyroid conditions and Table 2 for hypothyroidism. Thus, hyperthyroidism has been described as a risk factor for the development of pancreatic [66] and oesophageal [67]. Also, Hellevik et al., [68], found a higher risk of lung and prostate cancer in patients with hyperthyroid function. The risk was elevated both in subclinical hyperthyroid patients, as well in those with overt hyperthyroidism, being the risk stronger in this last patients [68]. Biochemical alterations in thyrotropin and thyroid hormone levels could be related to a non-thyroidal disease status caused by cancer, so the association would be caused by cancer leading to low thyrotropin levels instead of a hyperthyroid function. To rule out this possibility, the authors started follow-up 2 years after laboratory measurements and with this approach, the association of hyperthyroid function with cancer risk was strengthened [68].

Also, for prostate [71] and breast [70] cancer an association between high levels of T3 and cancer development has been shown. Furthermore, for prostate cancer an association between T3 levels and a higher risk of disease recurrence in those with advance disease (stages T2c and T3) was found [69]. Despite hyperthyroidism was also shown to be a risk factor for ovarian cancer [72], no significant association of self-reported history of hypothyroidism and hyperthyroidism with either endometrial or ovarian cancer risk was found in a large-cohort study performed by Kang et al. [73].

Respect to digestive system cancers, TH signaling has been associated to the prevention of disease [63], and accordingly it was demonstrated that long-term thyroid hormone replacement treatment in hypothyroid patients was related to a significantly reduced relative risk of colorectal cancer [74,75]. Also, increased risk of hepatocellular carcinoma in hypothyroid subjects was also demonstrated by 2 case-control studies [76,77]

However contradictory results were found in the relation between hypothyroidism and the development of other cancer types. Thus, Cristofanilli et al. [78] have described a lower incidence of breast carcinoma in patients with hypothyroidism and Backwinkel and Jackson [79] found a 5 month longer survival in hypothyroid respect to euthyroid breast cancer patients. However, in this last study a significantly lower survival time was found associated to hypothyroidism in the presence of metastasis. Also, hypothyroidism was shown to be a risk factor for the development of breast cancer [80] and a negative correlation between proliferation index and free T3 levels were found in HER2 positive breast cancer patients [81]. Contributing to this controversy, a recent meta-analysis showed no association with increased risk for breast cancer and THs replacement therapy does not reduce breast cancer prevalence [82].

Hypothyroidism was also shown to reduce the risk for prostate [83] and, to improve the survival of head and neck cancer patients [84]. Hercbergs et al. [85] have shown the spontaneous remission of a nonsmall cell lung cancer in a patient that survives a mixedema coma, and prolonged recurrence-free survival and 3-fold increased survival rates have been reported in association with chemical- induced hypothyroidism in two clinical trials for glioblastoma [86,87].

Experimental evidences using tumor models in hyperthyroid or hypothyroid animals were not able to clarify the role of thyroid status on tumor establishment and progression. Most studies demonstrate that tumor-bearing hypothyroid animals displayed

Table 1
Some studies on hyperthyroidism relation with different types of cancers.

Hyperthyroidism				
Cancer type	Study type	No. of cases	Clinical relevance	Refs.
Pancreatic	Case-control	532 Pts, 1701C	Increased risk	[66]
Oesophageal	Prospective	102 Pts, 160C	Significantly higher incidence in Pts than in C	[67]
Colorectal	Nested case-control	20990 Pts, 82054C	Modestly elevated risk	[75]
Lung (LC)	Prospective	192 LC Pts	Increased risk	[68]
Prostate (PC)		326 PC Pts		
Prostate	Comparative	68 Pts	Association with high risk of disease recurrence	[69]
		161 Pts, 27C	Mean serum T3 in Pts increased significantly vs C	[71]
Ovarian	Case-control	767 Pts, 1367C	Increased risk	[72]
Endometrial (EC)	Prospective	1314 EC Pts,	No association	[73]
Ovarian (OC)		1150 OC Pts		
Breast	Prospective cohort	2185 Pts	Association with risk of cancer development in peri/postmenopausal women	[70]

Pts: Cancer patients; C: Controls.

Table 2
Examples of hypothyroidism impact on different types of cancers.

Hypothyroidism				
Cancer type	Study type	No. of cases	Clinical relevance	Refs.
Colorectal	Nested case-control	20,990 Pts, 82054 C	Modestly elevated risk in untreated Pts Decreased risk with long-term hormone replacement therapy	[75]
Hepatocellular	Case control	420 Pts, 1104 C	Increased risk in women	[77]
carcinoma	Case-control[a]	54 Pts, 57 HCV,49 ALD	Increased risk in Pts with unknown etiology	[76]
Lung	Case report	1 Pts	Spontaneous remission following myxedema coma	[85]
Prostate	Randomized controlled trial	402 Pts, 800 C	Reduce Risk	[83]
Endometrial (EC)	Prospective	1314 EC Pts,	No association	[73]
Ovarian (OC)		1150 OC Pts		
Breast	Comparative	280 Pts	Pts 5 months more survival than C	[79]
			Significantly lower survival time in the presence of metastasis	
	Case control	1136 Pts, 1088 C	Reduce risk	[78]
Head and neck	Retrospective	155 Pts	Improved survival and increased recurrence-free survival	[84]
Glioblastoma	Clinical trial[b]	22 Pts	3-fold increase in survival duration	[86]
multiforme	Case report	1 Pts	Extended remission period and prolonged overall survival	[87]

Pts: Cancer patients; C: Controls.
[a] Cross-sectional associations between underlying liver disease in hepatocellular carcinoma (HCC) and hypothyroidism. HCC Pts seen with no underlying etiology for chronic liver disease; HCV: HCC patients with Hepatitis C virus infection; ALD: HCC patients with alcoholic liver disease.
[b] Chemoterapy plus chemical induce hypothyroidism with propylthiouracil.

reduced tumor growth and prolonged survival than euthyroid counterparts [62]. Thus, analysis of MNU-induced mammary carcinogenesis in rats with different thyroid status showed that the hyperthyroid group had a statistically higher tumor burden than euthyroid animals after 38 weeks post MNU injection, while hypothyroid rats had no tumors of mammary tissue origin at the same time [88]. Similarly, T4-induction of a hyperthyroid state increased sarcoma tumor growth and dissemination in syngeneic mice [89]. Otherwise, hypothyroidism lead to the inhibition of local growth rate of Morris Hepatoma implanted in rats, while decreasing tumor spreading and prolonging rat survival [90]. However, Frau et al. [91] has recently reported that hypothyroidism induction in an experimental model of liver carcinogenesis, favors the progression of preneoplastic lesions to a malignant carcinoma. This was accompanied by a decrease in the expression of TRs and their target genes, while T3-induced hyperthyroidism leads to contrary effects and to the regression of hepatic nodules [91]. The physiological loss of TR, either by gene deletion or mutation, was already related to the development, progression and dissemination of several cancers [for review see 92]. Therefore, the possible participation of this additional factor has to be considered.

