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Protective Effects of Immunization with *Tetrahymena pyriformis* on Murine Toxoplasmosis

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Introduction

A significant body of evidence has been accumulated which documents that a number of bacteria, among them *Mycobacterium bovis* BCG and *Propionibacterium acnes* (*Corynebacterium parvum*), confer upon injection an increased nonspecific resistance in the host against a variety of viral (Larson *et al.*, 1971), bacterial (Senterfitt and Shands, 1970; Adlam *et al.*, 1972) and protozoal infections (Nussenzweig, 1967; Ortiz-Ortiz *et al.*, 1975; Tabbara *et al.*, 1975; Clark *et al.*, 1976; Clark *et al.*, 1977; Smrkovski and Larson, 1977; Smrkovski and Strickland, 1978). They are most widely recognized as immunostimulators and nonspecific resistance by their administration is associated with cell-mediated immunity. On the other hand, it has also been shown that infections with intracellular protozoa such as *Toxoplasma gondii* and *Besnoitia jellisoni* provide resistance in mice against challenge with phylogenetically unrelated intracellular organisms (Ruskin and Remington, 1968 a, b). However, there has, so far, been little attempt to elucidate the efficacy of free-living organisms as an immunological adjuvant.

Tetrahymena pyriformis, a free-living ciliate protozoan, is widely and extensively studied in the fields of cell biology and biochemistry. We chose this protozoan from among many free-living organisms because it was known that the organism proliferates as fast as bacteria and can be easily cultured in axenic condition, and numerous informations with regard to morphological and biochemical characteristics of it have been accumulated.

We considered it of interest to determine whether immunization of mice with this organism could induce nonspecific resistance against *Toxoplasma* challenge infection.

Materials and Methods

Mice: Six- to 8-week-old female outbred ddY mice were used in most experiments. BALB/c derived nu/nu and nu/+ mice, 6- to 8-week-old female, were also used in some experiments. All mice were purchased from the Shizuoka Agricultural Cooperative Association for Laboratory Animals, Hamamatsu, Japan.

BCG vaccine: Lyophilized BCG vaccine of Japanese substrain was obtained from Dr. T. Tokunaga, the National Institute of

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Health of Japan, which was a product of the Japan BCG Laboratory, Tokyo. It was suspended in sterile saline and adjusted to an appropriate concentration before use. Heat-killed BCG was prepared by heating viable organisms for 1 hr at 70 C.

Tetrahymena: The W-strain of *Tetrahymena pyriformis* was obtained from Dr. Y. Watanabe, Institute of Biological Sciences, Tsukuba University, and cultivated in 3 l Fernbach flasks each containing 300 ml of PYD medium (1% proteose peptone, 0.5% yeast extract, and 0.8% dextrose) under sterile conditions (Watanabe and Ikeda, 1965). The culture flasks were kept shaken horizontally. The organisms were harvested by centrifugation at 850×g for 5 min and washed once with inorganic medium (NaCl 100 mg, KCl 4 mg, $CaCl_2$ 6 mg in 1 l of distilled water) (Watanabe and Ikeda, 1965). For lysis, the organisms in inorganic medium were frozen-thawed twice. This entire preparation was referred to lysed *Tetrahymena* antigen.

Immunization: Mice were injected intraperitoneally (i.p.) with live *Tetrahymena* or its lysed antigen. Live or heat-killed BCG were injected similarly into mice as positive control. Dose and immunization schedules of *Tetrahymena* and BCG are described in particular experiments.

Challenge with Toxoplasma*:* Immunized and control mice were challenged with bradyzoites of the weak virulent Beverley strain of *T. gondii*. The inoculum of *Toxoplasma* was prepared as follows. Brains of the chronically infected mice were removed and triturated in 5 ml of phosphate-buffered saline at pH 7. 2 (PBS) with mortar and pestle. The number of cysts in a unit volume of the brain suspension was estimated. The supension was treated with 0.25% trypsin for 10 min and released bradyzoites were washed twice in PBS, centrifuged at 700×g for 10 min and resuspended in PBS. The inoculum for the challenge infection was adjusted to contain approximately 5,000 bradyzoites which were equivalent to those within one cyst of mean size. This number of bradyzoites usually caused death of 80% or more of normal mice when inoculated i.p.. Besides i.p. challenge, intravenous (i.v.), per oral (p.o.) and subcutaneous (s.c.) challenges were also performed in some experiments. The mice were observed until 1 month after the challenge and their mortality and average survival time were assessed. The dead mice in the experiment were each checked for the presence of toxoplasmas.

