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SENSITIVITY OF SYRIAN HAMSTERS TO INOCULATION OF TUMOR CELLS DURING PREGNANCY AND LACTATION

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KEY WORDS: SV40 virus; tumor cells; pregnancy.

The ability of embryonic antigens to induce antitumor immunity is being widely discussed at the present time. Some workers state that immunization with embryonic antigens can be used to prevent both primary induced and transplanted tumors [4, 5]. According to some workers, repeated pregnancy during the latent period of carcinogenesis led to a decrease in the frequency of appearance of tumors in parturient females compared with virgins, and this was interpreted as proof of immunization of the mother with embryonic antigens of the fetus [6]. However, some of the published data has not been confirmed by other workers [1, 7].

The writer previously studied the effect both of artificial immunization with embryonic tissues and of single and repeated pregnancies during the latent period on the frequency of onset of primary tumors and on growth of transplantable tumors induced by SV40 virus in Syrian hamsters [1, 2]. These investigations showed that the frequency of tumors was much lower in females which became pregnant 1-5 times during the latent period of SV40 carcinogenesis than in females not becoming pregnant. However, these differences were evidently not connected with immunization of the parous females with embryonic antigens, for the frequency and times of onset of primary tumors in males were the same as in the parous females.

In the writer's previous experiments [2] immunization of inbred hamsters with embryonic hamster tissue followed by transplantation of continuous strains of syngeneic tumors led to neither inhibition nor to stimulation of tumor growth.

Meanwhile, a considerable decrease in the frequency of onset of tumors in females becoming pregnant several times during the latent period could be due both to their more effective natural immunization with embryonic antigens during pregnancy and to an increase in the level of natural resistance of these females during pregnancy or lactation.

The object of the present investigation was to study the effect of pregnancy and lactation in syngeneic hamsters on the sensitivity of females to inoculation of tumor cells.

EXPERIMENTAL METHOD

Noninbred Syrian hamsters were used. Experiments were planned so that the sensitivity of the animals to inoculation was tested 1-6 days before the first day of pregnancy or during the 1st-8th day of pregnancy. In the last series of experiments tumor cells were injected into lactating females on the 1st or 2nd day after parturition. Males inoculated simultaneously with identical doses of tumor cells served as the control. Continuous strain E-1 of hamster sarcoma, induced by SV40 virus, was used as the test tumor.

To determine sensitivity of the hamsters to inoculation of tumor cells the transplantation test was used in its most sensitive modification [3], in which each animal was inoculated with doses of test tumor differing by a factor of 5-10 (starting with about one tumor cell).

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TABLE 1. Sensitivity of Female Syrian Hamsters to Inoculation of Tumor Cells before and during First Days of Pregnancy

Group of animals	Time of inoculation of tumor and of beginning of pregnancy	Results of transplantation tests					log ID_{50}	log ID_{e-c}	t
		2,0	$2,0 \cdot 10^1$	$2 \cdot 10^2$	$2 \cdot 10^3$	$2 \cdot 10^4$			
1	Nonparous females (control)	3/12	5/12	9/12	12/12	12/12	1,40±0,16	—	—
2	1-6 days before pregnancy	0/10	4/10	3/10	10/10	9/10	2,36±0,19	0,96	3,794
3	On 1st-8th day of pregnancy	6/26	7/26	17/26	25/26	26/26	1,70±0,05	0,30	1,765

Legend. Here and in Table 2: numerator gives number of animals with tumors, denominator gives number of animals inoculated with that dose of test tumor; log ID_{50}) dose of tumor cells injected giving rise to growth of tumors in 50% of inoculated animals; log ID_{e-c}) difference between log ID_{50} in experiment and control.

TABLE 2. Sensitivity of Lactating Female Syrian Hamsters to Inoculation of Tumor Cells

Exp. No.	Group of animals	Animals	Results of transplantation test with tumor cells of strain E-1					log ID_{50}	log ID_{e-c}	t
			1,2	$1,2 \cdot 10^1$	$1,2 \cdot 10^2$	$1,2 \cdot 10^3$	$1,2 \cdot 10^4$			
1	1	Males (control)	0/5	0/5	1/5	5/5	5/5	2,50±0,32	—	—
	2	Lactating females	0/3	1/3	0/3	2/3	2/3	2,60±0,40	0,1	0,2
			2	$2 \cdot 10^1$	$2 \cdot 10^2$	$2 \cdot 10^3$	$2 \cdot 10^4$			
2	1	Males (control)	1/5	1/5	3/5	3/5	5/5	2,00±0,24	—	—
	2	Lactating females	1/5	1/5	0/5	0/5	5/5	2,70±0,33	0,7	1,7

