Effect of *Toxoplasma* Lysate Antigen (TLA) on Feline Cytotoxicity against FeLV Positive Lymphoma Cells

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ABSTRACT. The cytotoxic activities of feline spleen cells treated with *Toxoplasma* lysate antigen (TLA) were assayed against feline leukemia virus (FeLV)-producing lymphoma, FL74 cells, and xenogeneic target lymphoma, mouse YAC-1 cells. The TLA treatments were performed *in vivo* alone, *in vitro* alone, and *in vivo* plus *in vitro*, respectively. *In vivo* plus *in vitro* treatments with TLA induced a marked augmentation in cytotoxic activity of spleen cells to FL74 cells. The treatment with TLA *in vivo* alone showed an enhancement of cytotoxic activity but *in vitro* alone did not. The cytotoxic effects of TLA-treated spleen cells obtained from the cats which had been previously immunized with live FL74 cells were similar to those of spleen cells from non-immunized cats treated with TLA. However, no increase of cytotoxicity was shown in the response to mouse YAC-1 cells regardless of TLA treatments. These results indicated that the *in vivo* TLA treatment augmented the cytotoxicity of feline spleen cells against FeLV-producing lymphoma cell.—**KEY WORDS:** feline cytotoxicity, FeLV-producing lymphoma cell, *Toxoplasma* lysate antigen.

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The *Toxoplasma* lysate antigen (TLA), an antigen derived from *Toxoplasma* tachyzoites is also critical in the augmentation of NK activity by inducing interferon (IFN)- α and - γ [7, 17, 19, 21]. The components of TLA responsible for enhancing the NK activity were proved to be proteins associated with cytoplasm and membrane of *Toxoplasma* but not DNA and RNA [21]. The infection with live *Toxoplasma* also causes the remarkable enhancement of the cytotoxic activity [6, 11].

The immune cytotoxic response of the peripheral blood lymphocytes (PBL) and spleen cells to FeLV-producing lymphoma cells, i.e., FL74 cells, has been studied as an effector mechanism that mediates the tumor protection [10, 14, 15, 24, 25]. The results on the cytotoxicity of feline PBL to FL74 cells differ from one investigator to another [10, 14, 15, 25]. These investigators, however, agreed that cytotoxicity of spleen cells to

FL74 cells is present in normal cats.

In this study, we determined whether TLA exerts any effect on the cytotoxic activity of feline PBL and spleen cells against FL74 cells.

MATERIALS AND METHODS

Animals: The healthy cats of 2–3 years old were housed at our laboratory. All cats utilized in this study were free from FeLV infection as examined by an enzyme-linked immunosorbent assay using a Leukassay F kit (Pitman Moore Inc., Washington Crossing, NJ).

Effector cells: The PBL and spleen cells were used as sources of effector cells in cytotoxicity assay. Briefly, the cells prepared by Ficoll-Hypaque density gradient were incubated for 1 hour at 37°C to remove adherent cells, and thereafter the nonadherent cells were cultured at a concentration of

1×10^6 /ml in medium RPMI-1640 (Nissui Pharmaceutical Co., Tokyo) supplemented with 2 mM L-glutamine, 0.02 mg/ml of gentamycin and 10% heat-inactivated fetal bovine serum, referred hereafter to as culture medium.

Target cells: The target cells utilized were FL74 and YAC-1 which were maintained in continuous culture with the culture medium.

Preparation of TLA: The TLA was prepared as for the procedure described previously [19, 20]. Ten milligram of TLA in sterile physiological saline as a stock solution were adjusted to 1 mg/ml and 0.5 mg/ml with culture medium.

TLA treatments of effector cells: 1) *in vivo* treatment; The TLA was administered intravenously (iv) to cats at a concentration of 0.1 mg per kilogram of body weight twice (7 and 3 days) prior to effector cell preparations, and the equal volume of sterile physiological saline instead of TLA was administered iv to the control animals. Before administration of TLA in the above manner, some cats were immunized *in vivo* by iv inoculation with 1×10^8 viable FL74 cells on three occasions with 1 week interval between inoculations. 2) *in vitro* treatment; The PBL was treated with TLA at a concentration of 0.05 mg/ml for 20 hours and the spleen cells were incubated with TLA for 20 hours or 5 days at 37°C under 5% CO₂ humidified atmosphere.

