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Original Research Article

Study of the Effect of Hypothyroidism and Thyrotoxicosis on the Proliferative Activity of the Red Bone Marrow in Experimental Animals with an Implanted Akatol Tumor

M.A. Ismayilova

Author's Affiliation:
Samarkand State University, Samarkand, Uzbekistan

***Corresponding author:**
M.A. Ismayilova
Samarkand State University, Samarkand, Uzbekistan
E-mail:
bbozorov@samdu.uz

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ABSTRACT:
Analysis of the morphological structure of histological preparations of the thymus of experimental animals showed that experimental hypothyroidism leads to significant rearrangements both in the cellular composition and in the structure of the organ. The absolute area of the cortical zone, in comparison with the control group, significantly decreases, signs of hypertrophy of epithelial cells and an increase in the intensity of intracellular differentiation processes are revealed. There is little or no tissue proliferation. The proportion of lymphocytes in the cortical zone is 65.26±1.50%, the proportion of epithelial cells is 2.1±0.45%, which is significantly lower than those in the control group IV–81.45±1.22% and 4.2±0.63%, respectively. There are areas of rarefaction and degradation of the thymus tissue, which demonstrates the high rate of involutional processes. The thymus sharply decreased in size relative to the control and was represented by two small lobes and fragments, or was divided into separate segments, often of an irregular shape.

Keywords: Tumor strain of colon adenocarcinoma AKATOL, Red Bone Marrow, Thyroid Hormones, Apoptosis, Hypothyroidism, Thyrotoxicosis, BALB /c mice with implanted AKATOL tumor.

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INTRODUCTION

Even 20 years ago, biological therapy for tumors was more of a dream than a reality. Since that time, the situation has changed significantly. Biological approaches to the treatment of oncological diseases have appeared, which are an integral part of modern clinical practice. New effective biotechnological methods have been developed, the use of which will undoubtedly bear fruit in the future. This was largely facilitated by understanding the problem of the relationship between the tumor and the immune system (Abduvaliev, Ismayilova, Gildieva & Saatov, 2005; Abduvaliev, Gildieva

& Saatov, 2006). The immune system is divided into two main systems - humoral and cellular. B-lymphocytes are mainly responsible for the functioning of the humoral system, and T-lymphocytes are responsible for the function of the cellular system. Both systems are involved in the antitumor response of the body, however, T cells control the growth and regression of the tumor (Bazarov, Rajamuradov, 2020). Antitumor antibodies formed during tumor growth block tumor - associated antigens and prevent tumor destruction by specific T-lymphocytes and contribute to its escape from immunological supervision (Abduvaliev, Gildieva & Saatov, 2006). Why do tumors appear and do not regress under the influence of the immune system? First, the regression of tumors in the early stages of its development is not recorded by modern methods, and it can be assumed that the immune system nevertheless destroys many emerging tumor cells. Second, as the tumor progresses, it acquires a number of properties that allow it to elude immunological surveillance (Agol, 1996; Appay, Sauce & Prelog 2010). It is generally accepted that spontaneously occurring tumors contain weak tumor- associated antigens and body reactions against such tumors are extremely difficult to identify. Moderate immune responses to a tumor or their complete absence have long been explained by the absence of foreign gene products in tumor cells, anatomical isolation of antigenic tumors from the immune system, or generalized immunosuppression in a cancer patient (Azimova, 2008; Akramova, Umerov, Saatov, 2002). The latter is characteristic of many disseminated tumors at later stages of development. Study of the features of the mechanism of regulation of apoptosis by thyroid hormonesand proliferation of tumor cells is impossible without revealing the signaling relationships in the "thyroid hormones-immunity-cancer cell" system (Axel, 2006; Appay, Sauce, & Prelog, 2010; Ismailov, 2007; Ipatov, 2003). Analysis of literary sources allows us to speak about the significant effect of thyroid hormones on the functioning of the immune system in the body. The created model conditions of hypothyroidism and thyrotoxicosis made it possible to assess the degree of influence of the thyroid status on the work of the immune system under conditions of tumor growth and to establish the morpho-functional features of immunocompetent cells in all major organs of formation of the body's immune response to a carcinogenic attack (Kelly, Lieberman, 2009; Zlamy, Prelog, 2009).

