The Decline in the Production of Interleukin 2 in Cats Spontaneously Infected with Feline Leukemia Virus

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ABSTRACT. Twelve cats, confirmed to be positive for group specific antigens of feline leukemia virus (FeLV) in peripheral blood lymphocytes (PBL) by an indirect immunofluorescent antibody test, were studied for interleukin 2 (IL-2) production. The production of IL-2, determined by the cell proliferation of an IL-2 dependent murine T cell line (CTLL-2), was remarkably lower in PBL from FeLV-infected cats, as compared to those from healthy controls. In particular, FeLV-infected cats with leukemia or with the thymic type of lymphosarcoma had substantially poor IL-2 production. These results suggest that the proliferative response of PBL from persistently FeLV-infected cats to Con A is reduced, associating with the lowered ability of IL-2 production at least in part.—**KEY WORDS:** feline, FeLV, IL-2, immunosuppression.

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Cats persistently infected with feline leukemia virus (FeLV) frequently develop leukemia/lymphosarcoma as well as a generalized immunological hyporeactivity, which is responsible for secondary infection caused by opportunistic pathogens. In FeLV-infected cats, several types of abnormalities have been reported in both humoral and cell-mediated immunity [2, 7, 15, 18, 21, 24]. These abnormalities suggest the impairment of the immunoregulatory systems. However, the immunological cascades mediating immunodepression are poorly understood in FeLV-infected cats.

In human and murine lymphocytes, interleukin 2 (IL-2), secreted by lectin- or antigen-activated T lymphocytes, is shown to be mandatory for *in vitro* differentiation and proliferation of effector T cells. A number of studies on IL-2 in human patients with a variety of diseases including infectious diseases [14], autoimmune-mediated diseases [17] and tumors [1] have demonstrated that the defects in the production of IL-2 and in the responsiveness to IL-2 contribute to the pathogenesis and clinical

stages of diseases. It is, therefore, of great importance to know how IL-2 is concerned with the abnormalities in FeLV-infected cats.

The purpose of the present study is to investigate IL-2 production of PBL from persistently viremic cats naturally infected with FeLV with or without leukemia/lymphosarcoma.

MATERIALS AND METHODS

Animals: Twelve cats, admitted to the Animal Hospital of the Faculty of Agriculture, University of Tokyo, were used for the present study (Table 1). These cats were consisted of 6 females and 6 males ranged in age 2 to 8 years old, and all of them were positive for FeLV, as examined by the indirect immunofluorescent antibody test and enzyme-linked immunosorbent assay (ELISA). An immunological evaluation including the IL-2 assay was carried out, before they received steroid or other immunosuppressive drugs. Eight clinically healthy adult cats, consisted of 5 females

and 3 males ranged in age 2 to 8 years old, serologically negative for FeLV, were used as controls (healthy controls).

Six-week-old rats (Wistar-Imamichi strain) were also used for the source of IL-2 to maintain an IL-2 dependent murine T cell line described below.

Detection of FeLV group specific antigens: FeLV group specific antigens were detected by the following two methods; the indirect immunofluorescent antibody test, previously described by Hardy *et al.* [13], and ELISA with a Leukassay F kit (Pitman Moore Inc., Washington Crossing, NJ).

Culture media: RPMI medium 1640 (GIBCO, Grand Island, NY) supplemented with 10% heat-inactivated fetal bovine serum (GIBCO) (v/v), 25 $\mu\text{g/ml}$ of gentamicin, and 0.1% sodium bicarbonate, referred to as complete medium (CM), was used. For the induction of IL-2 production, 10 $\mu\text{g/ml}$ phorbol miristate acetate (PMA; Sigma Chemical Co., St. Louis, MO), 10 mM N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acids (HEPES; Research Organic Inc., Cleveland, OH), 5×10^{-5} M 2-mercaptoethanol (2-ME; Wako Pure Chemical Industries, Japan) and an additional 1 mM of L-glutamine (Nissui Pharmaceutical Co., Japan) were added to CM.

