PHYSIOLOGY

Cytological Profile of the Thymus of Mice with Increased Resistance to P3-X63-Ag8.653-MOPC Plasmocytoma after Stress

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Pronounced stimulation of antigen-independent differentiation of T lymphocytes is found. Physical loads and immobilization stress are shown to considerably augment both the immigration of T lymphocyte precursors to the thymus and the emigration of differentiated lymphocytes, as well as to affect the rate of cell differentiation.

Key Words: *cytological profile of the thymus; chronic stress; antitumor effect*

Stress factors may either accelerate or inhibit the growth of experimental tumors [4]. We earlier found that physical loads (swimming) and immobilization stress increase the resistance to P3-X63-Ag8.653-MOPC plasmocytoma in mice [2]. The role of immunological factors in the realization of the antitumor effect of chronic stress is of great importance; however, this aspect is still poorly understood.

The objective of the present investigation was a morphological study of the structural and functional peculiarities of the thymus in mice with elevated antitumor resistance, induced by intensive and moderate physical loads and immobilization.

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MATERIALS AND METHODS

The experiments were carried out on 95 female BALB/c mice aged 6 to 8 months. The mice were exposed to stress during 2 weeks according to the scheme presented in Table 1, after which 7 mice from each group were sacrificed by cervical dislocation for histological examination, while the other mice (88 animals) from the control (C) and experimental (S1, S2, and S3) groups were subcutaneously inoculated with P3-X63-Ag8.653-MOPC plasmocytoma cells (4×10^3 cells/mouse) and the dynamics of tumor growth was assessed. The tumor strain was obtained from the Research Institute of Human Morphology, Russian Academy of Medical Sciences.

Specimens for morphological examination were fixed in 10% buffered formalin and embedded in paraffin. Histological sections were stained with azure II-eosin. The absolute number and percentage of different forms of lymphoid cells was evaluated in the subcapsular zone, cortex, and medul-

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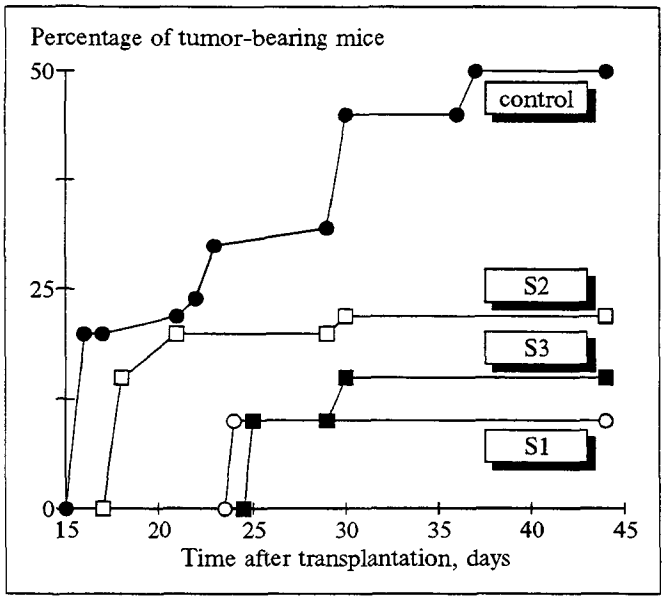

Fig. 1. Effect of chronic physical loads on the growth of P3–X63–Ag8.653–MOPC plasmocytoma.

lary substance of the thymus [3], and the reliability of the differences between the mean parameters in all experimental groups and the control was evaluated using the Wilcoxon-Mann-Whitney test. In the event that the differences were reliable, the ratio indexes (RI), reflecting the degree of changes of this parameter in comparison with the control were calculated by the formula:

$$RI_n = \frac{\text{mean content of cell elements in group Sn, \%}}{\text{mean content of cell elements in control C, \%}}$$

where n is experimental group 1, 2, or 3.

RESULTS

Chronic exposure to stress leads to an inhibition of tumor growth which manifests itself in a prolonged latent period and a 2- or more times reduced share of tumor-bearing mice in comparison with the control (Fig. 1).

