

Survival of Tumor Allografts in Rats Treated with Antithymocyte Serum

H. M. Abandowitz and P. K. Basrur

Department of Biomedical Sciences, University of Guelph, Guelph, Ontario, Canada

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Considerable evidence now exists to indicate that tumors in man and animals can provoke a host immune response against the tumor^{1,2}. Transplantable animal tumors avail themselves readily to further our knowledge in the study of the rejection phenomenon. Thus an antigenic tumor could, if induced to grow in an allogeneic animal whose rejection mechanisms had been suppressed by antithymocyte serum (ATS), provide a useful immunological model for investigating tumor rejection.

In the present investigation an attempt was made to transplant a nickel sulphide-induced tumor in allogeneic hosts treated with ATS. The chemically-induced tumor, a fibrosarcoma, was maintained by serial passage in syngeneic Fischer rats for ten generations before being used in this study. Earlier attempts to transplant this tumor into untreated inbred Hooded rats had failed.

Rabbit anti-rat (Hooded) thymocyte serum was prepared by the two pulse method of Levey and Medawar³, in female New Zealand white rabbits. The antiserum was pooled and stored at -20°C . Normal rabbit serum (NRS) was also collected and stored. Before use, serum was inactivated by heating at 56°C for thirty min and adsorbed with one-third of its volume of packed Hooded rat erythrocytes, at 4°C .

The immunosuppressive potency of the ATS used was determined by its ability to prolong female Fischer rat skin grafts on female Hooded rats given ATS according to the schedule outlined below.

The technique of skin grafting was as previously described⁴. In this strain combination, grafts on untreated rats or rats given NRS were invariably rejected within ten days. With the ATS used, the average graft survival was 28.1 days and the range of graft survival was 22–37 days.

Inbred Hooded rats aged between 10 and 12 weeks were treated with 0.5 ml aliquots of ATS or NRS injected intraperitoneally every day for four days before tumor implantation. On the day of

implantation and every other day for ten days, rats received 1 ml aliquots of ATS or NRS. All experimental animals were implanted subcutaneously in the left flank with a uniform plug of a solid tumor piece ($1 \times 1 \text{ mm}$), using a 12 gauge trocar. The growth of the tumor implants was followed by palpation, and regular recordings of two-dimensional measurements taken with vernier calipers.

Rats treated with ATS developed tumors at an accelerated rate as compared to rats treated with NRS (Table I). This growth rate approximated the

Table I. Effect of antithymocyte serum on tumor growth rate. a. For induction of the primary tumor, six week old female inbred Fischer rats were injected intramuscularly in the left thigh with 10 mg of finely powdered nickel sulphide in 0.2 ml Ayercillin. The tenth transplant generation was employed in this study. b. Animals given ATS or NRS received 0.5 ml of serum daily for four days before tumor implantation, and 1 ml serum just before implantation and thereafter every other day for ten days. ATS, rabbit anti-rat (Hooded) thymocyte serum; NRS, normal rabbit serum.

Animal strain	Treatment	Tumor incidence		Mean tumor diameter [mm]	
		at day 10	at day 25	at day 10	at day 25
Hooded	ATS	10/10	10/10	7.0	26.7
	NRS	5/5	0/5	5.1	0.0
Fischer	Nil	5/5	5/5	7.4	32.2

growth of the fibrosarcoma in untreated syngeneic Fischer rats. All rats were killed on day 25. At this time, the size of the tumors in rats treated with ATS measured 26.7 mm (range 19.5–31.0 mm), whereas in NRS-treated rats, tumors had totally regressed. Furthermore, animals treated with ATS developed metastatic nodules within the lungs and/or regional lymph nodes, whereas metastases were not encountered in any of the NRS-treated controls. On the other hand, only two out of five syngeneic Fischer rats developed metastases in the ipsilateral regional lymph nodes by day 25.

The immunosuppressive effect of antilymphocyte serum has been well documented in skin grafting^{3,5}, in tumor induction by oncogenic viruses^{6,7}, in tumor formation after heterotransplantation of tumor cells^{8–10}, in tumor induction by chemical carcinogens^{11–13}, and in other instances^{14,15}. Heterologous antilymphocyte serum therefore, is a potent and effective immunosuppressive agent affecting primarily the cells responsible for cell-mediated immunity¹⁶.

The results of this study indicate that treatment with ATS enhanced tumor growth and increased the incidence of metastases of this transplantable Ni_3S_2

Requests for reprints should be sent to H. M. Abandowitz, Department of Biomedical Sciences, University of Guelph, Guelph, Ontario, Canada.



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induced tumor in allogeneic hosts. The ATS therefore, was effective in suppressing the rejection response evoked in Hooded rats implanted with the transplantable tumor. However, following implantation to NRS-treated allogeneic recipients, the tumor was rejected within 15 days or so.

Allogeneic tumor acceptance it seems, may have a counterpart in human transplant recipients treated with immunosuppressants. A number of investigators

have observed the development of neoplasms in renal transplant recipients while maintained on immunosuppressive therapy¹⁷⁻¹⁹. Hence it is important to emphasize the potential hazards to patients receiving allografts which may contain malignant cells.

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