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原　　著

Immunological Response in the Mouse Brain: I. Transplantation Immunity to Mouse Lymphoma Graft

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Abstract

The immune responses in the mouse brain to intracranially and intradermally transplanted mouse lymphomas were compared by means of an appropriate design of a genetic distance between host and tumor. Antilymphoma graft resistance in the brain was clear not only in the allogeneic combinations, but also in those of the semisyngeneic host and challenging tumor. Enhanced resistance against the second intracranial tumor injection was also observed in all combinations of host mice and tumors. Furthermore, after rejection of the tumors whether implanted intradermally or intracranially, the allogeneic cytotoxic responses were induced to the same extent in the spleens using an in vitro cell-mediated cytotoxicity assay. Using athymic nude mice as recipients, the transplantation resistance detected in the brain was suggested to depend on T-cell mediated immunological responses.

In conclusion, we propose that the brain is not an "immunological privileged" site. The resistance to lymphoma graft in the brain is mediated by T-cells and is dependent on immunological responses which are essentially the same as those seen in peripheral sites.

Introduction

Several reports have been published concerning the transplantation immunity in the brain. In the 1920s, both Shirai[27] and Murphy[19] demonstrated that tumors transplanted to the brain would often grow, although the same tumors transplanted subcutaneously were rejected. These observations were extended by Medawar[17], who showed that histoincompatible skin graft,

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索引語：脳腫瘍，実験腫瘍，免疫，脳内，リンパ腫

* The abbreviations used are: BBB, blood-brain barrier; B6D2F$_1$, (C57BL/6×DBA/2)F$_1$; CB6F$_1$, (BALB/c×C57BL/6)F$_1$; CNS, central nervous system; FCS, fetal calf serum; HBSS, Hanks balanced salt solution; IC, intracranial; ID, intradermal.

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that underwent rapid rejection when transplanted subcutaneously, would grow indefinitely when transplanted to the brain, but distant from the ventricular system. Since Medawar's description of the brain as an "immunologically privileged" site, conflicting reports have been made on the ability of the brain to support the growth of transplanted allografts of normal and neoplastic tissues for prolonged periods. GREEN[9~11] studied the transplantation of heterologous tissues to the brain, and found that metastatic human cancer, as well as human glioblastomas and medulloblastomas, can grow in the brains of laboratory animals[11]. However, there has been a need for additional critical studies using inbred strains as hosts in order to define the limitation of the brain as a so-called privileged site. SCHEINBERG et al.[24~26] published analytical studies using a mouse ependymoblastoma and various inbred strains of mice as hosts. They reported that the intracerebral tumor isotransplants grew progressively with a negligible lymphocytic response in the brain, whereas intracerebral isotransplants to specifically immunized mice were associated with a massive lymphocytic infiltration of the tumor periphery with necrosis of tumor cells.

Successful intracerebral sensitization against mouse gliomas was also shown by SCHEINBERG et al.[26]. In these experiments, gliomas were transplanted to the brains of isologous mice and cured by irradiation. Subsequent tumor isotransplants to the skin or brain were rejected in significant numbers when compared to unexposed hosts. However, MEDAWAR[17] had previously shown that, although skin homografts transplanted to the brain of unsensitized animals could survive indefinitely, such a graft placed in the brain of a sensitized animal underwent rapid destruction mainly by lymphocytes, which also accumulated in the surrounding brain. According to these observations, SCHEINBERG et al.[25,27] concluded that "immunological privilege" was far from complete and that an initial exposure to a tumor transplant within the brain could provide some degree of immunity to a subsequent subcutaneous or intracerebral injection. Recently, other reports have shown that primary sensitization can take place in rats grafted with allogeneic skin in the brain[8,22]. These studies have also shown the occurrence of primary allograft reactions directed against tumor associated histocompatibility antigens[7,21].

In this paper, we demonstrate the presence of host resistance against intracerebral lymphoma graft not only against tumor-associated histocompatibility antigens in allogeneic models, but also against tumor-associated transplantation antigens in histocompatible recipients. The cell-mediated immune responses to the tumor graft in the brain were not essentially different from those seen in other tissues.

