eISSN: 09748369

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Biology and Medicine

Review Article

BIOLOGY AND MEDICINE
BM
www.biolmedonline.com

Volume 7, Issue 1, Article ID: BM-060-15, 2015
Indexed by Scopus (Elsevier)

www.biolmedonline.com

The follicle function and thyroid gland cancer

Eugeny Petrovich Kolpak[1,*], Sergy Alexsandrovich Kabrits[1], Volodymyr Bubalo[2]
[1]Saint Petersburg State University, Universitetskaya nab., 7/9, Saint-Petersburg, 199034, Russia.
[2]Research Institute of Epidemiology and Infectious L.V. Gromashevsky NAS of Ukraine, Mykolu Amosova Street, 5, 03038, Kyiv, Ukraine.

***Corresponding author**

Citation: Kolpak EP, Kabrits SA, Bubalo V (2015) The follicle function and thyroid gland cancer. Biol Med 7(1), Aritcle ID: BM-060-15, 6 pages.

Received: 12th Dec 2014; Accepted: 3rd Jan 2015; Published: 12th Feb 2015

Abstract
The author studies the structure of the thyroid gland, its vessels and nerves at macroscopic and microscopic levels. The follicle function and the process of thyroid tumor formation are studied as well. The maintaining mechanisms of morphological homeostasis of the thyroid gland and its structural and functional units are thoroughly studied. The author emphasizes that under modern ecological, social conditions which may lead to thyroid gland disorders and diseases, the study of morphofunctional features of the thyroid in normal and pathology state is urgent for sure. It is defined by morphological changes, including irreversible, of the thyroid gland against quick changes of the environment, insufficient safety for an organism from environment, slow structural and functional adaptation of the thyroid gland under different exogenous factors.

Keywords: Follicle; tumor; carcinoma; thyroid.

Introduction

The international scientists' interest to the further research of thyroid gland morphology is caused by an increased number of thyroid gland diseases, an important endocrine organ as its hormones are directly involved in organism development, growth, and adaptation to dynamic factors of environment [1,2]. The structure of the thyroid gland, its vessels and nerves at macroscopic and microscopic levels is studied in detail by medical practitioners and theorists. The thyroid gland function disorders leading to pathologies of various severities require for anatomic and experimental researches of the thyroid gland [3,4].

To preserve morphofunction stability of the biological system under significant deviation of the main environment values from optimal is one of the key functions of an organism. Realization of dynamic integrity and regulatory stability of functional processes in the thyroid gland as in any organ is defined by the structural homeostasis state provided by metabolic stability, the required system elements compound and quantity and their optimum spatial interposition [5,6].

Follicle

A spherical follicle, composed of follicular cells (thyrocytes) surrounding the colloid, is a functional unit of the thyroid gland [7,8]. Two other types of cells are located among follicles: B-cells (Hurthle) and C-cells. The main function of the thyroid gland is secretion of thyroid hormones of thyroxin (T4) and triiodothyronine (T3), 95% of which is thyroxin. Synthesis and release of thyroid gland hormones represent a complicated process schematically shown as follows [9-11]:

- Iodine uptake an extra into follicular cells.
- Oxidation of iodine transferred into colloid.
- Thyreoglobulin uptake from follicular cells into colloid.
- Active iodine molecules bound to thyreoglobulin with formation of intermediate products MIT (3-monoiodotyrosine) and DIT (3,5-Diiodthyrosinum).
- Connection of two DIT molecules in thyreoglobulin structure with formation of thyroxin (T4) or MIT and DIT molecules with triiodothyronine (T3) formation.
- Transfer of the thyreoglobulin-bound hormones into follicular cells and the

subsequent thyreoglobulin breakdown with release of free iodine–thyronines and iodine–thyrosines.
- Uptake of the released hormones from follicular cells into the blood flow.

Transfer of Iodide

Iodide accumulation in the thyroid gland represents the first step in thyroid hormones production. Iodide ions passage from blood capillaries through the basal membrane of polarized follicular cells of the thyroid gland is provided by human sodium-iodide symporter (hNIS). Molecular tools generated by *NIS* gene cloning are used to analyze different aspects of NIS expression in the thyroid tissues [12]: NIS passes two sodium ions with iodide–anion to a cell; Na+ transmembrane gradient transfers iodide against its electrochemical gradient. Gradient of Na+ concentration is supported by a sodium-potassium pump, adenosine triphosphatase transporting amino acids and sugars. Free iodine concentration becomes 30-40 times higher in follicular cells than in plasma at active transport. Iodine passes a concentration gradient into the colloid after activation in thyrocytes.