Cytotoxicity assay: The cytotoxic activity of feline PBL and spleen cells was tested by standard ⁵¹Cr releasing assay as described elsewhere [12, 22]. Briefly, the effector cells (0.1 ml) were distributed into each well of 96 well-microplates. The target cells were pelleted and labeled with 0.03 mCi of ⁵¹Cr sodium chromate (New England Nuclear, Boston, MA) for 1 hour at 37°C. To minimize the spontaneous release of target cells, ⁵¹Cr labeled cells were preincubated in 10 ml of culture medium for 2 hours at 37°C. Subsequently, these target cells were plated

in each well at a final volume of 0.2 ml with effector to target (E:T) ratios ranging from 12.5:1 to 50:1. The plates were centrifuged at $55 \times G$ for 3 minutes to increase E:T contact and then incubated for 6 hours or 18 hours at 37°C. At the end of incubation the plates were recentrifuged at $500 \times G$ for 6 minutes and half-aliquots of supernatant from each well were removed to measure the radioactivity. The percentages of specific release were calculated as follows: % specific release = (cpm in test release - cpm in spontaneous release/cpm in maximal release - cpm in spontaneous release) $\times 100$, where the maximal release indicates the release of target cells by adding 0.1 ml of 1% sodium dodecyl sulfate solution instead of effector cell suspensions, and the spontaneous release was the counts released by target cells in culture medium alone.

Statistics: The significance of differences between experimental groups was determined by Student's *t*-test and values of $p < 0.05$ were considered significant.

RESULTS

Effect of TLA treatment on cytotoxicity of feline PBL and spleen cells: The cytotoxicity of PBL and spleen cells to FL74 cells is shown in Table 1. All the PBL tested in 6-hour assay failed to lyse FL74 cells regardless of the treatments with TLA. In contrast, the cytotoxic activity of spleen cells was augmented by *in vivo* plus *in vitro* treatments with TLA as compared with that of untreated control animals ($p < 0.02$).

Cytotoxicity of spleen cells against FL74 cells: In order to determine the possibility that *in vivo* TLA-induced cytotoxicity of spleen cells is further augmented by prolonged culture periods in the presence of *in vitro* TLA (0.05 mg/ml), an experiment in which culture periods of splenic effector cells were prolonged to 5 days was performed (Fig. 1). No increase in the treat-

Table 1. Cytotoxic activity of PBL and spleen cells sensitized with TLA against FL74 cells

Effector cells	TLA treatments		% specific ^{51}Cr release ^{c)}		
	<i>in vivo</i> ^{a)}	<i>in vitro</i> ^{b)}	12.5:1	25:1	50:1
PBL	—	—	$-2.9 \pm 4.1^{\text{d)}$	-2.5 ± 3.6	-5.8 ± 5.6
	+	—	-0.6 ± 1.9	-0.4 ± 8.4	-6.6 ± 0.3
	+	+	0.9 ± 3.2	-4.2 ± 2.7	-5.0 ± 5.9
Spleen cells	—	—	1.8 ± 2.7	4.6 ± 3.6	4.8 ± 1.3
	+	—	2.1 ± 0.9	5.5 ± 3.2	10.3 ± 3.2
	+	+	3.4 ± 3.0	5.5 ± 2.3	18.2 ± 3.0

a) Effector cells from cats administered with TLA (0.1 mg/kg, body weight, iv) twice (7 and 3 days) prior to effector cell preparations(+) or saline solution(—), respectively.

b) After *in vivo* TLA treatments, effector cells were cultured with TLA (0.05 mg/ml) (+) or without TLA(—) for 20 hours before cytotoxicity assay.

c) Cytotoxicity assay was performed for 6 hours at E: T ratios of 12.5:1, 25: 1 and 50: 1.

d) Values represent mean $\pm$ SE.