Materials and Methods

Mice: We used male and female mice between 6 and 10 weeks of age. These were highly inbred BALB/c, C57BL/6, DBA/2 strains and their hybrids, (BALB/c×C57BL/6)F_1 ($CB6F_1$*) and (C57BL/6×DBA/2)F_1 ($B6D2F_1$). These mice were maintained in the Facilities of Experimental Animals, Faculty of Medicine, Kyoto University. We also used male and female BALB/c- and $CB6F_1$-nu/nu mice, maintained under pathogen free conditions and between 8 and 14 weeks of age.

Tumors: RL♂1 (kindly provided by Dr. E. NAKAYAMA, The Center of Adult Disease, Osaka, Japan), is a radiation-induced leukemia of BALB/c origin. Other tumors used in the present study were P815 (a methylcholanthrene-induced mastocytoma of DBA/2 origin) and EL-4 (a dimethylbezanthrecene-induced leukemia of C57BL/6 origin). All tumor cells had been maintained in our laboratory, in syngeneic strains in ascitic form.

Transplantation of Tumor: Tumor cells were harvested, washed three times and resuspended at the desired concentrations in Hanks' balanced salt solution (HBSS). For intradermal (ID) injection, tumor cells in a volume of 0.1 ml were injected on the back of the mice with 1 ml disposable tuberculin syringe and a 26-gauge needle, and for intracranial (IC) injection tumor cells in a volume of 0.01 ml were injected under sterile conditions through the right cranial bone to 2 mm in depth with the aid of a 0.05 ml glass microsyringe (Hamilton Co., Reno, NA.) and a 27-gauge YAOI needle[13]. In the mice of tumor rejection, the ID tumor grew to 5–10 mm in diameter in 2 weeks, and then regressed within 3–4 weeks as reported by ours in $CB6F_1$ mice injected with RL♂1 cells[14,16]. The macroscopical disappearance of the ID tumor, and survival of the mouse for more than 60 days after the IC injection of tumors was considered to be a tumor rejection.

Preparation of Spleen Cells: The spleen cells of C57BL/6 mice which had been injected with 1×10^5 RL♂1 cells intracranially or intradermally were aseptically removed at indicated time points after injection. Then, the spleen cells were crushed gently on a stainless steel mesh in HBSS. After removing large cell clumps and debris by passing through cotton wool, the spleen cells were centrifuged, washed three times and then resuspended in RPMI-1640 (Grand Island Biological Co., Grand Island, NY) supplemented with 10% fetal calf serum (FCS) (Flow Laboratories, Inc., Rockville, MD) in order to perform cell-mediated cytotoxicity assay.

Cell-mediated Cytoxicity Assay: Target cells were labeled with ^{51}Cr by incubating 5×10^6 cells with 0.1 mCi of Na_2CrO_4 (Japan Atomic Research Institute, Tokyo, Japan) in 0.1 ml RPMI-1640 with 10% FCS. Effector cells (2×10^6) were mixed with 1×10^4 ^{51}Cr-labeled target cells in a total 0.2 ml in the wells of a V-bottomed microculture plate (Limbro Scientific, Hamden, CT). After centrifugation at $200\times g$ for 1 min., the cultures were incubated at 37°C for 5 hrs in a humidified atmosphere of 5% CO_2 in air. Following incubation, the plate was centrifuged at $200\times g$ for 5 min. and 0.1 ml of supernatant was removed and assayed for radioactivity. Spontaneous release was determined by incubating ^{51}Cr-labeled target cells alone, and total labeling was determined by counting the radioactivity of 1×10^4 target cells directly. The following formula was used to compute percent cytolysis:

$$\frac{\text{Test cpm}-\text{Spontaneous cpm}}{\text{Total cpm}-\text{Spontaneous cpm}}\times100\ (\%)$$

Results

Primary Graft Resistance: Table 1 shows the genotypical relationship between host mice and tumors used in the present study. The relationship between host mice and tumors

Teble 1. Genotypical relationship between host mice and tumors.

