THE ROLE OF ANTIBODIES IN THE PATHOGENESIS OF CANCER

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In the last few years, data have been accumulated testifying to the significant role of antigens and antibodies both in normal and pathological processes. We are well acquainted with the role of immunological reactions in blood transfusion, and their significance for analyzing embryological relationships and tissue incompatibilities, as well as incompatibility of the fetus and the maternal organism.

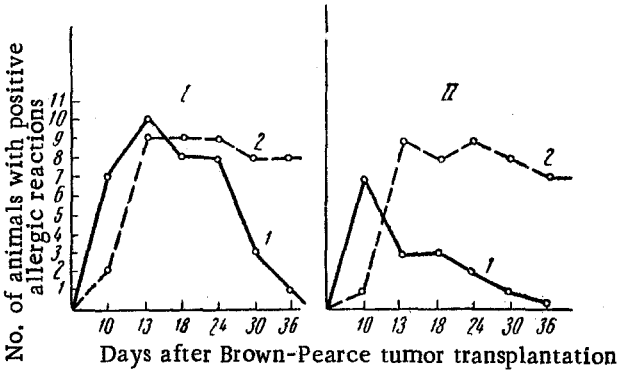

Fig. 1. Dynamics of allergic reactions in rabbits with Brown-Pearce tumor and in healthy animals, associated with immunization of rabbits with a vaccine against tularemia. Intracutaneous test with tularin after 24 h (I) and after 48 h (II)

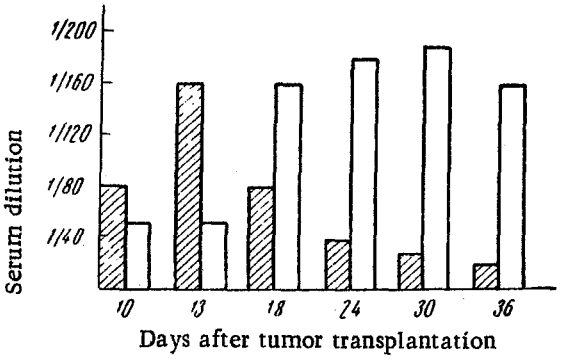

Fig. 2. Dynamics of agglutinin formation in the sera of rabbits with transplanted tumor (experimental) and in controls.

Autoantibodies are formed in diseases of the liver, kidneys, in rheumatism, lupus erythematosis, certain blood diseases, and other pathological states.

The autoantigens, causing the formation of autoantibodies in pathological processes, are the protein complexes of the given organism; their composition includes, as a rule, polysaccharides, lipids, nucleoproteins, chemically altered under the influence of various factors: physical, genetic, biological (bacteria, viruses), ionizing radiation, certain medicinal preparations.

There is much evidence indicating that autoantibodies formed in the organism in association with malignant neoplasms may manifest a definite cytotoxic or antiblastic activity. Thus, a study of cytotoxic sera in cancer is of the utmost importance for a profound understanding of many pathological processes.

With the purpose of resolving the question on the role of antibodies in the pathogenesis of malignant neoplasms, the Laboratory of Noninfectious Immunology of the Institute of Experimental Biology, AMN SSSR, was used to carry out experimental investigations, studying the action of antitumor, organ-specific, antienzymatic, and other sera.

Individual works contain evidence pertaining to the possible influence of immunological reactions on the processes of malignization and proliferation of cells [21, 23]. Experimental investigations devoted to studying the role of autoantibodies in the pathogenesis of cancer are few in number, and they have not yet attracted due attention.

TABLE 1. Appearance of the Arthus Phenomenon in Healthy Rabbits and Rabbits with Transplanted Brown-Pearce Tumor

Rabbits with Brown-Pearce tumor		Rabbits without tumor	
No. of rabbit	phenomenon appearance	No. of rabbit	phenomenon appearance
50	–	1141	+++
3940	++	3216	++++
2347	++	3810	++++
2212	–	2610	+++
3351	++	2234	+++
95	–	49	+++
18	–	3386	++++
74	–	88	+
82	++++	385	+
76	++++	1829	+++
85	–	2225	++++
	–	3812	++
		73	++++
		90	++++

Legend: – absence of the phenomenon; + minimal edema of the skin; ++ edema of the skin and hyperemia; +++ edema of the skin plus hyperemia plus hemorrhage plus minimal necrosis; ++++ edema of the skin plus hyperemia plus hemorrhage plus minimal necrosis plus subsequent necrosis at earlier intervals and in a more manifest form than in +++.

