Non-genomic Actions of Thyroid Hormones Regulate the Growth and Angiogenesis of T Cell Lymphomas

Florencia Cayrol1, Helena A. Sterle1, Maria Celeste Díaz Flaqué1, Maria Laura Barreiro Arcos1 and Graciela A. Cremaschi1,2*

1 Instituto de Investigaciones Biomédicas, Consejo Nacional de Investigaciones Científicas y Técnicas, Facultad de Ciencias Médicas, Pontificia Universidad Católica Argentina, Buenos Aires, Argentina. 2 Laboratorio de Radioisótopos, Cátedra de Física, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Buenos Aires, Argentina

T-cell lymphomas (TCL) are a heterogeneous group of aggressive clinical lymphoproliferative disorders with considerable clinical, morphological, immunophenotypic, and genetic variation, including ~10–15% of all lymphoid neoplasms. Several evidences indicate an important role of the non-neoplastic microenvironment in promoting both tumor growth and dissemination in T cell malignancies. Thus, dysregulation of integrin expression and activity is associated with TCL survival and proliferation. We found that thyroid hormones acting via the integrin αvβ3 receptor are crucial factors in tumor microenvironment (TME) affecting the pathophysiology of TCL cells. Specifically, TH-activated αvβ3 integrin signaling promoted TCL proliferation and induced an angiogenic program via the up-regulation of the vascular endothelial growth factor (VEGF). This was observed both on different TCL cell lines representing the different subtypes of human hematological malignancy, and in preclinical models of TCL tumors xenotransplanted in immunodeficient mice as well. Moreover, development of solid tumors by inoculation of murine TCLs in syngeneic hyperthyroid mice, showed increased tumor growth along with increased expression of cell cycle regulators. The genomic or pharmacological inhibition of integrin αvβ3 decreased VEGF production, induced TCL cell death and decreased in vivo tumor growth and angiogenesis. Here, we review the non-genomic actions of THs on TCL regulation and their contribution to TCL development and evolution. These actions not only provide novel new insights on the endocrine modulation of TCL, but also provide a potential molecular target for its treatment.

Keywords: VEGF, proliferation, angiogenesis, integrin αvβ3, thyroid hormones, T-cell lymphoma

INTRODUCTION

Thyroid hormones (THs), triiodothyronine (T3), and thyroxine (T4), are involved in different biological processes as cell growth, development, differentiation, and the regulation of metabolism and homeostasis (1). The classical mechanism of action of THs is mediated by the binding of T3 to nuclear receptors (TR) that interact with specific responding elements (TREs) in the promoters of target genes. The binding of T3 to TRs promotes a conformational change that induces the
exchange of corepressors for coactivators, thus leading to gene transcription on responsive genes (2, 3). THs can also trigger their actions by a non-classical mechanism that does not implicate direct gene transcription regulation by nuclear TRs. These non-genomic actions indirectly modulate gene transcription through the activation of intracellular pathways and other transcription factors (3, 4). Despite many of the non-genomic actions have been demonstrated to be initiated by THs through the activation of a membrane receptor (mTR), they can also be initiated at receptors located in the mitochondria or cytoplasm (5).

In the last years, several studies have identified the integrin αvβ3 as the membrane receptor for THs in normal tissues as blood vessels and heart (5); but also in several types of cancer cells (4, 6–9). Integrin αvβ3 is a member of a large group of heterodimeric transmembrane receptors that regulate cell-cell and cell-extracellular matrix (ECM) interactions and enable cells to respond to their environment (10). Several studies related to cancer have implicated the activity of this group of adhesion receptors in the proliferation, migration, and survival of different types of tumor cells (11). Many aspects of the cellular microenvironment, like the composition and structure of the ECM, the signals generated by growth factors or the stimulation of cytokine secretion are regulated by integrins (12, 13). Particularly, integrin αvβ3 mediates the interaction between the cells and the ECM as a result of its binding to plasmatic and ECM ligands that express the peptide sequence RGD (Arginine–Glycine–Aspartate) (14). Interestingly this integrin is highly expressed in proliferating cells, like malignant cancer cells and cells from the endothelial and vascular smooth muscle (14).

It is well-known that the growth, invasiveness, and dissemination of a tumor are highly associated with angiogenesis. In recent studies, our group demonstrated that the interaction of THs with integrin αvβ3 triggers intracellular pathways in T-cell lymphoma (TCL) cells. This further activates transcription factors, thus stimulating gene transcription and the production of angiogenic factors (15). Therefore, the expression of integrin αvβ3 in tumor cells and their vascular network could explain the proangiogenic and proliferative effects of THs on different cancers, including gliomas (9), breast (4), thyroid (6, 8), and renal cancer (7), among others.

In this review, we will focus on the role of integrin αvβ3 as the membrane receptor for THs and how its activation induces the proliferation and survival of different types of cancer cells. Specifically, we will discuss the influence of THs non-genomic actions through integrin αvβ3 activation on TCL malignant phenotype, and the inhibition of this receptor as a potential clinical target.

ROLE OF INTEGRIN αVβ3 IN CANCER AND ANGIOGENESIS

Integrins and Cancer

Despite integrins were initially described as cell adhesion receptors, current studies highlight the idea that these receptors have essential roles in cancer. In fact, one of the well-known mechanisms of cancer is the abnormal function of integrin receptors (16). Cancer is a complex disease and its progression is deeply related with the dynamically evolving extracellular matrix that regulates many aspects of the tumor and tumor-associated cells (16). Integrin bi-directional signaling is essential to sense, modulate, and respond to changes in extracellular stimuli (17). The signal transduction mediated by these receptors usually occurs through direct or indirect interactions between the cytoplasmic domain of the integrin and intracellular effectors, which occasionally can be supported by the interactions with other cell surface proteins that are associated to integrins (14). For example, it has been reported that caveolin is required for the association between Src-family kinases and β1 integrins; moreover the loss of this association results in the loss of FAK phosphorylation induction and the correct development of focal adhesion sites (18). Tetraspanins, on the other hand, are essential for rapid cell migration mediated by α3β1, α6β1, α6β4, and α7β1 integrins, making these integrin partners potential antimetastatic targets (19). In cancer cells, FAK and Src are two of the best-studied integrin-mediated signaling effectors. Different types of solid tumors, including pancreatic, colon, and breast cancers, show high expression and activation of FAK and Src, thus contributing to the progression and the malignant phenotype of these pathologies (20–22). Inhibition of FAK and Src signaling reduces tumorigenic and metastatic potential of breast cancer cells (23). When integrin-mediated cell adhesion occurs, FAK is activated by autophosphorylation, generating a high-affinity binding site for the SH2 domain of Src. These activated FAK/Src complexes are the link between integrins and the downstream signaling effectors such Rac1 GTPase or the MAPKs (24). The interaction of integrins and their ligands, and the consequent activation of these complexes and the intracellular pathways, can influence cancer cells behavior by increasing cell proliferation, survival, and gene expression; therefore contributing to tumor growth and metastasis (24). All these findings point out the mentioned pathways as potential therapeutic targets in different types of cancer (23, 24).