In addition, decreased tumor growth was reported for human prostate and lung adenocarcinoma xenografts in hypothyroid athymic nude mice [62,93]. Martinez-Iglesias et al. [94] showed that hypothyroidism resulted in a decreased rate of tumor growth, but an increased development and number of metastases, in murine xenograft models of human hepatocarcinoma and breast cancer. We have described similar findings on the *in vivo* growth of murine TLC in syngeneic animals with different thyroid status [58,95]. Hyperthyroid mice exhibited increased tumors along with increased expression of proliferating cell nuclear antigen and cell cycle regulators compared to hypothyroid and control tumor-bearing mice [58,95]. Also, they displayed an increased intratumoral and peritumoral vasculogenesis [58] and a lower number of tumor-infiltrating T lymphocytes with lower percentage of functional IFN-γ-producing CD8+ T cells [95]. However, hypothyroid mice showed a higher frequency of metastases than the other groups, similar to was found in breast cancer patients in which hypothyroidism was associated with significantly lower survival in the presence of metastasis [79]. In our hypothyroid animals, tumor dissemination was shown to be related to the thyroid status modulation of anti-tumor immunity, as lower number and activity of splenic NK and cytotoxic $CD8^+$ T cells were found in the spleens of hypothyroid respect to hyperthyroid tumor-bearing mice [95]. This results can be explained under the light of thyroid status influence on immunity as discussed before, and poin out that in addition to hormones, immune cells in tumor microenvironment also influence tumor destiny. Remembering that TH exert proangigenic actions on TCL cells that display increased levels of the integrin αvβ3, while normal T cells do not, inhibition of TH actions

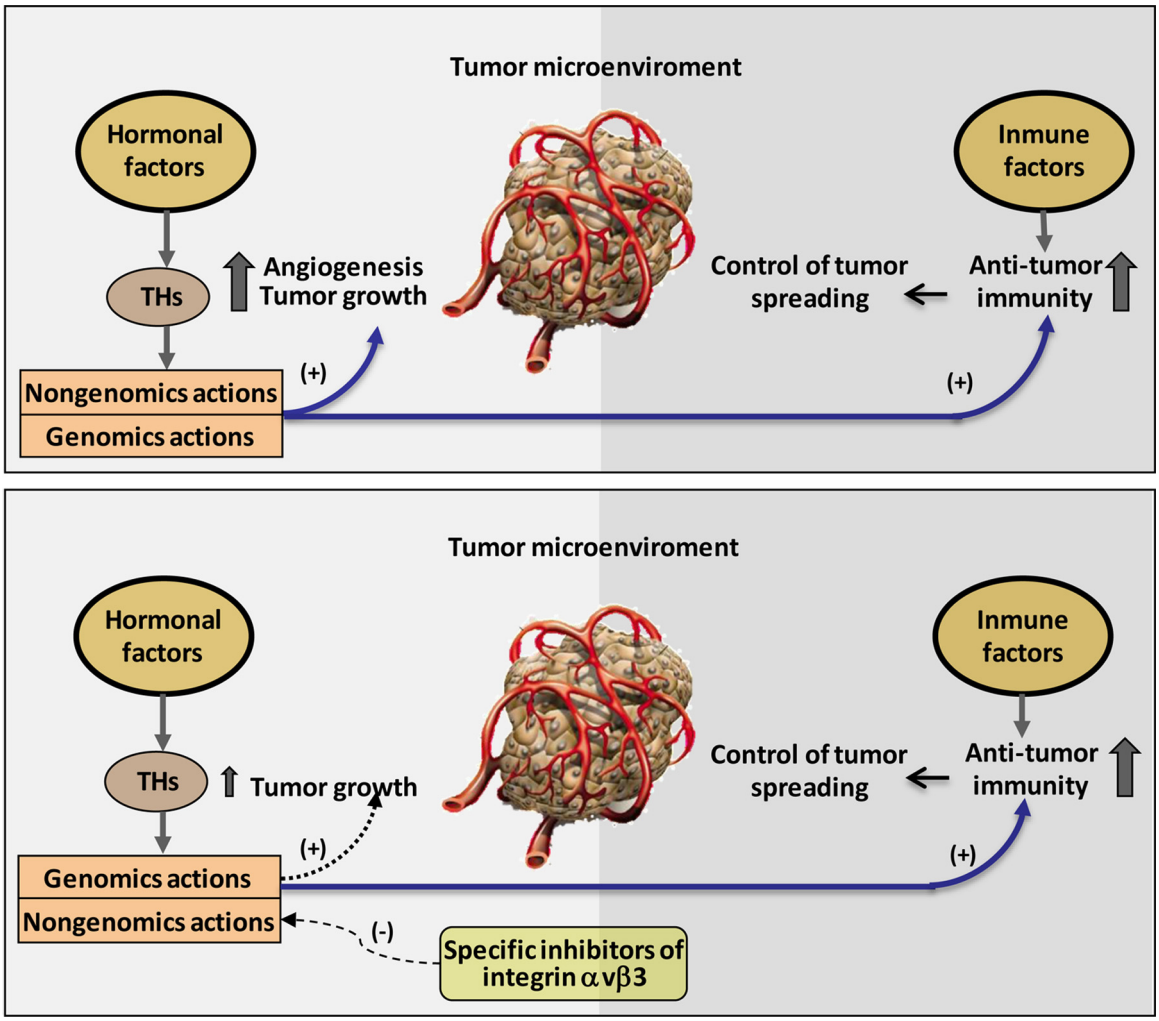

Fig. 2. Hormonal and inmune factors of the tumor microenviroment interplay to regulate T lymphomas growth and metastases dissemination.
THs induce tumor proliferation and angiogenesis through activation of nongenomic and genomic pathways. In addition, THs stimulate antitumor immunity contributing to control of tumor spreading (*upper panel*). Specific inhibitors of integrin αvβ3 block the nongenomic actions mediated by THs, which leads to a lower rate of tumor growth. Inhibition of integrin αvβ3 does not affect the antitumor response, which is modulated by the THs mainly through of the genomic pathways. Furthermore, the selective inhibition of the integrin αvβ3 could be an attractive therapeutic target for TCL patients therapy (*bottom panel*).

at this levels would be a potential adyuvant therapy against TCL progression.

