Thymus endocrine function disturbances in skin melanoma: association with change of functioning of the immune system peripheral link (review of published and authors' own research data)

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Summary This review presents data evidencing for the association of disturbances of the functions of the key organ of the immune system, thymus, and its peripheral link, as well as the dependence of their change upon melanoma biological properties. It was shown the results of treatment melanoma patients of thymic biological factors and preparations with activated influence endocrine function of thymus. Substantiation has been given for the significance of study of thymus endocrine function in patients with melanoma for objective evaluation of the immune system functioning and its changes after main treatment with the use of immune therapy methods.

Key words: thymic hormones, immune system, skin melanoma, biotherapy

The epidemiology of cutaneous melanoma. Melanoma of the skin was previously considered a relatively rare cancer, but recently marked its sustained and widespread growth [1, 20]. It is shown that the incidence of melanoma of the world population doubles every 10 years in Ukraine over the last 25 years the annual growth of this indicator is 5.4%. Melanoma is one of the most malignant human tumors and is characterized by infiltrative growth, early metastasis to regional lymph nodes and distant organs [3, 19]. The clinical course of melanoma, the absence in many cases of positive results from the basic methods of treatment - surgical and combined - determine the need for further study of the pathogenesis of the disease and the development on this basis of approaches to improve the effectiveness of its treatment.

Currently, the primary treatment schemes melanoma patients, more attention is paid to the use of methods of biotherapy, including immunotherapy and, because of the role of immune factors in the pathogenesis of this disease [5, 8, 27].

The functional state of the immune system in the skin melanoma. The possibility of developing melanoma active specific immune responses confirm the literature of a higher frequency of spontaneous regression of the tumor as compared to other malignancies, the presence of tumor-associated antigens as well as the results of studies of the immune system in patients [5]. In particular, in the peripheral blood of melanoma patients can detect T lymphocytes specifically sensitized to tumor antigens and cytotoxins active against these antigens. Patients seen the development of delayed-type hypersensitivity (DTH) response to intradermal injection of the polysaccharide fraction of the melanoma antigen.

At the same time, most authors point out that even with the localized form of melanoma develop changes antitumor immune responses, which are exacerbated by the extension of tumor [30, 43]. It has been established that patients with melanoma reduced the total number of lymphocytes, their T-population of CD4 + - and CD8 + T-lymphocyte subpopulations, increasing the proportion of zero T cells. At the localized form of melanoma is increasing the number of CD4 + CD25 +-cells, which contain and regulatory T-cells that exhibit immunosuppressive properties. Changes in melanoma functional properties of T-lymphocytes are characterized not only weakening the introduction DTH 2,4-dinitrochlorobenzene (DNCB), but also proliferative capacity of these cells to mitogens action; patients reduces the number and functional activity of natural killer cells (NK) and macrophages , in serum increases the amount of immunoglobulin (Ig) of class G and circulating immune complexes (CIC) having blocking properties. Already at an early stage of the disease revealed signs of the activation of immune system dysfunction: the proportion of lymphocytes expressing the activation antigens HLA-DR and CD25 +, but with the progression of the disease increases the proportion of CD69 + and CD95 + lymphocytes.

It is known that the operation of the peripheral immune system link is under the influence of its central governing organ – the thymus [2, 16-18, 45]. As an endocrine organ thymus produces a range of hormones, which belongs thymic serum factor (TSF) or thymulin, thymosin-alpha 1, thymopoietin II [2, 37, 38]. Thymic hormones affect antigen-independent and antigen-dependent stages of T lymphocyte differentiation, stages of regulatory T-lymphocyte subpopulations maturation in the thymus, the functional properties of T-lymphocyte and macrophage activity, etc. (Fig. 1) [Cit. N. 16].