Assay of Toxoplasma *antibodies:* An indirect latex agglutination (LA) test (Toxotest-MT, Eiken Co.) was used to determine the serum level of *Toxoplasma* antibodies (Kobayashi *et al.*, 1978).

Results

Effect of immunization with various doses of Tetrahymena *against* Toxoplasma *challenge*

To establish the minimum effective dose of *Tetrahymena,* mice were immunized i.p.

Table 1 Effect of immunization with various doses of *Tetrahymena* against *Toxoplasma* challenge*

Immunization†	Dose	No. mice dead/ no. inoculated (%)	Average days survival‡
Th§(live)	0	6/10(90)	12.2
	1×10^5	6/10(60)	11.7
	1×10^6	1/10(10)	14
	1×10^7	1/10(10)	13
Th(lysed)	0	10/10(100)	11.7
	1×10^5	10/10(100)	17.3
	1×10^6	5/10(50)	15.7
	1×10^7	5/10(50)	19.0

* Mice were challenged i.p. with 5,000 bradyzoites of the Beverley strain of *Toxoplasma* and investigated up to 30 days after the challenge.

† Immunization was made by i.p. route 7 days before *Toxoplasma* challenge infection.

‡ Average surviving days of mice that died.

§ Th, *Tetrahymena*.

with different doses of live or lysed *Tetrahymena* antigen equivalent to 1×10^5, 1×10^6 or 1×10^7 of original organisms. Seven days after the immunization, mice were challenged i.p. with *Toxoplasma*. As shown in Table 1, there was observed obvious decrease in death rate by increasing dose from 1×10^5 to 1×10^6, in both immunization regimens. The same protective value was obtained by immunization with 1×10^6 and 1×10^7. This suggests that the lowest dose necessary for eliciting maximum protection in either immunizaiton is 1×10^6. The size of inoculum for immunization was therefore fixed at 1×10^7, for the safety's sake, in the following experiments.

Comparison of effects of immunization with Tetrahymena *before and/or after* Toxoplasma *challenge*

To evaluate the protective effects by different schedules in relation to immunization and *Toxoplasma* challenge infection, mice were divided into 3 groups consisting of 10 mice each, and inoculated i.p. with 1×10^7 live *Tetrahymena* as follows; Group 1: a single injection on day −7; Group 2: 5 injections on days −7, 1, 3, 5 and 7; and Group 3: 4 injections on days 1, 3, 5 and 7 of the challenge infeciton. Results are shown in Table 2. Significant resistance against *Toxoplasma* challenge infection was shown in mice with the pretreatment (Groups 1 and 2), while 4 injections (Group 3) after the challenge were found to be non-effective.

Table 2 Comparison of effects of immunization with *Tetrahymena* before and/or after *Toxoplasma* challenge

Group	Days of immunization before and/or after challenge*	No. mice dead/ no. inoculated (%)	Average days survival
1	−7	2/10(20)	16.5
2	−7, 1, 3, 5, 7	0/10(0)	——
3	1, 3, 5, 7	9/10(90)	14.1
	Control	8/10(80)	14.4

* Mice were injected i.p. with 1×10^7 live *Tetrahymena*. For *Toxoplasma* challenge see footnote of Table 1.

Table 3 Duration of protective effect of *Tetrahymena* against *Toxoplasma* challenge

Immunization*	Days before challenge†	No. mice dead/ no. inoculated (%)	Average days survival
None		8/10(80)	11.8
Th(live)	7	0/10(0)	——
	14	0/10(0)	——
	21	2/10(20)	14.0
	28	5/10(50)	12.4
	35	9/10(90)	13.9
Th(lysed)	7	0/10(0)	——
	14	1/10(10)	14
	21	7/10(70)	15.6
	28	7/10(70)	13.9
	35	8/10(80)	11.4

* Mice had a single injection (i.p.) with 1×10^7 live or lysed Th.

† For *Toxoplasma* challenge see footnote of Table 1.

