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MECHANISM OF REGRESSION OF MAMMARY GLAND CARCINOMA IN LACTATING RATS

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The effect of the conditions of lactation on the frequency of regression of a transplantable mammary gland carcinoma RMK-1 was studied in albino rats. In rats feeding 8 ± 1 young the tumor underwent regression in 47% of cases. After ovariectomy and administration of cortisone and oxytocin, which have an indirect inhibitory action on the secretion of FSH by the pituitary, the frequency of regression of tumors in rats feeding the same number of young rose to 71-81%. In rats with prolonged lactation, feeding 8 ± 1 young for 2-2.5 months, and in rats with intensive lactation feeding litters of 13 ± 2 young, regression of the tumors did not increase. The results confirm the validity of the hypothesis that, besides high secretion of pituitary FSH, a decrease in the secretion of pituitary LH plays a role in the regression of mammary gland carcinoma in the course of lactation.

KEY WORDS: *carcinoma; regression; lactation.*

The view is held that lactation, like pregnancy, stimulates growth of breast cancer and is categorically contraindicated during the treatment of this form of tumor. However, there have been isolated reports that regression of spontaneous, induced, and transplanted mammary gland carcinomas may be observed in lactating animals. Regression of tumors in such cases has been shown to depend on the intensity of lactation and on the number of young in the litter [8]. The present writer also found the same relationship during a study of the effect of lactation on growth of transplantable mammary gland carcinoma RMK-1 in rats [4]. Regression of the tumors took place in 53% of cases in properly lactating rats feeding seven to nine young, but was not observed in weakly lactating rats with only two to four young in the litter. Data on the importance of the intensity of lactation in the regression of mammary gland carcinoma suggested that an important role in the mechanism of tumor regression is played by intrinsic luteinizing hormone (LH) of the pituitary, the production of which during lactation depends on the number of young in the litter [9, 4]. However, there are observations to show that regression of tumors, even in properly lactating rats, is observed only in half of the animals and, moreover, at the end of the period of lactation, although LH secretion reaches the optimal level during the first half of lactation [10]. Hence it follows that regression of tumors is due not only to the action of pituitary LH.

In the course of lactation, the increase in pituitary LH secretion is accompanied by a decrease in the secretion of pituitary follicle-stimulating hormone (FSH), as a result of the stimulation connected with the act of suckling [1, 11]. According to the results of the writer's investigations inhibition of pituitary FSH production is a leading factor in the mechanism of the antitumor action of certain hormones on mammary gland cancer [2, 6]. In particular, the LH preparation prolactin, isolated from bovine pituitary glands, induces regression of mammary gland carcinoma in rats because one of its properties is to inhibit the secretion of pituitary FSH [3]. Consequently, it can be tentatively suggested that for the regression of mammary gland carcinoma during lactation, besides high pituitary LH secretion,

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another important factor is the decrease in the secretion of pituitary FSH. If this hypothesis is correct, lactation combined with factors inhibiting pituitary FSH secretion should lead to an increase in the frequency of regression of tumors, whereas a further increase in the intensity of lactation, aimed at increasing pituitary LH secretion *in vivo*, will not necessarily have that effect.

The object of this investigation was to study the relationship between the frequency of regression of transplantable mammary gland carcinoma in albino rats and the conditions of lactation.

The following conditions which lead to a maximal increase in the intensity of lactation were used: feeding litters with a large number of young (13 ± 2), and prolonged lactation, where, in litters of 8 ± 1 young, the growing rats were frequently replaced by newborn rats. Among the factors inhibiting pituitary FSH secretion, ovariectomy and injection of corticosteroids were chosen. This choice was based on previous observations showing that ovariectomy and corticosteroids increase the antitumor action of hormones inhibiting the secretion of pituitary FSH on mammary gland cancer [2, 3, 6]. Some data on the physiology of lactation also point to the advantages of ovariectomy and corticosteroid administration. The onset of lactation is known not to be always accompanied by regression of the corpora lutea of pregnancy and by a decrease in the secretion of progesterone by the ovaries [8]. Progesterone, according to the writer's data, is the only stimulator of pituitary FSH secretion and of growth of mammary gland cancer [2, 5, 6]. Functioning ovaries, and after their removal, the adrenals of lactating rats as sources of progesterone, may thus have a stimulating action on the secretion of pituitary FSH and may reduce the frequency of regression of mammary gland tumors in the course of lactation. The effect of ovariectomy and corticosteroids on lactation is known: Some decrease in lactation after the operation can be prevented by intensive suckling. Corticosteroids do not stimulate lactation [12, 4].

