Review Article

The Emerging Roles of Thyroglobulin

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Thyroglobulin (Tg), the most important and abundant protein in thyroid follicles, is well known for its essential role in thyroid hormone synthesis. In addition to its conventional role as the precursor of thyroid hormones, we have uncovered a novel function of Tg as an endogenous regulator of follicular function over the past decade. The newly discovered negative feedback effect of Tg on follicular function observed in the rat and human thyroid provides an alternative explanation for the observation of follicle heterogeneity. Given the essential role of the regulatory effects of Tg, we consider that dysregulation of normal Tg function is associated with multiple human thyroid diseases including autoimmune thyroid disease and thyroid cancer. Additionally, extrathyroid Tg may serve a regulatory function in other organs. Further exploration of Tg action, especially at the molecular level, is needed to obtain a better understanding of both the physiological and pathological roles of Tg.

1. Introduction

The thyroid gland is comprised of thyroid follicles, in which thyrocytes surround a follicular lumen with the apical surface of a thyrocyte facing the lumen while the basal surface faces a basket-like capillary network evenly surrounding each thyroid follicle. Thyroglobulin (Tg), which is well known as the macromolecular precursor of thyroid hormone, is the most important and abundant protein produced and stored in thyroid follicles [1].

In the last decade, in addition to its well-established role as the precursor of thyroid hormone, we have revealed important novel roles for Tg. We found that Tg can serve as a negative regulator of thyroid function-related genes and an inducer of thyrocyte growth. In this review, we will summarize these studies of newly recognized Tg action and discuss the potential involvement of Tg in the development of thyroid disorders. Despite enormous advances in understanding the structure and the role of Tg in hormonogenesis, our understanding of the molecular function of Tg remains incomplete. Therefore, we will also include discussion of unanswered questions regarding Tg in this review that we hope will inspire further studies.

2. The Synthesis of Tg and Secretion of Thyroid Hormones

Tg is synthesized as a 12S molecule (330 kDa) and in its most stable state forms a 19S dimer (660 kDa). Biosynthesis of thyroid hormones and their release in the circulation include the following sequence of events [1, 2]. (1) Iodide from the blood stream is concentrated by the sodium iodide symporter (NIS) [3] at the basolateral surface of a thyrocyte and is transported into the follicular lumen by the proposed transporter pendrin [4, 5] on the apical surface. (2) The Tg polypeptide chain is synthesized on the cytosolic surface of the rough endoplasmic reticulum (rER) and translocated into the ER lumen to undergo a series of conformational modifications while an N-linked carbohydrate chain is synthesized and added to the polypeptide chain. (3) The properly folded Tg dimer then enters into the Golgi complex, where carbohydrate units are modified and sulfation occurs. (4) Mature but uniodinated Tg is transferred from the Golgi complex to the apical surface of the thyrocyte in exocytotic vesicles where Tg undergoes iodination mediated by thyroperoxidase (TPO) and H2O2. Thus, iodine is covalently bound to tyrosine residues in the Tg molecule to form monoiodotyrosine (MIT)
and diiodotyrosine (DIT). TPO also catalyzes the coupling of these iodotyrosine residues to form thyroxine (T4) and triiodothyronine (T3). (5) The iodinated Tg is retrieved by micropinocytosis or phagocytosis, reenters the thyrocytes through the apical surface, and finally passes into lysosomes where Tg is degraded to release T4 and T3 from their peptide linkage. Finally, T4 and T3 enter the capillary basket surrounding each follicle.

3. Follicular Heterogeneity Caused by Unknown Mechanisms Other Than Thyroid Stimulating Hormone (TSH) Signaling

TSH is considered to be a master regulator controlling all aspects of thyroid function [6–9]. TSH has the ability to stimulate almost every essential event in thyroid hormone production, including iodide uptake from the bloodstream into thyroid follicles, the synthesis, iodination, reabsorption, and degradation of Tg, and the release of thyroid hormone into the circulatory system. Since TSH levels are reasonably constant in the blood and the expression of TSH receptor (TSHR) has a homogeneous distribution among follicles in normal human thyroid [10], one might expect that the effects of TSH signaling should be similar in each follicle. Accordingly, follicular functions, such as expression of thyroid functional genes, Tg production and iodination, and thyroid hormone secretion, should theoretically also be similar among follicles.