EXPERIMENTAL RESULTS

To study the effect of pregnancy on the rate of successful inoculation of tumor cells, 50 female Syrian hamsters aged about 3 months were mated with 30 males in 10 cages (in the ratio of 5:3). After 7 days – the time which usually coincided with the early period of pregnancy for most females, or preceded pregnancy – the sensitivity of all the females to inoculation of different doses of the test tumor of strain E-1 was investigated. The males were removed from the cages 10 days after the beginning of mating. The times of the beginning of pregnancy and of parturition were recorded for each female. Depending on the time of pregnancy and of transplantation of the tumor cells the animals were divided into the following groups: 1) females into which tumor cells were inoculated 1-6 days before pregnancy, 2) on the 1st-8th days of pregnancy, and 3) the control group of nonparous females.

The results of the study of the sensitivity of these groups of animals to inoculation of strain E-1 cells are given in Table 1. The results of the transplantation tests showed that females inoculated with tumor cells 1-6 days before pregnancy were more resistant to inoculation of tumor cells than the control females (ID_{e-c} = 0.96; the differences between the results of the transplantation test were significant: $t = 3.7$). Females into which tumor cells were transplanted on the 1st-8th day of pregnancy, however, did not differ from nonparous females in their sensitivity to inoculation of tumor cells.

In the next series of experiments the sensitivity of females to inoculation of strain E-1 tumor cells during lactation was studied. Groups of males, inoculated at the same time with the same doses of tumor cells, served as the control. The results of two experiments of this series are given in Table 2. They showed that differences between the sensitivity of the animals of the two groups to inoculation of the test tumor was not significant ($t = 1.7$). Lactation thus had no significant effect on the sensitivity of the animals to inoculation of tumor cells. Between 1 and 6 days before pregnancy, i.e., on the first days after the beginning of mating, the females were more resistant to inoculation of tumor cells than nonparous females. However, on the 1st-8th day of pregnancy and also during lactation, no significant differences in sensitivity to inoculation of tumor cells could be found between the two groups of animals compared.

The results of this investigation are evidence that an increase in the resistance of females to tumors in the period before pregnancy cannot be due to immunization with embryonic antigens of the fetus, but is more likely to be due to an increase in the level of natural resistance of the animals, possibly connected with changes

in the hormonal status of these animals. This interpretation is also supported by data on the different levels of sensitivity to tumors in females during lactation and in males. The considerably higher level of resistance to tumors in multiparous females, which the writer observed previously [1], may perhaps be due to selection of the animals for two features important for preservation of the species: a higher level of natural resistance to tumors and higher fertility.

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REVERSIBILITY OF THE STATHMOKINETIC REACTION AFTER MALIGNANT TRANSFORMATION OF CELLS

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There have been many observations of changes in the mitotic regime in tumors, including the presence of numerous pathological mitoses in them. Analysis of pathological forms of cell division in tumor tissue has shown that a high proportion of them are due to pathology of the division spindle [1-3, 5, 7].

The appearance of polyploid and aneuploid cells in tumors is also evidently the result of injury to their division spindle, which is responsible for the uniform distribution of the chromosomes to the poles of the dividing cells. The mechanisms of these disturbances are not yet clear. Previous investigations of differences in the sensitivity of normal and transformed cells to metaphase inhibitors showed [10] that increased sensitivity of transformed cells to colcemid compared with that of cells of primary cultures is due, not to a change in binding of the alkaloid with the tubulins of the transformed cells, but to a change in the permeability of their plasma membrane. This has been confirmed by biochemical studies also [8, 9]. It remained to be discovered whether the processes of polymerization of tubulins are disturbed in tumor cells.

In the investigation described below this question was studied on a model of reversibility of the stathmokinetic reaction induced by colcemid. The writers showed previously that the reversibility of this reaction is associated mainly with repolymerization of the microtubules of the spindle from tubulins of the precursor pool [4]. This model thus enables processes of tubulin polymerization in the cells to be judged during formation of the division spindle.

EXPERIMENTAL METHOD

Experiments were carried out on cells of line KOKh-1, which have undergone malignant transformation, generously provided by the K. I. Skryabin Veterinary Academy, where this strain was obtained as follows. A tumor (sarcoma) was induced in newborn Syrian hamsters by subcutaneous injection of type 3 bovine adenovirus (BA-3). Tumors developed in 50% of animals. The present culture was obtained from the 23rd passage of this tumor in vivo. This cell line proved to be highly tumorogenic for hamsters (the value of TD_{50} varied between 10^1 and $10^{3\cdot6}$). Tumors formed at the site of injection of KOKh-1 cells within a short time attained a large size in adult animals and quickly caused their death [6].

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