EXPERIMENTAL METHODS

Experiments were carried out on noninbred rats with transplantable mammary gland carcinoma RMK-1 [4]. Rats producing young for the first time were obtained from the Nursery of Experimental Animals, Oncologic Scientific Center, Academy of Medical Sciences of the USSR.

To obtain intensive lactation with feeding of a double litter, the tumor was transplanted into pregnant rats 1-5 days before parturition and the rats were kept in pairs in cages. After parturition one female was removed from the experiment, leaving the other rat with a litter of 13 ± 2 young. In the experiment to study the effect of prolonged lactation the tumor was transplanted at the 25th-30th day of lactation into females feeding 8 ± 1 rats, when the first litter was weaned and was replaced by another litter with the same number of newborn rats. To maintain continuous lactation of 1.5 months, the young were replaced again by newborn rats every 2-3 weeks, the number of rats in the litter remaining constant.

In the experiment in which lactating rats were treated by ovariectomy or corticosteroids, the tumor was transplanted into pregnant rats 1-5 days before parturition. After birth of the young the lactating rats feeding 8 ± 1 young were divided into groups. Ovariectomy was performed on the animals of one group, a second group of animals received cortisone, a third underwent ovariectomy and treatment with cortisone, and the fourth group was ovariectomized and received cortisone and oxytocin, which was given to increase the evacuation of milk. Ovariectomy was performed during the first 2 or 3 days after parturition, and injections of cortisone and oxytocin began on the same day. Cortisone was injected subcutaneously as a suspension in physiological saline in a dose of 0.25 mg daily or 0.5 mg on alternate days. Oxytocin also was injected subcutaneously in a dose of 0.5 unit daily.

Virgin rats or lactating rats feeding 8 ± 1 young, of the same age as the experimental rats and into which a tumor was transplanted simultaneously with the experimental animals, served as the control for all experiments. The tumor was measured every 4-5 days. The results were assessed as the number of animals with tumors undergoing regression and as the duration of survival of the rats with tumors which did not undergo regression.

EXPERIMENTAL RESULTS

Data showing how the frequency of regression of mammary gland cancer depends on the conditions of lactation are summarized in Table 1. They show that in three groups of lactating rats which received no additional treatment and which differed only in the intensity and dur-

TABLE 1. Effect of Different Conditions of Lactation on Frequency of Regression of Carcinoma RMK-1 in Rats

Group of rats	Mean number of young		Duration of lactation, days		Absorption of tumors		Duration of survival of rats with nonregressing tumors	
	at beginning of lactation	at end of lactation	before transplantation	after transplantation	absolute number	%	absolute number	increase, %
Virgin (control)	—	—	—	—	5/26	19	32±5.4	
Lactating (control)	8±1	7±1	—	26±4.1	8/17 $P_1 < 0.05$	47	26±2.2	
Intensively lactating	13±2	12±1	—	32±2.7	3/12	25	31±3.9	+19
Long-lactating	8±1	7±1	28±3.1	37±5.6	3/14	21	83±4.8	+219
Lactating + ovariectomy	9±1	6±1	—	29±2.2	2/6	33	33±3.2	+27
Lactating + cortisone 0.5 mg on alternate days	8±1	4±1	—	21±2.3	1/7	14	26±0.02	0
Lactating + ovariectomy + cortisone 0.5 mg on alternate days	9±1	8±1	—	29±2.5	5/7 $P_2 < 0.05$	71	42±1.0	+61
Lactating + ovariectomy + cortisone 0.25 mg daily + oxytocin 0.5 unit daily	8±0	6±1	—	28±3.1	9/11 $P_2 < 0.05$	81	36±3.6	+38