Statistical analysis revealed a reliably decreased number of lymphoid cells per square unit (concentration) in the examined zones of the thymus after exposure to all types of stress (Table 2), but no serious destructive reactions differing from the control were noted. The only exception was the subcapsular zone of the thymus after an intensive physical load, where the destruction of cells was markedly increased (RI 1.8). The decreased concentration of lymphoid cells in the thymus zones together with a practically unchanged level of destruction (except for the subcapsular zone) suggests an intensified emigration of lymphocytes in the studied structures. This was also confirmed by the absence of a "naked" reticular framework of the thymus under the experimental conditions. On the contrary, the percentage of reticulocytes in the thymus of mice exposed to stress not only did not rise, but even sharply decreased (except for the subcapsular zone), the RI of epithelioreticulocytes in groups S2 and S3 being far lower than unity. The only exception, once again, is the subcapsular zone of the thymus after an intensive physical load (Table 2). At the same time, an augmented immigration of T lymphocyte precursors may be hypothesized. Indeed, a considerably elevated number of blasts and of large and (in part) medium lymphocytes was observed in the studied structural components of the thymus in practically all experiments, against the background of a mitotic activity little different from the control (differences are unreliable) (Table 2). Of interest are peculiarities of the concentration of cells in different zones of the thymus. For example, for all kinds of stress used the content of blasts maximally rose in the subcapsular zone (in S1 and S2 4-fold and in S3 7-fold) and in the cortex (in S1 8.7-fold, in S2 3.7-fold, and in S3 5.6-fold), while the content of large lymphocytes rose maximally in the medulla (9.19- and 10-fold, respectively). This argues for the scheme of independent differentiation of cortical and medullary thymocytes described earlier [1]. Changes in the content of medium lympho-

TABLE 1. Scheme of Stress Factors

Group (number of mice)	Stress
C (26)	Control, intact female BALB/c mice
S1 (22)	Intense physical load (swimming): the mice swam 3 times per day during 20 min 4 days a week ($t°$ water = 38°C)
S2 (25)	Immobilization stress: the mice were placed in plastic tubes for 6 h per day, 4 days a week, with free access to food and water
S3 (22)	Moderate physical load (swimming): the mice swam 3 times per day during 6 min, 4 days a week (3 min – $t°$ water = 28°C and 3 min $t°$ water = 38°C)

TABLE 2. Content of Cells (%) and RI of Cells in Different Structures of the Thymus of BALB/c Mice with Increased Antitumor Resistance

Cells	Structure of thymus	Content of cells, %				Index		
		C	S1	S2	S3	S1	S2	S3
Epitheliore-ticulocytes	1	16.4±2.3	24.1±1.5	9.95±1.1	10.4±1.1	1.46*	0.61*	0.63*
	2	12.4±1.5	0	3.1±0.72	2.54±0.2	0	0.25**	0.2**
	3	39.6±1.9	0	25.7±1.85	24.9±0.9	0	0.65**	0.63**
Blasts	1	0.76±0.9	3.04±0.3	3.2±0.5	5.6±0.8	4**	4.2**	7.0**
	2	0.16±0.1	1.4±0.5	0.6±0.2	0.9±0.2	8.7*	3.7*	5.6*
	3	0	0	0	0	0	0	0
Large lymphocytes	1	3.5±0.9	8.4±1.0	11.7±1.9	11.6±0.8	2.4**	3.4**	3.3**
	2	0.9±0.4	2.3±0.3	2.9±0.9	4.7±0.7	2.6*	3.2**	5.2**
	3	0.1±0.03	0.9±0.3	1.9±0.8	1.0±0.4	9.0*	19.0**	10**
Medium lymphocytes	1	19.2±1.1	0	31.6±1.5	33.6±2.4	0	1.6**	1.8**
	2	13.9±1.2	0	26.5±1.4	37.6±4.7	0	1.9**	2.7**
	3	19.1±1.3	13.9±1.8	29.7±2.5	32.3±2.3	0.7*	1.6*	1.7**
Small lymphocytes	1	55.8±3.7	37.7±2.3	38.8±4.9	34.8±2.1	0.7**	0.7*	0.6**
	2	69.4±2.9	59.6±2.5	0	51.4±4.7	0.9*	0	74**
	3	34.2±1.8	41.6±2.1	0	0	1.2**	0	0
Mast cells	1	0	0	0	0	0	0	0
	2	0.31±0.1	0	0.9±0.1	0	0	2.8**	0
	3	0.16±0.06	0	0.7±0.2	0.9±0.2	0	4.4*5.6**	
Mitotic cells	1	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0
	3	1.1±0.4	0	0	0.09±0.1	0	0	0.1**
Destroyed cells	1	1.0±0.2	1.8±0.2	0	0	1.8*	0	0
	2	0	0	0	0	0	0	0
	3	3.4±0.5	0	2.1±0.5	0	0	0.6*	0
Total number of cells per square unit (absolute number)	1	57.3±1.9	51.2±0.9	37.0±1.6	35.7±1.2	0.9*	0.6**	0.6**
	2	65.5±1.4	56.4±1.2	49.7±2.3	45.7±1.4	0.9**	0.8**	0.7**
	3	52.6±1.9	0	34.1±1.1	33.0±1.2	0	0.6**	0.6**

