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INDUCTION OF SARCOLYSIN RESISTANCE IN PLASMACYTOMA MOPC/406

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Sarcolysin is highly effective in the treatment of multiple myeloma [1. 4]. However, after several successful courses of treatment with this agent resistance has been observed to develop. In recent years a number of transplantable mouse plasmacytomas have been obtained [3, 4].

Plasmacytoma MOPC/406 was obtained in 1967 in BALB/c mice by injection of mineral oil and immunization with sheep's and bovine red blood cells. It is an experimental model which is similar in histogenesis and morphology to the corresponding human tumors. At the same time, this strain is sensitive to sarcolysin and cyclophosphamide, both of which are widely used clinically for the treatment of multiple myeloma.

The aim of this investigation was to obtain an adequate experimental model of a sarcolysin-resistant plasmacytoma.

EXPERIMENTAL METHOD

Experiments were carried out on 250 BALB/c mice. Plasmacytoma was transplanted by intraperitoneal injection of a suspension of ascites cells. Transplantations were 100% successful after 14 days. Sarcolysin began to be administered 72 h after transplantation.

Induction of resistance to sarcolysin began after the fifth dose of the drug per os or subcutaneously in doses of 0.25, 0.5, and 1 mg/kg. The dose per course was gradually increased, to reach 7.5 mg/kg by the 15th generation, 15 mg/kg by the 17th, and 20 mg/kg by the 18th-20th generations.

The antileukemic effect was assessed by the increase in mean duration of survival. During induction the leukemic cells were preserved by freezing in stages in liquid nitrogen, using a 5% solution of diethyl sulfoxide in the ratio of 1:1 with ascites fluid as the protective agent. The material was poured into polyethylene ampuls, previously sterilized by irradiation. The cells were frozen according to the following program: at the rate of 1° C/min to −40°C, 5°C/min to −80°C, and 20°C/min to −130°C, and then transferred into liquid nitrogen.

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TABLE 1. Therapeutic Effectiveness of Sarcolysin Against Strain MOPC/406, Sensitive and Resistant to Sarcolysin (20th generation)

Strain MOPC/406	Dose of sarcolysin, mg/kg	Duration of survival, days	% of surviving animals	P
Sensitive	Control	19,6(16,6:22,6)	0	
	20	22,8(0,4:45,2)	33,3	>0,1
	10	>50	100	
	5	>50	100	
	2,5	36,8(19,21:54,9)	50	<0,05
	1,25	32,16(17,56:46,76)	33,3	<0,05
Resistant	Control	15,0(12,8:17,2)	0	<0,02
	20	7,0	0	
	10	23,3(21,0:25,6)	0	<0,05
	5	17,5(10,1:24,9)	0	>0,1

Legend. Intraperitoneal transplantation of 5×10^6 ascites cells. Sarcolysin injected in a single dose, intraperitoneally, 72 h after transplantation. Duration of survival shown as mean values with confidence intervals at P = 0.05.

EXPERIMENTAL RESULTS

Resistance of the plasmacytoma developed slowly and required a cautious increase in the inducing dose per course. By the 20th generation stable resistance to the action of sarcolysin could be obtained.

The action of sarcolysin on the initial and resistant strains are compared in Table 1.

The original strain was highly sensitive to sarcolysin, and even a dose of 1.25 mg/kg caused an average increase in the duration of survival by more than 64.1% ($P < 0.05$) and one-third of the animals survived. With doses of 5 and 10 mg/kg all the treated animals survived, and on the 50th day they were clinically healthy with no signs of leukemia. At autopsy no ascites fluid was found. No leukemic cells were present in squash preparations from the organs.

Animals with a transplanted resistant strain of plasmacytoma, treated with sarcolysin, died before the 23rd day, and only in the group of mice receiving the optimal dose of 10 mg/kg was a small (18.8%) increase in the duration of survival observed ($P < 0.05$). An increase in the dose up to 20 mg/kg shortened the animals' survival on account of the toxic effect.

The much gerater toxic effect in the group with the resistant strain was evidently due to weaker binding of sarcolysin by cells of the resistant plasmacytoma than by those of its sensitive variant. A similar effect was observed previously in other types of leukemia [2].

A new strain of plasmacytoma MOPC/406 highly resistant to sarcolysin was thus obtained and can serve as a model of human plasmacytoma with which to study some of the important problems concerned with the nature of resistance to sarcolysin, and to develop rational experimental approaches to methods of overcoming it.

The resistant strain fully preserves its properties when preserved in the frozen state in liquid nitrogen.

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