However, contrary to this expectation, follicular heterogeneity has long been observed in both human and rat thyroid. The function of each follicle is not synchronized with that of its neighbors. Thyroid follicles are heterogeneous not only at the histological level but also at the functional level [11–16]. Heterogeneity has been observed in normal thyroids by measurement of iodide uptake, Tg synthesis, diffusion of iodinated Tg, thyroid hormone accumulation, enzyme activity, thyrocyte proliferation, and even expression of thyroid-specific transcription factors [17–19]. Thus, follicular heterogeneity exists despite equal TSH signaling at each follicle, suggesting that some unknown regulators other than TSH contribute to follicular heterogeneity [20].

Tg has been proposed, but not proven, to be this endogenous thyroid functional regulator. Gerber et al. discussed the possibility that Tg within the colloid might be a factor determining the viscosity of the colloid and thereby creating different diffusion velocities of iodinated Tg and thyroid hormones [12]. Using an in situ hybridization study of the thyroid-specific transcription factor Nkx2-1 in rats, we have directly implicated follicular Tg as a regulator of thyroid-specific gene expression independent of TSH [17]. These data established for the first time that Tg can act as a feedback autoregulator of thyroid functional gene expression and follicular function. Since then, we have made substantial progress in the exploration of Tg negative feedback in rat thyrocytes. Based on this negative feedback effect of Tg, we have proposed a “thyroid follicular cycle” model to explain follicular heterogeneity [21–28].

4. Tg Negatively Regulates Thyroid Follicular Function through Regulation of Thyroid Functional Gene Expression

4.1. Tg Suppresses Gene Expression Needed for Thyroid Hormone Synthesis. Using cultured rat thyroid FRTL-5 cells, we have shown that Tg is a strong negative regulator of thyroid function that acts by suppressing the expression of thyroid function-related genes in both a time- and dose-dependent manner [17]. Moreover, this significant suppressive effect was not duplicated in cells treated with thyroid hormones, iodide, or other appropriate controls, such as bovine serum albumin and mannitol. On the other hand, this suppressive effect on thyroid functional genes has also been observed with gel-fractionated Tg moieties increasing in the order of 12S, 19S, and 27S [18]. 27S shows the strongest effect to suppress Nkx2-1 expression [18]. These results indicate that this suppressive effect is specific to Tg. Thus, by suppressing the expression of thyroid functional genes, Tg can negatively regulate nearly every event that is essential for Tg iodination and thyroid hormone synthesis [17].

First, we showed that at physiological concentrations (as measured in vivo in colloid) Tg suppresses Tg mRNA and protein levels, thus acting as a negative feedback regulator of its own expression [18]. Iodine transport by NIS from the bloodstream into thyrocytes through the basal surface is one of the most important events in thyroid hormone synthesis. Using in vitro studies we have shown that Tg treatment can suppress promoter activity and mRNA and protein levels of NIS; moreover, this suppression of NIS by Tg was associated with a reduction of TSH-induced uptake of radiolabeled iodine in Tg-treated FRTL-5 cells, indicating that suppression of NIS expression by Tg indeed resulted in reduced iodide uptake in FRTL-5 cells [27]. Furthermore, using immunohistochemical and autoradiographic analysis of rat thyroid gland sections we showed a clear negative correlation between levels of Tg accumulated in the follicle and the amount of both radiolabeled iodine and newly synthesized Tg in follicular cells [24, 27].

Another essential event in Tg maturation and thyroid hormone synthesis is Tg iodination at the apical surface of the thyrocyte. As mentioned before, this process is mainly catalyzed and mediated by TPO and H2O2. TPO, which liberates iodine for addition onto tyrosine residues on the Tg molecule for the production of thyroid hormones [2], was also shown to be significantly suppressed by Tg in our initial study [17]. We additionally showed that Tg suppresses the expression of thyroid restricted dual oxidase 2 (Duox2) as well as its maturation factor Duoxa2 [29]; these enzymes are responsible for the generation of the H2O2 required for iodide organification. In contrast to Duox2 and Duoxa2, Duox1 and Duoxal, which contribute little to the generation of H2O2 in the thyroid, seem not to be regulated by Tg. We further showed that suppression of Duox2 and Duoxa2 by Tg dramatically reduced H2O2 production and consequently suppressed iodination in FRTL-5 cells [29]. We have recently confirmed the observations made in rat FRTL-5 cells and in vivo rat thyroid using primary cultures of normal human ...
thyroid [30]. Thus, Tg can suppress its own synthesis, iodination, and maturation.