Synthesis of Hormones

Thyrocite-produced thyroglobulin is iodinated on the thyrocite–colloid boundary. Thyroglobulin is the main thyroid protein with about 660,000 dalton molecular weight, and serves as a matrix for the thyroid hormone synthesis. Thyroid hormones are produced with iodine–triiodothyronine contains three molecules of iodine and thyroxine—four. Iodinated thyroglobulin with attached T3 and T4 is accumulated in the follicles as a colloid. Colloid droplets begin to move in the thyrocyte direction during the thyroid activation and T4 and T3 hormones are released under these enzymes action near the thyrocite–colloid division. The released hormones diffuse through the basal membrane of thyrocytes penetrating to the blood capillaries. The gland secretes about 100 nmol of T4 hormone and about 7 nmol of T3 hormone into the blood per day [13-15].

Thyroid Hormones in the Blood

Most of the thyroid hormones in the blood are bound to proteins and are inactive. The concentration of T4 bound hormone is one of the main markers to estimate a functional state of the thyroid gland. Normal T4 concentration makes 9.0-25.0 pmol/l, and T3 blood in healthy people is within 4-8 pmol/l—3-4 times less than T4.

Regulatory functions in the body are provided by free (biologically active) hormones. Free T4 hormone in healthy people is within 65-160 nmol/l, and free T3 hormone level in healthy people is within from 1.04 to 2.5 nmol/l. In most clinical cases, free T3 hormone level correlates with free T4. However, free T3 level can remain within norm (e.g., in hypothyroidism patients) at lowering of free T4 level at the iodine deficiency. It can be associated with switching of the biologically active T3 onto the synthesis in the gland for maximal uptake of iodine penetrated into the gland. At the same time T3 level decreases in patients without thyroid pathology against certain serious somatic diseases. In many cases, free T4 and T3 levels do not show a functional state of the thyroid gland, it can be caused by changed concentration of transport proteins. Increased T4 and T3 content (without clinical symptoms) is predetermined by genetically determined increase in thyroid-stimulating hormone (TSH) concentration [16].

Hormone Secretion

Hormone secretion is regulated by the TSH affecting the thyrocyte: while blood hormones are decreased, TSH synthesis and secretion is increased, but at increasing—it decreased. Thyroid gland disorders at any level of hormone secretion, iodine uptake in the thyroid functional space, regulation of hormone transfer in the blood flow may lead to diseases of the gland and other organs [16]. The increased T3 and T4 thyroid production causes hyperthyroidism, and decreased production causes hypothyroidism. At long iodic insufficiency, thyrocyte hyperplasia and hypertrophy are developed, their focal dystrophy, necrobiosis. Hormone-inactive compounds (thyreoalbumen, etc.) appeared in patients' blood decreasing thyroxin synthesis, increasing thyreotropine level and leading to the further increase of the thyroid gland and to node formation [17].

Hypophysis-produced TSH blood content is the main regulator of the thyroid gland function, its secretion activity quickly reacts

even to minimal changes of thyroid hormones in blood. Blood TSH level is considered as a marker for the thyroid gland function. The lower border of sensitivity of blood TSH assessment methods makes 0.002 mod/l. For norm, blood TSH concentration in healthy people is: for children under 1 yr old—1.4 mU/l and for other ages—0.5-5.0 mU/l.

Analyzing the results of examinations basing on which these referential fluctuations of blood TSH in healthy patients are offered, the conclusion can be made that in 95% of healthy adult people a blood TSH level makes less than 2.5 mod/l. Therefore at high normal values of TSH (>3.0 mod/l), an early phase of hypothyroidism is not excluded, and these cases are considered in clinical practice as necessity of another test of TSH in blood and antibodies to thyroid gland antigens [3].