Cell lines: A FeLV-producing T cell lymphoma cell line, FT-1, derived from a cat with the thymic type of lymphosarcoma, established in our laboratory by Dr. H. Tsujimoto in 1982, was used for the detection of serum antibodies to this cell line cells.

An IL-2 dependent and cloned murine cytotoxic T cell line (CTLL-2) [10] was used for the detection of IL-2 activity. The cell line has been maintained at intervals of 3 days.

Determination of anti-FT-1 cell antibodies: Anti-FT-1 cell antibodies were measured by a minor modification of the method of Essex *et al.* [8]. The titers were

expressed as the reciprocal of the highest dilution giving 50% fluorescein-positive cells.

Lymphocyte preparation: Lymphocytes from the spleen of cats and rats, and PBL from cats as well as lymphoid cells from pleural fluids of FeLV-infected cats were prepared by the Ficoll-Hypaque gradient centrifugation technique, as described previously [11]. The resultant cell suspension was consisted of more than 90% lymphocytes. The viability of cells was greater than 95%, as determined by the trypan blue (0.25%) dye exclusion test.

Test procedure for E-rosette: E-rosettes were detected by the method described earlier [23]. At least 200 lymphocytes were counted, and those bound with three or more erythrocytes were considered as E-rosette forming cells.

Test procedure for surface immunoglobulin positive ($s\text{Ig}^+$) cells: $s\text{Ig}^+$ cells were detected by the method of Taylor *et al.* [23]. The percentage of fluorescein-positive cells was determined by counting 200 cells at a magnification of $\times 400$ under a fluorescence microscope.

Lymphocyte blast transformation assay: The assay was performed according to the procedure described previously [3, 11]. PBL (1×10^6 cells/ml) were added to each well of 96-well flat-bottomed microtiter plates (Falcon; Becton Dickinson Labware, Oxnard, CA) containing 12.5 $\mu\text{g/ml}$ of Con A (Sigma) or 1 $\mu\text{g/ml}$ of pokeweed mitogen (PWM; Sigma). The plates were incubated for 72 hr at 37°C in a humidified atmosphere of 5% CO_2 and 95% air. Cells were pulsed with 0.25 μCi of tritiated thymidine (^3H -TdR; 6.7 Ci/mM, New England Nuclear, Boston, MA) 18 hr before harvested, and then harvested with a semiautomatic multiple-sample harvester (Labo Mash; Labo Science Co., Japan) and counted by a liquid scintillation counter (Aloka-LSC 2000; Aloka Co., Japan). Net counts per minute

(cpm) of triplicate wells were averaged for mean cpm.

Preparation of IL-2 from splenic lymphocytes and PBL: Crude IL-2 preparations were made from Con A-stimulated splenic lymphocytes from rats and cats, and Con A-stimulated PBL from cats, as previously described [11]. A batch of the culture supernatant from Con A-stimulated splenic lymphocytes of a healthy cat was used as a standard feline IL-2 sample. For the preparation of IL-2 samples, PBL (2×10^6 cells/ml) were cultured with Con A ($10 \mu\text{g/ml}$) for 12 hr at a humidified atmosphere of 5% CO_2 in air. After incubation, the culture supernatant was harvested and stocked at -20°C until used.

Culture supernatants prepared from Con A-stimulated PBL of FeLV-infected cats were subjected to a high speed centrifugation at 100000 g for 2 hr, to exclude the possible FeLV contamination. The resultant supernatant was free of FeLV, as determined by the reverse transcriptase assay [5] and ELISA using a Leukassay F kit.

Assay for IL-2 activity: The culture supernatant and pleural fluid were measured for IL-2 activity by the CTLL cell proliferation assay as previously described [9]. CTLL cells were washed twice to remove residual rat IL-2 and then seeded at 4×10^4 cells/ml in each well of 96-well flat-bottomed microtiter plates (Falcon 3072). The cells were cultured in the presence of each culture supernatant for 24 hr at 37°C in 5% CO_2 -humidified atmosphere. The cells received a 4-hr terminal pulse with ^3H -TdR ($0.4 \mu\text{Ci/well}$) before harvested onto glass fiber filters. The amount of incorporated radioactivity was measured in a liquid scintillation counter and the results were expressed as the mean cpm for triplicate cultures. IL-2 activity in test samples was also scored in units according to the following formula as previously described by Nakayama *et al.* [20].

$$\text{IL-2 activity (units)} = \frac{A-C}{B-C} \times 100$$

A is the mean cpm of a test sample at 12.5% of the concentration, B indicates the mean cpm of a standard feline IL-2 sample, and C is the mean cpm in the presence of CM instead of a test sample.