Duration of protective effect of Tetrahymena *against* Toxoplasma *challenge*

To determine how long protective effect of *Tetrahymena* persists, mice were immunized i.p. by a single injection of 1×10^7 live organisms or the lysed antigen 7, 14, 21, 28 or 35 days before challenge i.p. with *Toxoplasma* and the protective effects by those immunizations were compared. As shown in Table 3, protective effect was observed significantly for 21 days after immunization by the live *Tetrahymena* and 14 days by the lysed antigen. These effects diminished thereafter and no more effects were observed after 35 days in both groups.

Comparison of protective effects by Tetrahymena *and BCG against* Toxoplasma *challenge*

To compare the protective effect by *Tetrahymena* with that by BCG, a well known immunostimulant, mice were injected i.p. with 1×10^7 *Tetrahymena* antigen or 1×10^7 BCG and then challenged i.p. with *Toxoplasma*. For the immunization, live and lysed tetrahymenas and also live and heat-killed BCG were adopted, and injected into

mice once or twice. For two immunizations, the interval was 14 days. Mice non-treated or inoculated with inert substances such as glycogen and sheep erythrocytes (SRBC) were served as controls. *Toxoplasma* challenge was performed 7 or 4 days after a single or two injections with *Tetrahymena* or BCG. Mice that received 0.5 ml of 0.1% glycogen or 1×10^9 SRBC were challenged 1 day and 7 days after inoculation, respectively. The results are shown in Table 4. All groups of immunized mice were significantly protected from death, i.e., smaller mortal rate as compared with control mice. The degree of protection afforded by live *Tetrahymena* was comparable to that induced by live or heat-killed BCG, but lysed *Tetrahymena* antigen conferred lesser degree of resistance than did both live and heat-killed BCG vaccines. There was no significant difference in mortality between the groups of mice immunized with a single injection and with two injections of *Tetrahymena* or BCG.

Table 4 Comparison of protective effects of *Tetrahymena* and BCG against *Toxoplasma* challenge

Immunization*	No. mice dead/ no. inoculated (%)	Average days survival
None	52/54(96.3)	11.1
Glycogen	10/10(100)	11.1
SRBC	10/10(100)	14.1
Th(live), once	4/40(10.0)	18.3
Th(lysed), once	14/30(46.7)	12.8
BCG(live), once	6/30(20.0)	16.3
BCG(heat-killed), once	6/30(20.0)	12.8
Th(live), twice†	3/15(20.0)	14.7
Th(lysed), twice	18/28(64.3)	13.4
BCG(live), twice	6/28(21.4)	14.3
BCG(heat-killed), twice	1/15(6.7)	19

* 1×10^7 organisms for both Th and BCG, 0.5 ml of 0.1% glycogen or 1×10^9 sheep erythrocytes (SRBC) were each injected i.p. into mice. Mice were challenged i.p. with *Toxoplasma* 7 days after a single injection or 4 days after second injection with Th or BCG. Mice that received glycogen or SRBC were challenged 1 day and 7 days after inoculation, respectively. For *Toxoplasma* challenge see footnote of Table 1.

† Interval between two immunizations was 14 days.

Effect of immunization with Tetrahymena *against* Toxoplasma *challenge by various routes*

To evaluate the effect of immunization with *Tetrahymena* against *Toxoplasma* challenge by various routes, mice were injected i.p. with 1×10^7 *Tetrahymena* and challenged i.p., i.v., p.o. or s.c. with *Toxoplasma*. For the comparison, BCG was also used as an immunostimulant. Results are shown in Table 5. All control mice died from i.p. or i.v. challenge, whereas considerable degree of reduction in mortality was observed in *Tetrahymena*-immunized mice. The result of i.p. challenge with *Toxoplasma* was similar to that obtained in the previous experiment; the degree of protection afforded by live *Tetrahymena* was greater than that by

Table 5 Effect of immunization with *Tetrahymena* against *Toxoplasma* challenge by various routes

Immunization* (i.p.)	No. mice dead/no. inoculated (%) and average days survival after *Toxoplasma* challenge by route† of			
	i.p.	i.v.	p.o.	s.c.
None	10/10(100)11.3	10/10(100)12.9	6/10(60)14.8	6/10(60)16.0
Th(live)	1/10(10)17	6/10(60)15.2	3/10(30)19.7	6/10(60)18.0
Th(lysed)	6/10(60)11.8	3/10(30)16.3	4/10(40)13.8	3/10(30)19.7
BCG(live)	2/10(20)19.3	6/10(60)14.5	1/10(10)14	3/10(30)19.7

* For immunization and *Toxoplasma* challenge see footnotes of Table 1 and 4.

