EFFECT OF HOMOTRANSPLANTATION OF SKIN ON THE DEVELOPMENT OF A BROWN-PEARCE CARCINOMA IN RABBITS

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The opinion has been expressed that a relationship exists between the course of development of a neoplasm in the body and the state of its immunobiological factor [6]. Sometimes conditions may be created in the body which are unfavorable to the development of a malignant tumor. An example of this is given by the cases of spontaneous regression of tumors in man [8-10], and the more frequent cases of regression of primary tumors in experimental animals [4]. In this connection it is important to look for methods and substances which could raise the general resistance of the organism to a malignant tumor. As we have previously reported [5], one such method is homotransplantation of the skin into an experimental animal, after which the growth of a transplanted tumor in the animal is retarded. When planning these experiments the following considerations were used as a basis. It has been found that rejection of skin homografts develops as a result of the appearance of transplantation immunity in the recipient [1, 2, 3, 7]. Simonsen and co-workers [11] found that this immunity does not exhibit organ specificity and is directed not only against the transplanted tissue, but also against other tissues of the same donor. After skin transplantation the general reactivity of the body is increased and the immunological factors are stimulated, which leads to rejection of the skin grafts. It is evident that the resulting transplantation immunity has some effect on the course of tumor development.

We have studied the effect of homotransplantation of the skin in rabbits on the transplantability, growth, and metastasization of a Brown-Pearce carcinoma in these animals. Rabbits were selected as experimental animals because they have a higher level of reactivity than animals of other species, notably rats.

EXPERIMENTAL METHOD

Experiments were conducted on 48 male rabbits of the chinchilla breed, weighing 3.0-3.5 kg, distributed among 4 groups. In the rabbits (15) of the first group skin transplantation was followed 8 days later by transplantation of a Brown-Pearce carcinoma, in the rabbits of the second group (7) the skin and tumor tissue were transplanted at the same time, and in the rabbits of the third group (11) the tumor tissue was transplated first, and the skin 8 days later. The rabbits of the fourth group (15) were controls: only tumor tissue was transplanted into these animals.

The Brown-Pearce carcinoma was injected into the right testicle of all the animals in a dose of 0.5 ml of a 20% suspension of tumor cells in physiological saline.

The following criteria were considered when studying the development of the tumors in the experimental animals: the total number of positive and negative transplantations; the number of animals in which temporary growth of the tumor was observed, followed by absorption; the period after which the animals died from the tumor, the intensity of metastasization and the organs most frequently and severely affected. Each experimental animal was subjected to a thorough postmortem examination after natural death or sacrifice.

Homotransplantation of the skin was performed by the method described by E. A. Zorikov [3]. For this purpose a piece of skin measuring 24-30 cm^2 was excised from the donor in sterile conditions. The edge of the excised piece of skin was seized with forceps and slightly raised, so that the skin could be separated from the subcutaneous tissues and underlying muscles. With careful separation of the skin it remained undamaged and as a rule the operation was bloodless.

The skin graft was usually smaller in size than the wound surface. This was so that the graft was under tension and was more closely applied to the wound. The operation was performed without ether anesthesia and without the use of antibiotics. It should be noted that of the 33 animals undergoing operation, not one developed wound sepsis.

TABLE 1. Effect of Homotransplantation of the Skin on Development of Brown-Pearce Carcinoma in Rabbits

Group of rabbits	No. of rabbits	Tumor		Temporary growth of tumor followed by regression	Mean time of death of rabbits after operation (in days)	No. of resistent rabbits
		Took	Did not take			
First	15	8	7	8	Animals survived	15
Second	7	7	0	2	23.0	2
Third	11	11	0	1	33.5	1
Fourth	15	13	2	2	31.1	4

TABLE 2. Distribution of Macroscopically Visible, Viable Metastases by Organs in Experimental Rabbits

