INVITED COMMENTARY

On the origin of circulating thyroglobulin

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Introduction

The presence of thyroglobulin (Tg) in the blood circulation in a wide variety of concentrations is an intriguing phenomenon in thyroid pathology, taking into account that no physiological role for Tg outside the thyroid is known. However, the tissue-specific origin of Tg has made this protein very applicable as a diagnostic marker in various diseases of the thyroid, such as differentiated thyroid cancer, subacute thyroiditis, Graves’ disease and congenital thyroid diseases. This, in spite of the fact that the mechanisms by which Tg is released and the molecular structure in which it appears in the circulation are poorly understood. The paper by Druetta et al. (1) aims to provide more insight into these questions.

Tg synthesis and processing

Tg is synthesized by thyrocytes, organized in follicular structures. Both the synthesis and secretion are regulated by thyroid-stimulating hormone (TSH) and other factors such as insulin-like growth factor-I. Regulation occurs via transduction, and the cAMP, kinase A, inositol phosphate, kinase C and tyrosine kinase pathways (2) regulating the phosphorylation of, for example, the transcription factors TTF-1 and -2 and Pax 8 (3).

The Tg gene is located on chromosome 8q24.2-q24.3 and contains over 40 exons (4), holding 8307 bp of coding sequences (5). Because of its size of more than 300 kb, still not all the intron/exon boundaries have been mapped. The coding sequence of human Tg was elucidated in 1987 (6), and has been revised recently (5). Besides the main splicing product, alternative splicing transcripts of Tg are also found. The formation of mature Tg requires complex processing, e.g. glycosylation, folding and dimerization of the Tg subunits. The many disulide bridges keep, even after partial proteolysis, the spatial structure of Tg largely intact. Via transport vesicles Tg is secreted into the follicular lumen. At the apical border tyrosine residues of Tg are iodinated and coupled to iodothyronine residues, a process taking place most likely extracellularly. Both reactions, iodination and coupling, are catalyzed by thyroid peroxidase, a transmembrane enzyme that protrudes with its active center into the follicular lumen (7). The iodothyronine residue preferentially formed in Tg is thyroxine (T4) by coupling of two diiodotyrosine residues (8). The pro-hormone remains part of the polypeptide chain, until it is split off by proteolytic enzymes after endocytosis of Tg.

Tg release from the thyroid

The function of the thyroid is the production and secretion of thyroid hormones, mainly T4 and some triiodothyronine. Up till the 1960s it was believed that leakage of Tg out of the thyroid follicles was completely prevented by the follicular wall, consisting of thyroid cells connected to each other by tight junctions. But the demonstration of Tg in the blood circulation by hemagglutination-inhibition tests and by RIA changed this hypothesis. It became clear that in addition to thyroid hormone, Tg and other (iodinated) proteins were released by the thyroid (for review see also (9)). Considering the large amounts of Tg synthesized by the thyroid only minute amounts are released from a healthy thyroid. This release is often raised under pathological conditions, especially under the influence of TSH or thyroid-stimulating antibodies. Despite the availability of sensitive immunological assays, there is still no consensus on the absolute amounts of Tg released into the circulation. The measurement of Tg concentrations in serum, even with a uniform Tg preparation as a standard (10) gives large variations, possibly due to the molecular heterogeneity of the circulating Tg. Besides Tg, iodoalbumin has also been shown to be present in serum of patients with a variety of diseases of the thyroid. This is serum albumin that is taken up by the thyroid gland either by diffusion via the tight junctions (11) or via basolateral endocytosis (12), iodinated in the follicular lumen and subsequently released into the circulation, probably via the same mechanisms involved in the release of Tg.

Postulated routes for Tg release are:

(i) Vesicles, containing newly synthesized Tg, secrete their content into the extracellular space on fusing with the basolateral membranes. Consequently Tg released into serum will be iodine free, having a molecular mass of about 660 kDa, being that of the Tg dimer. It might be expected that this Tg secretion...
mechanism will be under the influence of TSH or TSH receptor-stimulating antibodies.

(ii) Tg, internalized by (micro)pinocytosis from the follicular lumen, has been found to be present in early and late endosomes. In these organelles, containing proteolytic enzymes, thyroid hormones may possibly be split off before Tg is degraded (more) completely in the late endosomes and in the lysosomes (13). The involvement of endosomes in Tg transcytosis has been shown in experiments with isolated inside-outside follicles (14) and in ultra-thin cryosections of intact thyroid tissue (13), providing evidence that this process will also occur in vivo. In this model, Tg secreted into the extracellular space might be partly hydrolyzed, but held together by the many disulfide bridges. Also these processes will be under the influence of TSH or TSH-mimicking antibody stimulation.

(iii) A third possibility is that proteins will pass the follicular cell wall via the intercellular route, by a modification of the sealing elements of the epithelium, the tight junctions (15). Indeed Van Uijen et al. (15) showed that the tight junctions of TSH-stimulated thyroid glands are narrower and composed of less strands than those of normal thyroids. In this mechanism Tg, as found for iodoalbumin, will be iodinated and intact.

In their publication Druetta et al. (1) describe the quality of the circulating Tg and they use these observations as a starting point for deducing the mechanism by which Tg is released by the thyroid gland in vivo. If the epithelial wall and cell polarity remain intact then the mechanism of secretion in thyroid carcinoma might follow the first and/or third postulated routes. For Graves’ disease and subacute thyroiditis the mechanism might be the first route, together with the second and possibly the third. However, besides these secretion mechanisms it has to be taken into consideration that Tg might be released by destruction of the follicular epithelium. This can be caused by inflammation of the thyroid tissue. It can be expected that in that case Tg is partly broken down, as is shown in the paper of Druetta et al. If the structure of the follicles is impaired, as in thyroid carcinoma, it is also possible that Tg is released into the blood circulation not only by the basolateral but also via the apical membrane pathway.

Druetta et al. found that Tg in serum of patients with Graves’ disease was slightly affected; besides Tg of normal size, Tg with a somewhat smaller molecular mass was found. Moreover, after reduction of the disulfide bridges Tg appeared to be partly hydrolyzed. For this reason Druetta et al. suggested a transcellular transport, by which Tg is partly degraded in the late endosomes or lysosomes.

By investigating the characteristics of circulating Tg under various pathological conditions, using sensitive methods, Druetta et al. are the first to indicate how Tg will be released in vivo. These studies can be considered as a start to obtaining more information about the pathways of Tg release under normal and pathological conditions.

References


