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Anvar Abduvaliev,
ScD, Associate Professor,
Tashkent Medical Academy;

Elvira Ibragimova,
ScD, Senior Researcher,
Institute of Bioorganic Chemistry;

Bakhtigul Azimova,
ScD,
Tashkent Medical Academy;

Alisher Rahmanov,
MD (Doctor in Medical sciences),
Interuniversity Scientific Research Laboratory,
Tashkent Medical Academy;

Ta'lat Saatov
ScD , Professor, Academician,
Institute of Bioorganic Chemistry,
Tashkent

The Hormonal Regulation of Immunocompetent System at Carcinogenesis

Key words: *thyroid gland, thyroid hormones, thymus involution, carcinogenesis*

Annotation: *The study showed that it is possible to make a conclusion about the relationship modeled in experimental animals thyrotoxicosis group II, a high proliferation of thymocytes and thymic lymphocytes and a significant inhibition of tumor growth AKATON. Experimental hypothyrosis modeled in mice in-group I, leads to significant rearrangements in cellular structure, and the structure of the thymus. The lack of thyroid hormone in the body induces an involution immunocompetent organ, which negatively affects the immune and oncological tread function of the body in terms of carcinogenesis.*

Introduction

The thymus is the central organ of immunogenesis, where the maturation and differentiation of T-lymphocytes. Mature thymocytes continuously leaving thymus in blood and replenish peripheral concentration of T-lymphocytes. Peripheral T cells do not return into the thymus. They constantly recirculate in the body, and exercise control over the formation of malignant, damaged or virus-infected cells and destroy them. Therefore, constant maintenance of peripheral T lymphocytes and their functional activity is important for the body, and their violation causes the development of immune deficiency with serious consequences for human health (1).

Thymus with the years constantly decreasing, the lymphoid part of organ replaced by fat and connective tissue (age involution of the thymus). At a number of diseases, the lymphoid part of thymus may reduce for a few days or hours, and this phenomenon is call accidental involution of the thymus, but in the case of convalescence, the thymus is restore. Long ago known that at tumor growth is also reduced thymus. In experimental tumor growth in mice thymus decreases significantly not only by the number of lymphocytes, but also by its weight. Considered that the involution of the thymus and the associated violation replenishment peripheral T lymphocytes underlies the development T-cell immunodeficiency and the insufficient protection against tumors (3).

There are hormonal and cytokine hypothesis; also suggest that the involution of the thymus can cause decay products of the tumor extracellular matrix components, metabolic factors (2).

Purpose of the present study is to investigate the effect of hypothyroidism and thyrotoxicosis on thymus involution in terms of development carcinogenesis in experimental animals.

Materials and methods

The material of the study based on samples of thymus, peripheral blood serum, tumor tissue AKATON mice BALB/c mice implanted with an experimental tumor AKATON.

Animals weighing 20-22 g kept in plastic cages (6 per cage) under standardized conditions of relative humidity (50-60%), temperature (22° C) and light conditions (12 h light and dark). Mice received standard commercial feed and drinking water *ab libitum.*

All painful manipulations performed with laboratory animals under ether anesthesia, and in strict accordance with the Declaration of Helsinki of the humane treatment of animals (World Medical Association, Edinburgh, 2000).

Definition of mitotic activity in the thymus of the experimental animals was carried out on sections of histological preparations 4-5 microns thick, stained with hematoxylin + eosin mixture by counting the number of cells under a microscope in the division, from which calculated the mitotic index (MI) MI = Number of cell division / 1000 . In each case calculated the mitotic index in the tumor sections 20-25, in the sum should be count 1000 cells per one animal.

Determination of apoptotic activity in the thymus of experimental animals performed on sections of histological preparations thickness of 4-5 microns, staining them with hematoxylin + eosin mixture and they counted under the microscope stage apoptotic cells in accordance with the following criteria:

plasma membrane blebbing, condensation of nuclear chromatin at the nuclear periphery, reducing its size (pyknosis), the formation of DNA fragments from high molecular weight (karyorrhexis) digested DNA fragments oligonukleosomalnye (ladder type), sealing the cell organelles, shrinkage of cytoplasm, vesicular form cell membrane fragments budding cells to form discrete apoptotic bodies, surrounded by a membrane and containing compacted remains of organelles and the nucleus.

The number of apoptotic cells expressed as a percentage relative to the total number of cells counted.

ELISA using commercial kits «Alkorbio», Russia, determined the concentration of endogenous L-thyroxine in the blood serum of experimental animals.

Results and Discussion

In the experiment in vivo on the model of tumor strain of adenocarcinoma of the small intestine AKATON studied the effect of hypothyroidism and thyrotoxicosis on thymus involution in terms of carcinogenesis in experimental animals. Experimental animals were divided into 4 groups: I group - the animal was carried out thyroidectomy (removal of the thyroid gland), causing hypothyrosis ie disadvantage thyroxine (T4) in the body; Group II - animals receive per os T4 in a high (5 mg/kg), a dose that resulted in the development thyrotoxicosis, i.e. an excess of T4 in the body; Group III - control, tumor-bearing animals are not subjected to any influence; Group IV - intact healthy animals, which have not performed the implantation of the tumor.

Table 1 shows the results of experimental carcinogenesis AKATON tumors in mice BALB/c mice with induced hypothyroidism (group I) and hyperthyroidism (group II). Statistically significant reduction of weight and volume of tumor tissue was observed only in the group II, where mice model invoked hyperthyroidism by administering high doses (5 mg/kg) T_4. Inhibition of tumor growth in this group by mass was 90.7%, the actual development of carcinogenesis in these animals occurred. This can be explained by factors influence the metabolic T4 various processes occurring in the organs and tissues of the body that leads to a change in the proliferative activity in cells of various etiologies.