Organ	First group		Second group		Third group		Fourth group	
	Metastasization in organ							
	Single*	Multiple	Single*	Multiple	Single*	Multiple	Single*	Multiple
	Number of rabbits							
Spermatic cord	0	0	0	5	0	10	0	11
Omentum	0	0	0	2	2	8	0	8
Mesentery	0	0	2	2	3	4	4	3
Peritoneum	0	0	0	4	2	3	0	3
Diaphragm	0	0	0	2	0	5	5	2
Small and large intestine	0	0	0	1	0	5	0	2
Liver	0	0	1	1	0	6	4	5
Kidneys	0	0	1	1	1	7	1	2
Lungs	0	0	0	0	1	6	1	3
Urinary bladder	0	0	0	0	1	0	1	0
Auxillary lymph glands	0	0	0	0	1	0	1	1
Stomach	0	0	0	0	0	0	0	0
Heart	0	0	0	0	0	0	0	0
Eyes	0	0	0	0	3	0	0	0

* Single means not more than 10 metastases present in an organ; multiple means continuous growth of tumor tissue throughout an organ or too many metastases to be counted.

EXPERIMENTAL RESULTS

Four experiments were carried out on the first group of rabbits (Table 1). The tumor initially took in 8 of the 15 rabbits. After the eighth-fifteenth day, however, the tumor tissue in these animals began to regress and on the twentieth day it had completely absorbed. No rabbit of this group died. All 15 animals were sacrificed on the fiftieth-sixtieth day after transplantation of the tumor, and 14 appeared healthy, with no macroscopically visible metastases in any organ. In one rabbit (No. 167) one completely necrotic metastasis the size of a cherry was found on the parietal peritoneum.

Two experiments were performed on the second group of rabbits. The tumor took in all 7 animals, but in 2 of them it subsequently regressed and then became completely absorbed. Five rabbits (71.4%) died on the average on the twenty-third day.

Three experiments were performed on the third group of rabbits. The tumor took in all 11 animals, but in one of them it subsequently regressed completely. Ten rabbits (90.9%) died from the tumor on the average on the thirty-fourth day.

In the control group, the tumor took in 13 of the 15 animals, and subsequently regressed in two. Eleven rabbits (73.3%) died from the tumor on the average on the thirty-second day.

It can be seen from Table 2 that no metastases were found in the rabbits of the first group. In the rabbits of the second group the distribution of metastases among the organs was approximately the same as in the controls. The spermatic cord, mesentery, omentum, liver, and kidneys were affected by metastases. In the rabbits of the third group an increase in the degree of metastasization in the organs was observed. The principal sites of metastasization were the spermatic cord, the omentum, the mesentary, the large and small intestine, the liver, the lungs and, in particular, the kidneys. Organs such as the urinary bladder, the auxillary lymph glands and the eyes also were affected by metastases.

Rejection of the skin grafts in the rabbits of the first three groups took place, as a rule, on the eighth-tenth day, in agreement with the findings obtained by most workers [3]. In the rabbits of the third group, however, in some cases the skin grafts survived for sixteen-twenty-three days. The question of the survival periods of skin homotransplants in rabbits with carcinoma is one that requires special investigation.

These results show that the transplantation immunity produced in rabbits after skin grafting raises the general resistance of the animal to the development of malignant tissue (first group of rabbits). This immunity leads to rejection of the skin grafts, and its subsequent course is directed against other tissues of the same animal species, especially against malignant tissues.

When the skin and tumor were transplanted into the animal at the same time the transplantation immunity acted only against the skin grafts and had no effect on the growth of the tumor. The probable explanation of this fact is that during the first few days the intensity of the transplantation immunity is very low and the tumor tissue can adapt itself to the immunological factor which is only in the initial stages of activation. Furthermore, malignant tissue possesses a high growth potential, which cannot be said of skin tissue. As a result of these two factors transplantation immunity, in its initial stage, does not affect tumor development.

In the presence of a developing tumor, skin transplantation leads to more intensive growth and metastasization of tumor tissue than in control animals. In this case it seems that the developing tumor weakens the organism, and the subsequent transplantation of skin introduces an unfavorable factor which stimulates growth of the tumor.

SUMMARY

A complete inhibition of the tumor growth (100%) is observed following transplantation of the skin in rabbits 8 days before inoculation of Brown-Pearce metastasis of tumors following simultaneous skin transplantation and inoculation of Brown-Pearce carcinoma. Transplantation of the skin 8 days after tumor inoculation caused intensified growth of Brown-Pearce carcinoma, manifested in the greater percentage of positive takes and a more vigorous metastasization.

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