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Regulation of Gene Expression by Thyroglobulin

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Abstract

Thyroglobulin (Tg) is a large glycoprotein consisting of 2,768 amino acid residues and the precursor of thyroid hormones (THs). Since abnormalities in Tg function and expression may naturally affect thyroid function, there has been much interest in the mechanisms that regulate the expression and maturation of Tg. By contrast, Tg found in the blood, because of leakage from thyroid follicles, is used as a marker of thyroid goiters and inflammation. However, the precise structure and function of the huge Tg macromolecule are still unclear. Recently, it was shown that Tg at its physiological concentration in follicles dynamically regulates the expression of various thyroid-specific genes responsible for counteracting the effect of TSH. In addition, it was also shown that Tg induces thyroid cell proliferation. Thus, follicular Tg is now recognized as an autocrine negative-feedback regulator tightly controlling follicular function. In this review, we will briefly summarize recent advances of Tg function.

Keywords: Thyroid; Thyroglobulin; Thyroid hormones; TSH

Introduction

Thyroglobulin (Tg), a dimetric glycoprotein whose molecular weight reaches approximately 660,000, is a TH precursor protein that accumulates in the colloid of thyroid follicles [1,2]. Tg is synthesized in thyroid follicular cells and secreted into the follicular lumen, where it undergoes iodination of its tyrosine residues, using the substrate hydrogen peroxide generated by dual oxidase 2, *via* thyroid peroxidase activity [3,4]. A condensation reaction between the iodinated tyrosine residue pairs (acceptor and donor tyrosine's) results in the formation of thyroxine (T4) or triiodothyronine (T3) residues [5]. Iodinated Tg is taken up by follicular cells *via* endocytosis in response to stimulation by the thyroid-stimulating hormone (TSH); after subsequent proteolysis by lysosomal enzymes, T4 or T3 is detached from the Tg molecule and released into the blood circulation [6].

The thyroid gland has a unique microvascular structure with a basket-like capillary network organized around each follicle, which constitutes the basic functional unit of the thyroid [7]. The Tg concentration within an individual follicle varies from less than 1 mg/mL to over 600 mg/mL, a histological characteristic of thyroid follicles called follicular heterogeneity [8,9]. Thus, the functions of thyroid follicles, e.g., storage of THs, iodide uptake and gene expression, are not uniform but rather heterogeneous, despite the same blood-derived supply of TSH and nearly uniform expression of TSH receptors in thyrocytes [10-12]. The nature of this follicular heterogeneity is unclear.

We have shown that the physiological concentration of Tg in each follicle dynamically regulates the expression of various thyroid-specific genes responsible for the follicular function of counteracting the effects of TSH [10,13]. In this review, we provide evidence for the emerging role of Tg in the active regulation of thyroid function.

Autocrine Negative-Feedback Regulation of Follicular Function by Tg

TSH and iodide are well known regulators of thyroid function. TSH is thought to act uniformly on individual follicles in the thyroid gland. Indeed, significant differences in TH accumulation and radioiodine uptake have been observed in neighboring follicles, but the mechanism of these differences is unknown [10]. We reported that Tg itself, which is a major protein abundant in intrafollicular colloids and whose concentration is not uniform among individual follicles, regulates follicular function in a concentration-dependent manner [10,11,13-18]. Thus, we evaluated the effect of follicular concentrations of Tg on the expression of thyroid-specific genes and demonstrated that the expression of all thyroid-specific genes necessary for TH synthesis is strongly suppressed at the transcriptional level by follicular Tg in a concentration-dependent manner, thereby antagonizing the effect of TSH. Specifically, in rat thyroid FRTL-5 cells and primary cultures of human thyroid follicular cells, gene expression of *Tg*, *solute carrier family 26 member 4* (*Slc26a4*), *Slc5a5*, *thyroid peroxidase* (*Tpo*), *dual oxidase 2* (*Duox2*), *dual oxidase maturation factor 2* (*Duoxa2*), *thyroid transcription factor* (*TTF-1* or *Nkx2-1*), *paired box 8* (*Pax8*) and *thyroid transcription factor* (*TTF-2* or *Foxe1*), was suppressed by follicular Tg in a dose-dependent manner even under maximal TSH stimulation. Moreover, it was found that follicular Tg also inhibited the uptake of radioiodine [10,11,13,14,17,18]. Immunohistochemical and autoradiographic analyses of rat thyroid sections showed that thyroid cells surrounding follicles with a low Tg concentration actively synthesize new Tg, whereas those surrounding follicles with a high Tg concentration synthesized hardly any Tg [10].