MATERIALS AND METHODS

The effect of hypothyroidism and thyrotoxicosis on the proliferative activity of red bone marrow in BALB/c mice was studied in an *in vivo* experiment using the model of a tumor strain of colon adenocarcinoma AKATOL. The experimental animals were divided into 4 groups: group I-the animals underwent thyroidectomy (removal of the thyroid gland), which caused hypothyroidism and a lack of T_4 in the body; Group II- animals received T_4 per os in a high (5 mg/kg) dose, which led to the development of thyrotoxicosis, i.e. excess T_4 in the body; group III–tumor-bearing animals were not exposed to any effect; Group IV - control, intact healthy animals that did not undergo tumor implantation.

Table 1 shows the results of the analysis of proliferative activity and cellular composition of red bone marrow in BALB/c mice with an implanted AKATOL tumor.

RESULTS AND DISCUSSION

Simulation of hypothyroidism conditions (group I) led to a decrease in the number of large, medium lymphocytes and blasts (by 32.3%, 32.4% and 37.88%, respectively, compared with the control group IV), the number of small lymphocytes, on the contrary, increased by 63.6 %. Mitotic and apoptotic activity of red bone marrow cells in group I did not differ statistically significantly from similar indicators in the control group (group IV). Decrease in the number of large, medium lymphocytes and blasts, as well as the predominance of small lymphocytes (Govallo cells) indicates active repair processes occurring in the bone marrow of mice under conditions of hypothyroidism (Fig. 3.13). It is believed that small lymphocytes are young forms that have come out directly from the bone marrow and have, to a certain extent, pluripotent properties. In particular, these lymphocytes are involved in the destruction of virus-infected and tumor cells, as well as in cellular immunity reactions. With a viral infection or tumor pathology, their content can increase significantly. At the same time, a

decrease in the percentage of large, medium lymphocytes and blasts demonstrates the suppression of antitumor immune defense in conditions of thyroid hormone deficiency.

Thyrotoxicosis conditions (group II) induced an increase in the number of large lymphocytes and blasts (by 45.6% and 13.79%, respectively, compared with the control group IV) (Figure 1). The number of small lymphocytes, on the contrary, decreased by 32.4%. Mitotic and apoptotic activity of red bone marrow cells in group I did not differ statistically significantly from similar indicators in the control group (group IV). The main number of large lymphocytes was represented by natural killers, taking part in the destruction of virus-infected, tumor, mutant and foreign cells using the spontaneous cytotoxicity reaction. An increase in the content of large lymphocytes in the blood is an adequate immune response in response to antigenic stimulation and demonstrates the activation of the body's immune defenses in response to the development of carcinogenesis.

Table 1: Effect of hypothyroidism and thyrotoxicosis on proliferative activity and cellular composition of red bone marrow in BALB / c mice with implanted AKATO L tumor

Groups	**Lymphocytes, %**			**Blasts, %**	**MI, %**	**AI, %**
	large	**medium**	**small**			
Group I. Hypothyroidism	10.1±1.05*	16.0±1.82*	48.6±2.62*	25.1±2.61*	0.62±0.1	0.40±0.1
Group II. Thyrotoxicosis	21.7±1.07*	18.6±0.47	20.1±1.29*	39.6±0.93	0.76±0.07	0.32±0.08
Group III. Intact tumor-bearing animals	19.5±1.02*	14.6±0.92*	26.8±2.78	39.1±2.42	0.7±0.1	0.43±0.06
Group IV. Healthy animals without tumor implantation	14.9±1.13	20.6±1.35	29.7±3.03	34.8±2.48	0.46±0.1	0.39±0.09

Note: * - p< 0.05 (compared to group IV)