† Challenge route: i.v.=intravenous, p.o.=per oral, s.c.=subcutaneous.

Table 6 Effect of immunization with *Tetrahymena* against *Toxoplasma* challenge in nude mice

Mice	Immunization*	No. mice dead/ no. inoculated (%)	Average days survival
	None	10/10(100)	12.6
Athymic	Th(live)	10/10(100)	16.5
nu/nu	Th(lysed)	10/10(100)	14.6
	BCG(live)	10/10(100)	17.0
Littermate	None	10/10(100)	10.3
nu/+	Th(live)	7/10(70)	15.8

* For immunization and *Toxoplasma* challenge see footnotes of Table 1 and 4.

lysed antigen and was comparable to that by BCG. Somewhat greater degree of resistance appeared in mice that received lysed *Tetrahymena* than in those immunized with live *Tetrahymena* or BCG when challenged i.v.. In contrast to challenge by i.p. or i.v., p.o. or s.c. challenge produced lower mortality in normal mice, where small reduction in mortality was observed in most of the immunized mouse groups than in the controls.

Effect of immunization with Tetrahymena *against* Toxoplasma *challenge in nude mice*

To determine whether protective effect of *Tetrahymena* against *Toxoplasma* challenge is elicited in nude mice, nu/nu and nu/+ mice were each inoculated i.p. with 1×10^7 live or lysed *Tetrahymena,* or live BCG and they were challenged i.p. with *Toxoplasma* 7 days later. The results are shown in Table 6. In nu/nu mice, all were killed by *Toxoplasma* infection, although there could be observed a tendency of prolonged survival in the immunized groups than in the control. In contrast, nu/+ mice revealed certain resistance to the challenge infection when immunized with live *Tetrahymena*; 30% of them survived.

Discussion

The results indicate that when *Tetrahymena,* a free-living ciliate, is inoculated i.p. into mice, it does produce a potent protection against a subsequent *Toxoplasma* challenge infection. It is clear from the result that an immunization of mice with *Tetrahymena* prior to *Toxoplasma* challenge is requisite for development of protective effect against the infection. Several conditions for elicitation of the protective effect by *Tetrahymena* have been clarified. The minimum effective dose was 1×10^6 organisms and equivalent for both live and lysed *Tetrahymena* antigens and the protective effect persisted for 2–3 weeks with decrease afterward.

Tetrahymena antigens behaved differently from inert subsances. Not only glycogen, which is often used to induce peritoneal macrophages, but also high dose of SRBC could not confer any protection against *Toxoplasma,* whereas *Tetrahymena* could elicit significant protection. This suggests that *Tetrahymena* is quite different from the mere inert substances like glycogen and SRBC as immunostimulant.

It was also demonstrated that there were differences in degree of resistance conferred by live *Tetrahymena* and lysed one depending on the challenge route of *Toxoplasma.* Live *Tetrahymena* produced greater degree of protection than did lysed antigen against i.p. challenges, while somewhat lesser resistance in mice when challenged i.v. or s.c.. There was no marked difference in the degree of protection by those antigens against p.o. challenge. Live *Tetrahymena* inoculated into mice may soon be killed and eventually digested since they are not parasitic. It remains to be elucidated how the live and lysed antigens behave differently as immunostimulant and also why the protective effect by *Tetrahymena* varies depending on route of the challenge. The facts that i.p. inoculation of *Tetrahymena* could also elicit certain protection against *Toxoplasma* challenge by various routes may suggest that the protective effect occurred not only locally but also somewhat systemically.

In this study, BCG was also used as refer-

ence immunostimulant to evaluate protective effect by *Tetrahymena*. Although some variations were observed in the effect of those immunogens depending on *Toxoplasma* challenge routes, there were essentially no marked differences in potency between *Tetrahymena* and BCG so far as judved by mortal rate of the mice.

It is clear from the results that two injections with *Tetrahymena* as well as BCG did not give increasing resistance as compared with a single immunization. Similar results have been reported by Smrkovski and Strickland (1978), who demonstrated that multiple doses of BCG did not induce a greater degree of protection in mice against malaria than did a single inoculation.