TABLE 2. Action of Antisera to Irradiated Tumor Cells on the Development of Ehrlich's Adenocarcinoma in Irradiated Mice

Type of serum	Volume of serum injected (ml)	No. of mice in group	No. of mice in which tumor developed
Against irradiated tumor cells	0.9	20	4
Against unirradiated tumor cells	0.9	20	13
From unimmunized rabbits	0.9	20	14
Serum not injected	–	20	15

In the investigations we began 10 years ago, we proceeded from the works of I. I. Mechnikov, A. A. Bogomolets, I. L. Krichevskii and other scientists [4,5,9, 1, 12], who attached general biological significance to immunological reactions. Over the last few years, this investigative trend was developed in the works of N. N. Zhukov-Verezhnikov [8].

The appearance of autoantibodies in the organism during malignant growth is completely regular, since there is a specific antigen in the malignant tissues, and the malignant cells are genetically different from the normal. The antigens newly formed in this case cannot be regarded as autoantigens.

A number of works testify to changes in the hereditary nature of malignant cells, including the investigations of a co-worker in our laboratory, M. S. Lomakin, and the Laboratory of Biochemistry, Yu. F. Malina [10]. They showed that the nucleoproteins of cancer cells differ from the nucleoproteins of normal cells in their chemical composition, since the relation of guanine and cytosine in them is different. Thus, regardless of whether or not there occurs a conversion of normal cells into malignant ones, under the influence of chemical (cancerogens), biological (viruses), radiation, or other cancerogenic factors, in the antigen sense malignant tissues are, to a definite degree, foreign to the organism. As a result of this, the tumor bearing organism cannot avoid reacting to the foreign antigen by defense reactions, including the formation of autoantibodies. The amount of the latter depends on the potential of the organism, and its responding system, for producing antibody. In the first stages of tumor development, the organism apparently possesses this capacity [3, 2]. Experiments on the appearance of autoantibody indicate that they are always easier to demonstrate during the first stages of the disease. The difficulty of demonstrating autoantibody in cancer is mainly due to the fact that in this disease, as a rule, the autoantibody exists in the fixed state. A large body of evidence [22, 24] has been presented recently on this question.

In this case, autoantibody should not only be considered from the point of view of their defense functions, but also from the aspect of their cytotoxic action. In essence, autoantibodies are cytotoxins, since their formation is caused by antigens from the protein complexes of cells and tissues of the same organism.

Studying the role of the autoantibody in the pathogenesis of cancer is only the beginning, and, from our point of view, the most correct approach to resolving this question is the general biological one. It is necessary to elucidate experimentally the role of antibodies from different origins: autoantibodies, isoantibodies, and heteroantibodies.

EXPERIMENTAL METHOD AND RESULTS

Various types of organ-specific, antitumor, and antienzymatic sera, as well as gamma-globulins (isolated

TABLE 3. Degree of Metastasis of the Brown-Pearce Carcinoma in Rabbits Subsequent to the Action of Antironidase Sera

Serum	Total amount of serum injected into each rabbit (ml)	Interval between serum injections (days)	Dose in a single injection (ml)	No. of organs containing metastases per individual rabbit				No. of metastases per single organ				Interval between transplantation of the tumor and sacrifice of the rabbit (days)
				with serum injected		serum not injected		with serum injected		serum not injected		
				anti-ronidase	normal			anti-ronidase	normal			
Horse	25	1-2	3	5.1	7.4	9.0		5.1	51.7	65.6		25
	35	2	6	5.1	6.5	8.6		7.9	44.5	72.6		36
	47	2	6	5.9	7.3	6.0		7.3	24.8	9.6		26
	42	Daily	4	1.9	5.1	2.0		–	–	–		17*
Goat	21	2-3	5	3.0	8.8	8.3		5.8	224.8	184		21
	21	2-3	–	3.7	10.0	–		41.0	306.0	–		37

