TUMOR AND LIVER LIPIDS OF RATS WITH SVEC'S ERYTHROMYELOSIS

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Changes in the total tissue lipid content of the tumor in rats with Svec's erythromyelosis correlate with the increase in its size. Phospholipids are the main lipid component. The content of phospholipids and total cholesterol in the tumor lipids reached a maximum 10 days after transplantation. In the liver lipids of animals with tumors, a decrease in the phospholipid fraction and total cholesterol is observed.

Insufficient attention has been paid to the study of lipid metabolism in malignant blood diseases. In the accessible literature no data could be found on simultaneous investigation of the lipid composition of the blood, tumor, and organs with leukemic infiltration throughout the course of growth of an experimental malignant tumor.

In the investigation described below the lipid composition of the tumor and liver was studied in rats with a form of experimental leukemia: Svec's erythromyelosis [6].

EXPERIMENTAL METHOD

On the ninth day after transplantation, an intraperitoneal leukosarcoma was removed from the donor animals, and the tumor tissue was minced and a suspension of tumor cells injected subcutaneously into 90 noninbred rats (12×10^6 cells per animal). Ten animals were used as controls. Before sacrifice the animals were deprived of food for 14-16 h. The mean diameter of the tumor was measured in experimental rats 1, 2, 5, 8, 10, 12, 13, 14, 15, and 16 days after transplantation, after which the animals were killed under ether anesthesia, the tumor and liver were removed and weighed, impressions were made, and the material was left on solid CO_2 until analysis. Lipid metabolism was studied relative to three indices: the content of total lipids, total cholesterol, and phospholipids. A cooled homogenate was prepared from the tumor and liver tissues of 5-9 animals in 20 times the volume of a methanol–diethyl ether mixture (3:1). Extraction continued for 1.5 h on a water bath at 60° in the presence of traces of tocopheryl acetate. The tissue was then separated from the lipid extract by centrifugation and filtration, and the lipid extract was washed with water to remove nonlipid impurities, and dried with anhydrous sodium sulfate. The solvents were evaporated in vacuo and the lipids weighed and dissolved in hexane. Total cholesterol was determined by the Liebermann-Burchard method. The phospholipid content, calculated as lecithin, was found by multiplying the value obtained during determination of lipid phosphorous [2] by a coefficient of 25. Total lipids, phospholipids, and total cholesterol were determined in dried liver tissue from the animals. A sample of minced liver tissue was frozen in liquid nitrogen and dried lyophilically for 7 h. The subsequent analysis took place in the usual manner. The value plotted at each experimental point is the mean of the values determined for nine (1st-12th days) or five (13th-16th days) animals. The results of measurement of the mean diameter of the tumor were analyzed by statistical methods.

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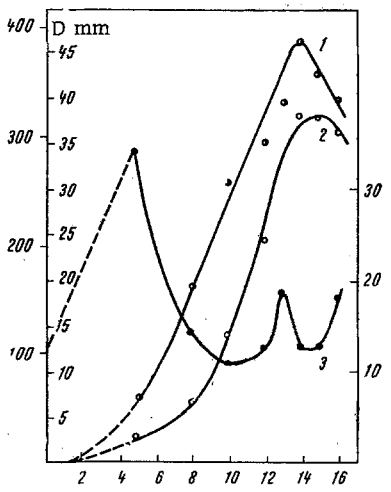

Fig. 1. Kinetic curve of increase in mean diameter of tumor (1) and change in total lipid content of whole tumor (2) and per gram of tumor tissue (3). Abscissa: time (in days); left) ordinate: total lipids (in mg), right) lipid content, in mg/g tissue.

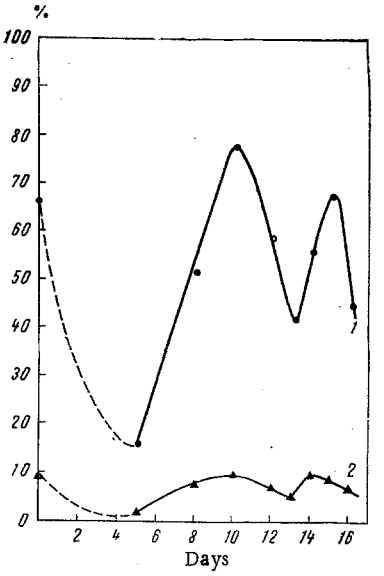

Fig. 2. Changes in percentage content of phospholipids (1) and total cholesterol (2) in tumor lipids.

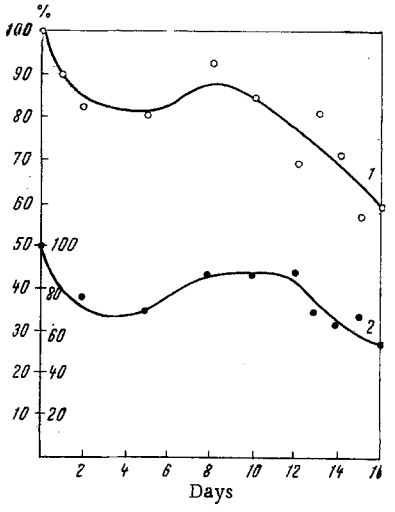

Fig. 3. Changes in content of phospholipids (1) and total cholesterol (2) in liver lipids (phospholipid and cholesterol fractions in liver lipids of healthy animals taken as 100).

