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RESEARCH ARTICLE

Documented and projected actions *in vitro* of thyroid hormone as L -thyroxine (T4) on basal cell carcinoma of the skin

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ABSTRACT

Thyroid hormone as L-thyroxine (T4) at physiological concentrations acts at its cell surface receptor on integrin $\alpha v\beta 3$ to stimulate cancer cell proliferation[1]. These proliferation studies have been conducted *in vitro*, but pharmacological reduction of T4 and substitution of nuclear receptor ligand 3,3',5-triiodo-L-thyronine (T3) is a state of euthyroid hypothyroxinemia that has been shown clinically to arrest tumor growth in patients with cancer. T3 is inactive at physiological levels at the plasma membrane integrin receptor. A preclinical study of human basal cell carcinoma (BCC) cells has shown that the integrin thyroid hormone receptor regulates BCC radiosensitivity. While the large majority of BCCs are very manageable clinically, a small number of such tumors are aggressive. In this review of documented and proposed effects of T4 on BCC cells, we raise the possibility that BCC aggressiveness reflects T4 actions on its thyrointegrin target. The functions affected by T4 at the integrin in other human cancers include enhanced cell proliferation, anti-apoptosis, immune checkpoint regulation and metastasis, as well as state of radiosensitivity. The importance of investigating this possible pathophysiology is that euthyroid hypothyroxinemia may be tested as a treatment option.

Keywords: integrin, thyrointegrin, radioresistance, apoptosis, metastasis, L-thyroxine (T4), 3,5,3;-triiodo-L-thyronine (T3).

Introduction

Classical genomic actions of thyroid hormone (TH) are initiated at nuclear TH receptors (TRs), for which the principal ligand is 3,5,3′-triiodo-L-thyronine (T3)[2]. The major product of the thyroid gland is L-thyroxine (T4), the prohormone for T3[1,2]. Nongenomic actions of TH are initiated at a cell surface receptor for thyroid hormone analogues on the extracellular domain of plasma membrane integrin αvβ3[1, 3]. Functionally, the principal TH ligand of this receptor is T4. Downstream of the integrin receptor for thyroid hormone, signal transduction systems may convert T4-generated signals into expression of specific genes[1]. In normal adult cells, integrin αvβ3 is modestly expressed and is largely in an inactive (folded) state[4]. In cancer cells and in rapidly-dividing endothelial cells, however, integrin αvβ3 is usually overexpressed and is in an activated (extended) state[1]. In such cells, T4 in physiological concentrations may importantly stimulate cell division via modulation of transcription of specific genes. Expression of a large number of other genes in cancer cells is differentially regulated by T4 at the integrin to foster anti-apoptosis[5], radioresistance[6] and angiogenesis[7,8], as discussed in this review. Many types of cancer cells have in preclinical studies been shown to respond to T4[1, 9-13]. Clinical evidence has shown that the growth of a variety of cancers is slowed by hypothyroidism[14-16] and that elimination of host T4 with maintenance of euthyroidism with T3 ('euthyroid hypothyroxinemia')[17] prolongs survival of cancer patients.

Cutaneous cancers shown to be responsive to thyroid hormone in clinical or preclinical studies are melanoma[18-21] and squamous cell carcinoma[22,23]. That both genomic and nongenomic molecular mechanisms of TH action are involved in these two types of cancer cells has been suggested. In an *in vitro* study of radioresistant human basal cell carcinoma (BCC) cells, Leith et al. described induction of radiosensitivity by tetraiodothyroacetic acid (tetrac)[24], a deaminated analogue of T4. This set of observations indicates that integrin αvβ3 is expressed by these cells and is in an activated state. The report also shows that BCC cells that are radioresistant can have the latter state reversed. Finally, Leith provides a basis for speculating—because of the expression and activation of the thyrointegrin—that when BCC is sometimes difficult to manage, the T4 receptor and its ligand T4 may be contributory[25]. In this brief review, we discuss possible contributions to BCC functional states that the thyrointegrin may support. These states described in BCC cells include radioresistance[24, 25], pro-angiogenesis,[26] immune checkpoint inhibition[27], anti-apoptosis[28, 29] and metastasis[30]. Much of this evidence has been developed via *in vitro* studies.

αvβ3 and Radioresistance in BCC cells

Lovett et al.[31] found that tumor control was achieved in 91% of BCC patients treated with one or more radiotherapeutic modalities (superficial ex-irradiation, electrons or megavoltage irradiation). Achievement of control was primarily related to lesion size, so that 97% of tumors <1 cm in diameter were successfully treated and control was obtained in 87% of lesions that were 1-to-5 cm in diameter. As noted above in the Introduction,

BCC patients with radioresistance are of particular interest to us because we have shown that radioresistance in BCC cells[24] and in other tumor cells[32] is subject to regulation by the cell surface integrin receptor for thyroid hormone and whether αvβ3 is activated/extended. The activated integrin is a basis for increased intercellular affinity (integrin-integrin and integrin-extracellular matrix protein interactions) and decreased intercellular space, resulting in inhibition of cell division and, thus, radioresistance[32].