Host mice	H-2 haplotype	Tumors RL♂1	Tumors P815	Tumors EL-4
BALB/c	d	MAHC[a]	MIHIC[b]	MAHIC[c]
DBA/2	d	MIHIC	MAHC	MAHIC
C57BL/6	b	MAHIC	MAHIC	MAHC
$CB6F_1$[d]	d/b	MAHC	MIHIC	MAHC
$B6D2F_1$[e]	b/d	MIHIC	MAHC	MAHC

a) Major histocompatible
b) Minor histoincompatible
c) Major histoincompatible
d) (BALB/c × C57BL/6)F_1
e) (C57BL/6 × DBA/2)F_1

was classified into three categories: 1) major histocompatible (syngeneic), 2) major histocompatible but minor histoincompatible and 3) major histoincompatible (allogeneic). The proper expression of mouse major histocompatibility antigens (H-2) on each tumor cells was confirmed by a complement-dependent cytotoxicity test using an appropriate anti-H-2 alloantiserum (data not shown). As shown in Table 2, tumor rejection was not seen in either ID nor in IC injection in the syngeneic combination of host and tumor. When BALB/c mice were injected with 1×10^5 RL♂1 cells either intradermally or intracranially, mean survival time was 25.5 days and 13.2 days, respectively. The mice injected with tumor cells intracranially began to lose weight on about day 10. Extracranial invasion of the intracranially-transplanted tumors was not noted.

In a semisyngeneic combination, as seen in the lower half of Table 2, some mice, especially $CB6F_1$ mice injected with RL♂1, survived after ID injection, on the other hand no mice survived

Teble 2. Lymphoma graft response against major histocompatible host.

Host	Tumors	Site	Doses of tumor cells injected 5×10^4	1×10^5	5×10^5	1×10^6
BALB/c	RL♂1	ID[a]	0/8[b]	0/9	0/8	0/9
		IC[c]	0/9	0/10	0/12	NT[d]
DBA/2	P815	ID	NT	0/9	0/11	0/7
		IC	0/9	0/10	0/9	NT
C57BL/6	EL-4	ID	0/6	0/9	0/8	NT
		IC	0/7	0/9	0/10	NT
$CB6F_1$	RL♂1	ID	8/8	7/7	8/8	6/9
		IC	0/8	0/9	0/8	NT
$CB6F_1$	RL♂1	ID	NT	0/5	0/6	0/5
-nu/nu		IC	0/5	0/5	NT	NT
$B6D2F_1$	P815	ID	3/6	2/7	0/8	NT
		IC	0/7	0/8	0/9	NT

a) Intradermal injection
b) Number of mice, rejected/tested
c) Intracranial injection
d) Not tested

Teble 3. Lymphoma graft response against minor histoincompatible host.

Host	Tumor	Site	Doses of tumor cells injected			
			5×10^4	1×10^5	5×10^5	1×10^6
BALB/c	P815	ID	NT[a]	6/6[b]	7/7	NT
		IC	2/5	3/9	1/8	NT
DBA/2	RL♂1	ID	5/5	6/6	3/6	NT
		IC	3/6	5/8	0/7	NT
$CB6F_1$	P815	ID	4/4	5/5	6/6	4/8
		IC	3/5	4/6	3/6	NT
$CB6F_1$	P815	ID	NT	0/5	0/5	NT
-nu/nu		IC	0/5	0/5	NT	NT
$B6D2F_1$	RL♂1	ID	5/5	5/5	4/4	NT
		IC	4/6	4/7	2/6	NT

[a] Not tested
[b] Number of mice, rejected/tested

after IC injection. $CB6F_1$ anti-RL♂1 effector cells are known to recognize a unique cell surface antigen on leukemia RL♂1 cells[20]. Therefore, the present results suggest that a primary immune response strong enough to reject the tumors could not ne detected in the brain in the present experimental protocol. Table 3 shows the graft resistance against minor histoincompatible lymphoma cells. Although all the mice injected with less than 1×10^5 tumor cells intradermally rejected the tumors, the rejection after the IC injection was not complete as seen in ID site. All the $CB6F_1$-nu/nu mice injected with P815 tumor cells in both sites died. These results indicate that the immunological response against the minor histocompatibility antigens expressed on the grafted tumors was demonstrated in the brain as well as in the peripheral tissue. However, clearly fewer mice rejected the IC tumors than the ID tumors in the tumor dose range examined in this experiment. This suggests that the course of tumor rejection in the brain may be different from that the ID tumor. The majority of the mice that received IC or ID injection of major histoincompatible tumors with less than 1×10^5 cells survived as shown in Table 4.