4.2. Tg Can Overcome TSH Action. In contrast to Tg, TSH, the conventional master hormone controlling thyroid function, has a positive regulatory effect on genes essential to thyroid hormone production as we mentioned above. Surprisingly, the negative regulatory effect of Tg seems to be strong enough to overcome this positive regulatory effect of TSH. First, we have shown that Tg suppresses the expression of TSHR and thereby weakens the influence of TSH on thyrocytes [17]. Furthermore, we have shown that Tg can significantly suppress the expression of Tg, Slc5a5 (Nis), Tpo, Duox2, and Duoxa2 in either the presence or absence of TSH [17, 27, 29].

Additionally, it is known that TSH can stimulate Tg reabsorption by thyrocytes, Tg degradation, and the release of thyroid hormone into the bloodstream through the capillary network surrounding the follicles. However, whether Tg itself influences these events involved in thyroid hormone release is still an open question. Nevertheless, we found that Tg can suppress the expression of vascular endothelial growth factor (Vegf), which contributes to increased vascular permeability, indicating that Tg might inhibit iodine uptake from the bloodstream not only by suppressing NIS expression but also by reducing vascular permeability [27].

Thus, our studies have shown that while TSH stimulates expression of genes that are essential for thyroid hormone production and release, Tg exerts an opposing effect, making Tg the first protein other than TSH known to have a significant regulatory effect on thyroid function. We propose that, in vivo, each thyroid follicle is regulated not only by TSH signaling received from the basal surface but also by colloid Tg signaling received from the apical surface. Follicles at different stages of the “follicular cycle” (see below) depending on the balance of TSH and Tg action might be the cause of follicular heterogeneity.

4.3. Tg Action Occurs at the Transcriptional Level. Our previous studies, including a recent one using DNA microarray analysis of FRTL-5 cells [31], indicate that the regulatory effect of Tg on thyroid functional genes is exerted at the transcriptional level, rather than by influencing mRNA stability or protein translation [5, 17, 18, 24, 32]. We have shown that Tg decreases the promoter activity of Tg, Slc5a5, Tpo, and Tshr [17, 27]. Nuclear extracts from Tg-treated FRTL-5 cells also exhibited a decreased ability to form protein/DNA complexes with their specific binding sites in promoters of Tg or Tshr [17]. Furthermore, we have shown that Tg has a strong suppressive effect on thyroid-restricted transcription factors, including Nkx2-1, Foxe1, and Pax8, which are responsible for the regulation of Tg, Slc5a5, Tpo, and Tshr expression in the thyroid [17].

These studies indicate that Tg can suppress Tg, Slc5a5, Tpo, and Tshr expression by suppressing promoter activity and the expression of thyroid-restricted transcription factors. We further revealed that two nuclear factor I (NFI) elements in the region between 5′-264 and 5′-153 bp in the Nkx2-1 promoter are involved in the suppression of Nkx2-1 by Tg [32]. Thus, we showed that Tg can reduce mRNA levels, protein levels, and binding activity of NFI to suppress Nkx2-1 expression. Although the regulation of Nkx2-1 by Tg has been extensively studied, the mechanisms by which Tg suppresses other thyroid-restricted transcription factors, as well as the reason why the suppressive effect of Tg only extends to thyroid-restricted transcription factors and genes, are still unclear.

4.4. The Biphasic Regulatory Effect of Tg on Pendrin. Unlike Slc5a5 and most other thyroid-specific genes, pendrin (encoded by the gene Slc26a4; Pds), the proposed transporter for iodine on the apical surface of follicles, is regulated by Tg in a biphasic manner in FRTL-5 cells. Thus, we have shown that Slc26a4 expression is significantly induced by low concentrations of Tg, while it is suppressed by high concentrations of Tg, which differs from the established role of Tg as a dose-dependent suppressor of thyroid-specific genes [5, 24]. One possible explanation for this stimulatory effect of low concentrations of Tg on Slc26a4 expression is that, despite its extremely low basic expression level compared with other thyroid functional genes in rat thyroid as shown in our other studies [33], pendrin is essential for providing sufficient iodine in the follicle when newly synthesized Tg awaiting iodination is transferred.