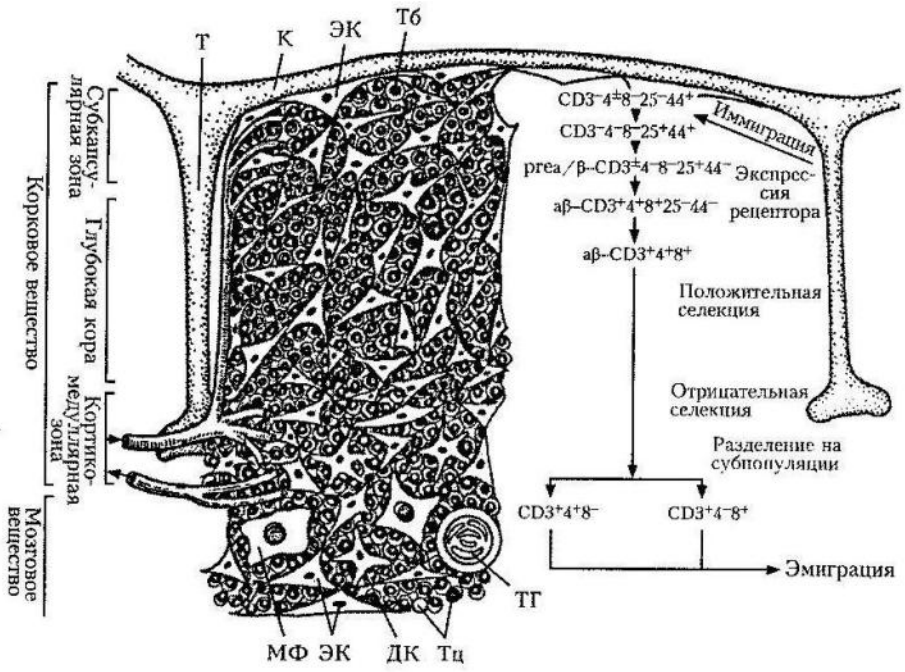

Fig. 1. Structure and differentiation in thymus of T cells

Among the thymic hormones attracts special attention TSF highly active, combining the features of all thymic hormones [37, 38]. The active form of TSF is associated with ions Zn^{2+}. In humans and animals TSF synthesized exclusively in the thymus, in its epithelial cells and secreted into the blood. TSF immunological activity manifests itself in effect all stages differentiation of T-lymphocytes (the bone marrow, the thymus, peripheral lymphoid organs) as well as their function. Thus, in the bone marrow suboptimal doses TSF influence expression Thy-1 antigen markers CD2, CD5 and CD7 precursor in T-lymphocytes, thereby

contributing to their transition into a more "mature" cells. TSF acts as a chemotaxic signal, which along with other factors (chemokine receptors CXCR4 and CCR9, P-selectin and its ligand PSGL-1) is set for the migration of T lymphocytes precursors from bone marrow to the thymus. In the thymus acts on the expression of TSF in thymocytes Thy-1, CD3 antigens, the balance of regulatory T subpopulations cytokine $CD4^{+}$-thymocyte transformation kortizol-sensitive into kortizol-resistant thymocytes. At the periphery of TSF enhances the proliferative response of T lymphocytes to mitogens, controls the balance of T-suppressor and T-helper cells, T helper type 1 and 2, as well as the production of T-helper cytokines and activity of NK cells.

In a number of malignant neoplasms (tumors of the breast, musculoskeletal, etc.) content in the blood is reduced TSF, at the same time, approaches aimed at restoring or activation of the endocrine function of the thymus, improve the clinical course of the tumor [18]. It is known that the involution of the thymus accompanied by a decrease in serum thymic activity, which is associated with increased incidence of malignancy (Fig. 2). [Cit. N 18].