TSH is a strategic marker at estimation of the thyroid gland function state. TSH secretion is regulated by the feedback mechanism: high concentration of bounded T4 and T3 is inhibited, and low ones stimulate TSH release. In case of primary hypothyroidism, TSH level raises. Increase of TSH level is characterized for subclinical hypothyroidism, thus blood free T4 and T4 concentration is normal. Low TSH level in lowered T4 concentration can indicate of insufficiency of hypophysis or hypothalamus (secondary hypothyroidism). At hypothyroidism, TSH synthesis and secretion in hypophysis by the feedback principle are blocked by high T4 and T3.

The Gland Growth

The maintaining mechanisms of morphological homeostasis of the thyroid gland and the concept of a structural functional unit are thoroughly studied in modern researches. A structural functional unit is a complex microsystem equal to the body which includes various tissue components with an integrated link as the separate association of the microvessels, specifically oriented in space. This unit in the thyroid gland is not an individual follicle as it has been considered before, but a polyfollicular structure with the three-dimensional microvascular system and connective tissues with C-cells, tissue basophils and fibroblasts. The topographical cleavage is confirmed by a special fibroblast shell (F-shells) surrounding a group of 4-6 follicles and dividing the gland into independent structural functional units—microsegments. New functions of hemocapillaries, morphodynamic, and morphogenetic have been found in the thyroid gland providing coordinated change of spatio-temporal relations of elements. So insufficient morphodynamic and morphogenetic functions of hemocapillaries or their exception can underline pathogenesis of most thyroid gland disorders, including tumor growth.

At changing of the blood hormone level, hormone thyrotropin (TSH) produced in the hypophysis can not only change the produced hormone amount but also stimulate the gland growth. The gland growth can be accompanied with benign tumors (adenomas) or malignant tumors (carcinoma). The tumor can appear due to the genetic information change or affected by factors stimulating cell division. Predominantly follicles in the postnatal period are naturally formed by division of “maternal” follicles into several small ones. There are three types of follicle formation from the maternal one: (1) solid nest, (2) budding type, (3) lumen-dividing type [18].

Both follicular cells and Hurthle cells and C-cells can be source for the tumor development [19]. A follicular adenoma is a benign tumor as an ellipsoid, consisting of colloid containing (macrofollicular) or not containing (microfollicular) large follicles. Colloid is not contained in the adenoma follicles developed from Hurthle cells. Malignant tumors are formed by cells of different shapes and sizes, spread within the gland, and can grow into surrounding tissues and distributed to the lymph and blood systems.

Tumoral Growth

The works analyzing equal transcriptions of hNIS by the polymerase chain reaction method or NIS presence in paraffin blocks of the thyroid gland tissue by the immune-histochemical method specify data on general decrease or, sometimes, lost NIS expression in benign and malignant thyroid tumor. This information is confirmed by the fact that both in thyroid gland benign and malignant tumors with insignificant exception, iodide content decreased component comparing to its content in healthy tissues. On the contrary, other researches based on combination of Western blot, or only on the immune-histochemical method, have revealed a normal expression (sometimes, overexpression)

of hNIS in most cases of thyroid carcinoma and adenoma [9].

Researches in the molecular biology allowed to understand better mechanisms of tumoral growth in thyroid gland tissues. Proliferation of normal follicular cells of the thyroid gland is controlled by growth factors, which affecting membrane receptors cause different cascades of an intracellular signal transduction. Tumoral growth is caused by irreversible disorder of these regulation cascades which can arise at increased activity of the stimulation mechanism or at lost inhibitor activity [20]. Monoclonal character of most benign and malignant thyroid tumors assumes that they are caused by molecular disorders causing oncogene activation and antioncogene inactivation. Some genetic anomalies, such as dot mutations and reorganizations, have been revealed in *RAS*, *GSP*, *TSHR*, *RET*, *TRK* genes [2,21,22].

Formation of the thyroid gland tumor is accompanied with decreasing of the thyroid gland follicle volume and, finally, the "functional" space can be fully replaced with tumor cells. Thus tumor cells do not function in thyroid hormone synthesis. The appeared tumor constantly grows [23,24], generating many "non-functional" cells with few follicles or even with no formation. Tumor malignancy is accompanied with the metastasis into blood capillaries and the thyroid surrounding tissues [23,25]. Thus, the tumor growth and spread may stimulate not only the activity of the TSH hormone cells and its receptors [4,6] but also the background thyroid parenchyma, causing thyroid gland cancer because background processes cause malignant transformation [24], though morphologically they are not direct predecessors of tumor [26,27]. Probably, a benign pathology of the thyroid gland, in particular, autoimmune thyroadenitis, can mask the thyroid cancer development [5].