Teble 4. Lymphoma graft response against major histoincompatible host.

Host	Tumor	Site	Doses of tumor cells inoculated			
			5×10^4	1×10^5	5×10^5	1×10^6
BALB/c	EL-4	ID	7/7[a]	7/7	8/8	6/8
		IC	5/5	5/6	2/7	0/6
BALB/c	EL-4	ID	NT	0/4	NT	NT
-nu/nu		IC	0/4	NT	NT	NT
DBA/2	EL-4	ID	5/5	5/7	3/8	1/8
		IC	3/6	2/7	1/6	0/8
C57BL/6	RL♂1	ID	7/7	8/8	9/9	8/8
		IC	9/9	10/10	9/9	4/8
C57BL/6	P815	ID	6/6	8/8	7/7	8/8
		IC	6/6	9/9	10/10	7/9

[a] Number of mice, rejected/tested

Teble 5. Secondary intracerebral antilymphoma graft response.

Host	Tumor (1×10^5)	Histocompatibility	Number of mice rejected/tested
$CB6F_1$	RL♀1	MAHC[a]	8/8(0/8)[b]
DBA/2	RL♀1	MIHIC[c]	6/6(5/8)
$B6D2F_1$	RL♀1	MIHIC	7/7(4/7)
BALB/c	EL-4	MAHIC[d]	8/8(5/6)
DBA/2	EL-4	MAHIC	3/9(2/7)

a) Major histocompatible
b) Primary response
c) Minor histoincompatible
d) Major histoincompatible

Fewer mice survived the IC injection of more than 5×10^5 cells than the mice with ID tumor cells as seen in minor histoincompatible combination. In this experiment and the next, in which EL-4 tumor cells were injected at the IC or ID site, the frequency of rejection was low both in BALB/c and DBA/2 mice. Generally, with EL-4, the mean survival time was shorter than that of other tumors. These findings suggest that the characteristics of EL-4 cells to grow rapidly after injection both in IC and ID sites (data not shown). Furthermore, the results that both $CB6F_1$-nu/nu and BALB/c-nu/nu mice injected with allogeneic tumors (Table 3 and 4) failed to reject the tumor indicated the importance of T-cell mediated immunocompetence both in IC and ID sites.

Secondary IC Graft Resistance: Next experiments were designed to assess whether the host extracranial presensitization would confer an enhanced transplantation resistance in the brain that could be measured by survival criteria. The mice that survived after ID injection of

Teble 6. No different cytotoxic activity was seen between intradermal and intracranial injection of MAHIC lymphoma graft.

Time[a] (week)	% Lysis[b]	
	ID	IC
1	10.6±3.3	8.4±3.7[c]
	(35.6±6.5	28.3±4.8)[d]
2	40.3±6.4	34.6±6.3
	(24.3±4.2	20.5±3.9)
3	34.3±5.7	33.1±5.9
	(6.5±3.1	5.8±2.1)
4	32.6±5.5	25.2±5.6

a) Time after injection of RL♀1 (1×10^5) in C57BL/6 mice.
b) Cytotoxic activity of spleen cells by 5-hr ^{51}Cr release assay, effector to target ratio 50 : 1.
c) Target cell: RL♂1. The differences of % lysis between ID and IC groups were not significant.
d) Target cell: YAC-1. The difference of % lysis between ID and IC groups were not significant ($p>0.05$).

1×10^5 cells were used as recipients of IC tumor injection 4 weeks after ID injection (Table 5). In the semisyngeneic combination, all presensitized $CB6F_1$ mice survived after IC injection (8/8). In contrast, none survived after the primary injection (0/8). Enhanced resistance against the second IC tumor injection was also observed in most of the combinations other than DBA/2 and EL-4.