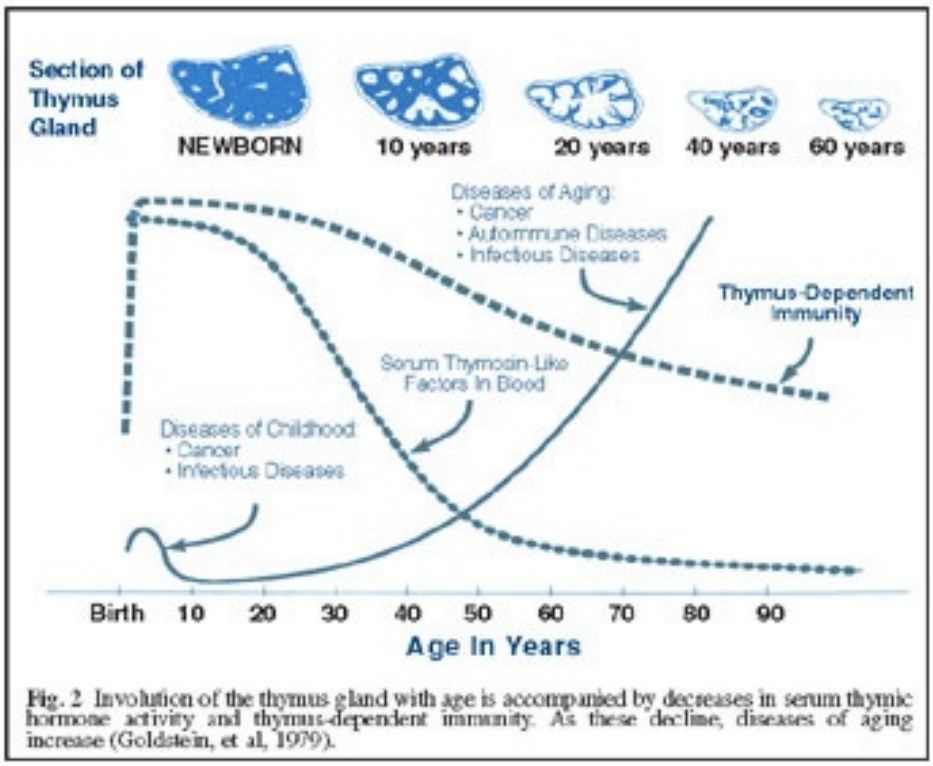

Fig. 2 Involution of the thymus gland with age is accompanied by decreases in serum thymic hormone activity and thymus-dependent immunity. As these decline, diseases of aging increase (Goldstein, et al, 1979).

Fig. 2. Age involution of the thymus accompanied by a decrease in blood levels of thymic hormones and activity of T-dependent immunity, as well as an increased frequency of age-associated diseases

So we imagined important to study the characteristics of the endocrine function of the thymus in melanoma patients with the biological properties of the tumor (primary tumor size, level of invasion into the dermis, the presence of regional lymph node metastases), and to identify the relationship of changes in endocrine function of the thymus and immunological parameters values. Furthermore, the nature of changes in the analysis parameters we considered patients sex. As established in male patients melanoma, change the functional properties of T-cells developed earlier and more pronounced than in women. [29] Shown more expressed mitotic activity of melanoma cell in male patients [4], indicating the most malignant tumor growth and a worse prognosis.

We examined 145 patients with both men and women with melanoma who had clinical stage I disease (only the primary tumor), and 64 patients of both sexes with clinical stage II (primary tumor + metastasis to regional lymph nodes), aged from 20 to 62 years. The control group consisted of 106 healthy men and women of the same age [11]. The diagnosis of melanoma and metastatic disease confirmed histologically. In patients with localized form of melanoma diagnosed IV levels of tumor invasion into the dermis, metastatic - III-IV levels [28].

Endocrine function of the thymus examined by titer (log_2) TSF [39]. Cellular and humoral links of immune system were studied using standard techniques [9]. In the peripheral blood the number of T-and B-lymphocytes, T-lymphocytes with suppressor and helper functions, the content of Ig class M, G, A and CIC were determined, estimated sensitivity of T lymphocytes in peripheral blood in vitro to thymostimulin (1 mg / ml), in production of leukocyte migration inhibition reaction as the antigen used patients autoplasma.

