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Comparison of the results of morphological changes observed in the spleen under the influence of carcinogens in the experiment

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Abstract: By means of morphological and immunohistochemical methods of a research the lymphoid device of a lien at rats at the age of 3 and 6 months which underwent a chemical carcinogenesis, the induced 1,2-dimetilgidraziny is studied. It is established that the entered carcinogen leads to decrease of the main morphometric indicators In - and T-dependent zones of a lien. After administration of carcinogen in these zones the number of CD79α+ cells (B-lymphocytes) and CD45RO+ cells (T-lymphocytes) is considerably reduced. It is taped that all quantitative and highquality changes of a white pulp of a lien are more expressed at rats at the age of 6 months. Revealed a decrease in the size of lymphoid nodules spleen, to reduce their number per unit area, improvement of relation (serotonin + histamine)/catecholamines. The changes of the immunodeficiency offspring are more pronounced. Carcinogenesis on the background of immunodeficiency stimulates migration CD-68+, NSE+ cells, as evidenced by the increase in their number in the red pulp.

Key words: lien, carcinogenesis, 1,2-dimethylhydrazine, white pulp; dendritic cells, B-lymphocytes, T-lymphocytes.

Relevance. In connection with the emergence of new research methods in morphology and the improvement of already known methods, the interest of immunologists in the structure of the spleen as an important and largest peripheral organ of the immune system is steadily growing [1]. The spleen is an organ of immunogenesis and lymphopoiesis, in which antigen-dependent differentiation of immunocompetent cells, the formation of effector and memory cells, as well as the elimination of obsolete and damaged hematopoietic cells take place [2]. It has a complex anatomical structure of an immunocompetent white pulp, including periarterial lymphoid muffs, lymphoid nodules with germinal centers, periarterial, mantle and marginal zones. This structure creates favorable conditions for effective cooperative interaction of cells involved in the immune response [3]. In addition to T- and B-lymphocytes, which form the corresponding T- and B-dependent zones, macrophages, reticular and dendritic cells (DC) are present in the white pulp of the spleen. There are two types of DC in the spleen: interdigitating (in the periarterial zones of lymphoid nodules) - cells of myeloid origin, interacting with naive T-lymphocytes and activating T-helpers, as well as suppressors of T- and B-lymphocytes; follicular - cells of non-bone marrow origin, are located in the germinal centers of lymphoid nodules, are not capable of movement, provide growth and differentiation of B-lymphocytes, take part in the formation of primary lymphoid nodules, forming a dense strong network for them [4]. Some authors emphasize the DC of reproduction centers, which are also cells of non-bone marrow origin, unlike follicular ones, they are capable of migration [5]. There is evidence in the literature that splenic DC are actively involved in antitumor immune surveillance. However, there are conflicting data on the functional orientation of these cells in the antitumor

immune response. Some authors believe that splenic DCs have a high antitumor potential and are able to suppress the growth of tumor cells, while thymic dendritic cells do not have such activity [6]. Others believe that splenic DCs, on the contrary, may contribute to the escape of the tumor from immune surveillance [7]. It is known that the introduction of a carcinogen triggers a number of processes in the body, leading to certain disorders in the organs of immunogenesis [8]. However, experimental studies on the effect of a carcinogen (1,2-dimethylhydrazine) on the morphology and DC of the spleen, in particular, have been carried out relatively recently, therefore, an in-depth study of the morphological and immunohistochemical pattern of spleen tissues during experimental carcinogenesis induced by 1,2-dimethylhydrazine is relevant.The steady growth of cancer incidence is a global medical and social problem. According to Rosstat, one of the most common tumor localizations is the large intestine, accounting for 11.4% of the total incidence of malignant neoplasms in the Russian population. There is evidence that approximately 80-90% of tumors in humans arise under the influence of various chemical carcinogens [1]. It is known that chemical carcinogenesis leads to certain disorders in the immune surveillance system [7]. There is evidence that the growth of malignant neoplasms is accompanied by the production of biologically active substances that inhibit the body's defenses. This, in turn, leads to a decrease in the antitumor immune response [10], as a result of which the tumor is not recognized by immune cells as foreign. This is probably due to the involution of the thymus against the background of carcinogenesis [5]. There is also evidence that the tumor has a direct toxic effect on immune organs [3], which, in turn, leads to a decrease in the production of immunocompetent cells by them, the production of defective and immunosuppressive cells [9]. One of the leading roles in the formation of antitumor immune defense belongs to the largest peripheral organ of immunogenesis - the spleen. Here the final antigen-dependent differentiation of B- and T-lymphocytes takes place, as well as the transformation of B-lymphocytes into plasma cells and the accumulation of memory cells. Despite the existing contradictions in the literature on the interaction between the tumor and immune organs, it can be argued that immunity plays a significant role in the pathogenesis of oncogenesis.

An important role in the formation of antitumor immune defense belongs to the spleen. There is evidence that tumors develop more intensively in splenectomy rats (Fedorov G.N., 2006). Our previous works have shown that the offspring of splenectomy female rats develop immunodeficiency (Mikhailova M.N., 2012), leading to accidental involution of the thymus

The aim of the study was to compare the results of studying the morphological and immunohistochemical characteristics of the rat spleen during chemical carcinogenesis 1 and 4 months after oncogenic exposure to cells.