Comparison of Cytotoxic Activity Induced in Spleens: Primary in vitro cytotoxic activities induced in spleens of tumor-rejected mice were compared between the two groups. As shown in Table 6, the peak of cytotoxic activity against RL♀1 cells was observed 2 weeks after the injection of RL♀1 in C57BL/6 mice in both ID and IC sites ($40.3\pm6.4\%$ and $34.6\pm6.3\%$). The peak of cytotoxic activity in the spleen coincided with the maximum size of the ID tumor. The ID tumor regressed thereafter, and disappeared macroscopically by day 30. No significant difference in cytotoxic activity was seen between ID and IC injection. These results indicate that both routes of injection with allogeneic tumors can induce killer cells to the same degree.

Discussion

The central nervous system (CNS) has been thought to be an "immunologically privileged site" because of its inability to develop allograft or even xenograft reactions[9,17,19]. Recent observations, however, suggest that immunological responses to intracranial tumors can be built[2,5,12,15,18,29]. Primary sensitization has been reported to occur in rats bearing allogeneic skin in the brain[22], and recently an occurrence of primary allograft reactions directed against tumor-associated histocompatibility antigens of lymphoma grafts was also demonstrated[7,21].

ALBRIGHT et al.[1] showed that gliosarcoma 9L in inbred rats exhibited parallel growth in subcutaneous and intracerebral sites, suggesting that the genetic control of tumor growth was the same whether in the brain or subcutaneously. The growth of a tumor on the brain is also subject to the establishment of tolerance[12]. This was studied by an experiment in which Lewis rat sarcoma cells were injected into the brain of rats of the AVN strain. If the recipients were first rendered tolerant to the donor strain by neonatal injection of bone marrow cells, graft survival was greatly enhanced[12].

In the present study, primary allogeneic and semisyngeneic resistance were clearly observed using lymphoma cells and various host combinations. Allogeneic resistance in the CNS seemed easier than semisyngeneic resistance as judged by survival criteria (Table 2, 3, 4). In the allogeneic combination of hosts and tumors, the resistance seen in the major histoincompatible combinations was more evident than that seen in the minor histoincompatible combinations (Table 3, 4). These results were grossly consistent with those obtained in ID sites. The different genetic distances of host and tumor combinations might be explained by the different antigens expressed on lymphoma grafts.

The immunological responses in the CNS may be due to the presence of the blood-brain barrier (BBB). The BBB is interposed between the blood vessels and the CNS, regulating the entry of substances into the brain. SHUTTLEWORTH[28] reported that the normal brain capillary endothelium lacked the fenestrations seen in other organs, and pointed tight junctions which

excluded large proteins from normal brain parechyma. The BBB was originally seen as a single exclusionary interface, but the situation is more complex. According to RAPOPORT[23], there is no single barrier but "a series of regulatory interfaces", which determine the rate at which various substances pass into the brain. It is now believed that, whereas an effective BBB exists in the normal brain, it is to some extent lost in a diseased brain. It would appear that, when the CNS is damaged, for instance, by the development of a tumor, the condition of immunological privilege could be substantially lost[6].

Another possible explanation that may also contribute to the BBB is the absence of lymphatic drainage in the cerebral parenchyma. The brain and spinal cord are generally considered to have no significant lymphatic vessels or lymphatic drainage system. There are minor pathways in the nasal olfactory lymphatics and peridural lymphatics of the nerve roots, but these are probably negligible as a method of lymphatic drainage from the cerebral parenchyma. Therefore, the absence of organized lymphoid tissue reflects the fact that the brain is not normally exposed to significant levels of antigenic stimulation. It is an inaccessible organ, shielded from attack by invading organisms, and relatively impermeable to antigens reaching it from the bloodstream.