Most solid tumors are originated from epithelial cells that are conferred with the ability to resist apoptosis, migrate, and disseminate through the epithelial-mesenchymal transition (EMT) (25). This process involves the remodeling of the ECM and changes in the interactions of cells with the ECM (26). Many integrins that are expressed by epithelial cells are retained in the tumor, but their levels and physiologic functions may be altered. Integrins α6β4, α6β1, αvβ5, α2β1, and α3β1, regulate the adhesion of epithelial cells to the basement membrane, however, in tumor cells they might involve and contribute to cell migration, proliferation and survival (11). However, during the differentiation into mesenchymal cells some epithelial integrins are downregulated and the expression of other integrins with key roles in EMT progression and tumor invasiveness are activated (24, 26). For example, the expression of α6β4 integrin is down-regulated during EMT in the mammary gland through the epigenetically silencing of the gene encoding β4 integrin (27). Also in mammary epithelial cells, enhanced expression of integrin αvβ3 is required for TGF-β-induced EMT (28). Likewise, α3β1, α5β1, αvβ1, and α2β1 integrins are overexpressed...
in different stages of EMT (24, 29). Indeed, the expression of many integrin subunits, including α3, α5, α6, αv, β1, β3, and β4 in different types of cancer cells, has been linked to their invasive and metastatic potential (30). The expression of integrins αβ3, α5β1, and αvβ6 are normally low or undetectable in most adult epithelia but in some tumors their protein levels are overexpressed (11). Elevated αvβ6 integrin levels are associated with fibrosis and cancer in lungs, skin and along the gastrointestinal tract (31). After its activation, α2β1 integrin promotes cell adhesion, proliferation and invasion in liver and lung metastasis (32). In prostate cancer (PCa) integrin α2β1 is overexpressed and its phosphorylation and consequent activation have been associated with the progression of this pathology (33). Also, integrin αvβ3 has been reported to contribute to PCa progression by promoting angiogenesis, survival, and invasion (34, 35). The overexpression of integrin αvβ3 in primary head and neck squamous carcinoma and metastatic lymph nodes was related to lymph node metastasis and worse prognosis (36). In breast cancer, the levels of integrin α6β4 and αvβ3 correlate with tumor size, grade and decreased survival (37, 38). The overexpression of integrin αvβ3 is also involved in the switch from a non-tumorigenic state of melanoma to a tumorigenic and invasive one (10) and increased bone metastasis in prostate cancer (39).

It is well-known that integrins are able to synergistically interact with cytokine receptors and growth factors, thus mediating some features of cancer progression as cell migration, invasion, and survival. In the last years, it has been described that integrin N-glycosylation is essential for integrin heterodimerization and interaction with ligands (16, 40, 41). Currently, several published works indicate that N-glycan alterations on integrin subunits influence their affinity for their ligands, thus contributing to the malignant phenotype. These studies propose the targeting of 1,6-GlcNAc structures, sialic acid, and fucose and their related enzymes, in combination with the inhibition of integrins, represent a promising new therapeutic approach (16).

Mainly two therapeutic strategies based on integrin target were developed in the last decades: inhibition of integrin function and the use of integrin expression patterns for drug delivery (42). The direct inhibition of integrin function with synthetic peptides and humanized antibodies, among others, has so far be the main therapeutic strategy in the clinic and until now is the only form of anti-integrin treatment shown to work in patients (43). The antibodies abituzumab, intetumumab, and the small molecule, cilengitide, are the most advanced molecules studied in clinical trials for the treatment of different types of cancer (44). Despite the promising preclinical results observed, poor efficacy was obtained in late-phase clinical trials (16). The problem in translating the preclinical data of anti-integrin therapies to the clinic, especially in cancer, would be related to the poor knowledge of integrin biology. For example, the profile and distribution of many integrins in normal and pathological tissues from cancer patients is somehow hard to achieve as there is a lack of good antibodies for integrin staining in formalin-fixed-paraffin embedded tissues. The use of integrins as biomarkers could improve the efficacy of anti-integrin cancer treatment (44).

In summary, if we improve the skills for the identification of integrins in patient samples and increases our knowledge on other integrin characteristics, as the internalization and intracellular trafficking response in the oncology process, new effective, and safe therapies would be generated.

Integrins and Tumor Microenvironment

The transformed cells are not capable of generating tumors with metastatic potential by themselves; this process requires a permissive tumor microenvironment (TME) that might be crucial for tumor progression. Recent works have begun to focus more deeply on the study of non-tumor cell components of the stroma and their involvement in the malignant progression (45). The TME include many host cell types, including fibroblasts, endothelial, perivascular, and inflammatory cells, that in some cases can contribute to tumor progression through different processes like angiogenesis, lymphangiogenesis or inflammation. Examples of tumor-associated stromal cells are tumor or cancer-associated fibroblasts (TAFs or CAFs) and tumor-associated macrophages (TAMs) (25, 45, 46). Reciprocal communication between cancer cells and these non-tumoral cells is essential and leads to high proliferation and metastatic capability of the tumor.

Integrins can bidirectionally transduce signals across the cell membrane, (24). The “outside-in” signaling is triggered by chemical or mechanical alterations in the ECM. The interaction of the integrin extracellular head domain with the ECM ligand or divergent cations induces integrin clustering and conformational rearrangements of the cytoplasmic tail that lead to the activation of several signaling pathways that regulate gene transcription and cell shape, survival and migration (47). The “inside-out” signaling, on the other hand, is triggered by a cytoplasmic signal that can alter the integrins’ affinity for extracellular ligands (48, 49). These mechanisms are essential for the communication of the cells with their microenvironment and regulate many important biological functions including cell proliferation, survival, and motility. The tumor cells use these same processes to acquire invasive and oncogenic survival properties and to orchestrate changes in the host microenvironment that lead to tumor growth and metastatic dissemination (17).

Additionally to their role in malignant cells, integrins expression on tumor-associated host cells can profoundly influence in the malignant potential of a tumor (17, 50). Integrins are expressed on all the cell types that compose the TME, and modulate functions of both, tumor and stromal cells, that promote the communication between different cell types of the TME, leading to tumor growth and malignant progression (50). For example, integrin α9β1 regulates the signaling that increases tumor growth and lymphatic metastasis via the recruitment of TAFs in breast cancer cells (51). In gastric cancer, C-X-C motif chemokine 12 (CXCL12) derived from CAFs promotes cell invasion by enhancing the clustering of integrin β1 in gastric cancer cells (52). Dr. Cress group demonstrated that the cleavage of integrin α6β1 by the serine protease urokinase plasminogen activator (uPA) induces tumor cell motility, invasion, and metastasis in a xenograft model of PCa cells placed within the living bone matrix (53). The same group described later
that TAMs stimulate the production of uPA inside the tumor, resulting in αvβ1 integrin cleavage in PCa cells (54).

The capacity of integrins to regulate cell adhesion and migration alone is enough to drive invasion. Tumor cells must break the ECM barriers to metastasize to a distant organ; this process requires not only the degradation and remodeling of ECM, but it can also involve ECM stiffening. For example, in human breast carcinoma, collagen fibers become bundled and align perpendicularly to the basement membrane, thus converting into tracks for cells to migrate (55). Likewise, in pancreatic ductal adenocarcinoma, increased collagen thickness and matricellular fibrosis in response to elevated β1-integrin mechano-transduction was related to a more aggressive pathology (17). ECM degradation and remodeling is carried out by several proteases. It has been shown that integrins can modulate the expression levels and the activity of those proteases, in particular matrix metalloproteinases (MMPs) and the uPA system (56). The ability to regulate matrix organization and remodeling is a critically important function of integrins (24). For example, the interaction between MMPs and integrin β2 is required for leukocyte migration, and the combined participation of MMPs and other integrins is also necessary for tumor metastasis (56).

The levels of MMPs are always elevated in the presence of tumors (57). The expression of MMP gene can be up-regulated by integrin signaling pathways (58). It has been reported in different studies that integrins αv and β1 are able to increase the levels of several MMPs. It was demonstrated that integrin αvβ6 increases the expression levels of MMPs in oral, ovarian and colon cancers (59–61). In oral squamous cell carcinoma (SCC), the increment of integrin αvβ6 expression activates MMP-3, thus promoting oral SCC cell proliferation and metastasis in vivo (61); on the other side, integrin β1 promotes invasion and migration of SCC cells via MMP7 (62). In ovarian cancer cells, high levels of integrin αvβ6 correlate with an augment of the expression and secretion of pro-MMP-2, pro-MMP-9 and high molecular weight uPA, thus increasing ECM degradation (59).