Fig. 1. Effect of TLA treatments on the cytotoxicity of spleen cells against FL74 cells. TLA (0.1 mg/kg, body weight, iv) was administered to cats twice (7 and 3 days) prior to spleen cell preparation, respectively (*in vivo* treatment), and spleen cells were cultured with TLA (0.05 mg/ml) for 5 days thereafter (*in vitro* treatment). The cytotoxicity assay for FL74 cells was performed for 6 (A) and 18 hours (B).

ment with TLA *in vitro* alone was observed in 6-hour response with FL74 cells when compared with untreated cells. Spleen cells taken from cats treated with TLA *in vivo* alone and *in vitro* plus *in vivo* showed significant cytotoxicity against FL74 cells ($p < 0.05$ and $p < 0.001$, respectively) when compared with that of *in vitro* alone at an E:T ratio of 50:1. There was, however, no

significant difference between treatments with TLA *in vivo* alone and *in vitro* plus *in vivo*, although *in vitro* plus *in vivo* treatments showed higher cytotoxicity than *in vivo* alone. The cytotoxicity of 18-hour assay as compared with 6-hour assay in each group resulted consistently in the enhanced activity as E:T ratios increased. The spleen cells of untreated control revealed 22.5% cytotoxicity to FL74 cells at an E:T ratio of 50:1, but its cytotoxic activity tended to be enhanced when treated with TLA *in vivo* or *in vitro*, and furthermore *in vivo* plus *in vitro* treatments with TLA induced a significant augmentation of cytotoxicity ($p < 0.05$).

Lytic effect on xenogeneic YAC-1 target cells: The YAC-1 cells in 6-hour assay were resistant to lysis by feline spleen cells regardless of treatments with TLA as shown in Table 2. The TLA-induced cytotoxic cells of spleen cells were also not capable of killing mouse YAC-1 cells in longer assay of 18-hour although there were some variations by *in vitro* alone and *in vivo* plus *in vitro* treatments of TLA in one experiment.

Effect of TLA treatment on cytotoxicity of PBL from FL74-immunized cats: To determine whether feline cytotoxic function

Table 2. Cytotoxic activity of feline spleen cells sensitized with TLA against xenogeneic mouse YAC-1 cells

Expt ^{a)}	TLA treatments		% specific ⁵¹ Cr release ^{d)}		
	<i>in vivo</i> ^{b)}	<i>in vitro</i> ^{c)}	12.5:1	25:1	50:1
1	—	—	0.8±2.5 ^{e)}	0.0±0.8	-0.5±0.5
	—	+	0.5±1.6	3.9±0.6	4.2±2.1
	+	—	-5.6±2.6	-7.6±2.2	-1.4±4.4
	+	+	-7.1±2.0	-5.3±2.5	-1.3±2.8
2	—	—	1.1±0.5	1.7±1.1	1.9±1.9
	—	+	8.3±6.1	8.2±6.0	9.9±2.4
	+	—	2.7±12.0	0.4±7.0	3.5±16.0
	+	+	0.4±7.0	0.8±19.0	9.7±13.0

a) Cytotoxicity assay was performed for 6 hours in experiment 1 and for 18 hours in experiment 2.

b) Spleen cells from cats administered with TLA (0.1 mg/kg, body weight, iv) twice (7 and 3 days) prior to spleen cell preparation (+) or saline solution(-), respectively.

c) After *in vivo* TLA treatments, spleen cells were cultured with TLA (0.05 mg/ml) (+) or without TLA(-) for 5 days before cytotoxicity assay.

d) Cytotoxicity assay was performed at E: T ratios of 12.5: 1, 25: 1 and 50: 1.

e) Values represent mean ± SE.

Table 3. Effect of TLA treatments on the cytotoxic activity of FL74-immunized PBL^{a)} against FL74 cells

Expt ^{b)}	TLA treatments		% specific ⁵¹ Cr release ^{e)}		
	<i>in vivo</i> ^{c)}	<i>in vitro</i> ^{d)}	12.5:1	25:1	50:1
1	—	—	3.0±4.9 ^{f)}	-0.9±4.8	1.7±0.5
	—	+	-2.2±1.8	-3.1±2.2	1.1±4.0
	+	—	4.1±4.1	4.1±5.4	-2.6±3.2
	+	+	1.5±6.1	2.0±6.4	-0.9±2.8
2	—	—	7.5±1.3	4.8±1.9	6.1±2.8
	—	+	6.9±2.5	4.6±1.8	5.6±2.9
	+	—	3.9±4.0	4.6±2.2	3.9±2.5
	+	+	6.8±1.9	7.1±1.3	8.0±2.4

a) Cats were immunized with 1×10⁸ viable FL74 cells/head (iv) on 3 times with 7-day interval before *in vivo* TLA administration.