*The rabbits died on the 16th-17th day. The ones that remained alive were sacrificed on the 17th day.

by precipitation in alcohol according to Cohn*), were studied The sera were obtained from goats, sheep, horses, and rabbits. The sera were investigated for specificity by determination of the height of the titer both for the specific antigen and for normal tissues of the animal.

Data on the action of cytotoxic antibodies against normal tissues in the organism of an animal with transplanted Brown-Pearce tumor have been presented in the work of I. N. Maiskii and L. L. Khundanova (see p. 77); it is apparent from these data that systematic introduction into the organism of antibodies against normal tissues leads to their sensitization, change in the immunological reactivity, lowering of resistance, and an increase in metastasis to the tissues of those organs for which the antibodies are specific. These data match the results obtained by R. B. Gragerova and Yu. A. Barshtein [7].

The data of G. P. Airapet'yan [1,2] serve as evidence of changes in the immunological reactivity associated with malignant neoplasms. She discovered that allergic and immunological reactions to the tularemia vaccine were depressed in rabbits with Brown-Pearce tumor (Fig. 1,2). In the work of M. N. Nilovskii [18], it was also shown that the Arthus phenomenon was less manifest in rabbits with Brown-Pearce tumor than in the controls (Table 1).

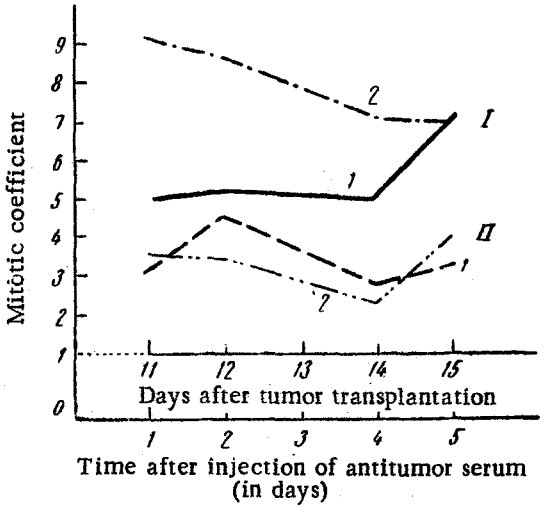

Fig. 3. Mitotic coefficient (‰) in Ehrlich's subcutaneous adenocarcinoma (I) and the corneal epithelium of mice, at various intervals following their injection with antitumor serum. 1) Experimental; 2) control.

The experiments of S. V. Sukhorukikh [20, 21] established that three injections of antitumor sera, including monospecific

*The gamma-globulin was prepared by co-workers of the I. I. Mechnikov A. A. Nikitenko Institute of Vaccines and Sera, for which we express our sincere thanks.

types, with a titer of 1 :160, leads to a lowering of the mitotic coefficient of those cells in the course of 4 days, after which the antiblastic effect ceases. This is a basis for postulating that the antibodies formed in the organism apparently initially serve a defense function, and subsequently begin to manifest their cytotoxic action. Further, it has been shown [19, 20] that anticancer antibodies possess a definite specificity. Thus, the injection of anticancer sera only effected the mitotic division of the cells in the tumors, and did not cause changes in the mitotic activity of the corneal epithelium or the epithelium lining the crypts of the small intestine (Fig. 3).

In the laboratory, tests were performed with sera against malignant tumors that had been irradiated with roentgen rays [15, 16]. It was established that anticancer antibodies are strictly specific. Sera against irradiated antigens manifest their greatest antiblastic activity in animals subjected to roentgen-ray exposure (Table 2).

As a result of numerous experiments, it was established that all sera against cell and tissue antigens possess a markedly manifested cytotoxic activity.

