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Thyroglobulin Synthesis of Oxyphilic Cells in Various Types of Neoplastic and Autoimmune Thyroid Diseases

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To determine the content of thyroglobulin in oxyphilic cells of the thyroid, which have been considered as non-thyroglobulin producing cells, the degree of stainability of the various oxyphilic cells for thyroglobulin was compared with that of non-oxyphilic follicular cells in either same or different lesion. A total of 13 oxyphilic lesions, including three follicular adenomas containing oxyphilic cell nodules, four pure oxyphilic cell adenomas, and six Hashimoto's thyroiditis were compared with 16 of non-oxyphilic lesions such as, seven follicular adenomas, four chronic lymphocytic thyroiditis, and five Graves' disease. Many oxyphilic cells stained positively for thyroglobulin regardless of their morphologic variation, but less intensely than the usual follicular cells in follicular adenomas, chronic lymphocytic thyroiditis, and Graves' disease. The stainability of oxyphilic cells for thyroglogulin did not show any significant correlation with morphologic features, whereas in follicular adenomas, the non-oxyphilic follicular cells forming microfollicles stained less strongly for thyroglobulin than the same cells lining large mature follicles in a reproducible way. With above findings, we concluded that oxyphilic cells maintain the functional activity in terms of thyroglobulin synthesis, although the content of the thyroglobulin is less than that of non-oxyphilic colloid forming follicular cells.

Key Words: *thyroglobulin, oxyphili cells, follicular adenoma, oxyphilic cell adenoma.*

INTRODUCTION

Histologic examinations have shown the occurrence of oxyphilic cells in the human thyroid, as well as in the parathyroids, and salivary glands (Lennox, 1948; Roth et al., 1962).

In the thyroid, this type of cells are commonly seen in the follicular neoplasm, Hashimoto's thyroiditis, Graves' disease, and nodular goiter (Heimann, 1966). Under the light microscopic examinations, this type of cells is polygonal and of a very large size (15-30 μm) with an abundant eosi nophilic finely granular cytoplasm. They contain irregular nuclei of variable size and shape. Nucleoli may be distinct. These cells have also been called as Askanazy cells, oncocytes, and Hürthle cells (Hemperl, 1950). Ultrastructurally, the dominating organelle of the oxyphilic cell is the mitochondrion (Hemperl, 1950; Feldman et al., 1972; Heimann et al., 1973). Other organelles such as ribosomes, Golgi apparatus, lysosomes, and vesicles can only be observed in the apical portion of the cell.

Although there were many theories (Heimann et al., 1973; Gardner, 1955) regarding the morphogenesis of this cell, recent ultrastructural studies have established that they are transformed follicular cells (Len-

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nox, 1948; Horn 1954 Feldman et al., 1972; Heimann et al., 1973).

Oxyphilic cells used to be thought to represent a degenerative change resulting from some unknown cellular injury (Hemperl, 1950). This belief, although once widely accepted, has been contradicted by enzyme histochemical studies (Tremblay and Pearse, 1960) demonstrating a very high mitochondrial activity in oxyphilic cells.

In spite of this mitochondrial activity, no biosynthesis of thyroxine or thyroglobulin could be demonstrated in a biochemical study of seven oxyphilic adenomas (Heimann et al., 1973).

However, there were a few recent reports which demonstrate presence of thyroglo bulin in the cytoplasm of oxyphilic cells by immunohistochemical technique (Albores-Saavedra et al., 1983; Gonzales-Campora et al., 1986; Johnson et al., 1987).

In present study, it is our understanding that the oxyphilic cells maintain thyroglobulin synthesizing activity although the content of the thyroglo bulin is less than that of non-oxyphilic colloid forming follicular cells.

MATERIALS AND METHODS

Thirteen oxyphilic cell lesions present in three follicular adenomas, four pure oxyphilic adenomas, and six Hashimoto's thyroiditis and 16 non-oxyphilic cell lesions in seven follicular adenomas, four chronic lymphocytic thyroiditis, and five Graves' disease were evaluated for the presence of thyroglobulin.

Areas showing diffuse infiltration of oxyphilic cells were selected and only cells possessing abundant eosinophilic granular cytoplasm either forming follicles or compact groups on routine hematoxylin-eosin stained slides were considered as oxyphilic cells.

Immunohistochemical studies were performed on formalin-fixed paraffin embedded tissue sections using the biotin-streptavidin method. Endogenous peroxidase activity was blocked by 10 minutes treatment at room temperature with three percent hydrogen peroxide in water. To minimize the non-specific background staining, preincubation with normal goat serum in phosphate buffered saline was done for 20 minutes at room temperature.

The sections were then incubated overnight in a humid chamber with the primary antibody (polyclonal goat antirabbit antibody to thyroglobulin) followed by incubation with linking antibody (biotinylated goat antirabbit immunoglobulin) and labeling with peroxidase conjugated streptavidin. The slides were developed using 3-amino-8-ethylcarbazole (AEC) as chromogen. The slides were counterstained with Mayer's hematoxylin.

The grading of immunoreactivity was performed on a scale of negative to three positive according to the degree of reactivity and percentage of reactive cells.

