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Review Article

Hypothyroidism: A Glimmer of Hope in Head and Neck Cancer?

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Abstract

Thyroid hormones play important roles in regulating normal metabolism, development, growth and differentiation of normal cells. Thyroid hormones have also been implicated in cellular transition, tumorigenesis and metastasis. They act via a cell surface receptor on integrin αvβ3 which regulate the expression of a large panel of genes relevant to cancer cell proliferation, cancer cell pathways and tumor-linked angiogenesis. Thus, thyroid hormones (T_3, T_4) and thyroid hormone antagonist, tetraiodothyroacetic acid (Tetrac) may have a role in respectively promoting & inhibiting metastasis.

Keywords: *Thyroid hormone, Integrin αvβ3, Overall survival, Metastasis, Tetrac*

Introduction

Thyroid hormones, by virtue of their influence on metabolic pathways, have been implicated in the processes of tumor cell proliferation, differentiation, and metastasis.[1,2]These actions of thyroid hormones are through a receptor on the extracellular domain integrin αvβ3. This integrin is expressed primarily by cancer cells and dividing endothelial cells that are related to cancer[3]. L-Thyroxine primarily binds to integrin αvβ3 at physiological concentrations and promotes cancer metastasis. As the thyroid gland falls in the field of treatment in most head and neck cancer cases, the effect of thyroid hormones on head and neck cancer needs to be fully understood.

Numerous animal and human tumors have shown enhanced survival and decreased tumorigenicity when exposed to hypothyroidism and very little is known about the effect of hypothyroidism on Head and neck cancer. A prospective study by Marc Nelson et al consisting of 155 patients out of which 59 patients developed hypothyroidism (defined as thyrotropin level greater than 5.5mIU/L), showed better survival than patients who did not develop hypothyroidism although a statistical significance was not achieved in this case[4]. A recent prospective trial was done to investigate the effectiveness of induced hypothyroidism on outcomes in patients with high-grade recurrent glioma.

In this study, 34 patients were given propylthiouracil and Lugol's solution, and 28 of the 34 patients were also given tamoxifen. Only one patient developed symptoms of hypothyroidism while eighteen developed biochemical hypothyroidism. The positive response by magnetic resonance imaging criteria was observed in 5 (28%) of the 18 hypothyroid patients compared to 0 (n=16) in the euthyroid group (P.04). According to preliminary findings, the median survival for the hypothyroid group was 10.6 months compared to 3.1 months for the euthyroid group (P.002) [5]. There are various mechanisms proposed by which thyroid hormones regulate cancer cell proliferation (Figure 1). Understanding the mechanisms by which thyroid hormones promote tumor cell proliferation and metastatic dissemination becomes important to devise preventive measures that could control the disease process and ultimately have an influence on the overall survival of the patient.

Relevant biological mechanisms of thyroid hormone activity in cancer metastasis

Angiogenesis and metastasis

Physiological T4 levels have been shown in animal studies to have proangiogenic effects [6]. The transcription of the VEGF, bFGF, and platelet-derived growth factor (PDGF) genes are all influenced by thyroid hormones. Thyroid hormone stimulates the expression of the EGFR gene, and epidermal growth factor (EGF) also possesses proangiogenic properties. [7,8]

Transforming growth factor β and metastasis

TGF β regulates functions like cell proliferation, differentiation, and functional behavior. In the context of cancer, the growth factor promotes metastasis through actions on angiogenesis, lymphangiogenesis, and transendothelial migration of prometastatic cancer cells. T4 has been shown to increase TGF β -induced normal airway smooth muscle cell proliferation, which is mediated by the hormone receptor on integrin αvβ3[9].

Matrix metalloproteinase gene expression and metastasis

The process of liberating cancer cells from a primary tumor or allowing circulating tumor cells to be seated at a distant site is dependent on the extracellular matrix being dissolved at the primary lesion and metastatic sites, respectively. MMPs are required for the dissolution of the extracellular matrices during cancer metastasis. Thyroid hormones have been shown to enhance the expression and activity of MMPs [10].

Epithelial-mesenchymal transition and metastasis

Thyroid hormone has been shown to promote EMT by acting on the hormone receptor on integrin αvβ3. EMT is linked with the formation of cells capable of metastasis. The process is based on the hormone-inducing β-catenin as well as certain downstream molecular targets of the catenin[11].

Fibronectin and metastasis

Thyroid hormone is known to regulate fibronectin expression via a signal transduction pathway involving PI3K/Akt and hypoxia-inducible factor-1 (HIF-1α). Plasma fibronectin has been shown to promote metastasis by inducing tumor cell invasiveness, which is dependent on integrin αvβ3 activation[12].