One of the characteristics that is important to consider is the physical location of MMPs because this dictates their biological functions and is critical for tumor progression. The localization of several MMPs in cell membrane through the interaction with integrins has been demonstrated; one example is the binding of MMP-2 to αvβ3 or MMP-9 to αVβ6 (56, 63). MMP-9 expression levels were found to be increased in colon cancer metastasis to liver, and this metalloproteinases co-localized with integrin αVβ6 at the invading border of the tumor (63). Consequently, integrins have a critical role in TME impact on tumor invasion and spreading.

Integrin αvβ3 and Angiogenesis
Angiogenesis is the formation of new blood vessels from pre-existing ones. Even though it is a fundamental physiological event, in certain situations angiogenesis can also be negative; the formation of new blood vessels contributes to the progression of several pathologies and is crucial in tumor growth and metastasis. Consequently, angiogenesis is essential for the growth, spreading and infiltration of malignant cells within tissues (64). In the beginning, tumors can proliferate and survive by taking advantage of the available vessel of their host and surroundings; nevertheless, malignant cells can become hypoxic if they are too far away from the oxygen and nutrients of those vessels (65). In response to hypoxia tumor cells are able to create new blood vessels to fulfill their metabolic needs.

Tumor angiogenesis depends on ECM disruption, the migratory ability of endothelial cells (ECs) and their adhesion to integrins. As we have already mentioned, integrins are expressed on ECs, lymphatic endothelial cells and pericytes (66) and for this reason, they have been pointed out as important players in cancer angiogenesis (11). They are involved in tumor angiogenesis by interacting with both axis that regulate the maturation and plasticity of the new vessels: the pathway of vascular endothelial growth factor (VEGF) and its receptor (VEGFR) (67) and that of angiopoietins and Tie receptors (ANG-Tie).

Among all integrins, αvβ3 has been thoroughly studied for its localized expression in neovascularure and in aggressive tumors (68). The membrane receptor integrin αvβ3 recognizes ECM proteins expressing the RGD peptide sequence. Despite the expression levels are low in resting endothelial cells and normal organ systems, integrin αvβ3 is highly expressed on activated tumor endothelial cells (11). The latter, makes this integrin an appropriate target for antiangiogenic therapeutics. Moreover, integrin αvβ3 is also express on tumor cells, thus both tumor cells and tumor vasculature can be target by anti-integrin therapy.

It was described that only 20% of integrin αv-null mice survive until birth, and that 100% die within the 1st day of birth (69). These mice develop intracerebral hemorrhage due to the defective interactions between blood vessels and brain parenchymal cells (70). On the other side, the β3 integrin-null mice can survive and apparently develop a normal vascular network (71). Furthermore, no integrin β3 protein levels are detected in quiescent blood vessels, but its expression increases during sprouting angiogenesis (72).

One of the roles of integrin αvβ3 during angiogenesis is to bind and activate MMP-2 on new blood vessels to disrupt ECM and facilitate tumor cell migration and infiltration (64). A cooperative action between activated integrin αvβ3 in tumor cells and platelets, that promotes extravasation and metastasis, has also been reported (73). Integrin αvβ3 also participates in the angiogenic switch. This process is referred the time during tumor progression where the balance between pro- and anti-angiogenic factors tilts toward a pro-angiogenic outcome, resulting in the transition from not vascularized hyperplasia to a vascularized tumor and malignant tumor progression (74). In this sense, it was described that the inhibition of tumor-associated αvβ3 integrin regulates the angiogenic switch in melanoma cells leading to reduced melanoma growth and angiogenesis in vivo (74).

In 2004, Davis et al. have shown that THs can induce angiogenesis through a cell surface receptor using a chick chorioallantoic membrane (CAM) model (75). In 2005, Bergh et al. have demonstrated that the membrane receptor for THs is near the RGD binding site of the integrin αvβ3 (76). Additionally, we found that the activation of integrin αvβ3 by THs mediates angiogenesis in malignant T cells (15). A number of in vitro and in vivo studies have supported a role for THs in the proliferation

Frontiers in Endocrinology | www.frontiersin.org 4 February 2019 | Volume 10 | Article 63
of tumor cells (75, 77–79) and as proangiogenic factor in many types of cancer (15, 75, 76, 80). These properties may be relevant to tumor biology and we will discuss them later in this review.

All the mentioned findings highlight integrin αβ3 as a fundamental tumor angiogenic promotor. Antagonists of αβ3 integrin were developed and some proved to be very successful antiangiogenic agents both in vitro and in preclinical angiogenesis assays in vivo. In accordance, integrin αβ3 antagonists could inhibit tumor growth in several cancer animal models of human breast cancer (81) and glioblastomas (82). Cilengitide, a specific inhibitor of integrin αβ3, was able to decrease tumor growth in two different angiogenic and invasive glioblastoma models, by decreasing the diameter of tumor vessels thus reducing the infiltration of cells around the tumor center (83). Associated with its function as membrane receptor for THs actions, the effects of the deaminated analog of L-thyroxine, Tetraiodothyroacetic acid (TETRAC) and its nanoparticulate formulation have been reported as antithyroid agents at the integrin (84).

THYROID HORMONE NON-GENOMIC ACTIONS IN T CELL LYMPHOMAS

THs Effects on T Cell Lymphoma Growth and Proliferation

As we have already mentioned, THs are critical for many processes like cell growth, differentiation, metabolism, and homeostasis maintenance (1). The classical effects of THs are initiated when T3 binds to their nuclear receptors (TRs) that interact with specific responding elements (TREs) in the promoters of target genes. The conformational change promoted by the binding of T3 to TRs induces the exchange of corepressors for coactivators, thus leading to gene transcription on responsive genes (2, 3). TRs are encoded by two different genes: the THRA located in chromosome 17, and the THRβ located in chromosome 3, codifying for the TRα and TRβ proteins, respectively (2, 3). The expression of these isoforms differs during the embryonic development and in adult tissues (1). Mutations of TRs have been detected in several cancers, such as erythroleukemia and liver, kidney and thyroid cancers (13). These mutations have been suggested to be a selective advantage for malignant transformation (85). Thus, the mutation (86, 87) or aberrant expression (88) of TRs has been demonstrated in several cancer cell lines. Also, biopsies of patients with gastrointestinal tumors showed increased levels of TRα1 that correlate with Wnt pathway activation and tumor proliferation (89).

Several clinical studies show controversial results related to THs status and cancer. On one side, some studies show that hypothyroidism might be a risk factor for the development and progress of different types of tumors like breast, thyroid and prostate cancers (85, 90, 91), while hypothyroidism could favor the clinical outcome of cancer patients (92, 93). However, hypothyroidism was associated with an increased risk of colorectal cancer and hepatocellular carcinoma, that would be explained by the increased generation of reactive oxidative species associated with lipid peroxidation, that result in chronic inflammation and DNA damage leading to neoplastic transformation (94, 95). The association between THs and cancer is now better understood following the discovery of the αβ3 integrin plasma membrane receptor for T4 and T3 (see below).

In the last decade several studies reported the proliferative effect that physiological concentrations of T3 and T4 have on different cancer cell lines, such as glioma, papillary, and follicular thyroid carcinoma, lung carcinoma and breast adenocarcinoma, among others (26, 77, 78, 96). These actions induce the activation of intracellular signaling pathways and transcription factors that increase cell proliferation.