In assessing the relationship between the studied parameters used coefficient of correlation ratio "η", which is characterized not only by its strength, but also the form [26].

Endocrine function of the thymus in melanoma. It is found that patients with localized melanoma form has TSF titer significantly ($p < 0.05$) decreased relative to healthy individuals, and the number of patients with reduced levels of thymic hormone among patients with melanoma T2 higher than among patients with melanoma T1 (75% versus 54,5%) [10, 12]. In male patients titer reduction TSF recorded more frequently than in women (100 and 65%, $P < 0.002$).

The dependence of the reduction of the level of TSF titer on invasion of melanoma in the dermis [28]. If the level III invasion value of the indicator decreased by 1.7 times against the norm, then the IV - is a factor of 2.9. At the same time an increasing number of patients with a thymic hormone, which is less than the lower limit of its fluctuations in healthy individuals (with level III invasion – 46.6% of cases, with IV - already 83.3% of cases).

TSF titer decreases when melanoma metastases are in regional lymph nodes than in patients with localized form (more than 4 times, $p < 0,05$) [25]. Thus values of an indicator which below limits of its normal fluctuations, meet practically at all surveyed patients that more often ($p < 0,05$), than at sick of the localized melanoma form.

Thus, according to our data, in malignant skin melanoma endocrine function of the thymus is inhibited. The degree of dysfunction of the gland is directly related to the biological properties of the tumor: the size of its primary focus, depth of invasion into the dermis and the presence of metastases in regional lymph nodes. Hypofunction of the thymus is more apparent in male patients. All it specifies that decrease of the endocrine function of the thymus - objective criterion of the adverse forecast of this disease.

Impaired function of the thymus in melanoma patients may be due to the development of degenerative changes in the epithelial component and it is due to a direct effect on the products the disturbed metabolism and tumor growth. Thymic hormone levels decline in melanoma may also be subject to activation in patients with glucocorticoid-adrenocortical function, which, according to our data, more apparent in male patients [23]. It is well known that steroids in high concentrations have a depressing effect on the structure and endocrine function of the thymus, acting through receptors in the epithelial component of the organ [18, 42, 50].

Communication malfunctions of the thymus and peripheral link the immune system in melanoma. We have established melanoma patients consistency nature and severity of disorders of the endocrine function of the thymus, on the one hand, and the dysfunction of the peripheral immune system, on the other. Thus, such a contingency investigated parameters identified in a localized form of melanoma with different levels of its invasion into the dermis [28]. It is shown that reduction of T-lymphocytes in the peripheral blood of patients with IV-V levels melanoma invasion into the dermis greater than level III ($p < 0.05$) It noted that the relative number of T-lymphocytes in patients with (III-IV infestation levels) increases after in vitro incubation with thymostimulin ($p < 0.05$). These results indicate that immature (nonrosette-forming) cells circulate in peripheral blood of patients, they have increased sensitivity to the differentiating factors of the thymus.

Violation of the ratio T-helpers and T-suppressors at melanoma patients with III and IV invasion levels is characterized by accumulation of the last (immunoregulatory index values are 2,1:1,0 and 2,7:1,0 at a rate of 3.5: 1.0). As it is known, excessive activation of T-suppressors in tumor growth may be important in the pathogenesis of tumor progression, including melanoma [7, 48]. Given the important role of thymic hormones in the differentiation of T-helpers and T-suppressors, as well as control of their quantitative ratio and functional activity, it is believed that the decline in TSF for melanoma - an important condition for

changes in patients with a balance of these subpopulations of T-lymphocytes and their functions. We have also established experimentally that in norm in the conditions of activation of the endocrine thymic function the $CD4^{+}25^{+}$-cells quantity in the thymus, decreased [22].