Results of the study and their discussion. The introduction of 1,2-dimethylhydrazine one month after the end of the course leads to the transformation of the colon mucosa, which is manifested by cellular dysplasia, polymorphism, nuclear hyperchromia and increased mitotic activity of glandular epithelial cells. After 4 months, the carcinogen causes the formation of one, less often two tumors in the large intestine ranging in size from 0.3 to 1.0 cm, which have the structure of a highly differentiated adenocarcinoma. Lymphoid tissue of the rat spleen forms two main B- and T-dependent zones, which are represented by periarteriolar lymphoid muffs (PALM) and lymphoid nodules. There are primary lymphoid nodules that do not have reproduction centers, and secondary

lymphoid nodules with germinal centers (HC), which appear only after antigenic stimulation. They, in turn, form a B-dependent zone, where differentiation, proliferation of B-lymphocytes and accumulation of memory cells take place. The T-dependent zone is the periarterial zone of lymphoid nodules and PALM, which consist of T-lymphocytes and interdigitating cells. The place where B- and T-lymphocytes interact with each other and meet with antigens is the marginal zone, which is located on the periphery of lymphoid nodules [8]. The quantitative and qualitative composition of these structures indicates the functional state of the spleen and reflects the state of its local immune status. In the spleen of intact rats, each lymphoid nodule has a rounded shape, a clear zonal structure, and smooth boundaries. At the same time, the proportion of large lymphoid nodules (more than 500 microns in diameter) prevails over small (less than 300 microns) and medium (300-500 microns). Our studies have shown that during carcinogenesis, lymphoid nodules not only acquire a changed shape, but also lose clear contours between zones, the boundaries between them become blurred and erased. The introduction of a carcinogen leads to an increase in the number of small and medium-sized lymphoid nodules by 2 times, and the number of large ones decreases by 10%. The diameter of the lymphoid nodules of the spleen 1 month after the administration of 1,2-dimethylhydrazine significantly decreases by 19%, and after 4 months it is more significant - by 22%.

As a result of the study, it was revealed that carcinogenesis induced by the introduction of 1,2-dimethihydrazine leads to a decrease in the weight of rats: 1 month after the administration of the carcinogen by 20%, and 4 months later - 24% (Table 1). Changes in other anthropometric data (length of the body, tail, ears) are unreliable at both periods of exposure to the carcinogen. The introduction of 1,2-dimethylhydrazine is accompanied by a decrease in the mass of the spleen: 1 month after injection by 22%, and 4 months later - by 27% (Table 1). When staining sections of the spleen of rats with hematoxylin and eosin, red and white pulp is visualized. At the same time, the proportion of red pulp in the total mass of the organ is on average 75–85%. In the lymphoid nodules of the white pulp of intact animals, the central artery is determined, often located eccentrically and surrounded periarterially by a T-dependent zone, the germinal center, the mantle and marginal zones. Among the lymphoid nodules, there are primary nodules without germinal centers and secondary nodules with reproduction centers that appear only after antigenic stimulation (Fig. 1, A). The ratio between secondary and primary lymphoid nodules is 2.6:1 in one field of view. Immunohistological examination reveals S100+-dendritic cells in the germinal centers of secondary lymphoid nodules, which form the stromal framework of reproduction centers (Fig. 2). When determining morphometric parameters, it was revealed that 1 month after the course administration of 1,2-dimethylhydrazine, the white pulp of the spleen retains its zonal structure. Borders of lymphoid nodules and periarterial lymphoid muffs are preserved, but become less distinct.

The study showed that after the introduction of a carcinogen in the offspring of rats of both experimental groups, the number of lymphoid nodules of the spleen in the field of view increases by 2-3 times, while the area of germinal centers decreases by 1.5-1.6 times. In the offspring of immunodeficient rats, lymphoid nodules acquire a varied shape and indistinct contours. The average number of luminescent granular cells (LGC) in the white and red pulp of the spleen of rats of the experimental groups increased by 23% and 31%, respectively. Against the background of carcinogenesis, there is an

increase in the level of biogenic amines in all LHA of the white and red pulp of the spleen by 2-4 times. At the same time, the introduction of a carcinogen into the offspring of intact rats leads mainly to an increase in the level of histamine, and against the background of congenital immunodeficiency - serotonin. The ratio (serotonin + histamine) / catecholamines, showing the total-directed action of biogenic amines (Struchko G.Yu., 2003), significantly increases in both experimental groups in all the studied structures of the spleen, which indicates the suppression of their functional activity. It has been established that carcinogenesis in the offspring of intact rats is accompanied by a decrease in the number of S100+ cells by 1.5 times, and in the offspring of immunodeficient rats, on the contrary, by an increase in their number by 1.3 times. The introduction of a carcinogen against the background of immunodeficiency leads to an increase in the number of CD-68+ and NSE+ cells by 2-3 times in the marginal zone of the white pulp, perifollicular and deep zones of the red pulp, which is probably due to the migration of macrophages and dendritic cells from the blood (Luzikova E. M., 2011). Thus, our data indicate significant structural and functional changes in the spleen against the background of carcinogenesis in the colon, manifested in an increase in the number and shape of lymphoid nodules, a decrease in their size, an increase in the number of dendritic cells and macrophages, and an increase in the level of biogenic amines. It was found that changes in the spleen during carcinogenesis in the offspring of rats with congenital immunodeficiency are more pronounced.

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