In this sense, our group has investigated the effect of genomic and non-genomic actions of THs on normal T lymphocytes (97, 98) and in TCL cell (15, 79, 99–103) proliferation and survival. We found that TH induced cell proliferation of murine TCL cells by triggering a non-genomic intracellular signaling that involves the activity of PKCζ that leads to ERK1/2 and NF-κB activation and the increase of transcriptional levels of TRs and the inducible nitric oxide synthase (99). We have also found that THs can regulate the balance between proliferation and apoptosis of TCL cells both in vitro and in vivo assays (79, 100). Additionally, we studied how the thyroid status modulates the in vivo growth of EL4 TCL cells and how the antitumor immune response is affected in euthyroid, hypothyroid, and hyperthyroid mice. The appearance of palpable solid tumors was earlier in hyperthyroid animals, which also developed tumors with a higher growth rate and an increased volume when compared with tumors in euthyroid controls or hypothyroid mice (79). In addition, the larger tumor size in hyperthyroid mice was accompanied by higher expression levels of the proliferating cell nuclear antigen and cell cycle regulators; and with an increase of intratumoral and peritumoral vasculogenesis (79).

Despite TCL tumor growth was not significantly different between hypothyroid and euthyroid mice, hypothyroid animals showed a higher frequency of metastases (102). This was associated to an increased percentage of regulatory T (Treg) cells in their tumor draining lymph nodes, a decrease number and activity of splenic NK cells and a decreased number of splenic myeloid-derived suppressor cells (MDSCs) when compared to control euthyroid tumor-bearing mice (102) (Figure 1). Also, tumor-bearing hyperthyroid mice displayed the lowest metastatic dissemination. This was related with an increased systemic antitumor immunity in hyperthyroid mice, reflected by the low number of MDSCs and increased number and activity of both NK and CD8+ cytotoxic T lymphocytes (Figure 1), thus strengthening the fact that low levels of circulating THs are related to TCL spreading and metastatic dissemination. These results highlight the importance of monitoring the thyroid status in patients with TCL.

Integrin αβ3 as the Thyroid Hormone Membrane Receptor in TCL Cells

As we have already mentioned, both T3 and T4, play important roles in regulating the proliferation of several cancer cell types. Their metabolic, developmental and growth effects in normal tissues are mediated primarily by TRs (104), while their surface
The identification of αβ3 integrin as the mTR provides the molecular basis to many actions of TH at cancer cells. THs can influence cell proliferation, survival and angiogenesis in different cancer cells via integrin αβ3 (110–112). Thus, myeloma cell adhesion to fibronectin is increased by T3 and T4 which induces αβ3 clustering. In addition, THs induce MMP-9 expression and activation via integrin αβ3 and MAPK induction, suggesting a role for TH-mediated activation of integrin αβ3 in myeloma migration and progression (110). THs also promote the proliferation of ovarian cancer cells via integrin αβ3 that activates extracellular regulated kinase (ERK1/2) (112). In breast cancer cells, THs regulate cell migration via integrin αβ3 that activates SRC/FAK/PI3-K pathway (111).

**Integrin αβ3 in the Malignant Phenotype of T Cell Lymphomas**

T cell lymphomas (TCL) are a broad group of aggressive lymphoproliferative disorders with significant variation clinical, immunophenotypic, and genetic features. This group of hematologic disorders that is characterized by a clonal growth of T cells at different stages of maturation represents ∼10–15% of Non-Hodking lymphomas (113, 114). The last World Health Organization classification has divided this group of hematopoietic malignancies according to its predominant presentation: leukemic (disseminated), nodal, extranodal, or cutaneous (115). The most frequent subtypes include peripheral T cell lymphoma not otherwise specified (PTCL-NOS), anaplastic large cell lymphoma (ALCL) and angioimmunoblastic T cell lymphoma (AITL) (116, 117). Although cutaneous T cell lymphomas (CTCL) are less frequent, is important to note that the skin is the second location in frequency of extranodal primary lymphomas (118). As in other neoplastic disorders, TCL are exposed to a complex environment that comprises among others, growth factors, cytokines, and hormones that are produced by either lymphoma cells or normal cells present in the surrounding or distal tumor microenvironment (119, 120). As we already mentioned, we have demonstrated that one of those factors are THs (15, 79, 99, 100, 103).

Studies of our group demonstrated that both, genomic and non-genomic actions triggered by THs increase cell proliferation of human and murine TCL lines. Moreover, these results described the contribution of the mTR, the integrin αβ3, in the non-genomic actions of THs in TCL cells (15, 99, 103). The signaling induced by THs through the mTR in murine TCL cells includes the rapid translocation of the ζ isoform of PKC to the cell membrane (99, 103), ERK 1/2 phosphorylation and the activation of the transcription factor NF-κB (15, 99), all molecular processes that are essential for the proliferation and survival of TCL cells.

Recently, we have also demonstrated that integrin αβ3 is the mTR in human TCL cells. Both T3 and T4 were able to induce in vitro the proliferation of tumor, but not normal T lymphocytes (99, 103), being the presence of physiological concentrations of both hormones the most effective to trigger the growth of human TCL cell lines (15). Thus, in a panel of 9 human TCL cell lines, representing the different subtypes of the disease, we showed that the proliferative actions triggered by THs were mediated by the

---

**TUMOR MICROENVIRONMENT**

![Diagram of tumor microenvironment with NK cells, Regulatory T cells, Myeloid-derived suppressor cells, CD8+ T lymphocytes, and NK cells](image)

**FIGURE 1 | Regulation of antitumor immune cells by circulating levels of THs.** In hyperthyroid conditions (blue arrows) increased number and activity of NK and cytotoxic CD8+ lymphocytes, while decreased number of myeloid-derived suppressor cells, were found in the spleens of TCL tumor-bearing mice. However, thyroid hormone-binding animals displayed higher numbers of T regulatory lymphocytes (Treg) in tumor-draining lymph nodes and lower number and activity of splenic NK and CD8+ lymphocytes than control, indicating that the hypothyroid status favors the dissemination of TCL cells.
activation of integrin αvβ3. This effect was blocked when the mRNA levels of the integrin αv, β3, or both were downregulated using siRNA (15). Additionally, we have evidenced that these effects were accompanied by the regulation of cell cycle markers. According to this, it has been reported in breast cancer cells that TETRAC inhibits the effects of THs on the integrin αvβ3 leading to an increment in the expression of proapoptotic genes, demonstrating that THs non-genomic actions are required for the survival of these cells (4, 121).

We identified the genetic programs activated by THs through their actions on integrin αvβ3 in TCL cells. To this aim we performed RNA sequencing techniques on TCL cells and analyzed results using bioinformatic tools. We found that genes involved in protein translation, lymphocyte proliferation/differentiation, DNA replication and angiogenesis were mobilized by THs through the mTR activation. Remarkably, we found that the intracellular pathways activated by THs through the mTR significantly induced the transcriptional levels VEGFA and VEGFB genes. This induction was abrogated by siRNA against integrin αvβ3 in TCL cells either from immature or mature origins; and dependent on the activation of the transcription factor NF-κB (15). Importantly, when we performed these experiments in the presence of vitronectin, the “natural” ligand of integrin αvβ3, we found that the pathways triggered by THs are different.

It is important to note that it was also evident an association between integrin αvβ3 and VEGF expression in samples from patients with PTCL. By bioinformatic analysis of PTCL tissue microarrays we found a positive correlation between the transcriptional levels of integrin αv or β3 and those of VEGFA or VEGFB. We also verified that the induction of VEGF production in TCL that is regulated by THs functions in a paracrine or autocrine manner. The induction of VEGF production mediated by THs increased the migration of human endothelial cells, and tumor cell proliferation. Moreover, the blocking antibody against VEGF, bevacizumab, abrogated all the mentioned effects. We also found that the proliferative action triggered by THs on TCL cells was impaired by the inhibitor of VEGF receptor, Axitinib, (15, 122). All these findings are resumed in Figure 2.