Tetrac binds to the thyroid hormone receptor on integrin ntegrin αvβ3, reduces integrin-integrin affinity and restores radiosensitivity[25, 32]. The liganding of T4 by the integrin has activating functions that deal largely downstream (signal transduction) with differential expression of a large number of genes related to cancer cell self-protection[1], as discussed below. A systematic investigation of possible effects of T4 on radioresistance has not yet been carried out.

αvβ3, T4 and Angiogenesis

Examined in the fertilized chicken egg chorioallantoic membrane (CAM) model, T4 at physiological concentratiomns has been shown to enhance significantly the transcription of a variety of genes relevant to angiogenesis[7, 8]. These include genes coding for vascular endothelial growth factor (*VEGF*), basis fibroblast growth factor (*bFGF*), platelet-derived growth factor (*PDGF*) and epidermal growth factor (*EGF*)[1, 7, 8]. T3 is active only at supraphysiological levels in the CAM system. These effects of T4 on angiogenesis are initiated at the thyroid hormone analogue receptor on αvβ3. We propose that this activity of T4 on vasculature is likely to be reproduced in BCC that is metastatic.

αvβ3, T4 and Immune Checkpoint Proteins

A cohort of BCC patients was recently reported to have substantial circulating levels of soluble immune checkpoint proteins[33]. These proteins included PD-1/PD-L1, CTLA-4 and TIM3. More than 50% of the 40 patients studied had infiltrating tumors, suggesting that the patients were in a state of systemic immunosuppression imposed by the checkpoint proteins and fostering aggressive skin disease. This raises the possibility that administration of checkpoint inhibitors might improve BCC management when the disease is extensive.

Acting at tumor cell surface αvβ3, T4 has been shown to regulate signal transduction pathway activities that determine cellular accumulation of PD-L1 and PD-1 that is anti-apoptotic[34, 35]. This may also serve to reduce the effectiveness of host immune checkpoint-based anti-cancer defense. Thyroid function testing and measurements of immune checkpoint proteins is needed in additional patient populations with aggressive BCC, e.g., metastatic BCC.

αvβ3, T4 and Anti-Apoptosis

Thyroid hormone as T4 has anti-apoptotic properties in cancer cells[36]. The mechanisms include blockade of Ser-15 phosphorylation (activation) of p53 and upregulation of expression of anti-apoptotic genes such as X-linked inhibitor of apoptosis (*XIAP*) and hypoxia-inducible factor-1α (*HIF-1χ*). The excessive ultraviolet (UV) light that induces

BCC is also known to inhibit p53-dependent apoptosis and, via the hedgehog signaling pathway, to upregulate transcription of anti-apoptotic genes[37]. Other anti-apoptotic mechanisms may be operative in BCC[38] and, as mentioned above, T4 action on certain immune checkpoint proteins may inhibit apoptosis. We raise the possibility that borderline elevated levels of T4, e.g., in the upper tertile of the normal range or frankly elevated free T4 levels that may occur in non-thyroidal illness syndrome (NTIS)[39], may synergize with continuing host UV exposure to support aggressive behavior of BCC cells.

αvβ3, T4 and Metastasis

Metastasis of BCC occurs infrequently, but can be fatal[40-42]. Mechanisms supporting BCC metastasis are incompletely defined. Because thyrointegrin αvβ3 is functional in BCC cells[24], we raise the possibility here that endogenous T4 that is elevated in NTIS[39] or simply in the upper tertile of the normal range may contribute to metastasis of tumors of many types[1, 43]. We propose that this applies to BCC and that host free T4 be measured clinically in BCC patients with and without metastases to test this hypothesis.

Mousa et al.[43] have reviewed the mechanisms by which T4 at the TH receptor on αvβ3 may support metastasis. Integrin αvβ3 molecules on tumor cells and on the platelet surface are both subject to activation—conversion of the folded state to the extended state of the extracellular component of the integrin—by physiological concentrations of T4[1,44]. In the T4-containing circulation in patients, platelets and free tumor cells bearing activated integrin will form complexes. The complexes are resistant to shear forces in the circulation and resistant to natural killer (NK) cells[45]. Platelet ATP freed up by T4 in the complexes may be additional support for tumor cell invasiveness[44]. T4 may also potentiate the local actions of any platelet-derived growth factors (PDGFs)[1].