RESULTS

In the initial stage of the diease the tumor is so small in diameter that it cannot be measured accurately (Fig. 1). On the fifth day after transplantation, its mean diameter was 7 mm and the mean weight of the tumor 0.68 g. Subsequently the tumor increased rapidly in size, so that 13 days after transplantation its diameter was 40 mm and its weight 20.3 g, 20% of the animal's body weight. The terminal stage of the disease, followed by mass death of the animals, then followed. The necrosis characteristic of this stage of the disease led to a decrease in size of the tumor.

As the tumor increased in size, the tumor lipid content also rose (Fig. 1). The lipid content per gram tumor tissue showed more complex changes. The tissue transplanted was taken from donor animals on the ninth day, when its lipid content was 9 mg/g tissue. The first experimental point, corresponding to the fifth day, shows that the lipid content per gram tumor tissue had increased to 34.2 mg. The hypothetical course of curve 3 (Fig. 1) from the time of transplantation to the fifth day is indicated by a broken line, and the position of the maximum is indicated conventionally, all that is certain being that it was reached at the beginning of growth of the tumor. Later, from the fifth to the 10th day, a decrease in the lipid fraction in the tumor mass down to 10 mg/g tissues was observed. A small increase in the relative content of lipids was observed from the 12th to the 16th day in the terminal stage of the disease. Comparison of the kinetic curves of the increase in tumor diameter with the change in relative lipid content shows that the decrease in lipids took place at a time of most rapid growth of the graft. This phenomenon perhaps reflects inadequacy of lipogenesis in the rapidly growing tumor tissue [3].

Changes in the relative percentage of phospholipids and total cholesterol (structural lipids) showed considerable fluctuations (Fig. 2). From the fifth to the 10th day, when the tumor was growing very rapidly, the phospholipid content rose from 15 to 78%, i.e., by more than five times. Later a sharp fall to 42% was observed, and the next maximum (65%) was reached in the terminal phase of the disease. The mean phospholipid content fluctuated around 50%, i.e., these compounds are dominant components of the tumor lipids.

The total phospholipid and total cholesterol contents in the tissues of the tumor as a whole increased in the same way as the total lipid content.

In the absence of information concerning the lipid composition of the tumor from the time of transplantation until the fifth day, only an indirect conclusion can be drawn regarding the character of its changes in this period. As was mentioned above, the tumor tissue was transplanted at the ninth day of its existence, at which time its lipid composition is known. Since the phospholipid content and total cholesterol content on the fifth day were lower than at transplantation, but the relative content of lipids at this time showed an increase, it can be postulated that this increase was due to an increase in the content of triglycerides utilized by the tumor to cover its energy requirements in the early stage of its development.

Investigation of the liver lipids showed a significant disturbance of lipid metabolism under the influence of growth of the malignant tumor. On the eighth day after transplantation of the tumor, impressions of the liver showed immature hematopoietic cells, and from this time the organ began to increase in weight. However, changes in the lipid composition of the liver tissue cannot be attributed entirely to leukemic infiltration, since the total content of lipids in it exceeded the original normal value throughout the course of the disease. So far as the content of phospholipids and total cholesterol in the liver lipids is concerned, the fraction of these components fell appreciably during the 24 h after transplantation (Fig. 3), and at the end of the experiment it was 60% of the normal value. The character of the kinetic curves of the change in content of total lipids, phospholipids, and total cholesterol in dry liver tissue was similar to the character of the curve obtained for fresh tissue. No increase in the water content of the liver tissue was observed during experimental leukemogenesis, and the dry weight of the organ from the time of transplantation up to death of the animals fluctuated only slightly, namely 25.24 $\pm$1.39% of its moist weight.

The most important of the experimental data obtained are those indicating the increase in content of structural lipids in the tumor tissue against the background of their decrease in the liver tissue. One possible explanation of this fact is that the tumor mobilizes components essential for its metabolism from the organs of the animals. Similar results are described in [4, 5], where it is demonstrated that the development of transplanted mouse gliomas, in whose tissues the principal lipid components were triglycerides, is accompanied by a decrease in the triglyceride content in the liver of the animal with the tumor. The tumor's need for a definite class of lipids may be specific and due to its origin from a particular type of tissue. The leukosarcoma which develops in transplanted erythromyelosis behaves as a local focus of leukemia and consists of undifferentiated hematopoietic cells. Shevchenko and Morozova [1] have shown that the content of structural lipids in leukemic leukocytes is lower than in normal, mature leukocytes. This is perhaps explained by the increased need of this tumor during a period of rapid growth for structural lipids, which are essential components of the cell membranes of dividing leukemic cells.

Another possible interpretation of the facts described above is the hypothesis that the tumor exerts some humoral influence on the host's metabolism, modifying it and adapting it to the needs of the growing malignant tissue.

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