Note. Numerator gives number of rats with regressing tumors, denominator total number of rats (spontaneous absorption of strain RMK-1 can be observed in 15-20% of cases).

ation of lactation, the frequency of tumor regression differed. The highest frequency of tumor regression was found in the control group of rats with ordinary proper lactation, feeding 8±1 young. Tumors growing during 14-19 days of lactation later underwent regression in 47% of animals (in eight of 17 rats). In the group of lactating rats feeding double litters of 13±2 young, the tumors were completely absorbed in only 25% of animals (in three of 12 rats). In the long-lactating rats feeding 8±1 young, which had started to feed a second litter with the same number of young at the time of transplantation of the tumor, the tumors also were absorbed in only 21% of animals (in three of 14 rats). However, in animals with intensive and prolonged lactation, the duration of survival of rats with tumors not undergoing regression was longer. Compared with the control lactating animals, in the rats with intensive lactation it was increased by 19% and in the rats with prolonged lactation by 219%. The most favorable conditions for tumor regression were thus ordinary proper lactation with feeding of 8±1 young, but not intensive or prolonged lactation.

If animals with ordinary proper lactation were treated by ovariectomy or by cortisone alone, the frequency of tumor regression in these animals was reduced. Regression of tumors in ovariectomized lactating rats amounted to only 33% (in two of six rats), but in rats receiving cortisone alone it was 14% (one of seven rats), and in the latter group the survival rate of the young also was sharply reduced. In these groups of animals the duration of survival of rats with tumors which did not undergo regression was not increased compared with the control lactating rats. If, however, rats with ordinary proper lactation were treated simultaneously by ovariectomy and cortisone, and in addition they were given oxytocin, the frequency of tumor regression increased sharply. In ovariectomized lactating rats receiving cortisone it was observed in 71% of animals (five of seven rats), but in those receiving oxytocin additionally in 81% (in nine of 11 rats). In these groups, compared with the control lactating rats, more animals in which the tumors did not undergo regression also lived longer (by 61 and 38%, respectively).

An intensive functional load on the mammary glands and high secretion of endogenous pituitary LH are thus not the decisive factors causing regression of tumors in the course of lactation, and there is no direct relationship between the intensity and duration of lactation and the frequency of tumor regression. However, intensive and prolonged lactation does not stimulate growth of mammary gland cancer but, on the contrary, it increases the survival period of animals with tumors that do not undergo regression, and this is especially true of prolonged lactation. Meanwhile, in properly lactating rats feeding 8±1 young, on which ovariectomy was performed at the beginning of lactation and cortisone and oxytocin administered simultaneously in order to exert an indirect inhibitory action on the secretion of pituitary FSH, the frequency of tumor regression rose sharply. These data confirm the validity of the

hypothesis that, besides high secretion of pituitary LH, a decrease in the secretion of pituitary FSH also plays an important role in the regression of mammary gland carcinoma during lactation.

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MIGRATION OF NUCLEOLI AND KARYOPLASM INTO THE CYTOPLASM OF RETICULAR CELLS IN LYMPH NODE CULTURES

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The successive stages of a process characterized by migration of the nucleoli and part of the contents of the nucleus into the cytoplasm of reticular cells were recorded in primary cultures of lymph nodes from albino mice with transplantable leukemia NK/LY. Comparison of the results with data of autoradiography, indicating high proliferative and metabolic activity of the reticular cells, leads the author to suggest that the phenomenon reflects, at the morphological level, the secretory function of the stromal cells of the hematopoietic organs.

KEY WORDS: *experimental leukemia; lymph nodes; reticular cells; tissue culture.*

Among the many problems which face the investigator studying proliferation and differentiation of cells one of the most central is that of the intimate relations between the nucleus and cytoplasm in the living cell.

The object of this investigation was to study the morphological and functional state of the stromal cells of lymph nodes from albino mice with transplantable leukemia NK/LY, in which the successive stages of a process characterized by migration of the nucleoli and of part of the karyoplasm from the nucleus into the cytoplasm of the cells were recorded.

EXPERIMENTAL METHODS

Cultures of lymph nodes were prepared by A. A. Maximov's method. The nutrient medium for culture consisted of two phases: solid and liquid. The solid phase of the nutrient me-

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