Thus the induction of pendrin by low concentrations of Tg might be a mechanism to meet the needs of Tg iodination in the rodent thyroid. Our recent study [30] has clearly shown that this is not the case in the human thyroid, where SLC26A4 is highly expressed [4]. Thus, we showed that SLC26A4 expression was reduced in a dose-dependent manner in primary cultures of normal human thyroid cells [30]. Of interest, none of TSH, insulin, or iodine seems to have a significant effect on Slc26a4 expression. This observation that Tg has different effects on the apical iodine transporter pendrin and the basolateral transporter NIS in rodents indicates that Tg regulates gene expression to maintain thyroid hormone production rather than simply suppressing thyroid-specific gene expression [24].

4.5. Exploration of the Underlying Molecular Mechanism of Tg’s Negative Feedback Effect. Although more and more thyroid-specific genes involved in thyroid hormone production have been found to be negatively regulated by Tg, the mechanism by which Tg, the huge 660 kDa macromolecule, could modulate transcription still remains largely unknown. Nevertheless, efforts to explore potential mechanisms of Tg action have been ongoing. It has been suggested that newly synthesized Tg attaches to a specific binding protein related to the lectin-like asialoglycoprotein receptor (ASGPR) expressed on the apical surface of thyrocytes, and only after sialylation and iodination of Tg has finished does ASGPR release Tg to allow it to be vectorially transferred into the follicle lumen or reabsorbed into thyrocytes [34–36]. We have partly shown that ASGPR has been shown to be associated with regulation of Nkx2-1, Tg, and Tpo expression by Tg [37].
However, there is so far no clear evidence that supports the idea that Tg binding to ASGPR specifically induces an intracellular signaling cascade leading to thyroid-specific gene suppression, and thus the molecular signal transduction process downstream of Tg binding to ASGPR still remains a black box. Moreover, we showed that the ASGPR-specific ligand orosomucoid did not duplicate the Tg’s suppressive effect, indicating that Tg action requires more than just binding to the proposed receptor, ASGPR [37]. The involvement of ASGPR in the negative feedback effects of Tg and the process of downstream signal transduction after Tg binding to ASGPR both need to be explored further.

5. Follicular Cycle Model

5.1. Concept of the Functional Cycle of a Follicle. Based on previous studies, we have proposed a “follicular cycle” model, in which each thyroid follicle is regulated by both TSH action at the basal surface (which is similar among follicles) and Tg action at the apical surface of the thyrocyte (which is significantly variable, reflecting the different Tg concentrations in each follicle) [21–28]. The size, volume, and function of the follicle depend on the balance of TSH and Tg action. TSH action stimulates Tg synthesis, iodination, reabsorption, thyroid hormone release from the Tg molecule, and secretion into the blood. By measuring follicular Tg using immunogold labeling after TSH stimulation, it was found by our group and others that the rate of TSH-induced Tg reabsorption and degradation significantly exceeded the rate of TSH-induced Tg synthesis [7, 16, 20, 25]. In contrast to the immediate significant increase in reabsorption of Tg in pinocytotic vesicles after TSH stimulation, we showed that newly synthesized Tg in rER increased only gradually, and colloid Tg content did not return to its original level before TSH stimulation, indicating a discrepancy between the kinetics of Tg synthesis and Tg reabsorption [25].

Based on the observations described above, we propose the following. (1) TSH has a stimulatory effect on both Tg synthesis and Tg reabsorption; however, the process of TSH-induced Tg reabsorption and degradation significantly exceeded the rate of TSH-induced Tg synthesis [7, 16, 20, 25]. (2) Tg has a strong negative feedback effect on the synthesis of Tg itself, and this suppressive effect can overcome the stimulatory effects of TSH. (3) Low concentrations of Tg induce pendrin expression whereas high concentrations of Tg suppress it.