RESULTS

The oxyphilic cells in follicular adenomas and pure

Table 1. Stainability for thyroglobulin in neoplastic conditions

Disease	Stainability for thyroglobulin
Oxyphilic cells	
Follicular adenoma	
case 1	++
case 2	+
case 3	++
Pure oxyphilic adenoma	
case 1	++
case 2	++
case 3	++
case 4	+
Non-oxyphilic cells	
Follicular adenoma	
case 1	+ (small follicle), (large follicle)
case 2	+++ (large follicle)
case 3	++ (small follicle), +++ (large follicle)
case 4	+ – +++ (variable pattern)
case 5	+++ (large follicle)
case 6	++ (small follicle)
case 7	+ (small follicle), ++ (large follicle)

Table 2. Stainability thyroglobulin in autoimmune thyroiditis

Disease	Stainability for thyroglobulin
Oxyphilic cells	
Hashimoto's thyroiditis	
case 1	−
case 2	−
case 3	+
case 4	+
case 5	++
case 6	+ − ++
Non-oxyphilic cells	
Chronic lymphocytc thyroidits	
case 1	+ − +++
case 2	+++
case 3	+++
case 4	+++
Grave's disease	
case 1	+++
case 2	+++
case 3	+++
case 4	+++
case 5	+++
case 6	+++

oxyphilic adenomas stained positively for thyroglobulin and the reactivity occurred throughout the cytoplasm of the majority of the cells, but in general, the cytoplasmic thyroglobulin content was reduced compared to the usual non-oxyphilic follicular cells. The stainability of the oxyphilic cells for thyroglobulin varied considerably but did not appear to show any significant correlation with the morphologic pattern (Table 1).

The stainability of non-oxyphilic follicular cells in follicular adenomas showed wide variation. The staining reaction was stronger and more intense in cells lining the large mature follicles than in those forming small abortive follicles (Table 1).

The oxyphilic cells in Hashimoto's thyroiditis showed marked reduction in cytoplasmic reaction for thyroglobulin (Table 2).

The non-oxyphilic reactive follicular cells in chronic lymphocytic thyroiditis and Graves' disease stained very intensely for thyroglobulin (Table 2).

DISCUSSION

It has been emphasized by Lennox (1948), that the large oxyphilic granular epithelial cells known as Hürthle cells were in first described by Askanazy (1894) and that these bear no relatinoship to the parafollicular cells described by Hürthle (1894) in thyroid glands of dogs. These are also called as Askanazy cells, oxyphilic cells, and oncocytes.

Although there were many theories regarding the morphogenesis of this cell, recent ultrastructual studies have established that they are transformed follicular cells (Horn, 1954; Heimann et al., 1973). Previous workers (Lennox, 1948; Hamperl, 1959) assumed that oxyphilic cells are degenerative dying cells representing a morphological expression of an unknown cellular injury.

Recent enzyme histochemical studies (Tremblay and Pearse, 1960), however, contradicted this widely accepted view and clearly demonstrated a very high mitochondrial enzymatic activity (Lennox, 1948; Tremblay and Pearse, 1960; Roth et al., 1962). Based on histochemical findings, it was suggested that oxyphilic cells are highly active cells with rich content of mitochondrion and of oxidative enzyme system such as DPN diphorase, succinate dehydrogenase, and TPN-linked isocitrate dehydrogenase (Tremblay and Pearse, 1960).

In spite of this high mitochondrial enzymatic activity, the result of biochemical investigation of seven oxyphilic adenomas revealed biosynthesis of thyroglbulin or thyroxine in their cytoplasm (Heimann et al., 1973). Ultrastructural studies have also failed to detect any evidence of hormonal hyperactivity in proliferating oxyphilic cells; dilated cisternae of the endoplasmic retic-

ulum which are characteristically present in the thyroid hormone secreting follicular cells, were almost completely absent in the cytoplasm of the oxyphilic cells (Lennox, 1948; Heiman, 1950; Feldman et al., 1972; Heimann et al., 1973).

In spite of above findings, their rich content of mitochondrion and of oxydative enzyme system and presence of a few enzymes for thyroid hormone production (Valenta et al., 1974), it is very suggestive that oxyphilic cells produce thyroglobulin.

This speculation was also supported by recent immunohistochemical studies by previous workers. Albores-Saavedra et al. (1983) have demonstrated relatively wearker but positive staining of the Hürthle cell carcinoma for thyroglobulin and Johnson et al. have also demonstrated reactivity for thyroglobulin in Hürthle cell neoplasm although in lesser degree than in conventional follicular lesions.

Böcker et al. (1978) have emphasized the distinction made by Tremblay and Pearse between Hürthle cells and mitochondrion rich cells and that only few oxyphilic cells had positive staining reaction for thyroglobulin while the so-called mitochondrion rich cells revealed moderate amount of thyroglobulin in the apical portion of the cell. The validity of distinction between Hürthle cells and mitochondrion rich cells have been questioned lately (Albores-Saavedra et al., 1983; Gonzales-Campora et al., 1986) and we believe that these two cell types should be considered as a common cell. This interpretation is supported by the facts that the so-called mitochondrion rich cells have considered as a disctinct prescursor of Hürthle cells (Tremblay and Pearse, 1960) and distinction between mitochondrion rich cells and Hürthle cells based on the number of mitochondria is not an easy task (Böcker et al., 1978).

In present study, the oxyphilic cells revealed positive cytoplasmic reaction for thyroglobulin although the content of thyroglobulin is less than that of non-oxyphilic colloid forming follicular cells.

In neoplastic lesions, the stainability of the oxyphilic cells varied widely from case to case, and even in the different area of the same case. Therefore, the stainability can not be predicted on the light microscopic examination. However, stainability of non-oxyphilic follicular cells in follicular adenomas revealed significant correlation with the morphologic patterns; stronger reactivity in the cells lining the large mature follicles and weaker reactivity in the cells forming small abortive follicles.

In autoimmune thyroiditis, the oxyphilic change of the follicular epithelium paralleled with diminished reactivity to thyroglobulin which directly indicated the functional status of thyroglobulin production; strong positive staining reaction in Graves disease and very weakly positive reaction in Hashimoto's thyroiditis. With above findings, we concluded that the oxyphilic cells maintain the functional activity in terms of thyroglobulin synthesis, although the content of thyroglobulin is less than that of non-oxyphilic colloid forming follicular cells.

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