b) Cytotoxicity assay was performed for 6 hours in experiment 1 and for 18 hours in experiment 2.

c) PBL from FL74-immunized cats administered with TLA (0.1 mg/kg, body weight, iv) twice (7 and 3 days) prior to PBL preparation (+) or saline solution (-), respectively.

d) After *in vivo* TLA treatments, PBL was cultured with TLA (0.05 mg/ml) (+) or without TLA(-) for 20 hours before cytotoxicity assay.

e) Cytotoxicity assay was performed at E: T ratios of 12.5: 1, 25: 1 and 50: 1.

f) Values represent mean ± SE.

could be enhanced by immunization with live FL74 cells, a portion of PBL from cats immunized with FL74 cells was followed by TLA treatment as described in materials and methods. The PBL from cats immunized with FL74 cells did not cause the killing of FL74 cells in spite of TLA inoculation (Table 3).

Effect of TLA treatment on FL74-immunized spleen cells against FL74 cells: When spleen cells were treated with TLA *in vivo* and then incubated with TLA for 20 hours *in vitro*, the cytotoxicity was increased in proportion to the increase of ratios of E:T (Fig. 2). And the cytotoxic activity of immune splenic effector cells that were sensitized with TLA *in vivo* and thereafter incubated with TLA for 5 days *in vitro* was shown in Fig. 3. The treatment with TLA revealed a tendency to increase the cytotoxicity in 6-hour assay. A significant cytotoxic activity of immunized spleen cells showed in *in vivo* plus *in vitro* TLA treatments when compared with that of untreated cells at E:T ratios of 25:1 and 50:1 ($p < 0.02$). All the immunized spleen cells in 18-hour assay showed higher cytotoxicity than those of 6-hour assay. However, the TLA-induced cytotoxic activity of FL74-immunized spleen cells was not enhanced beyond that of non-immunized cats treated with TLA.

DISCUSSION

The results presented in this study demonstrated that TLA prepared from tachyzoites of *Toxoplasma* is capable of enhancing the cytotoxic activity of feline spleen cells against FL74 cells *in vivo*. It is conceivable that (i) antigenic components of TLA are responsible for the direct augmentation effect on splenic cytotoxic activity in cats; (ii) spleen cells sensitized with TLA may be able to react with target cells, FL74 cells, by producing soluble factors such as IFN and interleukin (IL)-2 that can

Fig. 2. Effect of TLA treatments on the cytotoxicity of spleen cells from FL74-immunized cats against FL74 cells. Cats were immunized with 1×10^8 live FL74 cells (iv) on 3 times with 1-week interval between injections. TLA (0.1 mg/kg, body weight, iv) was administered to FL74-immunized cats twice (7 and 3 days) prior to spleen cell preparation, respectively (*in vivo* treatment), and spleen cells were cultured with TLA (0.05 mg/ml) for 20 hours thereafter (*in vitro* treatment). The cytotoxicity assay for FL74 cells was performed for 6 (A) and 18 hours (B).

Fig. 3. Effect of TLA treatments on the cytotoxicity of FL74-immunized spleen cells cultured for prolonged periods (5 days *in vitro*). Cats were immunized with 1×10^8 live FL74 cells (iv) on 3 times with 1-week interval between injections. TLA (0.1 mg/kg, body weight, iv) was administered to FL74-immunized cats twice (7 and 3 days) prior to spleen cell preparation, respectively (*in vivo* treatment), and spleen cells were cultured with TLA (0.05 mg/ml) for 5 days thereafter (*in vitro* treatment). The cytotoxicity assay for FL74 cells was performed for 6 (A) and 18 (B).

induce cytostasis and proliferation on themselves or other cells; and (iii) TLA may induce the expression of surface receptors on spleen cells as a portion of endogenous

cytotoxic cells. Thus, it is most likely that spleen cells sensitized with TLA *in vivo* alone may be cytotoxic rather than those *in vitro* alone, and that spleen cells treated with TLA *in vivo* plus *in vitro*, would be more efficient to lyse FL74 target cells than those treated with TLA either *in vivo* alone or *in vitro* alone. Treatment with TLA *in vitro* alone did not augment the cytotoxicity of spleen cells against FL74 cells. It is not surprising that spleen cells treated with TLA *in vitro* alone would not be sufficient for cytotoxic activity against target cells, since the adherent cells such as macrophages were previously removed before *in vitro* TLA treatment. The macrophages are also involved in the mechanisms of cytotoxicity [4, 16]. When macrophages were activated by any stimulation, they produce a series of immunoregulatory products, including IFN [1] and lymphocyte activating factors, which have the activating effects on T cells [3, 5]. It is also suggested that macrophages, when treated with TLA *in vivo*, also seemed to play an important role in the enhancement of splenic cytotoxicity. From these points of view, the spleen cells and macrophages *in vivo* may interact with each other in a complex variety of ways of cytotoxic activity.

