Suppression of the Humoral Antibody Response in Natural Retrovirus Infections

Abstract. *The feline leukemia virus (FeLV) frequently causes death by predisposing the host to acute infections by other pathogens rather than by inducing leukemia. In a previous study, cats infected with FeLV were found to have prolonged homograft rejection responses but there was no evidence that the humoral immune response was impaired. In the present study, the humoral response to the synthetic multichain polypeptide (L-tyrosine-L-glutamic acid)-poly-DL-alanine-poly-L-lysine, denoted (T,G)AL, was found to be significantly depressed in healthy cats that were naturally infected with FeLV compared to uninfected controls. In cats with persistent FeLV viremia the major antibody response to (T,G)AL, normally seen at days 9 to 14 after immunization, was both delayed and greatly reduced.*

As a group, retroviruses often infect lymphoid tissues and many cause leukemias (*1*). Some, such as the feline leukemia virus (FeLV), cause many more deaths by predisposing the host to acute infections by other pathogens than by inducing leukemia (*2*). Cats infected with FeLV were previously shown to have prolonged homograft rejection responses (*3*), but, in the same study, no evidence was found that the humoral immune response was impaired. In the study reported here we found that the humoral response to the synthetic multichain polypeptide (L-tyrosine-L-glutamic acid)-poly-DL-alanine-poly-L-lysine, denoted (T,G)AL, was significantly depressed in healthy cats that were naturally infected with FeLV compared to uninfected controls. In cats that were persistently viremic with FeLV the major antibody response to (T,G)AL, normally seen at days 9 to 14 after immunization, was both delayed and greatly reduced.

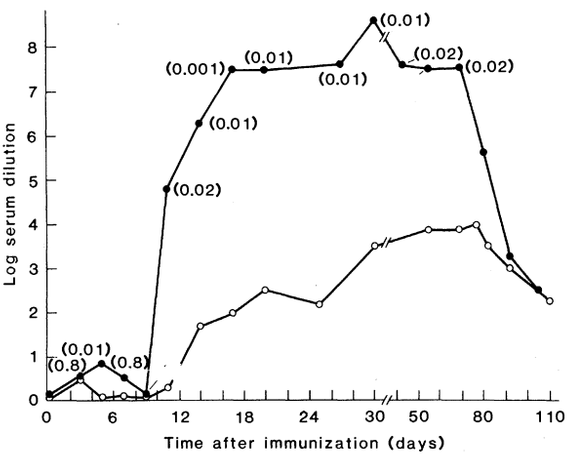

Fig. 1. Titer (geometric mean) of antibodies against the synthetic antigen (T,G)AL in (○) cats with natural, chronic infections of FeLV and (●) uninfected control cats. The numbers in parentheses represent the respective *P* values of the Student's *t*-test for the difference between the mean antibody titers for the two groups at each particular interval.

Eight outbred adult cats that became persistently viremic with FeLV in their natural environment were studied. By means of indirect fixed-cell immunofluorescence (*4*), viremia was confirmed in each cat for a period of at least 6 months at the time of inoculation with antigen. The FeLV-infected cats were also judged to be clinically healthy, both before and during the course of the experiments. Six uninfected healthy adult cats from similar environments were used as controls. Each animal was subcutaneously immunized with 1 mg of (T,G)AL in complete Freund's adjuvant. Blood was taken from the jugular vein at day 0, just before immunization, and subsequently every second day until day 11 and at intervals of several days thereafter for a total of about 110 days. The serum samples were tested for antibodies against (T,G)AL by means of an enzyme-linked immunoadsorbant assay (ELISA) as described by Ungar-Waron *et al.* (*5*).

The results are shown in Table 1 and Fig. 1. In the uninfected control group the first evidence of antibody production to (T,G)AL was detected between days 3 and 5. A major increase in antibody titer was detected at days 10 to 13 in the uninfected animals. The antibody titer increased rapidly to a very high level at about day 14, and then increased gradually to day 30 with individual end-point titers of 1:640 to 1:10,240 (Table 1). The antibody titers subsequently decreased at days 60 to 80.