RESULTS

Clinical features of FeLV-infected cats: Clinical findings on cats positive for FeLV group specific antigens in PBL using the indirect immunofluorescent antibody test are provided in Table 1. In case Nos. 1 and 2, common clinical features of neoplastic cells in the peripheral blood were found. Five FeLV-infected cats (case Nos. 3 to 7) had mediastinal mass and pleural fluid. The enlargement of systemic lymph nodes and splenomegaly were common features in case Nos. 8 and 9. The remaining three FeLV-infected cats had anemia (case Nos. 10 and 11) and fungal dermatitis (case No. 12), respectively, without neoplastic cells. On the basis of these findings, the FeLV-infected cats were diagnosed as leukemia (case Nos. 1 and 2), the thymic type of lymphosarcoma (case Nos. 3 to 7), the multicentric type of lymphosarcoma (case Nos. 8 and 9), hypoplastic anemia (case No. 11) and fungal dermatitis (case No. 12).

Immunological features of FeLV-infected cats: None of the FeLV-infected cats tested had greater anti-FT-1 cell antibody titers in the serum than 4-fold dilution (a titer of 4-fold dilution in case Nos. 3, 5 and 11) as shown in Table 2.

In the E-rosette forming cell assay, four FeLV-infected cats (case Nos. 1, 2, 4 and 5) had high values (69–88%), as compared to the mean value (31.2%) of 5 healthy controls. The values of case Nos. 5, 6, 8, 10 and 11 were within the range of the mean value of healthy controls (Table 2).

Table 1. Clinical features of FeLV-infected cats

Case No.	Age (years)	Sex ^{a)}	Breed	Clinical status
1	6	F	Mongrel	Neoplastic cells in the peripheral blood and splenomegaly
2	5	F	Persian	Neoplastic cells in the peripheral blood, splenomegaly and anemia with erythroid hypoplasia in the bone marrow
3	3	NF	Mongrel	Mediastinal mass and pleural fluid
4	4	F	Mongrel	Mediastinal mass, pleural fluid, neoplastic cells in the peripheral blood, splenomegaly and enlargement of the mandibular lymph node
5	2	M	Mongrel	Mediastinal mass and pleural fluid
6	2	NF	Mongrel	Mediastinal mass and pleural fluid
7	2	M	Mongrel	Mediastinal mass, pleural fluid and enlargement of the mandibular lymph node
8	8	NF	Mongrel	Enlargement of systemic lymph nodes and splenomegaly
9	8	NM	Mongrel	Enlargement of systemic lymph nodes and splenomegaly
10	2	NM	Mongrel	Anemia with erythroid hypoplasia in the bone marrow
11	4	M	Mongrel	Anemia and positive in anti-globulin test
12	4	M	Persian	Fungal dermatitis

a) F: female, M: male, NF: neutered female, NM: neutered male.

Four out of 12 FeLV-infected cats were examined for the proportion of sIg⁺ cells in PBL. Among them, 2 cats (case Nos. 1 and 4) had low values (0–7%), as compared to the mean value (26.3%) of 5 healthy controls. Case Nos. 8 and 11 were within the range of the mean value of 5 healthy controls (Table 2).

Seven FeLV-infected cats were studied for the blastogenic responses to Con A and PWM. As shown in Table 3, PBL from all FeLV-infected cats had a lower proliferative response to Con A than those from 7 healthy controls. A lowered response to PWM was observed in 6 FeLV-infected cats, except case No. 3 of which response was within the range of the mean value of 7 healthy controls. The depression of the proliferation of PBL from FeLV-infected cats was more apparent in the response to Con A than in that to PWM.