In the TLA-induced feline PBL and FL74-immunized PBL, no lysis of FL74 cells was seen. In contrast, NK-like activity of PBL is shown to be present in humans [23], rats [8], dogs [9] and pigs [2, 13]. This resistance of FL74 cells to PBL and FL74-immunized PBL is not due to a lack of TLA stimulation and a low level of IFN production but may be due to the weakness or inability to lyse FL74 cells with feline PBL by itself or the absence of NK-like cells in feline PBL as reported in previous studies [10, 25]. The absence of cytotoxicity in feline PBL is not consistent with the reports of McCarty and Grant [14, 15] who were able to measure NK-like lysis of FL74 cells.

The discrepancy between their results and our findings might be explained by ratios of PBL versus target cell and variation of cat breeds selected. The E:T ratios of 400:1 to 50:1 in their experiment were much higher as compared with 50:1 to 12.5:1 in the present study.

The ability of cytotoxic cells to kill the tumor target cells is substantially dependent on the intrinsic susceptibility of targets and whether the effector cells are stimulated by any agent capable of augmenting NK activity or not. Thus, we determined if TLA exerts any effect on cytotoxicity of feline spleen cells against mouse YAC-1 cell, a classical NK target cell [18]. This study showed that the cytotoxic activity of spleen cells by TLA treatments nearly exhibited no lysis of xenogeneic YAC-1 target cells. This finding, therefore, confirmed that the feline cells can not cross the species barrier and that lysis of xenogeneic target cells is dependent on the ability in which the effector cells recognize and bind with them.

McCarty and Grant [14] demonstrated that cytotoxic T lymphocyte (CTL) activity to FL74 cells was not detectable in spleen cells from cats immunized with the same cells *in vivo* when compared with those from normal cats. The cytotoxic activity found in TLA-treated spleen cells from immunized cats revealed a significant increase than that of cats without TLA treatment, but these levels of cytotoxic activity were, of interest, almost similar to the level of lysis detected in TLA-stimulated spleen cells of non-immunized cats, even when at an E:T ratio of 50:1 showing the highest levels of killing in each group. These results suggest that a significant portion of cytotoxicity in feline spleen cells is primarily mediated by NK-like cells rather than by CTL-like cells, which may be due to the lack of alloreactive CTL-like activity in cats. The possibility is existent that FL74 cells as a target tumor cell may be sensitive to NK-like cells but resis-

tant to CTL-like cells.

Further studies are warranted to determine whether TLA-induced NK cells contribute to the defence of FeLV-producing lymphoma cells or feline sarcoma virus (FeSV) related tumor cells.

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要 約

ネコリンパ球の FeLV 産生腫瘍細胞株に対する細胞障害活性へのトキソプラズマ溶解抗原 (TLA) の及ぼす影響：梁 萬表・後飯塚 僚・小野憲一郎¹⁾・鈴木直義¹⁾・長谷川篤彦 (東京大学農学部獣医内科学教室, ¹⁾ 獣医臨床病理学教室)——TLA を *in vivo* あるいは *in vitro* で処置したネコの末梢血リンパ球および脾細胞のネコ白血病腫瘍細胞株 (FL74) に対する細胞障害活性を検索した。末梢血リンパ球の FL 74 細胞に対する細胞障害活性は TLA 処置によっても変化は認められなかったが、脾細胞の細胞障害活性は *in vivo* の TLA 投与により増強される傾向がみられ、特に *in vivo* および *in vitro* の両方で処理した場合は有意な増強効果が観察された。ネコに FL 74 細胞を免疫した場合にも細胞障害活性は免疫しなかった時とほぼ同様であった。以上の結果から TLA はネコの脾細胞の細胞障害活性を増強させることが明らかになった。