Note. *1* – subcapsular zone; *2* – cortex; *3* – medulla. * – $p \leq 0.05$; ** – $p \leq 0.01$; 0 – unreliable differences.

cytes in all structural zones of the thymus in groups S2 and S3 were less expressed than the increase in the number of large lymphocytes, while the content of small lymphocytes was mostly lower than control values (Table 2). This may be related to both the inhibited cell differentiation and stepped-up emigration of medium and small lymphocytes from the thymus. Stimulated migration and recirculation of the cells are indirectly confirmed by the relatively high value of the index of mast cells in the medullary substance in groups S2 (4.4) and S3 (5.6).

It may be assumed that the complex of changes in the cytological profile of the thymus induced by repeated intensive and moderate physical loads in the form of swimming as well as by immobilization is connected with the development of increased resistance to P3-X63-Ag8.653-MOPC plasmocytoma in mice. The revealed cell rearrangements in the thymus parenchyma are indicative of an elevated functional activity of the thymus in response to physical loads and, particularly, of stimulated processes of antigen-independent differentiation of T lymphocytes. Analysis of the obtained results suggests that under these conditions the migration of T lymphocyte precursors to and of differentiated thymocytes from the thymus is

greatly intensified. The dynamics of the number of large, medium, and small lymphocytes suggests a probable change in the rate of cell differer tiation.

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PATHOLOGICAL PHYSIOLOGY AND GENERAL PATHOLOGY

Changes in Rhythmoinotropic Reactions of the Myocardium in Chronic Ischemia: Pathology or Adaptation?

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Changes in the organization of the Ca^+-transporting systems but not disturbances in the contractile apparatus of cardiomyocytes are shown to occur in chronic coronary heart disease. During a certain stage of CHD the change in rhythmoinotropic relations may reflect adaptive changes induced by functioning of the myocardium under conditions of ischemia.

Key Words: *myocardium; rhythmoinotropic activity; ischemia*

The pumping function of the heart depends first of all on its contractility and on the rhythmic pattern of heart-beats. These two properties are acted upon by regulatory influences which adjust heart functioning to adequately meet the physiological requirements of the organism.

Whereas the gross and often irreversible changes in the myocardium during acute ischemia are almost always pathological in nature, chronic ischemic heart disease (IHD) is characterized by the parallel development of hypoxemic damage and adaptation to it [4]. However, current approaches to the study of myocardial ischemia and to the search for protective measures are unable to reveal the first step in the development of adaptive reactions in cardiomyocytes [6].

The aim of the present study was to investigate the effect of chronic IHD on the character of the rhythmoinotropic function of the human heart in comparison with the analogous reaction of intact myocardium of guinea pigs and rats.

MATERIALS AND METHODS

The study was carried out on biopsy material (auricular trabecula of the right atrium) obtained dur-

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