IL-2 production by Con A-stimulated PBL from FeLV-infected cats: PBL from 12 FeLV-infected cats and 7 healthy controls were evaluated for the ability to produce IL-2.

As shown in Table 4, IL-2 activity in FeLV-infected cats (0–77.0 units), except case No. 9 (118.2 units), was lower, as compared to that of healthy controls (94.5 units). The synthesis of IL-2 was found to be severely impaired in FeLV-infected cats with leukemia (case Nos. 1 and 2), the thymic type of lymphosarcoma (case Nos. 4, 6 and 7) and hypoplastic anemia (case No. 10), which had lower levels of IL-2 activity less than 10 units.

Culture supernatants of Con A-stimulated PBL from case Nos. 1, 2, 4, 6, 7 and 10, containing a remarkably low level of IL-2 activity, were further investigated for the possible existence of factors inhibiting

Table 2. Immunological features of FeLV-infected cats

Case No.	Anti-FT-1 cell antibody titer ^{a)}	Cell markers (%)	
		E-rosette ^{b)}	sIg ⁺ ^{c)}
1	<4	81.7	7.0
2	<4	85.1	NE ^{d)}
3	4	NE	NE
4	<4	88.4	0
5	4	NE	NE
6	<4	45.2	NE
7	<4	NE	NE
8	<4	20.8	33.8
9	<4	NE	NE
10	<4	37.0	NE
11	4	39.7	37.1
12	<4	NE	NE
Mean±SE in healthy cats (n=5) ^{e)}		31.4±2.2	26.3±4.5

a) Anti-FT-1 cell antibody titers, determined by an indirect immunofluorescence test using a FeLV-producing feline lymphoma cell line, FT-1, are given as the reciprocal of the highest dilution giving 50% fluorescein-positive cells.

b) Lymphocytes forming rosettes with guinea pig erythrocytes.

c) Surface immunoglobulin positive cells.

d) Not examined.

e) Number of cats tested.

the CTLL cell proliferation. The CTLL cell proliferative responses were not substantially affected by the addition of each culture supernatant to a standard feline IL-2 sample (7059–10144 cpm), as compared with those cultured standard feline IL-2 sample alone (9219 cpm).

In addition, the pleural fluid from FeLV-infected cats (case Nos. 3 to 7) was examined with no detection of spontaneous IL-2 activity, and Con A-stimulated lymphoid cells from the pleural fluid of these 5 FeLV-infected cats failed to produce IL-2. Furthermore, a FeLV-infected cat (case No. 1) with leukemia, in which the repeated IL-2 assay was run at a 7-day interval during the therapy, showed no significant increase in IL-2 production, despite of the temporary improvement in the clinical status.

DISCUSSION

We previously reported that feline IL-2 activity was detectable in the CTLL cell proliferation assay, as described for human and murine IL-2 [11]. In the present study,

Table 3. Proliferative responses of PBL from FeLV-infected cats and healthy cats to Con A and PWM

Group	Proliferative response ^{a)}		
	Medium	Con A	PWM
FeLV-infected cats			
Case No. 1	2081	9176	4396
3	136	16006	11946
6	452	8566	3123
8	405	19793	1953
10	239	2108	565
11	846	18166	2640
12	576	11597	3331
Healthy cats			
Mean±SE (n=7) ^{b)}	339±49	31836±2379	8063±940

a) PBL (1×10^6 cells/ml) were cultured for 72 hr at 37°C with Con A and PWM at the concentration of 12.5 µg/ml and 1 µg/ml, respectively. Each value represents the mean in cpm of ³H-TdR incorporated in triplicate cultures.

b) Number of cats tested.