CIC content in serum of patients with melanoma tumor invasion IV level in the dermis higher than III (as compared with a norm respectively 1.7 times and 1.3 times) [28] . Known activating effect of the thymic hormones on functional status of macrophages, particularly in the liver, whose role in the removal of circulating immune complexes is significant [18, 47]. Therefore, the lack of thymic hormone in melanoma contributes to the accumulation in the blood of patients elevated concentrations of the "antigen-antibody", which long circulation promotes development of immunosuppression in an organism.

At the same time in melanoma patients in the accumulation of immune complexes in the blood increases the frequency of manifestation of the effect of increased migration of leukocytes [6, 13]. If inhibition of leukocyte migration shows maintaining the ability of sensitized T-lymphocytes produce migration inhibitory factor (MIF), but its strengthening - the presence in blood plasma factors blocking the formation of cell-mediated immune responses. According to our data, 40% of patients with level III melanoma invasion into the dermis, and 47% of patients with level IV have index of leukocyte migration (IML) above 110%. Importantly, the reduction in titer of TSF is more apparent in melanoma patients with enhanced migration of leukocytes. As thymic hormones modulate the production of MIF by sensitized T lymphocytes, it is possible to conclude about the importance of reducing the function of the thymus to suppress the production of this mediator by lymphocytes of melanoma patients and the accumulation in the blood of blocking factors.

So, installed by us dependence severity of disorders of the immune system of the level of tumor invasion into the dermis in localized melanoma patients may be caused degree of decrease of thymic hormone level at patients.

When the melanoma metastases in regional lymph nodes dysfunction of the peripheral immune system, as well as the thymus, further exacerbated [25]. Thus, in the peripheral blood of patients with metastatic melanoma in comparison with localized form "0"-cells are accumulate and the number of T-lymphocytes, which in the test in vitro exhibit enhanced sensitivity to thymic differentiating factors, is reduces. The content of immune complexes in the blood of patients with metastatic melanoma is higher than in patients without metastases. Moreover, among patients with metastatic melanoma increased number of patients in which the accumulation of immune complexes is shown the effect of enhancing the migration of leukocytes (67% vs 46% of patients with a localized form, $p < 0.05$). In the blood of patients with metastatic melanoma is increasing levels of IgA and IgG ($p < 0.05$). It is shown that, along with the CIC, Ig not only class G, but A can have properties that block cell-mediated immune responses [9]. At the same time, in the form of localized melanoma of the CIC are mainly associated with IgM, which is part of the "antigen-antibody", which increased production in the immune response is important for the regulation of the dynamics of production of IgA and IgG.

In the analysis of the degree of change in the value of some immunological parameters in patients with melanoma with different tumor size differences according to gender of patients were set. Thus the degree of reduction in the total number of lymphocytes, T- and B-lymphocyte populations in melanoma patients T2 vs T1 melanoma greater in men than in women. IgM concentration is significantly higher than normal only in female patients ($p < 0.05$). It is possible that male patients more pronounced lack of thymic hormones, along with a reduction in the number of T- and B- lymphocytes, causes abnormal co-operation of the lymphocyte population in the synthesis of IgM plasma cells.

Thus, the results of our studies suggest that the quantitative and functional disorders of the peripheral immune system both in localized and metastatic melanoma are significantly associated with hormonal dysfunction of the thymus. Proof connection between the breach of the functioning of the central (thymus) and

peripheral organs of the immune system in melanoma may be a correlation between the values of the investigated parameters (Table) [13].

Table. Values of the correlation ratio coefficient (η), characterizing the degree of coupling of immunological parameters in patients with different clinical stages of melanoma

Stage	Thymus	The degree of dependence of values of immunological parameters and the thymic hormone level			
		The number of T-cells	The number of T helper	IML level	CIC level
I	FTS	+0,46±0,17*	+0,48±0,15*	–0,45±0,16**	–0,52±0,15**
II	FTS	+0,75±0,15*	+0,50±0,15*	–0,56±0,20*	–0,51±0,23*

The reliability of communication FTS level and immunological parameters:

*-P <0,05, ** - P <0,01; (+ / –) - direction of the parameters communication.