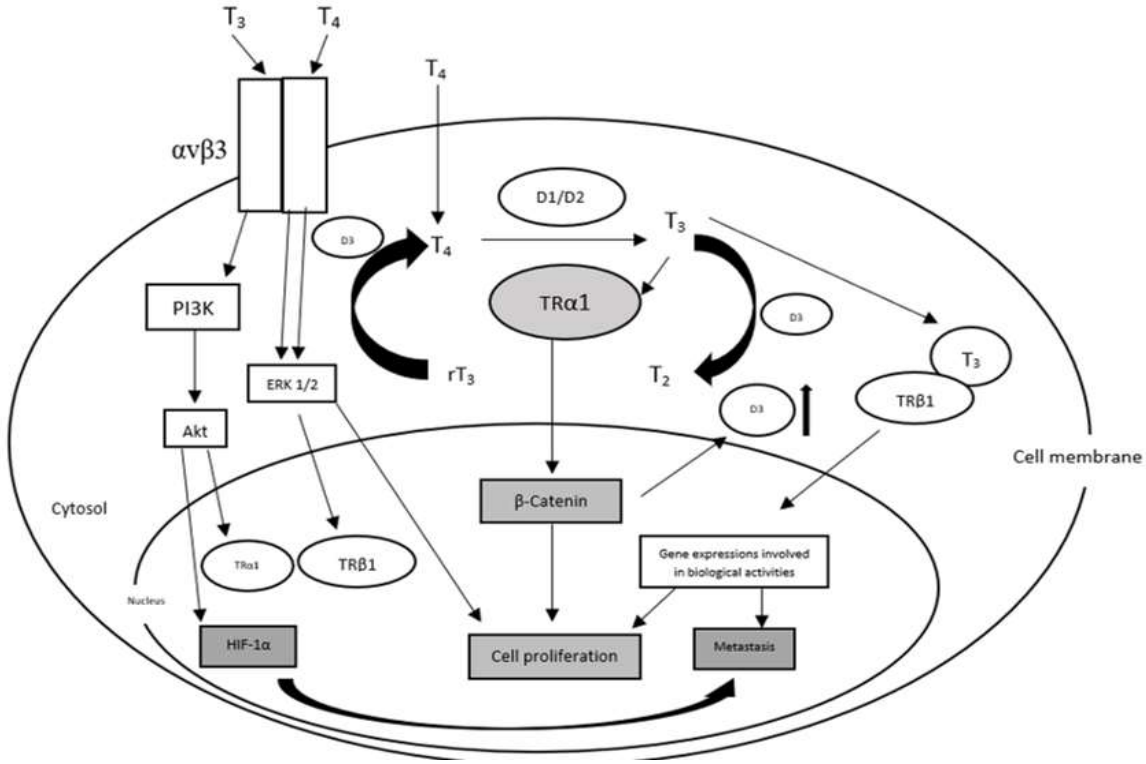

Figure 1 The schematic diagram depicts the proposed mechanisms by which thyroid hormone regulates cancer cell proliferation[13]. [Redrawn from Lin HY, Chin YT, Yang YC, Lai HY, Whang-Peng J, Liu LF, Tang HY, Davis PJ. Thyroid hormone, cancer, and apoptosis. Comprehensive Physiology. 2011 Jan 17;6(3):1221-37]

T4 enters the cell membrane via active transporters and is converted to T3 by a deiodinase in one mechanism (D1 or D2). When T3 binds to a nuclear thyroid hormone receptor 1, the protein β-catenin increases in abundance and translocates to the nucleus, where it stimulates cell proliferation. When T3 binds to TRα1, normal thyroid hormone-dependent biological activities occur, as well as an antiproliferative effect in cancer cells. However, TR1α's antiproliferative effect is diminished by D3 overexpression induced by TR-enhanced catenin-dependent mechanisms. T4 and, to a lesser extent, T3 binds to integrin αvβ3 and activate ERK1/2 phosphorylation, thereby non-genomically stimulating cancer cell proliferation. When T3 binds to integrin αvβ3, it not only phosphorylates ERK1/2 but also activates Akt by triggering PI3K phosphorylation. As a result, Akt increases HIF-1 expression, which then promotes cancer cell metastasis. The open boxes represent normal signal pathways, while the coloured boxes represent signals involved in cancer progression.

Role of tetraiodothyroacetic acid (tetrac)

Studies have shown that tetraiodothyroacetic acid (tetrac) which is a deaminated metabolite of T4, competitively inhibits the binding of T4 and T3 to αvβ3 and disorders the crosstalk between αvβ3 and tumor-promoting factors[14]. Tetrac also restores resveratrol's p53-dependent proapoptotic properties in cancer cells exposed to T4, which inhibits apoptosis[15].

Since the thyroid gland is in close proximity to most Head and neck cancers, patients receiving radiotherapy usually are prone to radiation-induced hypothyroidism (RIHT). This, however, can be beneficial in terms of the above-discussed mechanisms of thyroid hormones promoting cancer metastasis provided it is maintained at subclinical level. The optimal duration of hypothyroidism to achieve a better outcome is not extensively reported in the literature.

Conclusion

Limited data from trials indicate that maintaining patients at subclinical levels of hypothyroidism can be beneficial and in turn, increase overall survival in Head and neck cancer patients. Larger, prospective studies are necessary to test this hypothesis.

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