Table 4. IL-2 production by PBL from FeLV-infected cats and healthy cats

Group	IL-2 activity ^{a)} (units)
FeLV-infected cats	
Case No. 1	0
2	2.5
3	34.2
4	5.3
5	50.9
6	7.8
7	5.3
8	60.6
9	118.2
10	7.0
11	77.0
12	67.4
Healthy cats	
Mean±SE (n=7) ^{b)}	94.5±7.5

a) Each value was obtained from the mean in cpm of ³H-TdR incorporation in triplicate cultures by the formula described in MATERIALS AND METHODS.

b) Number of cats tested.

feline IL-2 activity was examined as one of the parameters of lymphocyte functions in persistently viremic cats spontaneously infected with FeLV.

All of FeLV-infected cats investigated in the present study had remarkably low titers of anti-FT-1 cell antibodies, which closely resemble antibodies to feline oncornavirus-associated cell membrane antigens (FOC-MA) [12], indicating the depressed humoral immunity to FeLV and FeLV-associated antigens.

The PBL from almost all FeLV-infected cats were proved to have significantly lower proliferative responses to Con A and PWM, as compared to those from healthy controls. This observation was similar to that of Cockerell *et al.* [2].

IL-2 activity in the culture supernatant of Con A-stimulated PBL, which was determined by the CTLL cell proliferation assay, was confirmed to be lower in all FeLV-infected cats, except case No. 9, than in

healthy cats. None of culture supernatants of Con A-stimulated PBL from FeLV-infected cats had a detectable inhibitory effect on the CTLL cell proliferation. Therefore, the observed lower IL-2 activity seems to be associated with a decreased ability of PBL to produce IL-2 in response to Con A.

In this study, the lowered IL-2 production does not seem to correlate with the proportion of E-rosette forming cells and of sIg⁺ cells in PBL.

The possible explanation for the mechanism of defective IL-2 production induced by viruses have been proposed by some authors. Copelan *et al.* [4] have suggested that the FeLV suppress the function of human T cells through direct inhibition of IL-2 production. Wainberg *et al.* [26] have suggested that viral interferences with IL-2 production occur at the level of the infected macrophage, presumably via altering interleukin 1 (IL-1) synthesis. In this respect, human monocytes infected with cytomegalovirus have been demonstrated to secrete inhibitors which inhibit IL-1 activity [22]. Wainberg *et al.* [25] have also reported that avian retrovirus binds human IL-2 to make it inactive.

In persistently viremic cats infected with FeLV, the decline in IL-2 mediated lymphocyte function may be responsible for immunological hyporeactivity, at least in part. Clonal expansion of helper, suppressor and cytotoxic T cells absolutely requires a proper amount of IL-2 [16, 19], and even natural killer cells need IL-2 for full expansion of their activity [6]. Therefore, inadequate availability of IL-2 could hamper the development of a normal immune response, possibly contributing to persistent FeLV infection in cats, and indicating FeLV-related diseases and leukemogenesis to escape host defence mechanisms. Further studies are required for more defined understanding on the relation of IL-2 activity to

the stage and/or type of the disease.

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要 約

ネコ白血病ウイルス感染ネコにおけるインターロイキン2産性の低下：後飯塚 僚・廣田好和・長谷川篤彦・友田 勇（東京大学農学部家畜内科学教室）——末梢血塗抹標本で間接蛍光抗体法によりネコ白血病ウイルス（FeLV）群特異抗原が検出された12例のネコについて、末梢血リンパ球のインターロイキン2（IL-2）産生能を検索した。これらのネコではいずれも、FeLV産性腫瘍細胞株（FT-1）に対する血清抗体価は低値であり、また末梢血リンパ球の concanavalin A（Con A）および pokeweed mitogen に対する幼若化反応も、健康ネコリンパ球のそれに比して低く、特に Con A 刺激の場合は、著明に低かった。FeLV 感染ネコ末梢血リンパ球を Con A で刺激し、その培養上清中の IL-2 活性をマウス IL-2 依存性T細胞株（CTLL-2）のトリチウムチミジンの取りこみによって測定すると、FeLV 感染ネコの IL-2活性は、健康ネコのそれに比較して低く、特に白血病あるいは胸腺型リンパ肉腫症例では著しく低かった。これらの事実から、FeLV 感染ネコにおける免疫抑制には IL-2 産生能の低下が関与していると考えられた。