Thyrotropin in the Development and Management of Differentiated Thyroid Cancer

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KEYWORDS

• Thyrotropin • Thyroid cancer • Recombinant human TSH • Thyroid hormone • TSH

KEY POINTS

- Thyrotropin (TSH) is the major growth factor and regulator of the thyroid.
- Further research is required to definitely show that higher serum TSH causes human thyroid cancer, whether prediagnostic serum TSH predicts ultimate prognosis, and how best to use serum TSH in determining which patients with thyroid nodules should undergo biopsy.
- TSH is important in the management of thyroid cancer, with TSH stimulation of thyroid cells (either by thyroid hormone withdrawal or recombinant human [rh]-TSH) facilitating radioiodine uptake and detection of occult persistent thyroid tissue via release of serum thyroglobulin.
- The development of rh-TSH was an important advance in thyroid cancer management, permitting TSH stimulation to occur without hypothyroidism, albeit at greater financial cost.
- Further work is required to prove that rh-TSH is equivalent to thyroid hormone withdrawal in patients with metastatic disease.
- A risk-benefit approach to TSH targets in thyroid cancer management may maximize clinical benefit of this therapy while minimizing complications.

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INTRODUCTION

Over the past decade, knowledge of the potential role of TSH in the development of differentiated thyroid cancer has expanded. In addition, the therapeutic role of TSH has continued to evolve. This review synthesizes current knowledge of TSH in both the development and management of differentiated thyroid cancer.

TSH BIOLOGY

History

The crucial role of the anterior pituitary in thyroid growth and function was recognized in the early twentieth century, initially with studies in amphibians,[1–3] followed by demonstration in mammals.[4,5] TSH was identified as a distinct hormone secreted from the anterior pituitary shortly after,[6] although it took until 1971 before its structure was elucidated.[7]

Physiology of TSH

TSH is the major regulator and growth factor of the thyroid. The approximately 28-kDa glycoprotein heterodimer is secreted under negative feedback from thyroid hormone, which occurs at both the levels of the pituitary and the hypothalamus (inhibiting secretion of TSH-releasing hormone, which as the name suggests, prompts release of TSH from the anterior pituitary).[8] TSH controls the processes that lead to increased thyroid hormone production and secretion from follicular thyroid cells. These include increasing the number, size, and secretory activity of thyrocytes; increasing the activity of the sodium-iodide symporter (NIS); increasing the organification of iodide; increasing the cleavage and release of preformed thyroid hormone from thyroglobulin; and increasing thyroid blood flow.[9] TSH does not influence parafollicular C-cells; therefore, it does not affect medullary thyroid cancer cells, and all subsequent discussion of thyroid cancer in this article refers to differentiated thyroid cancer (papillary and follicular thyroid cancer), which develops from thyroid follicular cells.

TSH exerts its effect by binding to the TSH receptor, a G protein–coupled receptor on the thyrocyte surface (**Fig. 1**). Classical TSH actions are mainly mediated through the $G_{\alpha s}$–adenylyl cyclase–protein kinase A–cyclic adenosine monophosphate (cAMP) second messenger system, with some actions through the $G_{\alpha q/11}$-inositol phosphate/diacylglycerol-protein kinase C pathway.[10] It has also been recognized, however, that TSH can cross-talk with many other cell signaling pathways, including those known to be associated with thyroid cancer development, including the mitogen-activated protein (MAP) kinase system[11] and phosphoinositide 3-kinase (PI3-K) system.[11,12]

Other factors may also play a role in regulating thyroid function, at least in experimental models. These include insulin, insulin-like growth factor 1, epidermal growth factor, transforming growth factor β, phorbol esters, fibroblast growth factor, and hepatocyte growth factor.[10]

TSH AND THYROID CANCER DEVELOPMENT

The role of TSH in thyroid biology makes it an appealing candidate as a possible cause of thyroid cancer. Evidence for this has accumulated over the past decade in animal models and human clinical studies.

Animal Model Evidence

Follicular thyroid cancer has been assessed in mice using a knock in mutation to the thyroid hormone receptor-β gene ($TR\beta^{PV}$)[13–16] that causes a dominant negative