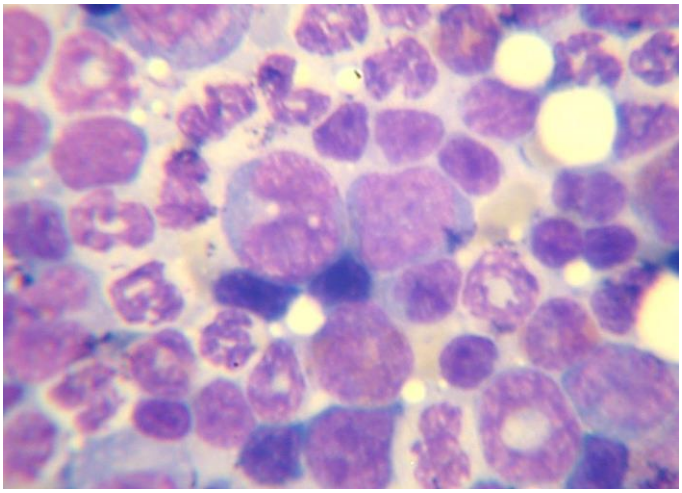

Figure 1: Red bone marrow. Group I (hypothyroidism) small lymphocytes. Coloring according to main- Grunwald. Magnification eyepiece 10 ×, objective 100 ×.

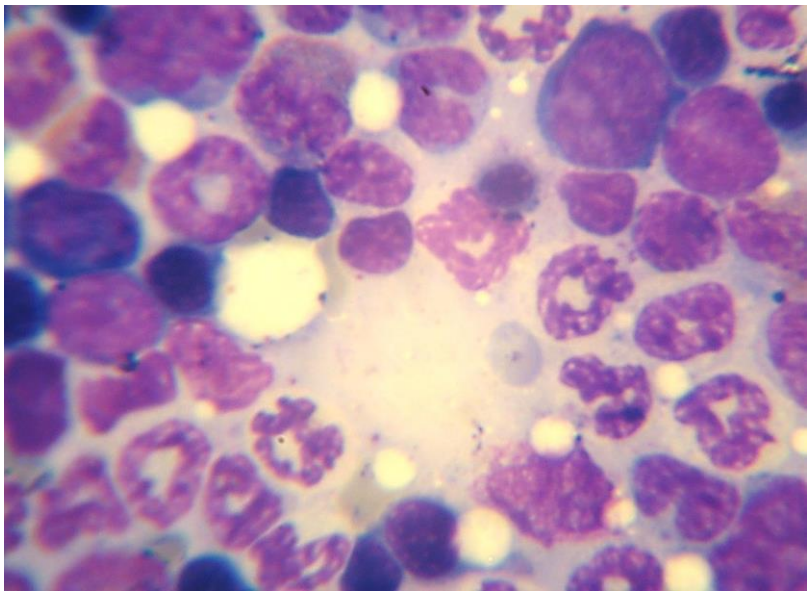

Figure 2: Red bone marrow. Group II (thyrotoxicosis). Cell composition. Coloring according to Main-Grunwald. Magnification eyepiece 10 ×, objective 100 ×

Group III (tumor-bearing animals without any treatment) was characterized by an increase in the number of large lymphocytes (by 30.87%) and a significant decrease in the percentage of medium lymphocytes (by 29.2%) compared to those in the control group IV. Medium lymphocytes have a diameter of about 10-12 microns and constitute the main pool of lymphoid elements, which include T- and B-lymphocytes, which are involved in the implementation of acquired immunity reactions directed against various pathogens. A decrease in the number of these elements of the cellular composition of the red bone marrow demonstrates the depletion of the antitumor immune defense of the body.

CONCLUSIONS

The course of carcinogenesis, in the case of induction of model hypothyroidism and thyrotoxicosis, proceeds differently. Deficiency of thyroid hormones leads to a significant increase in body weight of experimental animals, does not cause inhibition of tumor growth, and does not statistically significantly reduce the proliferation of cancer tissue. On the contrary, an excess of thyroid hormones does not allow the development of the process of carcinogenesis, inhibits the proliferation of cancerous tissue and induces apoptosis in tumor cells.

Thus, an excess of thyroid hormones stimulates specific antitumor immunity under conditions of experimental carcinogenesis. At the same time, thyroid pathologies or a decrease in thyroid status (as was demonstrated for group III) shift the cellular composition of the red bone marrow towards repair processes, which inhibits the body's specific antitumor immune defenses.

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