4.2. Inhibition of TH actions at the integrin αvβ3 receptor for TCL treatment

It has been well accepted that anti-angiogenic therapy can be an adjuvant treatment for various types of tumor with relative success [96]. Also, we have already discussed the pro-angiogenic action of THs on several types of cancer [11]. Taking into account our results on the proliferative and proangiogenic roles of THs mediated by the mTR in TCL lines, we used preclinical models to analyze whether these pathways could be capitalized for the treatment of patients with TCL. We performed xenografts of human TCL in NOD-SCID immunodeficient mice and we evaluated the effect of the inhibition of the integrin αvβ3 on the tumor growth. The negative regulation of the integrins αv or β3 in TCL by siRNA reduced the tumor volume and decreased the expression levels of VEGF and the blood vessel area in the tumor [21]. This suggests a decrease in the angiogenic potential of tumors originated from cells that do not express mTR. Moreover, the growth of tumors in immunodeficient animals transplanted with PLCT-NOS cells or patient-derived tumors xenotransplanted in mice was significantly reduced by treatment with cilengitide [21], a selective pharmacologic inhibitor for integrin αvβ3, at present used in the clinic for the treatment of other tumors [97]. It is worth to notice that no toxic effects of cilengitide were observed in these animals. Cilengitide is at the present time undergoing phase III clinical trials in patients with glioblastoma [98] and phase II clinical trials with other types of solid tumors [99–101]. Given that integrin αvβ3 is mainly expressed in malignant cells [102], these results point out the importance of these mechanisms for the development of an effective and low toxicity treatment for patients with TCL.

In support to the role of integrin αvβ3 in cancer, an observational study on unselected terminal patients with incurable solid tumors showed that medical induction of hypothyroxinemia, with T3 or the anti-thyroid drug methimazole plus T3, extended survival in the majority of patients [103]. This was based on the fact that the integrin αvβ3 affinity for T4 is greater than that for T3 in many cell types [9], and that T4 is a more potent inducer of tumor cell proliferation than T3 [104]. Furthermore, the inhibition of T4 and T3 binding to the integrin αvβ3 by the non-cell permeable T4 analog, tetraiodothyroacetic acid (tetrac), covalently attached to a nanoparticle (Nanotetrac), abolished the angiogenic activity of THs [105]. Thus, Nanotretrac suppressed expression of EGFR, VEGF, multiple cyclins, catenin, and multiple cytokines and was shown

to be an effective chemotherapeutic agent in preclinical studies of human pancreatic cancer cell xenografts [106]. In sum, all these evidences point out that targeting the mTR would be an attractive therapeutic tool for other neoplastic diseases.

5. Concluding remarks

In a tumor, cell growth is sustained by many factors of the microenvironment that also allow their invasion and escape to evade the anti-tumor immune response. This tumor microenvironment includes hormonal factors and THs were demonstrated to be one of these factors. A well-characterized biological mechanism through which THs may regulate tumor cell division and spreading involves THs binding to the mTR, namely the integrin αvβ3. This activates various pro-carcinogenic pathways leading to cell proliferation and angiogenesis. For TCL, THs were shown to induce, both *in vitro* and *in vivo*, their proliferation. This effect is mediated by the induction of signaling pathways in which both TR and integrin αvβ3 participate. Among the signaling initiated by the integrin, the activation of NF-κB plays a crucial role in TCL growth. This mechanism also involves the modulation of cell cycle regulators and angiogenic factors, thus ultimately leading to the tumor growth and vascularization. Despite slowing tumor growth, reduction of circulating THs levels paradoxically rises TCL dissemination by affecting the distribution of immune cell types in the tumor milieu and the nature of local and systemic antitumor immune responses. Thus, the mTR, that would not affect immune cell function, become an attractive target for TCL treatment. In fact, the selective inhibition of the integrin αvβ3 in different subtypes of TCL results in the inhibition of cell proliferation, tumor growth and impaired angiogenesis (see Fig. 2). In those cases in which tumor cells displayed an mTR with higher affinity for T4 than T3, the induction of hypothyroxinemia with normal levels of T3 would be a good and cheap adjuvant alternative for cancer treatment. In cases in which both T3 and T4 modulates tumor cell physiopathology *via* the integrin αvβ3, as in TCL, then selective inhibition of the integrin, with cilengitide or potentially by nanotetrac, would contribute to impair cancer progression. Nevertheless, the confirmation in preclinical models that both compounds do not affect antitumor immunity is still pending.

Conflict of interest

The authors declare no conflicts of interest.