Table 2 presents data on body weight and thymus of animals on the day of the experiment (21 days from the day of tumor implantation). Carcinogenesis flowing without affecting positive or negative factors for it leads, as seen in the group III, to significant involution of thymus. Mass fraction of thymus in relation to the body weight of mice in Group III was 0,28%, the ratio is nearly we observed in the group I, which were modeled conditions hypothyroidism - 0.3%. At the same time, the weight of the body was also small - for Group III, it amounted to 54,0±3,6 mg for group I - 56,0±4,0 mg, well below the norm: in healthy intact animals that are not implanted tumor of the thymus weight was 75,0±3,8 mg (Group IV), and the proportion of cancer of the average mouse weight in this group was equal to 0.45%. In group II, which in experimental animals were simulated conditions of hyperthyroidism, thymus involution did not occur - the mass of the body was 74,0±5,2 mg, which is correlated with that of the control group IV, and was the highest mass fraction of all the experimental groups - 0.55%.

To confirm the data obtained and to obtain an objective picture of the proliferation thymus tissue of the experimental animals we were set mitotic (MI) and apoptotic (AI) codes of thymic epitheliocytes and thymocytes (Table 3).

Table 1

The change in mass and volume of the tumor AKATON of experimental animals on the day of completion of the experiment (21 days)

Group	Weight tumor, g	tumor volume, $см^3$	tumor growth inhibition (TGI), %
Group I. Hypothyroidism	1,89±0,56	2,24±0,66	12,5
Group II. Thyrotoxicosis	0,2±0,07*	0,24±0,08*	90,7
Group III. Control - tumor-bearing animals	2,16±0,46	2,54±0,32	-

Note: * - $p < 0,05$

Table 2

The weight thymus in mice of BALB/c-induced hypothyroidism and thyrotoxicosis under conditions of experimental carcinogenesis

Group	Body weight, g	Weight of thymus, mg	Thymus weight ratio to body weight,%
Group I. Hypothyroidism	18,5±0,8	56,0±4,0*	0,30
Group II. Thyrotoxicosis	13,3±1,2	74,0±5,2	0,55
Group III. Intact tumor-bearing animals	19,1±1,3	54,0±3,6*	0,28
Group IV. Healthy animals without tumor implantation	16,5±1,2	75,0±3,8	0,45

Note: * - p <0,05 (in comparison with the group IV)

As can be seen from the data, hypothyroidism causes a significant decrease in mitotic activity of thymus tissue, the number of dividing cells in Group I at 94.7% less than the control group cortical zone IV. In addition, decline thymus cell proliferation observed in Group III in tumor-bearing animals without exposure - the number of mitoses cortical areas in this group was 65.5% less than the control. Terms thyrotoxicosis in mice of group II did not induce a decrease of mitotic activity in the thymus, these MI in this group did not differ statistically from those in healthy intact animal.

Table 3

Mitotic activity and apoptosis of thymic epitheliocytes and thymocytes in mice BALB/c mice with induced hypothyroidism and thyrotoxicosis under conditions of experimental carcinogenesis

Group	The number of the cells	Cortical area of thymus		Brain area of thymus	
		МИ, ‰	АИ, ‰	МИ, ‰	АИ, ‰
Group I. Hypothyroidism	10000	0,32±0,18*	1,3±0,4*	0,1±0,04*	0,08±0,02*
Group II. Thyrotoxicosis	10000	7,0±0,6	2,4±0,32*	1,5±0,2	0,9±0,4
Group III. Intact tumor-bearing animals	10000	2,1±0,62*	5,2±1,1	0,4±0,1*	1,2±0,3
Group IV. Healthy animals without tumor implantation	10000	6,1±1,02	5,6±0,6	2,2±0,3	2,4±0,6

Note: * - p <0,05 (in comparison with the group IV)

It should also be noted that the number of group I of apoptotic cells is significantly higher than the number of mitotically dividing cells - 75.3%, whereas in group II, which were modeled conditions thyrotoxicosis values exceed the values of the AI at 65.7%, which means

high proliferative activity of the cells of thymus. In the experimental groups I and III, we are dealing with regression thymus tissue, as the number of apoptotic cells in the cortical zone of thymus tissue of these groups exceeds the number mitoses: AI/MI for group I is 4.06; AI/MI group III - 2,47.

Table 4 shows the results of determining the concentration of thyroxine in the blood serum of mice BALB/c. The study T4 levels in the blood serum of experimental animals revealed that the model state of hypothyroidism and thyrotoxicosis in mice have been created correctly and given an adequate picture of the thyroid status.

Table 4

The concentration of thyroxine in the serum of mice BALB/c line with implanted tumor AKATON

Group	T_4, nmol/L
Group I. Hypothyroidism	5,0±1,2
Group II. thyrotoxicosis	100,5±5,12
Group III. Intact tumor-bearing animals	30,0±2,0
Group IV. Healthy animals without tumor implantation	60,0±4,0

Conclusion

The study showed that it is possible to make a conclusion about the relationship modeled in experimental animals thyrotoxicosis group II, a high proliferation of thymocytes and thymic lymphocytes and a significant inhibition of tumor growth AKATON.

Experimental hypothyrosis modeled in mice in-group I, leads to significant rearrangements in cellular structure, and the structure of the thymus. The lack of thyroid hormone in the body induces an involution immunocompetent organ, which negatively affects the immune and oncological tread function of the body in terms of carcinogenesis.

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