In sum, we found that the transcriptional programs initiated by THs through the activation of integrin αvβ3, stimulate cell proliferation and favor cell survival of TCL, thus, contributing to their malignant phenotype. Furthermore, they also lead to the production and release of angiogenic factors, thus favoring tumor dissemination.

**Inhibition of Integrin αvβ3 Receptor for TCL Treatment**

As we have already mentioned, integrin αvβ3 is highly expressed on activated tumor endothelial cells, but not on resting endothelial cells and normal organ systems (11). In addition, this membrane receptor is also highly expressed on tumor cells. This characteristic makes integrin αvβ3 an attractive target for both tumor cells and tumor vasculature.

Based on the proliferative and proangiogenic roles of THs mediated by the integrin αvβ3 in TCL cells, 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 integrin αvβ3 inhibition on tumor growth.

**FIGURE 2** | Non-genomic action of THs initiated at the surface receptor of TCL cells on the integrin αvβ3. THs induce signaling pathways triggered after binding to integrin αvβ3 include the activation of NF-κB, thus leading to the production of angiogenic factors such as VEGF and to cell proliferation, cell survival and angiogenesis. Figure adapted from Cremaschi et al. (122) with permission from Elsevier.
The negative regulation of the integrins αv or β3 in TCL cells by siRNA reduced the tumor volume and decreased the protein levels of VEGF and the blood vessel area in TCL tumors (15, 122). This suggests a decrease in the angiogenic potential of tumors derived from cells that do not express the integrin αvβ3. We then wondered whether integrin αvβ3 actions on lymphoma cells could be therapeutically capitalized for the treatment of TCL patients; and considering that PTCL-NOS is the most frequent subtype, we developed a xenograft model of human PTCL-NOS cells into SCID mice and evaluated the action of the selective inhibitor of integrin αvβ3 cilengitide. We found that cilengitide treatment reduced tumor volume by decreasing NF-κB pathway activation and the microvascular lumen size, while increasing tumor apoptosis (15). Moreover, similar effects were found in mice bearing ALCL patient-derived tumors (PDX) xenografts (15, 122). It is important to note that in mice treated with cilengitide no toxic effects were observed. These results highlight the importance of these mechanisms for the development of a more effective and less toxic therapy for patients who suffer these pathologies.

Cilengitide was the first integrin antagonist evaluated in clinical phase I and II trials for the treatment of glioblastoma and several other tumor types (123–125). No encouraging results were found in patients with glioblastoma when using cilengitide as a single agent. Some reasons for the unexpected clinical low efficacy in glioblastoma could be related to the fast off-rate of cilengitide from its targets, the rapid plasma clearance, or the poor perfusion of the brain tumor environment (43). However, it is important to note that a beneficial therapeutic action was found when administered in association with standard radiotherapy or chemotherapy (125, 126), and this was also found in other type of tumors (127, 128).

There is not much information on the role of THs and its action on integrin αvβ3 in other hematologic malignancies; however it was shown that this integrin enhance the proliferation of acute myeloid leukemia (AML) cells (129) and it is required for AML cell survival (130). Furthermore, integrin αvβ3 expressed on the worst prognostic AML cells mediates the interaction with stroma cell-derived ligands in the bone marrow niche, thus triggering a signaling cascade that is critical for the proliferation of AML cells (131). Activated integrin αvβ3/β-catenin signaling pathway in tumor microenvironment decreased the sensitivity of AML cells to tyrosine kinase inhibitor sorafenib, as well (132). Thus, inhibition of this integrin signaling pathway would also be of potential therapeutic impact in AML.

CONCLUDING REMARKS

Integrins are crucial mediators for the survival and migration of tumor cells, not only by acting directly on these cells, but also through the influence they exert on the cells of the microenvironment that surround the tumor. Due to the central role that integrins play in tumor angiogenesis and metastasis, they have become promising targets for the treatment of different types of aggressive cancers.

In this sense, integrin αvβ3 has a crucial role in inducing tumor cell migration and metastasis to distant organs. Moreover, being the membrane receptor for thyroid hormone non-genomic actions, integrin αvβ3 triggers intracellular pathways leading to TCL proliferation and survival and to tumor growth and vascularization via the production of angiogenic factors. The selective inhibition of the integrin αvβ3 in different subtypes of TCL results in the decrease of cell proliferation, tumor growth and impaired angiogenesis. The lack or low expression of integrin αvβ3 in non-active endothelial cells and in normal lymphoid cells, important actors in antitumor immune response, offers a rationale and attractive target for TCL treatment.

Moreover, integrin αvβ3 may be an attractive therapeutic tool for other neoplastic diseases. In fact, in patients with advanced solid tumors, as breast, ovary, and pancreas cancers, the benefit of medical induction of euthyroid hypothyroxinemia was demonstrated (133–136). These studies were based on the fact that integrin αvβ3 is overexpressed in these types of tumors, and, by reducing T4 levels, the cancer cell proliferation and survival and the tumor-related angiogenesis can be reduced, without affecting other important metabolic processes that are mainly regulated by T3 levels.

AUTHOR CONTRIBUTIONS

FC: conception and design, acquisition of data, writing/drafting manuscript, revising for important content, final approval of version to be published agreement for accountability of published material; HAS: writing/drafting manuscript, revising for important content, final approval of version to be published; agreement for accountability of published material; MD: revising for important content, final approval of version to be published; agreement for accountability of published material; MB: revising for important content, final approval of version to be published; agreement for accountability of published material.

FUNDING

This work was supported by the Agencia Nacional para la Promoción Científica y Técnica, PICT 2015/0874, PICT 2015/0876 and Grant for Basic Research Projects from Instituto Nacional del Cáncer, Ministerio de Salud de la República Argentina.

REFERENCES

1. Mendoza A, Hollenberg AN. New insights into thyroid hormone action. Pharmacol Ther. (2017) 173:135–45. doi:10.1016/j.pharmthera.2017.02.012
2. Lazar MA. Thyroid hormone action: a binding contract. J Clin Invest. (2003) 112:497–9. doi:10.1172/JCI19479
3. Brent GA. Mechanisms of thyroid hormone action. J Clin Invest. (2012) 122:3035–43. doi:10.1172/JCI60047
25. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell (2011) 144:646–74. doi: 10.1016/j.cell.2011.02.013

26. Lin HY, Sun M, Tang HY, Lin C, Luidens KM, Mousa SA, et al. L-Thyroxine vs. 3,3',5'-triiodo-L-thyronine and cell proliferation: activation of mitogen-activated protein kinase and phosphatidylinositol 3-kinase. Am J Physiol Cell Physiol. (2009) 296:C980–91. doi: 10.1152/ajpcell.00305.2008

27. Yang X, Purcell B, Lu S, Chang YK, Mercurio AM. Regulation of beta 4-integrin expression by epigenetic modifications in the mammary gland and during the epithelial-to-mesenchymal transition. J Cell Sci. (2009) 122(Pt 14):2473–80. doi: 10.1242/jcs.094148

28. Mori S, Kodaira M, Ito A, Okazaki M, Kawaguchi N, Hamada Y, et al. Enhanced expression of integrin αvβ3 induced by TGF-beta is required for the enhancing effect of Fibroblast Growth Factor 1 (FGF1) in TGF-beta-induced Epithelial-Mesenchymal Transition (EMT) in mammary epithelial cells. PLoS ONE (2015) 10:e0137486. doi: 10.1371/journal.pone.0137486

29. Lamouille S, Xu J, Derynk R. Molecular mechanisms of epithelial-mesenchymal transition. Nat Rev Mol Cell Biol. (2014) 15:178–96. doi: 10.1038/nrm3758

30. Carpenter BL, Chen M, Knifley T, Davis KA, Harrison SM, Stewart RL, et al. Integrin α6β4 promotes autocrine Epidermal Growth Factor Receptor (EGFR) signaling to stimulate migration and invasion toward Hepatocyte Growth Factor (HGF). J Biol Chem. (2015) 290:27228–38. doi: 10.1074/jbc.M114.688737