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References

[1] A. Oetting, P.M. Yen, New insights into thyroid hormone action, Best Pract. Res. Clin. Endocrinol. Metab. 21 (2007) 193–208, http://dx.doi.org/10.1016/j.beem.2007.04.004.
[2] M.A. Lazar, Thyroid hormone action: a binding contract, J. Clin. Invest. 112 (2003) 497–499, http://dx.doi.org/10.1172/JCI200319479.
[3] G.A. Brent, Mechanisms of thyroid hormone action, J. Clin. Invest. 122 (2012) 3035–3043, http://dx.doi.org/10.1172/JCI60047.
[4] S.Y. Cheng, J.L. Leonard, P.J. Davis, Molecular aspects of thyroid hormone actions, Endocr. Rev. 31 (2010) 139–170, http://dx.doi.org/10.1210/er.2009-0007.
[5] I.H. Chan, M.L. Privalsky, A conserved lysine in the thyroid hormone receptor-alpha1 DNA-binding domain, mutated in hepatocellular carcinoma, serves as a sensor for transcriptional regulation, Mol. Cancer Res. 8 (1) (2010) 15–23, http://dx.doi.org/10.1158/1541-7786.MCR-09-0425.
[6] M.D. Rosen, I.H. Chan, M.L. Privalsky, Mutant thyroid hormone receptors (TRs) isolated from distinct cancer types display distinct target gene specificities: a unique regulatory repertoire associated with two renal clear cell carcinomas, Mol. Endocrinol. 25 (2011) 1311–1325, http://dx.doi.org/10.1210/me.2010-0420.
[7] P.J. Davis, F.B. Davis, S.A. Mousa, M.K. Luidens, H.Y. Lin, Membrane receptor for thyroid hormone: physiologic and pharmacologic implications, Annu. Rev. Pharmacol. Toxicol. 51 (2011) 99–115, http://dx.doi.org/10.1146/annurev-pharmtox-010510-100512.
[8] P.J. Davis, F. Goglia, J.L. Leonard, Nongenomic actions of thyroid hormone, Nat. Rev. Endocrinol. 12 (2) (2016) 111–121, http://dx.doi.org/10.1038/nrendo.2015.205.
[9] J.J. Bergh, H.Y. Lin, L. Lansing, S.N. Mohamed, F.B. Davis, S. Mousa, P.J. Davis, Integrin alphaVbeta3 contains a cell surface receptor site for thyroid hormone that is linked to activation of mitogen-activated protein kinase and induction of angiogenesis, Endocrinology 146 (2005) 2864–2871, http://dx.doi.org/10.1210/en.2055-0102.
[10] E.K. Sloan, N. Pouliot, K.L. Stanley, J. Chia, J.M. Moseley, D.K. Hards, R.L. Anderson, Tumor-specific expression of alphavbeta3 integrin promotes spontaneous metastasis of breast cancer to bone, Breast Cancer Res. 8 (2006) R20, http://dx.doi.org/10.1186/bcr1398.
[11] M. Pinto, P. Soares, D. Ribatti, Thyroid hormone as a regulator of tumor induced angiogenesis, Cancer Lett. 301 (2011) 119–126, http://dx.doi.org/10.1016/j.canlet.2010.11.011.
[12] H.Y. Tang, H.Y. Lin, S. Zhang, F.B. Davis, P.J. Davis, Thyroid hormone causes mitogen-activared protein kinase-dependent phosphorylation of the nuclear estrogen receptor, Endocrinology 145 (2004) 3265–3272, http://dx.doi.org/10.1210/en. 2004-0308.
[13] H.Y. Lin, H.Y. Tang, A. Shih, T. Keating, G. Cao, P.J. Davis, F.B. Davis, Thyroid hormone is a MAPK-dependent growth factor for thyroid cancer cells and is anti-apoptotic, Steroids 72 (2) (2007) 180–187, http://dx.doi.org/10.1016/j.steroids.2006.11.014.
[14] H.Y. Lin, M. Sun, H.Y. Tang, C. Lin, M.K. Luidens, S.A. Mousa, S. Incerpi, G.L. Drusano, F.B. Davis, P.J. Davis, l-Thyroxine vs. 3,5,3′-triiodo-L-thyronine and cell proliferation: activation of mitogen-activated protein kinase and phosphatidylinositol 3-kinase, Am. J. Physiol. Cell Physiol. 296 (2009) C980–C991, http://dx.doi.org/10.1152/ajpcell.00305.2008.
[15] R. Meng, H.Y. Tang, J. Westfall, D. London, J.H. Cao, S.A. Mousa, M. Luidens, A. Hercbergs, F.B. Davis, P.J. Davis, H.Y. Lin, Crosstalk between integrin αvβ3 and estrogen receptor-α is involved in thyroid hormone-induced proliferation in human lung carcinoma cells, PLoS One 6 (2011) e27547, http://dx.doi.org/10.1371/journal.pone.0027547.
[16] G. Moriggi, C. Verga Falzacappa, C. Mangialardo, S. Michienzi, A. Stigliano, E. Brunetti, V. Toscano, S. Misiti, Thyroid hormones (T3 and T4): dual effect on human cancer cell proliferation, Anticancer Res. 31 (2011) 89–96.
[17] C. Jaffiol, L. Baldet, J. Torresani, J. Bismuth, C. Papachristou, A case of hypersensitivity to thyroid hormones with normally functioning thyroid gland and increased nuclear triiodothyronine receptors, J. Endocrinol. Invest. 13 (1990) 839–845, http://dx.doi.org/10.1007/BF03349636.
[18] P. Filipcík, J. Brtko, L. Rauová, V. Sedláková, Distribution of triiodothyronine nuclear receptors during the cell cycle in mouse leukemia cells, Folia Biol. (Praha) 38 (1992) 332–339.
[19] S. Meier-Heusler, A. Pernin, H. Liang, M.O. Goumaz, A.G. Burger, C.A. Meier, Quantitation of beta 1 triiodothyronine receptor mRNA in human tissues by competitive reverse transcription polymerase chain reaction, J. Endocrinol. Invest. 18 (1995) 767–773.
[20] M.L. Barreiro Arcos, H.A. Sterle, M.A. Paulazo, E. Valli, A.J. Klecha, B. Isse, C.G. Pellizas, R.N. Farias, G.A. Cremaschi, Cooperative nongenomic and genomic actions on thyroid hormone mediated-modulation of T cell proliferation involve up-regulation of thyroid hormone receptor and inducible nitric oxide synthase expression, J. Cell. Physiol. 226 (2011) 3208–3218, http://dx.doi.org/10.1002/jcp.22681.
[21] F. Cayrol, M.C. Díaz Flaqué, T. Fernando, S.N. Yang, H.A. Sterle, M. Bolontrade, M. Amorós, B. Isse, R.N. Farías, H. Ahn, Y.F. Tian, F. Tabbò, A. Singh, G. Inghirami, L. Cerchietti, G.A. Cremaschi, Integrin αvβ3 acting as membrane receptor for thyroid hormones mediates angiogenesis in malignant T cells, Blood 125 (2015) 841–851, http://dx.doi.org/10.1182/blood-2014-07-587337.
[22] N. Fabris, E. Mocchegiani, M. Provinciali, Pituitary-thyroid axis and immune system: a reciprocal neuroendocrine-immune interaction, Horm. Res. 43 (1995) 29–38.
[23] A.M. Genaro, A.J. Klecha, L.R. Frick, M.L. Barreiro Arcos, G.A. Cremaschi, Thyroid hormone modulation of immunity. Its participation in chronic stress-induced immune alterations, Curr. Immunol. Rev. 6 (2010) 339–347, http://dx.doi.org/10.2174/1573395511006040339.
[24] P. De Vito, S. Incerpi, J. Pedersen, P. Luly, F. Davis, P. Davis, Thyroid hormones as modulators of immune activities at the cellular level, Thyroid 21 (2011) 879–890, http://dx.doi.org/10.1089/thy.2010.0429.
[25] D. Roksandić, A. Radovanović, J. Danilović Luković, D.M. Marković Kovačević Filipović, M. Čolić, Stereological and immunohistochemical study of the spleen in hypothyroid juvenile rats, Acta Veterinaria 65 (2015) 246–259, http://dx.doi.org/10.1515/acve-2015-0021.
[26] S. Chatterjee, A.S. Chandel, Immunomodulatory role of thyroid hormones: in vivo effect of thyroid hormones on the blastogenic response of lymphoid tissues, Acta Endocrinol. (Copenh.) 103 (1) (1983) 95–100, http://dx.doi.org/10.1530/acta.0.1030095.