These changes in expression patterns indicate that follicular function is regulated by the concentration of Tg in individual follicles. Thus, when the Tg concentration is low, the synthesis and accumulation of newly formed Tg are enhanced. After accumulation of new Tg in a follicle, further Tg synthesis, iodine uptake and organification cease, and the follicle becomes a storage space for the TH precursor, awaiting re-absorption and TH secretion. The follicular Tg concentration decreases upon re-absorption, and when the concentration decreases to a certain level, new Tg synthesis is re-initiated. These cycles are repeated again and again asynchronously among follicles [19]. It is speculated that this mechanism serves to ensure slow accumulation and storage of low levels of dietary iodide to maintain a high concentration of the TH precursor in follicles, so that it can be supplied immediately when needed.

Induction of Thyroid Cell Proliferation by Follicular Tg

The physiological activity of TSH in the thyroid gland not only induces TH production and secretion but also promotes thyroid cell growth. In addition, follicular Tg was shown to induce thyroid cell growth. Thus, when FRTL-5 cells were treated with Tg in the absence of TSH, cell growth was induced as strongly as that induced by maximal TSH stimulation [20]. When Tg was subjected to gel filtration chromatography, the strongest effect on cell growth was obtained by the 27S tetramer and 19S dimer forms of Tg. The signal transduction pathway of Tg involved in cell growth is not dependent on the cAMP/PKA pathway, which is downstream of TSH, but rather on inhibition of the PKA pathway. Further studies revealed that Tg-induced cell growth was suppressed by inhibitors of either the PI3K/Akt pathway (LY294002) or the mitogen-activated protein kinase pathway (PD98059), suggesting that Tg regulates cell proliferation through at least these two pathways [20,21]. It was reported that Tg prepared from iodine-deficient goiters has stronger effects than those of Tg prepared from normal thyroid tissue, suggesting that poorly iodinated and/or poorly sialylated Tg may induce thyroid cell growth more effectively than fully iodinated and/or sialylated Tg [14,22]. Therefore, abnormalities in Tg-regulated cell growth mechanisms might be related to the pathogenesis of some thyroid disorders. It was also demonstrated that follicular Tg induces growth of kidney mesangial cells [23]. We cloned a short variant of Tg (kTg) from a kidney cDNA library and demonstrated its expression not only in mesangial cells but also in podocytes in the glomerulus, the heart, and lungs; sera from patients with Hashimoto's thyroiditis contain antibodies against kTg [24]. Thus, the role of Tg and its variant kTg may expand beyond our current knowledge and scope. Further elucidation of the cell recognition mechanism and signaling pathway of Tg will lead to further understanding of thyroid pathogenesis and physiology.

Conclusion

Tg is the major product of the thyroid gland and a substrate for TH synthesis, and it is clinically used as a blood marker. However, it has become clear that the concentration of Tg in follicles (not the blood) induces potent regulation of follicular function in thyrocytes. Tg has been found to antagonize the effect of TSH, which is the main regulator of thyroid function. Since mutations in the Tg gene and the appearance of autoantibodies are common in patients with cancer and autoimmune diseases, it is likely that follicular Tg serves to maintain thyroid homeostasis. In this review, we describe the function of Tg as an autocrine negative-feedback regulator of thyroid function. How Tg is recognized by the follicular epithelium and its role in signaling pathways are major questions that remain to be answered. In addition, Tg or its variant kTg may play unknown roles in other organs. Clarifying the whole picture of the actions of Tg will shed light on the development of new therapeutic strategies and the pathogenesis of thyroid and other disorders.

References

1. Berndorfer U, Wilms H, Herzog V (1996) Multimerization of thyroglobulin (TG) during extracellular storage: isolation of highly cross-linked TG from human thyroids. J Clin Endocrinol Metab 81(5): 1918-1926.