31. Koivisto L, Bi J, Hakkinen L, Larjava H. Integrin αvβ6: structure, function and role in health and disease. Int J Biochem Cell Biol. (2018) 99:186–96. doi: 10.1016/j.biocel.2018.04.013

32. Casal JJ, Bartolome RA. RGD catherdins and αβ1 integrin in cancer metastasis: a dangerous liaison. Biochim Biophys Acta Rev Cancer (2018) 1869:321–32. doi: 10.1016/j.bbcar.2018.04.005

33. Juan-Rivera MC, Martinez-Ferrer M. Integrin inhibitors in prostate cancer. Cancers (2018) 10:44. doi: 10.3390/cancers10020044

34. Goel HL, Li J, Kogan S, Languino LR. Integrinalfa6β6 regulates cell adhesion: identification and characterization of important N-glycosylation sites on integrinα6β6 for cell migration. Mol Cell Biol. (2017) 37:e00558-16. doi: 10.1128/MCB.00558-16

35. Kimmel CL, Lasinska I, Mackiewicz J. Integrins as a new target for cancer treatment. Trends Cancer (2018) 4:44. doi: 10.1016/j.trecan.2018.05.009

36. Friedrichs K, Ruiz P, Franke F, Gille I, Terpe HJ, Imhof BA. High expression level of α6β6 integrin in human breast carcinoma is correlated with reduced survival. Cancer Res. (1995) 55:901–6.

37. Tokmakidis SP, Leger LA. Comparison of mathematically determined blood lactate and heart rate “threshold” points and relationship with performance. Eur J Appl Physiol Occup Physiol. (1999) 82:97–106. doi: 10.1007/s00421-002-0129-5

38. Cai X, Thinn AMM, Wang Z, Shan H, Zhu J. The importance of N-glycosylation on beta3 integrin ligand binding and conformational regulation. Mol Cancer Ther. (2018) 17:328. doi: 10.1158/1051-4446.MCR-17-0220

39. Hsu CH, Bai Y, Ma Q, Wang Y, Chen J, Zhao H, et al. Targeted drug delivery with an integrin-binding knottin-Fc-MMAF conjugate produced by cell-free protein synthesis. Mol Cancer Ther. (2017) 16:3763–75. doi: 10.1158/1051-4446.MCT-16-0831

40. Huang R, Rofstad EK. Integrins as therapeutic targets in the organ-specific metastasis of human malignant melanoma. J Exp Clin Cancer Res. (2018) 37:92. doi: 10.1186/s13046-018-0763-x

41. Desgroiseller JS, Cheres DA. Integrins in cancer: biological implications and therapeutic opportunities. Nat Rev Cancer. (2010) 10:59–22. doi: 10.1038/nrc2748

42. Cheng SY, Leonard JL, Davis PJ. Molecular aspects of thyroid hormone actions. Endocrinol Rev. (2010) 31:139–70. doi: 10.1207/s15309247ero09001

43. Chan IH, Privalsky ML. 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. (2010) 8:15–23. doi: 10.1158/1541-7786.MCR-09-0425

44. Cai X, Thinn AMM, Wang Z, Shan H, Zhu J. The importance of N-glycosylation on beta3 integrin ligand binding and conformational regulation. Mol Cancer Ther. (2018) 17:328. doi: 10.1158/1051-4446.MCR-17-0220

45. Hang Q, Isaji T, Hou S, Wang Y, Fukuda T, Gu J. A key regulator of cell adhesion: identification and characterization of important N-glycosylation sites on integrinα6β6 for cell migration. Mol Cell Biol. (2017) 37:e00558-16. doi: 10.1128/MCB.00558-16

46. Kimmel CL, Lasinska I, Mackiewicz J. Integrins as a new target for cancer treatment. Trends Cancer (2018) 4:44. doi: 10.1016/j.trecan.2018.05.009

47. Friedrichs K, Ruiz P, Franke F, Gille I, Terpe HJ, Imhof BA. High expression level of α6β6 integrin in human breast carcinoma is correlated with reduced survival. Cancer Res. (1995) 55:901–6.

48. Tokmakidis SP, Leger LA. Comparison of mathematically determined blood lactate and heart rate “threshold” points and relationship with performance. Eur J Appl Physiol Occup Physiol. (1999) 82:97–106. doi: 10.1007/s00421-002-0129-5

49. Cai X, Thinn AMM, Wang Z, Shan H, Zhu J. The importance of N-glycosylation on beta3 integrin ligand binding and conformational regulation. Mol Cancer Ther. (2018) 17:328. doi: 10.1158/1051-4446.MCR-17-0220

50. Hang Q, Isaji T, Hou S, Wang Y, Fukuda T, Gu J. A key regulator of cell adhesion: identification and characterization of important N-glycosylation sites on integrinα6β6 for cell migration. Mol Cell Biol. (2017) 37:e00558-16. doi: 10.1128/MCB.00558-16

51. Cai X, Thinn AMM, Wang Z, Shan H, Zhu J. The importance of N-glycosylation on beta3 integrin ligand binding and conformational regulation. Mol Cancer Ther. (2018) 17:328. doi: 10.1158/1051-4446.MCR-17-0220

52. Hang Q, Isaji T, Hou S, Wang Y, Fukuda T, Gu J. A key regulator of cell adhesion: identification and characterization of important N-glycosylation sites on integrinα6β6 for cell migration. Mol Cell Biol. (2017) 37:e00558-16. doi: 10.1128/MCB.00558-16
64. Marucci F, Bellone M, Caserta CA, Corti A. Pushing tumor cells towards a malignant phenotype: stimuli from the microenvironment, intercellular communications and alternative roads. Int J Cancer (2014) 135:1265–76. doi: 10.1002/ijc.28352

46. Gehler S, Ponik SM, Riching KM, Keely PJ, Bi-directional signaling: extracellular matrix and integrin regulation of breast tumor progression. Crit Rev Eukaryot Gene Expr (2013) 23:139–57. doi: 10.1615/CritRevEukaryotGeneExpr.2013006647

57. Kessenbrock K, Plaks V, Werb Z. Matrix metalloproteinases: regulators of the tumor microenvironment. J Mol Med. (2005) 10:415–33. doi: 10.1006/scbi.2000.0379

50. Larsen M, Artym VV, Green JA, Yamada KM. The matrix reorganized: extracellular matrix remodeling and integrin signaling. Curr Opin Cell Biol. (2006) 18:463–71. doi: 10.1016/j.cub.2006.08.009

51. Ota D, Kanayama M, Matsui Y, Ito K, Maeda N, Kutomi G, et al. Tumor- 

52. Izumi D, Ishimoto T, Miyake K, Sugihara H, Eto K, Sawayama H, et al. CXCL12/CXCR4 activation by cancer-associated fibroblasts promotes integrin beta1 clustering and invasiveness in gastric cancer. Int J Cancer (2014) 134:1207–19. doi: 10.1002/ijc.28964

61. Li X, Yang Y, Hu Y, Dang D, Regezi JA, Schmidt B, et al. Macrophage-dependent cleavage of the laminin receptor v6 mediates the potential for colon cancer cells to extravasate and metastasize from the blood stream. Thromb Res. (2015) 36:208–27. doi: 10.1016/j.thromres.2017.09.007

62. Max R, Gerritsen RR, Nooijen PT, Goodman SL, Sutter A, Keilholz U, et al. CXCL12/CXCR4 activation by cancer-associated fibroblasts promotes integrin alpha vbeta3 expression on tumor-associated vessels of human carcinomas. Int J Cancer (1997) 71:320–4.

