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Review

Possible contributions of thyroid hormone replacement to specific behaviors of cancer

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ABSTRACT

L-Thyroxine (T_4) is the principal replacement hormone for patients who have hypothyroidism. Some preclinical and clinical evidence supports the possibility that T_4 can at least permissively affect certain features of established cancers and cancer-relevant angiogenesis. Thus, in the occasional patient with hypothyroidism and concomitant cancer, it appears reasonable to consider thyroid hormone replacement exclusively with 3,3′,5-triiodo-L-thyronine (T_3). This use of T_3 has been shown to be effective and safe in early experience with medical induction of euthyroid hypothyroxinemia in patients with advanced solid tumors.

Contents

1. Introduction

L-Thyroxine (T_4) is the principal secretory product of the thyroid gland. It serves as a prohormone for 3,5,3′-triiodo-L-thyronine (T_3) in the latter's intracellular functions [1,2]. T_3 mediates the critical intracellular actions of the hormone on transcription of specific genes that require primary interactions between T_3 and its nuclear receptor proteins (TRs) [1,2]. T_3 also regulates mitochondrial respiration [3]. Because its biological half-life is significantly longer than that of T_3, T_4 is the most commonly prescribed form of thyroid hormone replacement for clinical hypothyroidism and for suppression of endogenous thyrotropin (TSH) release in patients with differentiated thyroid carcinoma (DTC). In addition to serving as a prohormone for T_3, T_4 has a panel of distinctive cellular functions that are relevant to oncology [4,5] and that we briefly review here.

2. T_4 as a hormone

T_4 has actions that transcend the role of prohormone. For example, T_4 has been shown to regulate the state of the actin cytoskeleton [6,7] that is essential to cell structure and intracellular trafficking of proteins and other factors, whereas T_3 does not affect the state of actin (soluble vs. fibrous forms). A receptor site for thyroid hormone has also been described on the extracellular

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domain of the plasma membrane protein, integrin αvβ3 [8,9]. At physiological free hormone concentrations, T_4 is active at this receptor [8,10]. *In vitro* evidence [10,11] and clinical evidence [12] indicates that T_3, bound with a lower affinity by αvβ3 [8], is of low activity at physiological levels at the receptor. From this receptor and without entering the cell, T_4 regulates trafficking of specific proteins (e.g., ERα, TR, p53) and via signal transducing kinases influences transcription of specific cancer-relevant genes (Fig. 1) [4,5,13]. Because the integrin is primarily expressed by cancer cells and by dividing endothelial cells, actions of T_4 that are initiated at the cell surface relate importantly to oncology. T_4 can, however, stimulate angiogenesis that is not relevant to tumors and has been documented to be pro-angiogenic in a variety of non-cancer models [8,14–17].

