Thyrotropin Suppressive Therapy in Thyroid Carcinoma: What Are the Targets?

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Published guidelines on the treatment of thyroid carcinoma support TSH suppressive therapy as the standard of care for long-term follow-up after initial surgery and sequential radioiodine application (1, 2). This guidance based on large retrospective studies may be criticized on several grounds; in particular, they were not uniformly performed to current standards of surgical intervention, postoperative radioactive iodine treatment, standardized thyroxine preparations, or tailored TSH suppression using sensitive TSH assays (3). However, recent findings have largely resolved these uncertainties and confirm the beneficial effects of TSH suppressive treatment in patients with thyroid cancer (4, 5). Another important finding of these newer studies was that high-risk patients appear to respond better than patients carrying a low risk (5).

Pathophysiological Basis of TSH Suppressive Therapy

The pathophysiological basis of this beneficial effect of TSH suppression seems straightforward considering the wealth of literature on the growth-promoting effects of TSH, both in animal models and in humans (6). An increased prevalence of thyroid cancer in patients with Graves' disease, even though still controversial, seems to support further the concept of TSH or thyroid-stimulating antibody dependency in thyroid carcinomas (7). Small series of patients suggest that the risk for cancer recurrence or metastatic disease may be increased in Graves' disease. However, available results from thyroid carcinoma raise a number of serious questions concerning TSH receptor expression, activation, and the cellular response to TSH stimulation. As enumerated in the following paragraphs, the data suggest the possibility of direct thyroid hormone-dependent cellular effects rather than TSH-mediated actions.

First, TSH receptor expression may be partly or completely lost in thyroid carcinomas. Durante *et al.* (8) recently confirmed previous studies demonstrating a substantial decrease in TSH receptor mRNA levels in thyroid carcinomas with a complete loss in some of the most dedifferentiated tumors (7, 8). These findings were confirmed at the protein level with a complete loss of TSH receptor protein expression on Western blot analysis and a loss of TSH binding to the receptor preparation in some of the dedifferentiated tumors (9). These results cast serious doubt on a purely TSH driven effect, at least in dedifferentiated tumors.

Second, activation of the TSH receptor primarily induces a differentiation signal, and not a growth promoting, dedifferentiation signal. In an elegant study of patients treated preoperatively with TSH suppressive doses of thyroxine, markers of thyroid differentiation were significantly reduced compared with untreated controls (10). The effects of TSH on thyroid differentiation may explain why humans bearing constitutively active TSH receptor mutants do not have an increased rate of thyroid cancer. Furthermore, cell lines transfected with these mutant receptors show no consistent growth advantage compared with cells and transgenic animals with a constitutively active cAMP signaling pathway (11). Recent evidence suggests that the coupled regulation of growth and differentiation via the TSH receptor may be dominantly linked to the Gq/G11 coupled pathway. Transgenic animals with a thyroid specific knockout of the α-subunit of Gq/G11 lose the ability for iodine organification and develop hypothyroidism (12). These transgenic animals have normal-sized thyroid glands at birth and during the first 1–2 months of age, which argues against an essential role of this pathway in thyroid growth, at least during development. However, Gq/G11 may link thyroid function to thyroid growth because the transgenic animals are not able to respond with thyroid growth to a goitrogen diet or to hypothyroidism. Thus, in normal physiology TSH stimulates a closely coupled differentiation and proliferation program. This can be reactivated in dedifferentiated thyroid carcinoma cells as exemplified recently (13). If undifferentiated thyroid carcinoma cells are treated with a reverse transcriptase inhibitor, proliferation of the cells is reduced. In parallel, the TSH receptor and the human sodium/iodide symporter are reexpressed. Furthermore, *in vitro* and *in vivo* TSH-stimulated iodine uptake is restored, indicating that proliferation

Abbreviations: PI3K, Phosphatidylinositol 3-kinase; Pttg1, pituitary tumor transforming gene 1.

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is not dominantly controlled by the presence of the TSH receptor (14).

Third, TSH alone is a weak stimulator of thyrocyte proliferation *in vitro* and requires cooperation with insulin/IGF-I for full effects (6). In dog thyrocytes, TSH stimulates the expression of IGF-I receptors, and more recent work demonstrates a facilitating mechanism of TSH on cell cycle regulation via cyclin-dependent kinases, with p27 supporting a permissive function of TSH on IGF-I dependent growth stimulatory mechanisms. The concept that thyroid growth is not necessarily dependant on TSH stimulation is further supported by results from TSH receptor knockout animals that develop normal-sized thyroid glands. These animals show defects in the expression of a differentiation gene, the human sodium/iodide symporter, and fail to concentrate radioactive iodine in their glands (14). This may be mediated via a link to Gq/G11 signaling, which, as discussed previously, will impact on growth regulation, and can be activated by other known growth regulators such as epidermal growth factor and IGF-I.

Potential "Non-TSH" Driven Mechanisms

All these data question the importance of a TSH-mediated effect on tumor growth and aggressiveness. But what is the potential alternative mechanism behind the positive clinical effect seen with TSH suppressive therapy? With the known differentiation favoring effects of T_3, a direct T_3 receptor-dependent action on the tumor may serve as another, admittedly speculative, explanation. Recent findings of Cheng and colleagues (15–17) indicate such a direct T_3 mediated effect on thyroid proliferation at various levels, including phosphatidylinositol 3-kinase (PI3K), peroxisome proliferator activated receptor γ, and gelsolin. In experiments focused on the interaction of the T_3 receptor with pituitary tumor transforming gene 1 (Pttg1), these investigators showed that only the liganded normal T_3 receptor, but not the unliganded form or a mutated receptor, acts as an optimal degradation signal for Pttg1. This has important consequences because Pttg1 potentially stimulates an increase in transforming activity, induces hyperplasia, proliferation, and dedifferentiation in thyrocytes and other epithelial cells (18). Pttg1 expression is increased in thyroid carcinomas both on an mRNA level and immunohistochemically, and this has been related to nodal and distant metastases. TSH receptor activation may increase Pttg1 expression, but the expression of the protein is under the dominant control of various growth factors targeting the PI3K/AKT and MAPK/ERK signaling pathways (19). Mutations activating either pathway are frequently linked to the proliferation and aggressiveness of thyroid carcinomas. Although there is clearly much more work necessary, the current available data would fit the hypothesis of a direct T_3-T_3 receptor mediated action on Pttg1 acting as a downstream inhibitor of PI3K or MAPK signaling without a need to interact with TSH. Further direct, TSH independent, effects of thyroid hormones on the thyroid have been described. Thyroid fibroblast growth factor receptor expression appears to be controlled by T_3 receptor action on its promoter, and mutated forms of the T_3 receptor directly activate PI3K signaling and induce thyroid carcinomas in a mouse model (20). These findings are consistent with the idea that the concentration of T_3 within the tumor tissue is mediating the beneficial effects of thyroxine therapy, rather than TSH suppression *per se*. If this hypothesis is confirmed, measurement of circulating thyroid hormone levels, a better definition of their currently undefined uptake by tumor tissue (no data on thyroid hormone transporters are currently available), and local regulation through intratumor activation by deiodinases (21) may be more important for the long-term outcome of thyroid hormone therapy than the degree of TSH suppression. Serum TSH levels would only serve as a marker for the tissue effect of thyroid hormones. Furthermore, if this proposition is correct, it would support the testing of specific T_3 analogs to target T_3 receptor in tumor tissue rather than heart or bone, which are currently the most important targets for side effects of TSH suppressive therapy (22).

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