Thus, in a follicle with high colloid Tg accumulation, the Tg synthesis-promoting effect of TSH is counteracted by the Tg negative feedback effect. As a result, Tg synthesis in this follicle is suppressed and TSH predominantly functions to promote colloid Tg reabsorption, Tg degradation, and thyroid hormone secretion into the blood. Colloid Tg concentration in this follicle will soon significantly be decreased due to the faster Tg reabsorption and slower Tg synthesis, thus relieving the overwhelming negative feedback effect of Tg. Relief from the Tg negative feedback effect along with the positive effects of TSH will cause Tg synthesis to be restored in this follicle. A low colloid Tg concentration also maximizes pendrin expression to promote Tg iodination on the apical surface in cases of rodents. Thus, colloid Tg will gradually accumulate in this follicle. When accumulation of colloid Tg reaches a certain level, the Tg negative feedback effect will again predominate over the stimulatory effect of TSH on Tg synthesis and the whole process will repeat itself. Follicles at different stages of this “follicular cycle” would have different functions, thus contributing to follicular heterogeneity [22].

5.2. Pathological Consequences of Failure of Tg Regulation. In “follicular cycle” model we have proposed, follicular function is dynamically regulated by fluctuating concentrations of Tg. Therefore, it is not difficult to imagine that failure of physiological regulation of follicular function by Tg might result in thyroid disorders. Weakened Tg negative feedback (either due to an abnormality of Tg itself or due to the mechanism by which it suppresses gene expression) may result in constant activation of thyroid-specific gene expression and persistent accumulation of follicular colloid tissue, which may be related to the development of adenomatous goiters. In contrast, abnormal persistent activation of Tg negative feedback may overshoot serum thyroid hormone levels, which in turn could increase TSH levels and result in goiter development. Thus, more studies are needed to obtain a better understanding of the physiological function of Tg and to further explore the involvement of Tg in thyroid pathology.

Furthermore, in our recent study, we showed that the feedback effect of Tg remains intact in Graves’ thyroid but is lost from adenomatous goiter, follicular adenoma, and papillary carcinoma cells [30]. Although the loss of (or “escape” from) a response to Tg is likely a consequence of, rather than a cause of, neoplastic transformation, further research into thyroid autoregulation by Tg may help shed light on some of the unanswered questions of the etiology and progression of thyroid neoplasia and hyperplasia.

6. Other Functions of Tg

6.1. Tg Functions as a Strong Inducer of Cell Growth. In contrast to its marked effect on thyroid-specific gene expression, our group and others have shown that Tg has significant cell growth-promoting effects in FRTL-5 cells as well as in some nonthyrocyte cells [38, 39]. We showed that Tg induces growth of FRTL-5 cells independent of TSH, insulin, and insulin-like growth factor (IGF) stimulation [40]. Moreover, gel-fractionated Tg moieties 12S, 19S, and 19S also have this promoting effect on thyroid cell growth [40], and their promoting effect increases in the same order (12S < 19S < 27S) as the suppressive effect on genes [40], indicating that this promoting effect is also Tg specific. Interestingly, Tg exerts a biphasic regulatory effect on the growth of thyrocytes, which is similar to the effect we observed in the regulation of pendrin by Tg in rat FRTL-5 cells. Thus, low Tg concentrations maximize its growth-promoting effect, whereas high Tg concentrations exert a suppressive effect on cell growth.

Although the mechanism of Tg suppression of thyroid-specific genes remains largely unknown, several signaling
pathways that are responsible for Tg-induced cell growth in FRTL-5 cells have been identified. And these pathways partially overlap with the signaling pathways employed by TSH to stimulate thyrocyte growth. In TSH signal transduction, the binding of TSH to TSHR promotes the production of cAMP. In turn, cAMP activates protein kinase A (PKA) to induce the expression of various genes necessary for cell proliferation [41–43]. We have shown that a specific inhibitor of PKA, H-89, partially reversed TSH-induced cell growth in FRTL-5 cells [40]. However, unlike TSH, Tg does not increase cAMP levels, and H-89 did not modulate the effect of Tg on cell growth [40]. Tg regulates cell growth by activating the phosphatidylinositol 3-kinase (PI3K) pathway [40]. The PI3K inhibitor LY294002 reversed both TSH- and Tg-induced cell growth, indicating that the PI3K signal pathway is a common pathway for both TSH and Tg.