Tumor cell matrix metalloproteinase *(MMP) gene* expression *(MMP-2, MMP-9)* supports solubilizing the extracellular matrix at the primary tumor site and at potential sites of metastases[43]. Thyroid hormone analogues acting at αvβ3 regulate transcription of these genes; a synthetic T4 antagonist, nano-diamo-tetrac (NDAT), downregulates MMP gene expression in cancer cells and we have proposed that the primary endogenous ligand of the integrin, T4, facilitates metastasis by upregulating MMP genes[43].

As noted above, we have shown that T4 in the setting of cancer is highly pro-angiogenic via various mechanisms that are regulated from the thyroid hormone receptor on αvβ3[1]. The pro-angiogenic activity is an important support factor for tumor metastasis. Cancer driver genes are genes whose mutation may support cancer growth in the primary tumor and in metastases. Actions of thyroid hormone analogues at integrin αvβ3 modulate expression of at least a dozen driver genes[43]. We have suggested that this is another mechanism by which T4 stimulates metastasis and by which T4 antagonists retard the metastatic process[43].

The processes listed here are possible factors contributing to metastasis when the latter arises in s BCC.

Discussion and Conclusions

Skin cancers such as melanoma and squamous cell carcinoma (SCC) are aggressive clinical

entities that are difficult to manage. There is evidence that the TH receptor on integrin αvβ3 may mediate adverse clinical behaviors in melanoma[20]. A role for the integtrin TH receptor in SCC has not been fully established, but T4—the principal ligand for the integrin thyroid hormone receptor—may be a growth factor for this type of cancer[22, 23]. Our review here of the mechanisms that underlie aggressive behavior that occasionally complicates BCC was enabled by the demonstration by Leith[24, 25, 32] that thyroid hormone analogue actions in BCC cells can alter the state of radiosensitivity. This means that αvβ3 is in a functional (activated) state in BCC cells and can contribute additional pro-cancer actions we considered here, namely, anti-apoptosis, angiogenesis and metastasis.

We propose that *in vitro* comparison studies of aggressive BCC cells vs. non-aggressive BCC cells be carried out to look for T4-sensitive changes in cell proliferation, radiosensitivity and metastasis. We raised the issue of immune checkpoint function in BCC cells that have activated integrin TH receptors for two reasons: 1) Lin et al. have demonstrated T4 control of PD-1/PD-L1 immune checkpoints in several types of cancer cells[34, 35] and 2) BCC patients have been shown to have systemic evidence of increased immune checkpoint activity[33].

There are several clinical settings in which T4 actions on BCC cells at integrin αvβ3 may be manifested. First, systemically ill patients with the nonthyroidal illness syndrome (NTIS) may have elevated circulating T4 levels. [39]. Second, we feel that the sensitivity of the integrin to T4 is such that levels of endogenous free T4 or pharmacological T4 replacement may result in free T4 concentrations in the upper tertile of the normal range; these levels may be sufficient to induce αvβ3-mediated enhancement of cell proliferation. Third, patients with thyroid cancer whose management includes suppression of endogenous thyrotropin (TSH) with exogenous T4 may have elevated circulating free T4. While there may be an epidemiologic association of basal cell carcinoma of the skin with thyroid cancer[46,47], this has not yet been critically examined from the standpoints of relative dates of onset of the two conditions and aggressiveness of the skin disease.

There are potentially important therapeutic implications of the presence of activated, T4-responsive αvβ3 in aggressive BCC cells. We have pointed out above that induction of euthyroid hypothyroxinemia—ridding the patient of T4, but maintaining the normal metabolic acid (tetrac)—is an option. A hallmark of tumor support actions of T4 initiated at the cancer cell surface integrin is the susceptibility of such actions to blockade with tetrac[1]. In preclinical studies, tetrac and chemically-modified tetrac in the absence of T4 have anticancer activity against a variety of tumor types[11,12,50-54] and a clinical trial of chemically-modified tetrac as an anticancer against nervous system tumor is currently in progress (SA Mousa, J Lynch, PJ Davis). The immune checkpoint actions of tetrac mentioned above are attractive for application to locally aggressive BCC[55]. Tetrac will also disrupt T4 action on epithelial-to-mesenchymal transition (EMT)[56] because this action is αvβ3-mediated; BCC is EMT-dependent[57]. Actions of tetrac on *ERBB2* and *AKT* driver gene expression[1] may be relevant to Hedgehog pathway signaling[58] which is prominent in BCC[55,59]. Thus, from the standpoints of pathogenesis and possible treatment, roles for T4 in aggressive BCC require further examination.

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