63. Weber MR, Zuka M, Lorger M, Tschann M, Torbett BE, Zlijistra A, et al. Activated tumor cell integrin vβ3 cooperates with platelets to promote extravasation and metastasis from the blood stream. Thromb Res. (2016) 140 (Suppl. 1):S27–36. doi: 10.1016/S0049-3848(16)30095-0

65. Nussenbaum F, Herman IM. Tumor angiogenesis: insights and innovations. J Oncol. (2010) 2010:32641. doi: 10.1155/2010/32641

66. Silva R, D’Amico G, Hodivala-Dilke KM, Reynolds LE. Integrins: the keys to unlocking angiogenesis. Arterioscler Thromb Vasc Biol. (2008) 28:1703–13. doi: 10.1161/ATVBAHA.108.172015

67. Mahalebshwar GH, Teng W, Reddy K, Plow EF, Byzhou: mechanisms of integrin-vascular endothelial growth factor receptor cross-activation in angiogenesis. Circ Res. (2007) 101:570–80. doi: 10.1161/CIRCRESAHA.107.155655

72. Max R, Gerritsen RR, Nooijen PT, Goodman SL, Sutter A, Keilholz U, et al. Integrin β3 contains a cell surface receptor site for thyroid hormone that regulates extracellular matrix degradation via the plasminogen activation cascade. Cancerogene sis (2002) 23:237–44. doi: 10.1093/carcin/23.2.237

73. Kessenbrock K, Plaks V, Werb Z. Matrix metalloproteinases: regulators of the tumor microenvironment. Cell (2010) 141:52–67. doi: 10.1016/j.cell.2010.03.015

74. Bergh JJ, Lin HY, Lansing L, Mohamed SN, Davis FB, Mousa SA, et al. Thyroid hormone is a MAPK-dependent growth factor for thyroid cancer cells and is linked to activation of mitogen-activated protein kinase and induction of angiogenesis. Endocrinology (2005) 146:2864–71. doi: 10.1210/en.2005-0102

75. Hajizadeh A, Soltani S, Mostofizadeh S. The role of α6β1 integrin in breast cancer progression. Int J Cancer (2014) 21(Suppl. 3):21–4.
84. Davis PJ, Lin HY, Sudha T, Yalcin M, Tang HY, Herbergs A, et al. Nanotetrahedral targets integrin αvβ3 on tumor cells to disorder cell defense pathways and block angiogenesis. Onco Targets Ther. (2014) 7:1619–24. doi: 10.2147/OTT.S67393

85. Goemann IM, Romitti M, Meyer ELS, Wajner SJ, Maia AL. Role of thyroid hormones in the neoplastic process: an overview. Endocr Relat Cancer (2017) 24:R367–85. doi: 10.1016/j.erc.2017-09-0192

86. Wang CS, Lin KH, Hsu YC. Alterations of thyroid hormone receptor alpha gene: frequency and association with NM23 protein expression and metastasis in gastric cancer. Cancer Lett. (2002) 175:121–7. doi: 10.1016/S0304-3835(01)00722-4

87. Lin KH, Zhu XG, Hsu HC, Chen SL, Shieh HY, Chen ST, et al. Dominant negative mutant of thyroid hormone alpha receptors from patients with hepatocellular carcinoma. Endocrinology (1997) 138:5308–15. doi: 10.1210/endo.138.12.5625

88. Horkko TT, Tuppurainen K, George SM, Bhargava M, Wattenberg EV, Ingbar DH. T3 increases Na-K-ATPase activity via a MAPK/ERK1/2-dependent pathway in rat adult alveolar epithelial cells. Am J Physiol Lung Cell Mol Physiol. (2008) 294:L749–54. doi: 10.1152/ajplung.00335.2007

89. Uchuya-Castillo J, Aznar N, Frau C, Martinez P, Le Neve C, Maris A, et al. Induction of apoptosis in T lymphoma cells by long-term treatment with thyroid hormones in the neoplastic process: an overview. Endocr Relat Cancer (2017) 24:R367–85. doi: 10.1016/j.erc.2017-09-0192

90. Hellevik AI, Asvold BO, Bjoro T, Romundstad PR, Nilsen TI, Vatten LJ. Thyroid function and cancer risk: a prospective nationwide cohort study. J Intern Med. (2010) 267:165–9. doi: 10.1111/j.1365-2796.2009.01689.x

91. Goemann IM, Romitti M, Meyer ELS, Wajner SJ, Maia AL. Role of thyroid hormones in the neoplastic process: an overview. Endocr Relat Cancer (2017) 24:R367–85. doi: 10.1016/j.erc.2017-09-0192

92. Lin KH, Zhu XG, Hsu HC, Chen SL, Shieh HY, Chen ST, et al. Dominant negative mutant of thyroid hormone alpha receptors from patients with hepatocellular carcinoma. Endocrinology (1997) 138:5308–15. doi: 10.1210/endo.138.12.5625

93. Hassan MM, Kaseb A, Li D, Patt YZ, Vauthey JN, Thomas MB, et al. Different mitogen-mediated Beta-adrenergic receptor modulation in murine T lymphocytes depending on the thyroid status. J Cell Physiol. (2013) 226:3208–18. doi: 10.1002/jcp.22681

94. Barreiro Arcos ML, Sterle HA, Vercelli C, Valli E, Cayrol MF, Klecha AJ, et al. Induction of apoptosis in T lymphoma cells by long-term treatment with thyroxine involves PKCζeta nitration by nitric oxide synthase. Apoptosis (2013) 18:1376–90. doi: 10.1007/s10495-013-0869-8

95. MacLeod F, Mate A. Life enrichment for long-stay patients in acute care: an interdisciplinary program. Perspectives (1991) 1:52–6.

96. Sterle HA, Barreiro Arcos ML, Valli E, Paulazo MA, Mendez Huergo SP, Bliden AE, et al. The thyroid status program T cell lymphoma growth and modulates immune cell frequencies. J Mol Med. (2016) 94:417–29. doi: 10.1007/s00109-015-1363-2

97. Barreiro Arcos ML, Gorelik G, Klecha A, Genaro AM, Cremaschi GA. Thyroid hormones increase inducible nitric oxide synthase gene expression downstream from PKC-ζeta in murine tumor T lymphocytes. Am J Physiol Cell Physiol. (2006) 291:C372–376. doi: 10.1152/ajpcell.00316.2005

98. Lin HY, Cody V, Davis FB, Herbergs AA, Luidens MK, Mousa SA, et al. Identification and functions of the plasma membrane receptor for thyroid hormone analogues. Discov Med. (2011) 11:337–47.

99. Lei J, Mariash CN, Bhargava M, Wattenberg EV, Ingbar DH. T3 increases Na-K-ATPase activity via a MAPK/ERK1/2-dependent pathway in rat adult alveolar epithelial cells. Am J Physiol Lung Cell Mol Physiol. (2008) 294:L749–54. doi: 10.1152/ajplung.00335.2007

100. Lin HY, Cody V, Davis FB, Herbergs AA, Luidens MK, Mousa SA, et al. Molecular modeling of the thyroid hormone interactions with αvβ3 integrin. Steroids (2007) 72:165–70. doi: 10.1016/j.steroids.2006.11.008

101. Lin HY, Landersdorfer CB, London D, Meng R, Lim CU, Lin C, et al. Pharmacodynamic modeling of anti-cancer activity of tetraiodothyroacetic acid in a perfused cell culture system. PLoS Comput Biol. (2011) 7:e1001073. doi: 10.1371/journal.pcbi.1001073

102. Sterle HA, Barreiro Arcos ML, Valli E, Paulazo MA, Mendez Huergo SP, Bliden AE, et al. The thyroid status program T cell lymphoma growth and modulates immune cell frequencies. J Mol Med. (2016) 94:417–29. doi: 10.1007/s00109-015-1363-2