[27] A.J. Klecha, A.M. Genaro, A.E. Lysionek, R.A. Caro, G.A. Coluccia, G.A. Cremaschi, Experimental evidence pointing to the bidirectional interaction between the immune system and the thyroid axis, Int. J. Immunopharmacol. 22 (2000) 491–500, http://dx.doi.org/10.1016/S0192-0561(00)00012-6.
[28] A.J. Klecha, M.L. Barreiro Arcos, A.M. Genaro, G. Gorelik, D.M. Silberman, R. Caro, G.A. Cremaschi, Different mitogen-mediated beta-adrenergic receptor modulation in murine T lymphocytes depending on the thyroid status, Neuroimmunomodulation 12 (2005) 92–99, http://dx.doi.org/10.1159/000083581.
[29] A.J. Klecha, A.M. Genaro, G. Gorelik, M.L. Barreiro Arcos, M.D. Silberman, M. Schuman, S.I. Garcia, C. Pirola, G.A. Cremaschi, Integrative study of hypothalamus-pituitary-thyroid-immune system interaction: thyroid hormone mediated modulation of lymphocyte activity through the protein kinase C signaling pathway, J. Endocrinol. 189 (2006) 45–55, http://dx.doi.org/10.1677/joe.1.06137.
[30] G.D. Bendyug, Y.A. Grinevich, N.N. Khranovskaya, F.V. Fil'chakov, L.G. Yugrinova, A.G. Kad'kalenko, The state of the immune system in thyroidectomized rats, Bull. Exp. Biol. Med. 135 (2003) 154–157.
[31] K.A. El-Shaikh, M.S. Gabry, G.A. Othman, Recovery of age-dependent immunological deterioration in old mice by thyroxine treatment, J. Anim. Physiol. Anim. Nutr. (Berl.) 90 (2006) 244–254, http://dx.doi.org/10.1111/j.1439-0396.2005.00602.x.
[32] W. Watanabe, T. Shimizu, A. Hino, M. Kurokawa, A new assay system for evaluation of developmental immunotoxicity of chemical compounds using respiratory syncytial virus infection to offspring mice, Environ. Toxicol. Pharmacol. 25 (2008) 69–74, http://dx.doi.org/10.1016/j.etap.2007.09.003.
[33] P.S. Schoenfeld, J.W. Myers, L. Myers, J.C. La Rocque, Suppression of cell-mediated immunity in hypothyroidism, South Med. J. 88 (2005) 347–349.
[34] A. Jafarzadeh, M. Poorgholami, N. Izadi, M. Nemati, M. Rezayati, Immunological and hematological changes in patients with hyperthyroidism or hypothyroidism, Clin. Invest. Med. 33 (2010) E271–E279.
[35] S. Stagi, C. Azzari, G. Bindi, F. Galluzzi, S. Nanni, R. Salti, A. Vierucci, Undetectable serum IgA and low IgM concentration in children with congenital hypothyroidism, Clin. Immunol. 116 (2005) 94–98, http://dx.doi.org/10.1016/j.clim.2005.03.003.
[36] J. Collazos, S. Ibarra, J.A. Mayo, Thyroid hormones in HIV-infected patients in the highly active antiretroviral therapy era: evidence of an interrelation between the thyroid axis and the immune system, AIDS 17 (2003) 763–765.
[37] H.C. Ho, A.D. Chapital, M. Yu, Hypothyroidism and adrenal insufficiency in sepsis and hemorrhagic shock, Arch. Surg. 139 (2004) 1199–1203, http://dx.doi.org/10.1001/archsurg.139.11.1199.
[38] S. Afhami, V. Haghpanah, R. Heshmat, M. Rasoulinejad, M. Izadi, A. Lashkari, S.M. Tavangar, M. Hajiabdolbaghi, M. Mohraz, B. Larijani, Assessment of the factors involving in the development of hypothyroidism in HIV-infected patients: a case-control study, Infection 35 (2007) 334–338, http://dx.doi.org/10.1007/s15010-007-6163-3.
[39] D.N. Nandakumar, B.C. Koner, R. Vinayagamoorthi, N. Nanda, V.S. Negi, K. Goswami, Z. Bobby, A. Hamide, Activation of NF-κB in lymphocytes and increase in serum immunoglobulin in hyperthyroidism: possible role of oxidative stress, Immunobiology 213 (2008) 409–415, http://dx.doi.org/10.1016/j.imbio.2007.10.005.
[40] F.F. Bloise, F.L. Oliveira, A.F. Nobrega, R. Vasconcellos, A. Cordeiro, L.S. Paiva, D.D. Taub, R. Borojevic, C.C. Pazos-Moura, V. Mello-Coelho, High levels of circulating triiodothyronine induce plasma cell differentiation, J. Endocrinol. 220 (2014) 305–317, http://dx.doi.org/10.1530/JOE-13-0315.
[41] J.J. Goronzy, F. Fang, M.M. Cavanagh, Q. Qi, C.M. Weyand, Naive T cell maintenance and function in human aging, J. Immunol. 194 (2015) 4073–4080, http://dx.doi.org/10.4049/jimmunol.1500046.
[42] B.B. Yeap, Hormones and health outcomes in aging men, Exp. Gerontol. 48 (2013) 677–681, http://dx.doi.org/10.1016/j.exger.2012.07.012.
[43] C.F. Hodkinson, E.E. Simpson, J.H. Beattie, J.M. O'Connor, D.J. Campbell, J.J. Strain, J.M. Wallace, Preliminary evidence of immune function modulation by thyroid hormones in healthy men and women aged 55–70 years, J. Endocrinol. 202 (2009) 55–63, http://dx.doi.org/10.1677/JOE-08-0488.
[44] M.L. Barreiro Arcos, A.J. Klecha, A.M. Genaro, G.A. Cremaschi, Immune system modulation by thyroid axis includes direct genomic and nongenomic actions of thyroid hormones on immune cells, Immunol. Endocr. Metab. Agents Med. Chem. 10 (2010) 1–10, http://dx.doi.org/10.2174/187152210791171313.
[45] P. De Vito, V. Balducci, S. Leone, Z. Percario, G. Mangino, P.J. Davis, F.B. Davis, E. Affabris, P. Luly, J.Z. Pedersen, S. Incerpi, Nongenomic effects of thyroid hormones on the immune system cells: new targets, old players, Steroids 77 (2012) 988–995, http://dx.doi.org/10.1016/j.steroids.2012.02.018.
[46] E. Mezosi, J. Szabo, E.V. Nagy, A. Borbely, E. Varga, G. Paragh, Z. Varga, Nongenomic effect of thyroid hormone on free-radical production in human polymorphonuclear leukocytes, J. Endocrinol. 185 (2005) 121–129, http://dx.doi.org/10.1677/joe.1.05968.
[47] Y. Chen, M. Sjölinder, X. Wang, G. Altenbacher, M. Hagner, P. Berglund, Y. Gao, T. Lu, A.B. Jonsson, H. Sjölinder, Thyroid hormone enhances nitric oxide-mediated bacterial clearance and promotes survival after meningococcal infection, PLoS One 7 (2012) e41445, http://dx.doi.org/10.1371/journal.pone.0041445.
[48] I. Mascanfroni, M.M. Montesinos, S. Susperreguy, L. Cervi, J.M. Ilarregui, V.D. Ramseyer, A.M. Masini-Repiso, H.M. Targovnik, G.A. Rabinovich, C.G. Pellizas, Control of dendritic cell maturation and function by triiodothyronine, FASEB J. 22 (2008) 1032–1042, http://dx.doi.org/10.1096/fj.07-8652com.