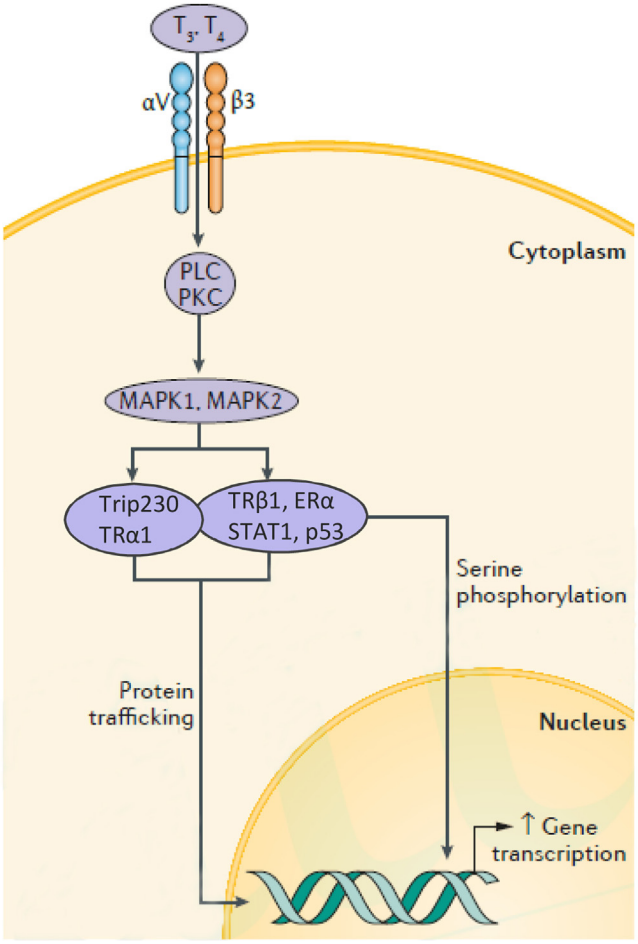

Fig. 1. Diagram of selected cellular actions of nongenomic thyroid hormone effects relevant to the cancer cell. Acting at a receptor on the extracellular domain of plasma membrane integrin αvβ3, thyroid hormone—primarily as L-thyroxine, T_4—activates phospholipase C (PLC) and protein kinase C (PKC) and, downstream, mitogen-activated protein kinase (MAPK; extracellular signal-regulated kinases, ERK1/2). MAPK promotes trafficking of specific proteins from cytoplasm into the nucleus and their phosphorylation. Among these proteins are the nuclear thyroid hormone receptor (TRβ1) resident in cytoplasm, nuclear estrogen receptor (ERα) in cytoplasm, signal transducing and activator of transcription-1α (STAT1α) and p53. Activation of such proteins via phosphorylation alters transcription of a number of specific genes and production of mRNAs whose products are relevant to cell division and cancer cell survival. T_4 also nongenomically regulates the state of actin and the cytoskeleton, but whether αvβ3 mediates this action is not known. These actions of thyroid hormone are reviewed in references [4,13] Davis et al. A number of extracellular matrix proteins (vitronectin, etc.) also bind to the integrin at sites unrelated to the thyroid hormone receptor.
Reprinted from reference [5], Davis et al. (2016).

3. T_4 and cancer biology

We have shown that T_4 in physiological free hormone concentrations stimulates proliferation of a variety of cancer cells *in vitro* and in xenografts [10,11,18–23]. The cancer cell genes regulated by T_4 are relevant to control of cell proliferation, to cancer cell defense pathways [5,13] and to angiogenesis [24,25]. Blocking of the binding of T_4 to nonmalignant cells does not affect cell proliferation (JT Leith, A Hercbergs, manuscript submitted, 2016).

Among the human cancer lines shown to proliferate in response to actions of physiological concentrations of T_4 at integrin αvβ3 are glioblastoma [26], non-small cell lung carcinoma (NSCLC) [27], triple-negative breast carcinoma [28], ovarian carcinoma [29], colon cancer [28] and myeloma cells [30]. Interestingly, follicular and papillary thyroid cancer cells also proliferate in response to T_4 *in vitro* [23] and this is discussed in more detail in section 5, Implications for Prescribing T_4, below. Depriving intraocular implants of melanoma cells of thyroid hormone arrests the cells [31]. Preclinical studies of the blocking thyroid hormone action at integrin αvβ3 in a variety of tumor xenografts with an inhibitory formulation of a thyroid hormone derivative, tetraiodothyroacetic acid (tetrac), have shown arrested tumor growth [4,5]. Among the xenografts subject to this effect are renal cell carcinoma [18], NSCLC [27], medullary carcinoma of the thyroid [20], pancreatic carcinoma [19] and multi-drug resistant breast cancer [32].

That there are clinical ramifications of these effects on cancer cells is supported by the results of induction of the state of euthyroid hypothyroxinemia in patients with advanced cancers with normal thyroid function [12]. Improved duration of clinical survival and solid tumor shrinkage have been described in such patients whose serum T_4 levels have been importantly reduced. The state is produced by a) administration of an antithyroid drug, methimazole, to block host thyroid gland synthesis of T_4 with b) the addition of T_3 as thyroid hormone replacement.

The molecular basis for these cancer-relevant thyroid hormone effects on cell proliferation (Fig. 2) initiated at αvβ3 includes dependence downstream of the receptor on mitogen-activated protein kinase (MAPK) activation [26] and nucleoprotein phosphorylation [5]. Studies of the deprivation of tumor cells of the actions of T_4 with tetrac or a tetrac formulation infer that there are integrin-mediated actions of the hormone on control of the cell cycle, prevention of apoptosis and support of chemoresistance [4,25,33]. We emphasize that these integrin-based effects of T_4 are largely limited to cancer cells and tumor-relevant dividing endothelial cells, because non-dividing, nonmalignant cells, except for osteoclasts, express low quantities of αvβ3 [1,4].

4. T_4, angiogenesis and apoptosis

As noted, T_4 is pro-angiogenic and this effect, in the absence of cancer, is desirable in the setting of wound repair and healing. In solid tumor management, however, anti-angiogenesis is a goal that remains under broadly based, if somewhat disappointing, investigation [34,35]. By multiple mechanisms [14,16,17,24,36], normal circulating levels of thyroid hormone may contribute to the limited effectiveness of anti-angiogenic agents in the setting of cancer. Among the molecular mechanisms by which the hormone stimulates angiogenesis are induction of transcription of vascular growth factor genes, such as basic fibroblast growth factor (bFGF) [14,37,38], vascular endothelial growth factor (VEGF) [39] and VEGFA [38]. The hormone also stimulates transcription of the gene coding for bFGFR [37], the receptor for bFGF. Expression of the polyfunctional, pro-angiogenic hypoxia-inducible factor-1α (HIF-1α) gene is also subject to induction by thyroid hormone [26,39]. Matrix metalloproteinase-9 (MMP-9) transcription is stimulated