Several reports have been presented with regard to nonspecific resistance to *Toxoplasma*. Tabbara *et al.* (1975) have found significant protection in rabbits against toxoplasmic retinochoroiditis when the animals were immunized with BCG i.v. but not by inoculation into retrobulbar space. On the other hand, Dubey (1978) reported that the pretreatment of hamsters i.v. or i.p. with BCG at the single dose of 2×10^7 did not afford any protection against oral challenge of *Toxoplasma* oocysts. Also, Swartzberg *et al.* (1975) have demonstrated that the pretreatment of mice with *P. acnes* activated macrophages to kill *Toxoplasma in vitro* but conferred only transient protection *in vivo* against the C56 strain of *Toxoplasma*. These reports cannot be compared directly with our study results because there exist many differences in experimental conditions, e.g., species of experimental animal used, the virulence and form of *Toxoplasma,* and the route and interval of immunization.

It may be natural that the specific immunization with live avirulent toxoplasmas would give more intensive protection from death caused by challenge infection with the virulent strain of *Toxoplasma* than vaccinations with the dead toxoplasmas (Krahenbuhl *et al.*, 1972) and possibly than the nonspecific vaccines as well. Comparison of these specific vaccines with *Tetrahymena* in respect to preventive effect is a matter of different scope.

Production of anti-*Toxoplasma* antibodies was negligible, if any, in both *Tetrahymena*-immunized and non-immunized mouse groups at least until days of their deaths so far as tested by LA test. Therefore it may be difficult to attribute the difference in mortality between the groups to different antibody productions. It was also found in our separate experiment that peritoneal macrophages from mice immunized with *Tetrahymena* were markedly activated to kill *Toxoplasma in vitro* as compared with those from control mice. Detailed informations on the *in vitro* study will be presented in elsewhere. Thus, cell-mediated immunity is considered to play most important role for the resistance against *Toxoplasma,* in which the activated macrophages should be regarded as the essential cells as suggested earlier by Remington and Krahenbuhl (1976).

While the effect of immunization with *Tetrahymena* or BCG was equivocal in nu/nu mice, nu/+ mice could elicit resistance to *Toxoplasma* challenge *in vivo* test. A possible participation of lymphocytes of mice in the immune system with *Tetrahymena* is under study.

Effectiveness of the immunizaiton with *Tetrahymena* for increasing resistance to other parasitic infections and elucidation of the degree and extent of possible side effect caused by *Tetrahymena* remain to be clarified.

Summary

Experiments were carried out to evaluate the effect of immunization of mice with *Tetrahymena pyriformis,* a free-living ciliate protozoan, on protection against *Toxoplasma gondii*. Significant protections was elicited when mice were injected with 1×10^6 or more of *Tetrahymena*. Immunization with

Tetrahymena was effective only when performed within 2–3 weeks before the challenge. Intraperitoneal immunization with 1×10^7 live tetrahymenas or the lysed antigen conferred a considerable protection in mice against intraperitoneal or intravenous challenge with *Toxoplasma,* while little protection against oral or subcutaneous challenge. The degree of protection by *Tetrahymena* was comparable to that by BCG so far as the present experimental system is concerned. Although no decrease in mortality was observed in nude mice immunized with *Tetrahymena,* longer survival time was observed as compared with control mice.

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マウス・トキソプラズマ感染症に対する *Tetrahymena pyriformis* の防御効果

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自由生活性繊毛虫 *Tetrahymena pyriformis* (Th) をワクチンとしてマウスに接種することにより，トキソプラズマ (Tp) 感染に対する抵抗性を非特異的に増強しうることが判明した．Th による防御効果の発現には，1×10^6 個以上の Th を感染前に接種（腹腔内）することが必要であり，その免疫効果は2～3週間維持され，その程度は Tp の攻撃接種ルートによつて異なつたが，Tp による腹腔内のみならず静脈内接種に対しても抵抗性を示した．また，Th は本研究での実験条件による限りでは，BCG 接種の場合とほぼ同等の防御効果を賦与しうることが示された．なお，免疫力低下個体のモデルとして，ヌードマウスを用いた場合は，Th 免疫群に，死亡率の減少を認めることはできなかつたが，生存日数の増加がみられた．