[49] I.D. Mascanfroni, M.M. Montesinos, V.A. Alamino, S. Susperreguy, J.P. Nicola, J.M. Ilarregui, A.M. Masini-Repiso, G.A. Rabinovich, C.G. Pellizas, Nuclear factor (NF)-kappaB-dependent thyroid hormone receptor beta1 expression controls dendritic cell function via Akt signaling, J. Biol. Chem. 285 (2010) 9569–9582, http://dx.doi.org/10.1074/jbc.M109.071241.
[50] M.L. Barreiro Arcos, G. Gorelik, A. Klecha, A.M. Genaro, G.A. Cremaschi, Thyroid hormones increase inducible nitric oxide synthase gene expression downstream from PKC-zeta in murine tumor T lymphocytes, Am. J. Physiol. Cell Physiol. 291 (2) (2006) C327–C336, http://dx.doi.org/10.1152/ajpcell.00316.2005.
[51] E.S. Jaffe, N.L. Harris, H. Stein, P.G. Isaacson, Classification of lymphoid neoplasms: the microscope as a tool for disease discovery, Blood 112 (2008) 4384–4399, http://dx.doi.org/10.1182/blood-2008-07-077982.
[52] A.A. Gru, Pathology of T-cell lymphomas: diagnosis and biomarker discovery, Cancer Treat Res. 165 (2015) 51–95, http://dx.doi.org/10.1007/978-3-319-13150-4_3.
[53] P.I. Boffetta, Epidemiology of adult non-Hodgkin lymphoma, Ann. Oncol. 22 (2011) iv27–iv31, http://dx.doi.org/10.1093/annonc/mdr167.
[54] M. Boi, E. Zucca, G. Inghirami, F. Bertoni, Advances in understanding the pathogenesis of systemic anaplastic large cell lymphomas, Br. J. Haematol. 168 (2015) 771–783, http://dx.doi.org/10.1111/bjh.13265.
[55] J.A. DeSimone, P. Sodha, D. Ignatova, R. Dummer, A. Cozzio, P. Guenova, Recent advances in primary cutaneous T-cell lymphoma, Curr. Opin. Oncol. 27 (2015) 128–133, http://dx.doi.org/10.1097/CCO.0000000000000161.
[56] V. Singh, S.M. Singh, Progressive tumor growth-associated altered tumor microenvironment: implications in a tumor stage-dependent modulation in survival of a murine T cell lymphoma, J. Cancer Res. Clin. Oncol. 135 (2009) 1015–1024, http://dx.doi.org/10.1007/s00432-008-0537-5.
[57] M.L. Barreiro Arcos, H.A. Sterle, C. Vercelli, E. Valli, M.F. Cayrol, A.J. Klecha, M.A. Paulazo, M.C. Diaz Flaqué, A.M. Franchi, G.A. Cremaschi, Induction of apoptosis in T lymphoma cells by long-term treatment with thyroxine involves PKCζ nitration by nitric oxide synthase, Apoptosis 18 (2013) 1376–1390, http://dx.doi.org/10.1007/s10495-013-0869-8.
[58] H.A. Sterle, E. Valli, F. Cayrol, M.A. Paulazo, D.J. Martinel Lamas, M.C. Diaz Flaqué, A.J. Klecha, L. Colombo, V.A. Medina, G.A. Cremaschi, M.L. Barreiro Arcos, Thyroid status modulates T lymphoma growth via cell cycle regulatory proteins and angiogenesis, J. Endocrinol. 222 (2014) 243–255, http://dx.doi.org/10.1530/JOE-14-0159.
[59] A.B. Glinskii, G.V. Glinsky, H.Y. Lin, H.Y. Tang, M. Sun, F.B. Davis, M.K. Luidens, S.A. Mousa, A.H. Hercbergs, P.J. Davis, Modification of survival pathway gene expression in human breast cancer cells by tetraiodothyroacetic acid (tetrac), Cell Cycle 8 (2009) 3562–3570, http://dx.doi.org/10.4161/cc.8.21.9963.
[60] S.A. Mousa, H.Y. Lin, H.Y. Tang, A. Hercbergs, M.K. Luidens, P.J. Davis, Modulation of angiogenesis by thyroid hormone and hormone analogues: implications for cancer management, Angiogenesis 17 (2014) 463–469, http://dx.doi.org/10.1007/s10456-014-9418-5.
[61] A.H. Hercbergs, O. Ashur-Fabian, D. Garfield, Thyroid hormones and cancer: clinical studies of hypothyroidism in oncology, Curr. Opin. Endocrinol. Diabetes Obes. 17 (2010) 432–436, http://dx.doi.org/10.1097/MED.0b013e32833d9710.
[62] L.C. Moeller, D. Führer, Thyroid hormone, thyroid hormone receptors, and cancer: a clinical perspective, Endocr. Relat. Cancer 20 (2013) R19–R29, http://dx.doi.org/10.1530/ERC-12-0219.
[63] A.R. Brown, R.C. Simmen, F.A. Simmen, The role of thyroid hormone signaling in the prevention of digestive system cancers, Int. J. Mol. Sci. 14 (2013) 16240–16257, http://dx.doi.org/10.3390/ijms140816240.
[64] M.T. De Sibio, M. de Oliveira, F.C. Moretto, R.M. Olimpio, S.J. Conde, A.C. Luvizon, C.R. Nogueira, Triiodothyronine and breast cancer, World J. Clin. Oncol. 5 (3) (2014) 503–508, http://dx.doi.org/10.5306/wjco.v5.i3.503.
[65] M. Ellis, K. Cohen, E.S. Maman, A. Hercbergs, P.J. Davis, O. Ashur-Fabian, The involvement of thyroid hormones in cancer, Harefuah 154 (2015) 512–515.
[66] A.H. Ko, F. Wang, E.A. Holly, Pancreatic cancer and medical history in a population-based case-control study in the San Francisco Bay Area, California, Cancer Causes Control 18 (2007) 809–819, http://dx.doi.org/10.1007/s10552-007-9024-6.
[67] A. Turkyilmaz, A. Eroglu, Y. Aydin, O. Yilmaz, N. Karaoglanoglu, A new risk factor in oesophageal cancer aetiology: hyperthyroidism, Acta Chir. Belg. 110 (5) (2010) 533–536.
[68] A.I. Hellevik, B.O. Asvold, T. Bjøro, P.R. Romundstad, T.I. Nilsen, L.J. Vatten, Thyroid function and cancer risk: a prospective population study, Cancer Epidemiol. Biomarkers Prev. 18 (2009) 570–574, http://dx.doi.org/10.1158/1055-9965.EPI-08-0911.
[69] S. Lehrer, E.J. Diamond, A.M. Bajwa, R. Kornreich, S. Stagger, N.N. Stone, M.J. Droller, R.G. Stock, Association between serum triiodothyronine (T3) level and risk of disease recurrence in men with localized prostate cancer, Prostate Cancer Prostatic Dis. 4 (4) (2001) 232–234, http://dx.doi.org/10.1038/sj.pcan.4500542.
[70] A. Tosovic, A.G. Bondeson, L. Bondeson, U.B. Ericsson, J. Malm, J. Manjer, Prospectively measured triiodothyronine levels are positively associated with breast cancer risk in postmenopausal women, Breast Cancer Res. 12 (2010) R33, http://dx.doi.org/10.1186/bcr2587.
[71] S. Lehrer, E.J. Diamond, N.N. Stone, M.J. Droller, R.G. Stock, Serum triiodothyronine is increased in men with prostate cancer and benign