103. Barreiro Arcos ML, Gorelik G, Klecha A, Genaro AM, Cremaschi GA. Thyroid hormones increase inducible nitric oxide synthase gene expression downstream from PKC-ζeta in murine tumor T lymphocytes. Am J Physiol Cell Physiol. (2006) 291:C372–376. doi: 10.1152/ajpcell.00316.2005

104. Lin HY, Cody V, Davis FB, Herbergs AA, Luidens MK, Mousa SA, et al. Molecular modeling of the thyroid hormone interactions with αvβ3 integrin. Steroids (2007) 72:165–70. doi: 10.1016/j.steroids.2006.11.008

105. Lin HY, Cody V, Davis FB, Herbergs AA, Luidens MK, Mousa SA, et al. Induction of apoptosis in T lymphoma cells by long-term treatment with thyroxine involves PKCζeta nitration by nitric oxide synthase. Apoptosis (2013) 18:1376–90. doi: 10.1007/s10495-013-0869-8

106. Lei J, Mariash CN, Bhargava M, Wattenberg EV, Ingbar DH. T3 increases Na-K-ATPase activity via a MAPK/ERK1/2-dependent pathway in rat adult alveolar epithelial cells. Am J Physiol Lung Cell Mol Physiol. (2008) 294:L749–54. doi: 10.1152/ajplung.00335.2007

107. Moeller LC, Cao X, Dumitrescu AM, Seo H, Refetoff S. Thyroid hormone mediated changes in gene expression can be initiated by cytosolic action of the thyroid hormone receptor beta through the phosphatidylinositol 3-kinase pathway. Nucl Recept Signal. (2006) 4:e020. doi: 10.1621/nrs.04020

108. Cody V, Davis PJ, Davis FB. Molecular modeling of the thyroid hormone interactions with αvβ3 integrin. Steroids (2007) 72:165–70. doi: 10.1016/j.steroids.2006.11.008

109. Lin HY, Landersdorfer CB, London D, Meng R, Lim CU, Lin C, et al. Pharmacodynamic modeling of anti-cancer activity of tetraiodothyroacetic acid in a perfused cell culture system. PLoS Comput Biol. (2011) 7:e1001073. doi: 10.1371/journal.pcbi.1001073

110. Cohen K, Hargrave P, Kamei N, Wattenberg EV, Ingbar DH. T3 increases Na-K-ATPase activity via a MAPK/ERK1/2-dependent pathway in rat adult alveolar epithelial cells. Am J Physiol Lung Cell Mol Physiol. (2008) 294:L749–54. doi: 10.1152/ajplung.00335.2007

111. Moeller LC, Cao X, Dumitrescu AM, Seo H, Refetoff S. Thyroid hormone mediated changes in gene expression can be initiated by cytosolic action of the thyroid hormone receptor beta through the phosphatidylinositol 3-kinase pathway. Nucl Recept Signal. (2006) 4:e020. doi: 10.1621/nrs.04020

112. Cody V, Davis PJ, Davis FB. Molecular modeling of the thyroid hormone interactions with αvβ3 integrin. Steroids (2007) 72:165–70. doi: 10.1016/j.steroids.2006.11.008
121. Glinskii AB, Glinsky GV, Lin HY, Tang HY, Sun M, Davis FB, et al. Modification of survival pathway gene expression in human breast cancer cells by tetraiodothyroacetic acid (tetrac). *Cell Cycle* (2009) 8:3562–70. doi: 10.4161/cc.8.21.9963

122. Cremaschi GA, Cayrol F, Sterle HA, Diaz Flaque MC, Barreiro Arcos ML. Thyroid hormones and their membrane receptors as therapeutic targets for T cell lymphomas. *Pharmacol Res.* (2016) 109:55–63. doi: 10.1016/j.phrs.2016.02.001

123. Beekman KW, Colevas AD, Cooney K, Dipaola R, Dunn RL, Gross M, et al. Phase II evaluations of cilengitide in asymptomatic patients with androgen-independent prostate cancer: scientific rationale and study design. *Clin Genitourin Cancer* (2006) 4:299–302. doi: 10.3816/CGC.2006.n.012

124. Friess H, Langrehr JM, Oettle H, Raedle J, Niedergethmann M, Ditrich C, et al. 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* (2006) 6:285. doi: 10.1186/1471-2407-6-285

125. Scaringi C, Minniti G, Caporello P, Enrici RM. Integrin inhibitor cilengitide for the treatment of glioblastoma: a brief overview of current clinical results. *Anticancer Res.* (2012) 32:4213–23.

126. Li M, Song X, Zhu J, Fu A, Li J, Chen T. The interventional effect of new drugs combined with the Stupp protocol on glioblastoma: a network meta-analysis. *Clin Neurol Neurosurg.* (2017) 159:125–32. doi: 10.1016/j.clineuro.2017.05.015

127. Cedra S, Wieggand S, Kolb M, Dietz A, Wichmann G. Reduced cytokine release in *ex vivo* response to cilengitide and cetuximab is a marker for improved survival of head and neck cancer patients. *Cancers* (2017) 9:E117. doi: 10.3390/cancers9090117

128. Massabeau C, Khalifa J, Filleron T, Modesto A, Bigay-Game L, Plat G, et al. Continuous infusion of cilengitide plus chemoradiotherapy for patients with stage III non-small-cell lung cancer: a phase I study. *Clin Lung Cancer* (2018) 19:e277–85. doi: 10.1016/j.clc.2017.11.002

129. Shah CA, Bei L, Wang H, Altman JK, Platianis LC, Eklund EA. Cooperation between αvβ3 integrin and the fibroblast growth factor receptor enhances proliferation of Hox-overexpressing acute myeloid leukemia cells. *Oncotarget* (2016) 7:54782–94. doi: 10.18632/oncotarget.10189

130. Miller PG, Al-Shahrour F, Hartwell KA, Chu LP, Jaras M, Puram RV, et al. In vivo RNAi screening identifies a leukemia-specific dependence on integrin beta 3 signaling. *Cancer Cell* (2013) 24:45–58. doi: 10.1016/j.ccr.2013.05.004

131. Zeisig BB, So CW. Linking MLL leukemia with integrin signaling. *Cancer Cell* (2013) 24:5–7. doi: 10.1016/j.ccr.2013.06.011

132. Yi H, Zeng D, Shen Z, Liao J, Wang X, Liu Y, et al. Integrin αvβ3 enhances beta-catenin signaling in acute myeloid leukemia harboring Fms-like tyrosine kinase-3 internal tandem duplication mutations: implications for microenvironment influence on sorafenib sensitivity. *Oncotarget* (2016) 7:40387–97. doi: 10.18632/oncotarget.9617

133. Hercregs A, Davis PJ, Lin HY, Mousa SA. Possible contributions of thyroid hormone replacement to specific behaviors of cancer. *Biomed Pharmacother.* (2016) 84:655–9. doi: 10.1016/j.biopha.2016.09.053

134. Hercregs A, Mousa SA, Leinung M, Lin HY, Davis PJ. Thyroid hormone in the clinic and breast cancer. *Horm Cancer* (2018) 9:139–43. doi: 10.1007/s12672-018-0326-9

135. Mousa SA, Glinsky GV, Lin HY, Ashur-Fabian O, Hercregs A, Keating KA, et al. Contributions of thyroid hormone to cancer metastasis. *Biomedicines* (2018) 6:357. doi: 10.3390/biomedicines6030089

136. Massabeau C, Khalifa J, Filleron T, Modesto A, Bigay-Game L, Plattianis LC, et al. Contributions of thyroid hormone to cancer metastasis. *Biomedicines* (2018) 6:357. doi: 10.3390/biomedicines6030089

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

*Copyright © 2019 Cayrol, Sterle, Díaz Flaque, Barreiro Arcos and Cremaschi. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.*