Antienzymatic sera present a different picture [13, 14]. Not having any cytotoxic action, they have a rather wide range of antiblastic activity (Table 3). Antienzymatic sera were obtained by immunizing goats and horses with the enzyme, ronidase (a preparation of hyaluronidase).

Using this sera, we attempted to inactivate the enzyme, hyaluronidase which, in our opinion, plays a major role in the processes of tumor metastasis. The experiments showed that injection of 21 ml of sera into rabbits with the Brown-Pearce tumor markedly inhibits the metastases processes in them. Increase of the serum dose to 47 ml, retaining the same intervals and means of injection, did not yield a markedly toxic effect and led to a decrease in the number of organs metastically involved. Along with this, the injection of 42 ml, but with shortening of the intervals between injections (the serum was injected daily, alternating between intravenous and intraperitoneal administrations), caused death of the animals on the 15th-16th day; in this case we observed pronounced pathologico-anatomical changes in the internal organs, especially the liver and kidneys; the number of organs with metastases were approximately the same in the experimental and control animals.

Thus, the duration of the intervals between injections, as well as the means of injection, were shown to have great significance, although the antironidase sera is observed to have toxic activity only when injected in very large doses.

The importance of the means of injection and the dose of the sera is apparent from the experiments on mice with the ascitic form of Ehrlich's adenocarcinoma, performed by G. P. Airapet'yan. Intraperitoneal injection of 0.2 ml of the gamma-globulins from antironidase serum, daily for 6 days, led to death of all the animals. When 6 injections of the same dose were administered, at intervals of 2 days, 50% of the animals were seen to survive.

The above data serves as evidence that anticancer sera are specific, since their injection leads to lowering of the mitotic coefficient only in the tumors, and does not influence other meristems of the organism (cornea, intestinal crypts). Anticancer sera in small doses possess a certain antiblastic effect, but with increases of the dose or the number of injections, the therapeutic effect is transformed into a cytotoxic one.

By injecting specific organs or anticancer antibodies into the organism of animals with malignant neoplasms, it is possible to regulate the metastatic processes, inhibit or intensify them, or effect the localization of the metastases in the corresponding organs and systems. By injecting antibodies into the organism, one can influence the intensity of tumor cell division in a definite manner, and shorten or prolong the life of animals with a malignant tumor.

Antironidase sera, which are not cytotoxic, show less cytotoxic activity, and the range of their antiblastic activity is markedly wider than that of the cytotoxic sera. The cytotoxic activity of sera against cancer cells and tissues is apparently connected with the presence in the sera of a large amount of nonspecific antibodies, which damage normal systems in the organism.

Obtaining monospecific sera in large quantities would afford the possibility of differentiating cytotoxic and antiblastic activity.

The presented data, from experiments and the literature, serve as evidence that the autoantibodies formed in the organism may play a definite role in the pathogenesis of cancer.

Apparently, the cancer cells, with their altered antigens, cause their own form of autoimmunization, which is accompanied by the production of antibodies that cause corresponding antigenic and pathological changes in several normal organs, not damaged by the cancer. In turn, these antigenically altered cells become autoantigens themselves;

the organism responds to the formation of these latter antigens by the production of cytotoxic antibodies, which act on other normal cells, altering their antigenic makeup. Apparently, autoimmunization is associated with harmful involvement of all systems and organs in the stricken organism, leading to reduction of the animal's defense reactions and the appearance of cachexia.

All this points up the fact that studying the role of antibodies in the pathogenesis of malignancies holds not only theoretical, but also practical, interest, and makes it possible to approach the resolution of problems in the prophylaxis and treatment of malignant neoplasms from a new position.

SUMMARY

On the basis of experimental data obtained in studying the anticancer, organospecific, antienzymatic sera and gamma-globulins, it was shown that a material role in the pathogenesis of cancer is played by the autoantibodies forming in the patient's organism in response to the foreign antigens present in the tumor. Phenomena of cachexia, reduction of protective reactions, time and site of metastasis are connected by the author with the sensitizing effect of autoantibodies exerted on the cells and diminished reactivity of the affected organism.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