In the present study, primary graft resistance was easily detected in murine brain against allogeneic lymphoma cells (Table 4). These resistance appeared relatively "weak" compared to that seen in ID sites. However, relatively similar degree of cytotoxic activity was detected in spleen cells in allogeneic lymphoma transplanted mice in both IC and ID sites (Table 6). This relatively "weak" resistance in the brain means that the number of mice which rejected the allogeneic tumor intracranially is significantly lower than that of the mice injected intradermally with the same number of tumor cells at both the IC and ID sites (Tables 3, 4). An important problem to be discussed is that the procedure to transplant the tumor cells injected IC in a volume of 0.01 ml with a 27 gauge needle could cause mechanical destruction of brain parenchyma and disruption of the BBB followed by perifocal brain edema. However, our control experiments of IC injection of 0.01 ml HBSS alone support to the contrary. Furthermore, temporary growth of IC tumor was found by histological examination (data not shown), and PUCCETTI et al.[21] found similar results to ours with radioisotopic techniques. In both cases, allogeneic tumors were completely rejected and the animal survived. In such a case, the mice that received allogeneic tumors intracranially would not to be survived because of the increased intracranial pressure due to the tumor growth and brain edema, even if an immune response, strong enough to lyse the tumors to some extent, was produced. This peculiar phenomenon may affect the results, since the intracranial space of mice is very small and limited. In this sense, the experiments using organ or skin grafts are essentially different from those using tumor grafts because an organ or skin graft would not proliferate as tumor grafts.

Another problem is whether the semistereotaxic procedure of the injection of tumor cells through the head skin and cranial bone could cause contamination of lymphoid cells from head skin or periphery. If it does, the results obtained after IC transplantation might not reflect completely the reaction occurring in the brain. Direct evidence to solve this problem is lacking now, but extracranial invasion of the tumors transplanted intracranially was not seen. If the intra-

cranial tumors should extend extracranially along the needle path, a systemic immune response could occur.

The primary response against tumor-associated transplantation antigen was investigated in histocompatible recipients. In this experiment of $CB6F_1$ grafted with RL♂1 cells which bear a unique cell surface antigen[20], no evidence of intracranial resistance was obtained, on the contrary, ID tumors induced by 5×10^5 cells (Table 2) were completely rejected. ID host sensitization with RL♂1 resulted in considerable protection against IC injection of the same tumor (Table 5).

CIRCOLO et al.[4] showed that the mouse brain can be considered an "immunologically privileged" site for natural resistance more than T-dependent classical graft response. They concluded that classical graft resistance was easily detected in the brain of allogeneic nonirradiated recipients, but that only marginal natural resistance could be detected in mouse brain by mortality studies in nonirradiated hemopoietic histocompatible hybrid or nude mice.

CHIU et al.[3] reported that no significant cell-mediated cytotoxity was seen in short term (4 hrs) cytotoxity assays with spleen cells obtained from C-6 glioma-bearing rats at any stage of tumor growth, and that the glioma-bearer serum, though not cytotoxic to the C-6 cells alone, became cytotoxic with the addition of rabbit complement. In our studies, allogeneic cell-mediated cytotoxity was detected in the 5-hr ^{51}Cr-release assay from 1 week after the IC injection of tumor cells. In our semisyngeneic system, no significant cell-mediated cytotoxity was detected using RL♂1 tumor cells and $CB6F_1$ mice in the 5-hr ^{51}Cr-release assay, but the humoral immune response is unknown.

We believe that the brain should no longer be called an "immunologically privileged" site, and that our findings could be helpful in explaining the effectiveness of systemic adoptive immunotherapy to the brain tumors.

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和文抄録

マウス脳内における免疫応答
1. マウスリンパ腫に対する移植免疫

京都大学医学部　脳神経外科
欅　　篤*，半田　　肇，山下　純宏

同　　免疫研究施設
栗林　景容，増田　　徹

*現籍　天理よろづ相談所病院　脳神経外科

実験腫瘍に対するマウス脳内における免疫応答を皮下移植モデルと比較し，脳内免疫応答の特殊性の有無につき検討した．

遺伝的背景の異なる3種類の純系マウスおよび同マウスに誘発された同系腫瘍3種類，又純系マウス間の第1代雑種を用い，腫瘍の移植後の拒絶の有無を同系，半同系，異系の腫瘍—マウス間の関係で皮下と脳内で比較観察した．その結果，基本的には皮下と同様に脳内においても半同系，異系間の移植腫瘍片の拒絶反応が認められ，ヌードマウスを用いた実験よりこれら拒絶反応がT細胞を主体とした免疫応答によりなされていることが観察された．しかし，脳内においては皮下と異なり移植細胞数によっては，異系間の腫瘍植片拒絶も完全に行われない場合があり，免疫応答能に差があるものと推察された．