prostatic hyperplasia, J. Urol. 168 (2002) 2431–2433, http://dx.doi.org/10.1016/S0022-5347(05) 64161-4.
[72] R.B. Ness, J.A. Grisso, C. Cottreau, J. Klapper, R. Vergona, J.E. Wheeler, M. Morgan, J.J. Schlesselman, Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer, Epidemiology 112 (2000) 111–117.
[73] J.H. Kang, A.S. Kueck, R. Stevens, G. Curhan, I. De Vivo, B. Rosner, E. Alexander, S.S. Tworoger, A large cohort study of hypothyroidism and hyperthyroidism in relation to gynecologic cancers, Obstet. Gynecol. Int. 743721 (2013), http://dx.doi.org/10.1155/2013/743721.
[74] G. Rennert, H.S. Rennert, M. Pinchev, S.B. Gruber, A case-control study of levothyroxine and the risk of colorectal cancer, J. Natl. Cancer Inst. 102 (2010) 568–572, http://dx.doi.org/10.1093/jnci/djq042.
[75] B. Boursi, K. Haynes, R. Mamtani, Y.X. Yang, Thyroid dysfunction, thyroid hormone replacement and colorectal cancer risk, J. Natl. Cancer Inst. 107 (2015) djv084, http://dx.doi.org/10.1093/jnci/djv084.
[76] A. Reddy, C. Dash, A. Leerapun, T.A. Mettler, L.M. Stadheim, K.N. Lazaridis, R.O. Roberts, L.R. Roberts, Hypothyroidism: a possible risk factor for liver cancer in patients with no known underlying cause of liver disease, Clin. Gastroenterol. Hepatol. 5 (2007) 118–123, http://dx.doi.org/10.1016/j.cgh.2006.07.011.
[77] M.M. Hassan, A. Kaseb, D. Li, Y.Z. Patt, J.-N. Vauthey, M.B. Thomas, S.A. Curley, M.R. Spitz, S.I. Sherman, E.K. Abdalla, M. Davila, R.D. Lozano, D.M. Hassan, W. Chan, T.D. Brown, J.L. Abbruzzese, Association between hypothyroidism and hepatocellular carcinoma: a case-control study in the United States, Hepatology 49 (2009) 1563–1570, http://dx.doi.org/10.1002/hep.22793.
[78] M. Cristofanilli, Y. Yamamura, S.W. Kau, T. Bevers, S. Strom, M. Patangan, L. Hsu, S. Krishnamurthy, R.L. Theriault, G.N. Hortobagyi, Thyroid hormone and breast carcinoma. Primary hypothyroidism is associated with a reduced incidence of primary breast carcinoma, Cancer 103 (2005) 1122–1128, http://dx.doi.org/10.1002/cncr.20881.
[79] K. Backwinkel, A.S. Jackson, Some features of breast cancer and thyroid deficiency. Report of 280 cases, Cancer 17 (1964) 1174–1176.
[80] J.L. Kuijpens, I. Nyklíctek, M.W. Louwman, T.A. Weetman, V.J. Pop, J.W. Coebergh, Hypothyroidism might be related to breast cancer in post-menopausal women, Thyroid 15 (2005) 1253–1259, http://dx.doi.org/10.1089/thy.2005.15.1253.
[81] I. Mourouzis, A. Tzovaras, B. Armonis, A. Ardavanis, M. Skondra, J. Misitzis, D. Pectasides, C. Pantos, Are thyroid hormone and tumor cell proliferation in human breast cancers positive for HER2 associated? Int. J. Endocrinol. 765406 (2015) 2015, http://dx.doi.org/10.1155/2015/765406.
[82] A.G. Angelousi, V.K. Anagnostou, M.K. Stamatakos, G.A. Georgiopoulos, K.C. Kontzoglou, Mechanisms in endocrinology: primary HT and risk for breast cancer: a systematic review and meta-analysis, Eur. J. Endocrinol. 166 (2012) 373–381, http://dx.doi.org/10.1530/EJE-11-0838.
[83] A.M. Mondul, S.J. Weinstein, T. Bosworth, A.T. Remaley, J. Virtamo, D. Albanes, Circulating thyroxine, thyroid-stimulating hormone, and hypothyroid status and the risk of prostate cancer, PLoS One 7 (10) (2012) e47730, http://dx.doi.org/10.1371/journal.pone.0047730.
[84] M. Nelson, A. Hercbergs, L. Rybicki, M. Strome, Association between development of hypothyroidism and improved survival in patients with head and neck cancer, Arch. Otolaryngol. Head Neck Surg. 132 (2006) 1041–1046, http://dx.doi.org/10.1001/archotol.132.10.1041.
[85] A. Hercbergs, Spontaneous remission of cancer-a thyroid hormone dependent phenomenon? Anticancer Res. 19 (6A) (1999) 4839–4844.
[86] A.A. Hercbergs, L.K. Goyal, J.H. Suh, S. Lee, C.A. Reddy, B.H. Cohen, G.H. Stevens, S.K. Reddy, D.M. Peereboom, P.J. Elson, M.K. Gupta, G.H. Barnett, Propylthiouracil-induced chemical hypothyroidism with high-dose tamoxifen prolongs survival in recurrent high grade glioma: a phase I/II study, Anticancer Res. 23 (1B) (2003) 617–626.
[87] O. Ashur-Fabian, D.T. Blumenthal, M. Bakon, D. Nass, P.J. Davis, A. Hercbergs, Long-term response in high-grade optic glioma treated with medically induced hypothyroidism and carboplatin: a case report and review of the literature, Anticancer Drugs 24 (2013) 315–323, http://dx.doi.org/10.1097/CAD.0b013e32835c7a47.
[88] M.L. Vermey, G.T. Marks, M.G. Baldridge, Effect of thyroid function on MNU-induced mammary, Carcinogenesis Zool. Sci. 32 (2015) 272–277 http://dx.doi.org/10.2108/zs140124.
[89] M.S. Kumar, T. Chiang, S.D. Deodhar, Enhancing effect of thyroxine on tumor growth and metastases in syngeneic mouse tumor systems, Cancer Res. 39 (9) (1979) 3515–3518.
[90] S.Y. Mishkin, R. Pollack, M.A. Yalovsky, H.P. Morris, S. Mishkin, Inhibition of local and metastatic hepatoma growth and prolongation of survival after induction of hypothyroidism, Cancer Res. 41 (1981) 3040–3045.
[91] C. Frau, R. Loi, A. Petrelli, A. Perra, S. Menegon, M.A. Kowalik, S. Pinna, V.P. Leoni, F. Fornari, L. Gramantieri, G.M. Ledda-Columbano, S. Giordano, A. Columbano, Local hypothyroidism favors the progression of preneoplastic lesions to hepatocellular carcinoma in rats, Hepatology 61 (2015) 249–259, http://dx.doi.org/10.1002/hep.27399.