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2. Heidelberger M, Svedberg T (1934) The molecular weight of thyroglobulin. Science 80(2079): 414.
3. BJÖRKMAN U, EKHOLM R (1984) Generation of H2O2 in isolated porcine thyroid follicles. Endocrinology 115(1): 392-398.
4. Ruf J, Carayon P (2006) Structural and functional aspects of thyroid peroxidase. Arch Biochem Biophys 445(2): 269-277.
5. Coscia F, Taler-Verčič A, Chang V T, Sinn L, O Reilly F J, et al. (2020) The structure of human thyroglobulin. Nature 578(7796): 627-630.
6. Citterio C E, Targovnik H M and Arvan P (2019) The role of thyroglobulin in thyroid hormonogenesis. Nat Rev Endocrinol 15(6): 323-338.
7. Fujita H, Murakami T (1974) Scanning electron microscopy on the distribution of the minute blood vessels in the thyroid gland of the dog, Rat and Rhesus Monkey. Arch Histol Jpn 36(3): 181-188.
8. Hayden L J, Shagrin J M, Young J A (1970) Micropuncture investigation of the anion content of colloid from single rat thyroid follicles. Pflügers Archiv 321(2): 173-186.
9. Smeds S (1972) A microgel electrophoretic analysis of the colloid proteins in single rat thyroid follicles. II. The protein concentration of the colloid in single rat thyroid follicles. Endocrinology 91(5): 1300-1306.
10. Suzuki K, Mori A, Saito J, Moriyama E, Ullianich L, et al. (1999) Follicular thyroglobulin suppresses iodide uptake by suppressing expression of the sodium/iodide symporter gene. Endocrinology 140(11): 5422-5430.
11. Suzuki K and Kohn L D (2006) Differential regulation of apical and basal iodide transporters in the thyroid by thyroglobulin. J Endocrinol 189(2): 247-255.
12. Tanaka K, Inoue H, Miki H, Komaki K, Monden Y (1996) Heterogeneous distribution of thyrotrophin receptor messenger ribonucleic acid (TSH-R mRNA) in papillary thyroid carcinomas detected by in situ hybridization. Clin Endocrinol (Oxf) 44(3): 259-267.
13. Suzuki K, Mori A, Lavaroni S, Miyagi E R I, Ulianich L, et al. (1999) In Vivo expression of thyroid transcription factor-1 RNA and its relation to thyroid function and follicular heterogeneity: identification of follicular thyroglobulin as a feedback suppressor of thyroid transcription factor-1 RNA levels and thyroglobulin synthesis. Thyroid 9(4): 319-331.
14. Suzuki K, Lavaroni S, Mori A, Ohta M, Saito J, et al. (1998) Autoregulation of thyroid-specific gene transcription by thyroglobulin. Proc Natl Acad Sci U S A 95(14): 8251-8256.
15. Suzuki K, Nakazato M, Ulianich L, Mori-Aoki A, Moriyama E, et al. (2000) Thyroglobulin autoregulation of thyroid-specific gene expression and follicular function. Rev Endocr Metab Disord 1(3): 217-224.
16. Ishido Y, Luo Y, Yoshihara A, Hayashi M, Yoshida A, et al. (2015) Follicular thyroglobulin enhances gene expression necessary for thyroid hormone secretion. Endocr J 62(11): 1007-1015.
17. Ishido Y, Yamazaki K, Kammori M, Sugishita Y, Luo Y, et al. (2014) Thyroglobulin suppresses thyroid-specific gene expression in cultures of normal but not neoplastic human thyroid follicular cells. J Clin Endocrinol Metab 99(4): E694-E702.
18. Yoshihara A, Hara T, Kawashima A, Akama T, Tanigawa K, et al. (2012) Regulation of dual oxidase expression and H2O2 production by thyroglobulin. Thyroid 22(10): 1054-1062.
19. Sellitti D F, Suzuki K (2013) Intrinsic regulation of thyroid function by thyroglobulin. Thyroid 24(4): 625-638.
20. Noguchi Y, Harii N, Giuliani C, Tatsuno I, Suzuki K, et al. (2010) Thyroglobulin (Tg) induces thyroid cell growth in a concentration-specific manner by a mechanism other than thyrotropin/cAMP stimulation. Biochem Biophys Res Commun 391(1): 890-894.
21. Sue M, Hayashi M, Kawashima A, Akama T, Tanigawa K, et al. (2012) Thyroglobulin (Tg) activates MAPK pathway to induce thyroid cell growth in the absence of TSH, insulin and serum. Biochem Biophys Res Commun 420(3): 611-615.
22. Suzuki K, Mori A, Lavaroni S, Ulianich L, Miyagi E, et al. (1999) Thyroglobulin regulates follicular function and heterogeneity by suppressing thyroid-specific gene expression. Biochimie 81(4): 329-340.
23. Sellitti D F, Suzuki K, Doi S Q, LaGranha C, Machado M, et al. (2001) Thyroglobulin increases cell proliferation and suppresses Pax-8 in mesangial cells. Biochemical Biophysical Research Communications 285(3): 795-799.
24. Wu H, Suzuki S, Sellitti D F, Doi S Q, Tanigawa K, et al. (2009) Expression of a thyroglobulin (Tg) variant in mouse kidney glomerulus. Biochem Biophys Res Commun 389(2): 269-273.

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