However, inhibition of the PI3K pathway did not completely suppress Tg-induced cell growth. We have confirmed that this is because Tg also induces activation of the c-Raf/MEK/ERK pathway of mitogen-activated protein kinase (MAPK), which is specific to Tg-induced cell growth [31]. In this study, we showed that the MEK1/2 inhibitor PD98059 suppressed Tg-induced phosphorylation of ERK1/2 and reduced Tg-induced DNA synthesis in FRTL-5 cells. Tg also induced expression of the essential transcription factors c-Myc, c-Fos, and c-Jun and phosphorylation of the retinoblastoma (Rb) protein to stimulate cell growth [31]. Interestingly, although insulin and Tg work together in an additive manner to increase cell proliferation, no additive cell growth-promoting effect was observed when TSH and Tg were both added to FRTL-5 cells. Instead, TSH partially reversed the effect of Tg on cell growth, indicating that TSH/cAMP signaling may counteract the signaling employed by Tg to stimulate cell growth [31, 40].

6.2. Functions of Tg outside the Thyroid Gland. Historically, Tg was considered to exclusively be produced and function within thyroid follicles; thus, serum follicular Tg content is clinically important for the diagnosis of thyroid diseases, especially for diagnosis of the reoccurrence and metastasis of thyroid cancer [44]. However, with the identification of renal expression of several "thyroid-specific" genes including Pax8 [45, 46], the expression of putative Tg receptors, including ASGPR, in nonthyroidal cells [47, 48], Tg binding to nonthyroid follicular cells [44], and the accumulation of Tg in the form of antigen-antibody complexes in the glomerular basement membrane in some cases of immune complex glomerulonephritis during autoimmune thyroid disease [48], the physiological and pathological roles of Tg outside the thyroid have received more attention.

The glomerular mesangial cell is an especially likely target for the extrathyroidal action of Tg due to that cell's expression of Pax8 and ASGPR. We have used mouse mesangial cells and shown that the suppression of Pax8 by Tg is probably correlated with reduced expression of B cell lymphoma 2 (Bcl2), a well-known apoptosis suppressor, indicating that Tg might be involved in apoptotic signaling in mesangial cells [39]. Moreover, we showed that Tg, but not thyroid hormone, can promote the proliferation of mesangial cells. These studies suggest a possible role of Tg as a gene transcription and cell growth regulator in mesangial cells.

Furthermore, we have found that Tg has a transforming growth factor- (TGF-) β-like transcriptional effect in mouse mesangial cells [49]. Intracellular signaling, including TGF-β autoregulation leading to increased TGF-β expression in mesangial cells, is thought to be involved in the pathology of some glomerular diseases. We showed that Tg increases Tgfβ and plasminogen activator inhibitor 1 (Pai1) expression and decreases the expression of Pax8 in a manner similar to TGF-β isoforms in mesangial cells [49]. In addition, using a pentacapeptide TGF-β antagonist, we demonstrated that this TGF-β-like effect of Tg is not mediated by Tg's binding to the TGF-β receptor. Thus, our studies suggest that, like TGF-β isoforms, Tg may also be involved in the initiation of glomerular injury by mimicking the action of TGF-β in mesangial cells.

Furthermore, we have cloned a variant Tg transcript (kTg) in a mouse kidney cDNA library [50]. kTg has a unique sequence beginning at intron 41, and translation of this mRNA is predicted to yield a protein of 367 amino acids (40 kDa) containing a unique 13-amino acid sequence serving as a potential signal peptide followed by a 354-amino acid segment identical to the carboxy-terminal end of thyroid Tg. Using an antibody directed against the C-terminus of thyroid Tg, we detected a 40 kDa protein in the kidney and showed that this protein was localized to podocytes and the mesangial area of the renal glomerulus [50]. Moreover, kTg protein was recognized by sera from patients with Hashimoto's thyroiditis but not that from controls, indicating that kTg may serve as a potential self-antigen that is recognized and bound by anti-Tg antibodies thus contributing to the pathology of immune complex glomerulonephritis during autoimmune thyroid disease [50].

7. Summary and Perspective

Novel functions of Tg have been recognized during the last decade, including a negative feedback effect of Tg on thyroid function via regulation of the expression of genes essential for thyroid hormone synthesis, a cell growth-promoting effect, and extrathyroidal functions. However, our knowledge of Tg action at the molecular level and its potential involvement in thyroid pathology (including autoimmune disease and cancer) is far less complete. Further investigation is needed to explore the mechanism of Tg recognition by thyrocytes, the signaling pathways responsible for Tg action, and the potential role of Tg in the development of all types of thyroid disease.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.
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