[92] W.G. Kim, S.Y. Cheng, Thyroid hormone receptors and cancer, Biochim. Biophys. Acta. 1830 (2013) 3928–3936, http://dx.doi.org/10.1016/j.bbagen.2012.04.002.
[93] C. Theodossiou, P. Schwarzenberger, Propylthiouracil reduces xenograft tumor growth in an athymic nude mouse prostate cancer model, Am. J. Med. Sci. 319 (2000) 96–99, http://dx.doi.org/10.1097/00000441-200002000-00005.
[94] O. Martinez-Iglesias, S. Garcia-Silva, J. Regadera, A. Aranda, Hypothyroidism enhances tumor invasiveness and metastasis development, PLoS One 4 (2009) e6428, http://dx.doi.org/10.1371/journal.pone.0006428.
[95] H.A. Sterle, M.L. Barreiro Arcos, E. Valli, M.A. Paulazo, S.P. Méndez Huergo, A.G. Blidner, F. Cayrol, M.C. Díaz Flaqué, A.J. Klecha, V.A. Medina, L. Colombo, G.A. Rabinovich, G.A. Cremaschi, The thyroid status reprograms T cell lymphoma growth and modulates immune cell frequencies, J. Mol. Med. (Berl.) (2015), http://dx.doi.org/10.1007/s00109-015-1363-2 (in press).
[96] L. Yadav, N. Puri, V. Rastogi, P. Satpute, V. Sharma, Tumour angiogenesis and angiogenic inhibitors: a review, J. Clin. Diagn. Res. 9 (2015) XE01–XE05, http://dx.doi.org/10.7860/JCDR/2015/12016.6135.
[97] C. Mas-Moruno, F. Rechenmacher, H. Kessler, Cilengitide: the first anti-angiogenic small molecule drug candidate design, synthesis and clinical evaluation, Anticancer Agents Med. Chem. 10 (2010) 753–768, http://dx.doi.org/10.2174/187152010794728639.
[98] R. Stupp, M.E. Hegi, T. Gorlia, S.C. Erridge, J. Perry, Y.K. Hong, K.D. Aldape, B. Lhermitte, T. Pietsch, D. Grujicic, J.P. Steinbach, W. Wick, R. Tarnawski, D.H. Nam, P. Hau, A. Weyerbrock, M.J. Taphoorn, C.C. Shen, N. Rao, L. Thurzo, U. Herrlinger, T. Gupta, R.D. Kortmann, K. Adamska, C. McBain, A.A. Brandes, J.C. Tonn, O. Schnell, T. Wiegel, C.Y. Kim, L.B. Nabors, D.A. Reardon, M.J. van den Bent, C. Hicking, A. Markivskyy, M. Picard, M. Weller, European Organisation for Research, Treatment of Cancer (EORTC), Canadian Brain Tumor Consortium, CENTIC study team, Cilengitide combined with standard treatment for patients with newly diagnosed glioblastoma with methylated MGMT promoter (CENTRIC EORTC 26071–22072 study): a multicentre, randomised, open-label, phase 3 trial, Lancet Oncol. 15 (2014) 1100–1108, http://dx.doi.org/10.1016/S1470-2045(14)70379-1.
[99] H. Friess, J.M. Langrehr, H. Oettle, J. Raedle, M. Niedergethmann, C. Dittrich, D.K. Hossfeld, H. Stöger, B. Neyns, P. Herzog, P. Piedbois, F. Dobrowolski, W. Scheithauer, R. Hawkins, F. Katz, P. Balcke, J. Vermorken, S. van Belle, N. Davidson, A.A. Esteve, D. Castellano, J. Kleeff, A.A. Tempia-Caliera, A. Kovar, J. Nippgen, A randomized multi-center phase II trial of the angiogenesis inhibitor cilengitide (EMD 121974) and gemcitabine compared with gemcitabine alone in advanced unresectable pancreatic cancer, BMC Cancer 6 (2006) 285, http://dx.doi.org/10.1186/1471-2407-6-285.
[100] K.W. Beekman, A.D. Colevas, K. Cooney, R. Dipaola, R.L. Dunn, M. Gross, E.T. Keller, K.J. Pienta, C.J. Ryan, D. Smith, M. Hussain, Phase II evaluations of Cilengitide in asymptomatic patients with androgen-independent prostate cancer: scientific rationale and study design, Clin. Genitourin. Cancer 4 (2006) 299–302 http://dx.doi.org/10.3816/CGC.2006.n.012.
[101] D.A. Bradley, R. Dunn, C. Ryan, R. Di Paola, D.C. Smith, K.A. Cooney, P. Mathew, M. Gross, A.D. Colevas, M. Hussain, EMD121974 (NSC 707544, cilengitide) in asymptomatic metastatic androgen independent prostate cancer (AIPCa) patients (pts): a randomized trial by the prostate cancer clinical trials consortium (NCI 6372), J. Clin. Oncol. 25 (2007) 18s (suppl; abstr 5137).
[102] E.K. Sloan, N. Pouliot, K.L. Stanley, J. Chia, J.M. Moseley, D.K. Hards, R.L. Anderson, Tumor specific expression of alphavbeta3 integrin promotes spontaneous metastasis of breast cancer to bone, Breast Cancer Res. 8 (2006) R20, http://dx.doi.org/10.1186/bcr1398.
[103] A. Hercbergs, R.E. Johnson, O. Ashur-Fabian, D.H. Garfield, P.J. Davis, Medically induced euthyroid hypothyroxinemia may extend survival in compassionate need cancer patients: an observational study, Oncologist 20 (2015) 72–76, http://dx.doi.org/10.1634/theoncologist.2014-0308.
[104] H.Y. Lin, M. Sun, H.Y. Tang, C. Lin, M.K. Luidens, S.A. Mousa, S. Incerpi, G.L. Drusano, F.B. Davis, P.J. Davis, L-Thyroxine vs. 3,5,3-triiodo-L-thyronine and cell proliferation: activation of mitogen-activated protein kinase and phosphatidylinositol 3-kinase, Am. J. Physiol. Cell Physiol. 296 (2009) C980–C991, http://dx.doi.org/10.1152/ajpcell.00305.2008.
[105] P.J. Davis, H.Y. Lin, T. Sudha, M. Yalcin, H.Y. Tang, A. Hercbergs, J.T. Leith, M.K. Luidens, O. Ashur-Fabian, S. Incerpi, S.A. Mousa, Nanotetrac targets integrin αvβ3 on tumor cells to disorder cell defense pathways and block angiogenesis, Onco Targets Ther. 7 (2014) 1619–1624, http://dx.doi.org/10.2147/OTT.S67393.
[106] M. Yalcin, H.Y. Lin, T. Sudha, D.J. Bharali, R. Meng, H.Y. Tang, F.B. Davis, S.C. Stain, P.J. Davis, S.A. Mousa, Response of human pancreatic cancer cell xenografts to tetraiodothyroacetic acid nanoparticles, Horm. Cancer 4 (2013) 176–185, http://dx.doi.org/10.1007/s12672-013-0137-y.