Using the methods of biotherapy in the plans of the primary treatment of melanoma patients.

Effect of primary treatment on the immune system of melanoma patients. It is known from the literature that in melanoma patients after surgical removal of the tumor is observed further decrease of the absolute peripheral blood lymphocyte and its T-population, reduction in the frequency of positive results in the inhibition of leukocyte migration reaction on tumor antigen, the weakening of blasttransformation reaction of lymphocytes under the action of phytohemagglutinin (PHA), ability infringement of lymphocytes to form a DTH response to the polysaccharide antigen complex from melanoma tissue [19, 21]. Inclusion in the treatment regimen of melanoma patients chemotherapy drugs in most cases accompanied by a decrease in the absolute content of peripheral blood T lymphocytes, decreased lymphocyte cytotoxic effect on tumor cells [36].

We have found that changes in a number of immunological parameters after surgical and combined methods (surgery + chemotherapy (PCT)) treatment associated with a further depletion of the endocrine function of the thymus in these patients [14]. For example, in melanoma patients against a significant falling titer TSF after surgery and especially the combined treatment significantly increased the frequency of reduced levels of T-lymphocytes ($p < 0.05$). In this case, between the decrease in the blood titer of TSF and the number of T-cells there is a significant direct relationship ($\eta = 0,57 \pm 0,27$, $p < 0,05$). In patients after treatment observed a further increase in the blood level of the CIC and the values of the IML. In addition, according to our data, after application of chemotherapy in patients' blood increases levels of cortisol, which can be one of the pathogenetic mechanisms worsening dysfunction of the thymus and T-cell-mediated immune system in melanoma patients [24].

Approaches to immunotherapy of melanoma. According to modern immunotherapy concepts, which is used for malignancy, divided into non-specific, impacting on the immune system in general and the specific, inducing the development of anti-cancer immune system reactions [7, 8, 34]. A distinction is also active and passive immunotherapy. The effectiveness on the immune system of methods for active specific and non-specific immunotherapy is most fully studied in melanoma.

Thus, methods of active specific immunotherapy in patients with localized melanoma researchers used vaccinotherapy based on tumor cells and tumor-derived antigens [46]. The authors noted improvement in T-cell-mediated immune system, these changes were correlated with the clinical course of the disease. Improving the efficacy of anticancer therapy of melanoma can be achieved using vaccinotherapy combined with a powerful adjuvant - dendritic cells [32, 33, 49, 51].

Among the methods of active nonspecific immunotherapy for melanoma using various biological response modifiers (cytokines, BCG, levamisole, splenin,

bioactive thymus factors, etc.). Thus, the efficacy of BCG is shown in patients with localized melanoma to prevent the recurrence and metastasis [5, 36]. Patients with primary melanoma localized limbs and trunk (I-II stage disease) to prevent development of metastases, the authors used course (within one year) α2ß recombinant interferon and interleukin-2 (IL) in schemes of main treatment [20 , 31]. An increase in the three-year survival rate of patients, especially by combination of interferon and interleukin-2, which was associated with positive changes in indicators of the state of the immune system was founded.

In the literature, there are data that demonstrate the effectiveness of biologically active factors of the thymus in melanoma. As the researchers note, the main benefit of immunotherapy by thymic factors is their ability to correcting violations in carcinogenesis of lymphoid cell differentiation, induction of maturation, regulating the activity of lymphocytes functioning, turn on depending on the initial state of the immune system helper, suppressor and cytotoxic lymphocyte functions [18, 44 45, 47].

In patients with non-metastatic melanoma form and low levels of T-lymphocytes used basic treatment (chemotherapy or surgery) or independently thymostimulin [40]. It is noted that all patients after receiving thymostimulin increased number of common and active E-rosette-forming T-lymphocytes to normal values. Such changes combined with the absence of metastases in patients within 34 months, while 87% of patients after chemotherapy DTIC and 81% of patients after surgery they appeared.

