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SENSITIVITY OF BALB/c AND WR MICE TO THE IMMUNOSUPPRESSANT ACTION OF CYCLOPHOSPHAMIDE AND THIOPHOSPHAMIDE

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UDC 616.277.3.065:612.017.1

KEY WORDS: cyclophosphamide; thiophosphamide; immunosuppression; genotype.

Previously [1] the writers found significant interlinear differences in sensitivity of mice to the immunosuppressant action of cyclophosphamide (CP) and thiophosphamide (thiotepa) *in vivo*. It was shown that the degree of sensitivity of mice of different lines to the immunosuppressant action of the compound is maintained whatever immunosuppressant is used.

The aim of this investigation was to determine how universal this phenomenon really is. The basis for the investigation consisted of previous findings indicating that WR/Y mice are highly sensitive to the mutagenic action of thiotepa [3] but relatively resistant to the mutagenic action of CP [2]. It was interesting to discover whether this rule also applies to the immunosuppressant action of these compounds.

EXPERIMENTAL METHOD

Male BALB/cIYsto and WR/Y mice (black mice) weighing 22-25 g were used. The immunosuppressants used were CP (as the Soviet preparation cyclophosphan) and thiotepa (synthesized at the S. Ordzhonikidze All-Union Pharmaceutical Chemical Institute). Sheep red blood cells (SRBC) were used as antigen. The mice were immunized intravenously with SRBC in a dose of 5×10^8 cells, after which the immunosuppressant was injected intraperitoneally. The interval between injection of antigen and compound was 24 h in the case of CP, but thiotepa was injected immediately after immunization. The number of antibody-forming cells (AFC) in the mouse spleen was determined by Jerne's method [6] 4 days after injection of the antigen. Animals not receiving immunosuppressant treatment served as the control. The results were expressed in percentages of the control and were subjected to statistical analysis by Student's test. Differences were considered to be significant at the $P \leq 0.05$ level.

EXPERIMENTAL RESULTS

Values obtained for relative immunosuppression of WR mice by the use of CP (Table 1) and thiotepa (Table 2) were compared with those obtained for BALB/c mice which, as previous investigations [1] showed, were highly resistant to the immunosuppressant action of these compounds.

It will be clear from Table 1 that the sensitivity of WR and BALB/c mice to the immunosuppressant action of CP was virtually equal, whereas WR mice were significantly more sensitive to the immunosuppressant action of thiotepa than BALB/c mice (Table 2). Interlinear differences were discovered when maximal and intermediate doses of the compound were used.

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0007-4888/84/9705-0647$08.50

TABLE 1. Immunosuppressant Action of CP *in Vivo* on Mice of Different Lines (mean values)

Line of mice	No. of group	Dose of CP, mg/kg	Number of mice in group	Number of AFC in spleen, percent of control: mean and confidence intervals	P
BALB/c	1	50	12	0,12 (0,05—0,28)	$P_{1-4}>0,05$
	2	25	23	7,7 (4,7—12,8)	$P_{2-5}>0,05$
	3	12,5	10	77,8 (44,7—135,8)	$P_{3-6}>0,05$
WR	4	50	11	0,11 (0,05—0,27)	
	5	25	21	4,1 (2,6—6,5)	
	6	12,5	11	50,1 (37,2—67,6)	

Legend. Here and in Table 2, pooled data of 4 experiments are given; confidence interval shown in parentheses. Number of AFC in control in BALB/c mice 95,280 (66,680-136,100; n = 20), in WR mice it was 43,650 (42,850-44,460; n = 18). These same figures were used when calculating the data given in Table 2.

TABLE 2. Immunosuppressant Action of Thiotepa *in Vivo* on Mice of Different Lines

Line of mice	No. of group	Dose of thiotepa, mg/kg	Number of mice in group	Number of AFC in spleen, percent of control: mean and confidence intervals	P
BALB/c	1	16	9	1,6 (0,7—3,8)	$P_{1-4}<0,001$
	2	8	22	36,0 (24,7—52,5)	$P_{2-5}<0,0001$
	3	4	10	76,6 (63,2—92,7)	$P_{3-6}>0,05$
WR	4	16	9	0,25 (0,15—0,44)	
	5	8	20	12,6 (8,5—18,5)	
	6	4	10	87,7 (46,8—114,8)	

Just as during investigation of the mutagenic action of CP and thiotepa, WR mice were thus relatively resistant to the immunosuppressant action of CP and highly sensitive to the action of thiotepa. It can be postulated on the basis of these results that a parallel may exist between the mutagenic and immunosuppressant action of these compounds. This view is supported also by data in the literature. In particular, it has been shown [1, 4] that DBA/2 mice are more sensitive to the immunosuppressant action of CP *in vivo* than mice of the highly resistant BALB/c line. The same relations between mice of these lines were found in a study of induction of sister chromatid exchanges *in vivo* in bone marrow cells [5] by means of CP.

The differences thus revealed in the response of WR mice to the immunosuppressant action of CP and thiotepa can thus perhaps be atributed both to differences in the pharmacodynamics of these compounds in WR mice and to the character of interaction of immunocompetent target cells with immunosuppressants.

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EXPRESSION OF HUMORAL ANTIBODIES TO MURINE MAMMARY TUMOR VIRUS-RELATED ANTIGENS IN BREAST CARCINOMA PATIENTS AND CONTROL SUBJECTS

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UDC 618.19-006.6-07:616.153.962.4-097:[578.828.4:578.74

KEY WORDS: cancer; virus; humoral antibodies; antigens.

Murine mammary tumor virus (MMTV) is an agent which produces a high percentage of spontaneous mammary gland carcinomas under natural conditions and in mice of laboratory strains. Expression of exogenous MMTV in mice of many strains is accompanied by the appearance of a malignant neoplasm in the mammary gland when the titer of antibodies against MMTV proteins is raised in the animal's serum [8]. Expression of antigens immunologically related to MMTV has been established in breast cancer patients [3, 5] in the tumor cells; antibodies reacting specifically with MMTV proteins have been found in the serum of various groups of normal subjects and cancer patients [1] and sequences with high homology with the genome of this virus have been found in the human genome [2]. However, the results so far are somewhat contradictory and do not reflect unambiguously a strict association between expression of MMTV-related antigens (or antibodies to them) with the appearance of a neoplastic process in the mammary gland [8].

In the investigation described below, highly sensitive immunologic methods were used to determine whether the malignant process in the mammary gland is accompanied by a humoral response to MMTV-related antigens, and to establish at what level these antigens are expressed normally and in neoplasms in other situations.

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(Presented by Academician of the Academy of Medical Sciences of the USSR D. S. Sarkisov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 97, No. 5, pp. 600-603, May, 1984. Original article submitted July 12, 1983.

0007-4888/84/9705-0649$08.50