Two main types of carcinoma may occur from follicular epithelium cells: papillary and follicular. These two types of neoplasms are different by the structure, molecular-biological characteristics, and also clinical behavior. Besides, medullary and anaplastic carcinomas are found out in the thyroid gland. The anaplastic carcinoma can develop from previous papillary, follicular or medullary tumors [28,29]. Nonepithelial neoplasms are possible to develop from lymphoid cells (thyroid gland lymphoma) or rare from connective tissues (thyroid gland sarcoma). The tumor tissue consists of small cells of different sizes, close to each other, located among maternal gland tissues and forming different structures [16,30] with microvessel high density [25,31].

Neoplasms

Seven types of neoplasms are revealed in most cases at definitive postmortem examination of patients, including benign: (1) nodular goiter, (2) adenomatous nodular goiter, and (3) follicular adenoma; malignant: (4) follicular, (5) papillary, (6) medullary, and (7) anaplastic carcinoma [32]. Histologically the nodular goiter usually has the heterogeneous structure—combined macrofollicular, norm-follicular with microfollicular and solid area. The necrosis and hemorrhage focus, and cystic transformation are often found out in these formations. Capsule is not typical. Nodes of the monomorphous structure, often with changed oxyphilous cells, necrosis, surrounded with a continuous capsule, indicate the adenomatous goiter.

The follicular adenoma differs from the nodular goiter by an accurate continuous capsule and more monomorphous histologic structure, different structure of the thyroid surrounding tissues [33]. Follicular adenomas are subdivided into macrofollicular (colloide), norm-follicular (simple), microfollicular (fetal), and solid/trabecular (embryonal). Certain heterogeneity, sites of the various histologic structure, is quite often observed in the follicular adenoma structure.

Carcinomas

Histologically follicular carcinomas are subdivided by expressiveness of invasive properties into minimum invasive and maximum invasive. Yamashina [34] and Gardner *et al.* [35] also noticed that follicular carcinoma was not characterized by the macrofollicular tissue structure, more often this is microfollicular formation. A wide nonuniform fibrous capsule (to 4 mm) is observed in these tumors. Follicular carcinoma, as follicular adenomas, can have the oxyphil cell structure (Hürthle cells).

Morphologically typical papillary carcinoma is characterized by two basic symptoms: papillae and characteristic changes in tumoral cell nucleus. Matsuzuka *et al.* [4] and Pacini *et al.* [36] noticed that in 45-70% of cases at papillary carcinoma micrometastases are pathohistologically revealed in counterlateral lobe of the thyroid gland.

Medullary carcinoma is a malignant tumor developed from parafollicular C-cells and makes 3-12% of thyroid carcinoma cases. Spontaneous (sporadic) and hereditary (family) medullary carcinoma is observed. At morphological examination, papillary, giant-celled, small-celled, oxyphil cell, and renal cell structures can be observed in tumor, which prevalence divides medullar carcinoma into corresponding subtypes.

Anaplastic carcinoma is aggressive undifferentiated malignant tumor of the thyroid gland making 10-13% of thyroid carcinoma. Histologically anaplastic carcinoma is subdivided into two main subtypes: giant-celled and small-celled [1].

Some researchers showed that for many kinds of thyroid carcinoma, the fatal risk of locally regional relapses and remote metastases grows with increased size [19]. Unlike follicular carcinoma, multifocal growth of papillary cancer is often observed. Purposeful studying of histologic cuts of the thyroid gland at papillary carcinoma of various sizes has shown that tumor multicentricity is revealed from 20% at normal postmortem examination to 80% at the systematized analysis of millimetric cuts [37].

At an estimation of thyroid tumor weight, its size, locally regional distribution, and remote metastasises [19] are taken into consideration. The analysis of results of different examinations connected with an estimation of the prognostic importance of the tumor size shows essential difference in specialists' opinions.

Conclusion

Thus, under modern ecological, social conditions which may lead to thyroid gland disorders and diseases, the study of morphofunctional features of the thyroid in normal and pathology state is urgent for sure. It is defined by morphological changes, including irreversible, of the thyroid gland against quick changes of the environment, insufficient safety for an organism from environment, slow structural and functional adaptation of the thyroid gland under different exogenous factors.

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