Trevisan G. et al [52] in patients with non-metastatic melanoma and without manifestations of immunodeficiency after surgery used thymopentin. Immunological studies were performed every three months during 29 months. The authors observed an increase of 40% of the content $CD3^+$ -, $CD4^+$ lymphocytes and NK cells in peripheral blood. Only 3 of the 33 patients at the end of line monitor recorded appearance of regional metastases.

Research Bodey B. et al [41] showed reduced hematopoietic toxicity of chemotherapy in the case of combinations with thymic factors as compared to using only chemotherapy.

With the simultaneous use of T-activin and chemotherapy in patients with metastatic melanoma authors observed a reduction in the frequency leukopenia, thrombocytopenia, as well as the manifestations of allergic reactions [35].

Upon receiving Thymosin alpha 1, patients with metastatic melanoma received DTIC with interferon and IL-2 increases the level of T cells, NK activity, combined with an increase in survival [44]. According to the authors, one of the ways of the positive impact of thymosin-alpha1on the immune system in patients with neoplasia is to increase the number of cytokine receptors on T cells, as well as increased production of cytokines. At the same time, there is evidence that patients with metastatic melanoma with low T-cell application of thimostimulin did not affect their level against DTIC, and the survival rate of patients did not differ from rate after receiving DTIC [40].

According to our data, the use of the drug with the inductor properties to the endocrine function of the thymus (biological preparation of a spleen – splenin) in schemes of the primary treatment of patients with localized form of melanoma leads to an improvement of the immune system [14]. If, after surgical and combined (surgery and chemotherapy) treatments TSF titer significantly ($p < 0,05$) decreased compared with baseline (from $1,38 \pm 0,17$ respectively to $0,36 \pm 0,1$ and $0,67 \pm 0,35$), after switching splenin to scheme surgical and combined treatment of patients its value significantly increased (respectively to $5,06 \pm 0,8$ and $4,0 \pm 0,61$, $p < 0.05$). The level of TSF does not differ from that of healthy subjects ($p > 0.05$). Application splenin in schemes of main treatment leads to a significant increase in the absolute quantity of T lymphocytes, and the detection rate discount levels of T cells is substantially reduced compared with the frequency in patients not treated with the drug (respectively 23% and 85%, $p < 0, 05$). Under the influence of splenin increased after primary treatment level of immune complexes

is reduced to values recorded in healthy subjects ($p > 0,05$). It also reduces the number of patients with increased migration of leukocytes.

Thus, it can be concluded that improved cellular and humoral immune responses in melanoma patients treated splenin, largely related to elevation of thymic hormone. Splenin has immunomodulatory effects only in the presence of abnormalities in the immune status. It is known that the biologically active substance may induce the appearance of splenic T-cell marker on lymphocytes. Immunomodulatory activity also has a splenin analog – Erbisol.

Also of interest are our experimental data on the study of the mechanism of antimetastatic effect of thymic factors for melanoma [15]. Found that in mice with B16 melanoma treated with thymic factors (timoptin, vilozen, timalin, taktivin), levels of TCF increased and the body's ability to develop interferon also increases. This is important for enhancing the cytotoxic activity of NK cells and macrophages.

Conclusion

Thus, these data demonstrate the importance of the study of the endocrine function of the thymus in localized and metastatic melanoma, which will give an opportunity to objectify the evaluation of patients with the initial state of the immune system and its changes during the primary treatment. Study of thymic function is also a prerequisite not only during immunotherapy by thymic factors (timalin, timogen etc.), but using approaches active nonspecific and specific immunotherapy. This is due to the fact that the impact of their influence on cellular and humoral immune system in melanoma depends on its initial state, which, in turn, largely determined by the state of the endocrine and cytocrine functions of the thymus [37]. It should be noted that no analysis of the endocrine function of the thymus it is hard to obtain objective conclusions on the functional status of the peripheral immune system in other forms of cancer.

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