Of the eight FeLV-infected cats, two showed a first peak of antibody response to (T,G)AL at day 3, which was similar to the peak seen in all six of the uninfected animals. No antibodies to (T,G)AL were found at days 3 to 5 in six of the eight immunized FeLV-infected cats. A significant difference could be shown between the two groups at day 5 after immunization (Student's *t*-test). In five of eight FeLV-infected cats a low level of antibody production against (T,G)AL could be detected by days 14 to 20. Two of the eight infected cats did not respond to (T,G)AL at all, and a third showed a response that was only barely detectable by days 27 to 31. The range of peak titers for the other five FeLV-infected cats

Table 1. Humoral antibody titers against (T,G)AL in FeLV-infected cats and uninfected control cats during the first month after immunization.

Cat number	Time after infection (days)					
	0	3 to 5	10 to 12	14 to 16	18 to 20	27 to 31
			Cats infected with FeLV			
1	< 10	< 10	< 10	10*	20	80
2	< 10	40	10	20	20	80
3	< 10	10			20	160
4	< 10	< 10	< 10	< 10	< 10	10
5	< 10	< 10	10	40	80	640
6	< 10	< 10		160	320	320
7	< 10	< 10	< 10	< 10	< 10	< 10
8	< 10	< 10	< 10	< 10	< 10	< 10
Geometric mean		1.15	1.22	6.62	10.15	34.27
			Uninfected control cats			
9	< 10	10	1,280	2,560	5,120	10,240
10	< 10	10	320	640	2,560	5,120
11	< 10	10	2,560	5,120	5,120	2,560
12	< 10	10	40	80	160	1,280
13	< 10	20	20	160	80	640
14	< 10	10	10	40	640	640
Geometric mean		11.22	141.56	402.72	903.65	2,032.36

*Reciprocal of the highest twofold dilution of serum that gave a positive reaction (starting with an initial dilution of 1:10).

was 1:80 to 1:640 (Table 1). Only one of the eight infected animals developed a titer that was as high as any of the six uninfected cats by day 31, and the geometric mean antibody titers were approximately 60 to 120 times higher for the uninfected cats. The antibodies present at the first peak (days 3 to 5) were predominantly immunoglobulin M for both groups, whereas the second peak (after day 10) was primarily immunoglobulin G as determined with ELISA (*5*).

Cats that are naturally infected with FeLV have a greatly increased risk of developing bacterial, viral, and parasitic diseases such as septicemia, stomatitis, peritonitis, pneumonia, haemobartonellosis, and toxoplasmosis (*2*). Presumably, many of these infections, which are usually controlled in part by the humoral immune system, would be subclinical in the absence of immune suppression by FeLV. We observed a delay in the humoral immune response in six of eight FeLV-infected cats and a diminished peak in the antibody response in six of the eight infected animals. These results indicate that FeLV infection causes a severe immune impairment which is expressed as a delayed humoral response and by prolonged depressed concentrations of detectable antibodies in the serum.

The polypeptide (T,G)AL is known to be a T-cell–dependent antigen in rodents (*6*). One would expect it to evoke the same general class of response in cats. That most of the infected cats could, after a certain time, respond to the antigen allows us to speculate that the impairment lies in the T-helper cell function, and that once the B cells are triggered antibodies can be produced. A specific impairment of OKT-4 positive T-helper cells occurs in cells from humans infected with the adult T-cell leukemia virus (*7*).

Little is known about the way in which FeLV causes immunosuppression. Results by Mathes *et al.* implicated a virion structural protein of approximately 15,000 daltons (*8*). In earlier studies, infection with FeLV was associated with prolongation of allograft rejection (*3*), thymic atrophy (*9*), depletion of paracortical lymphoid tissues (*9*), decreased response to T-cell mitogens (*10*), depressed peripheral blood lymphocyte counts (*2*), and diminished mobility of lymphocyte membrane capping (*11*). Despite these results, which appear to reflect both general impairment of lymphoid tissues and specific impairment of T-cell responses, earlier attempts to show that humoral immunity was depressed by FeLV infection were unsuccessful (*3*). Many of these studies were, however, conducted with cats that were inoculated in the laboratory with a particular strain of FeLV. Our results indicate that the humoral antibody response is diminished in cats that are naturally infected with FeLV.

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Antibodies to Cell Membrane Antigens Associated with Human T-Cell Leukemia Virus in Patients with AIDS

Abstract. *The acquired immune deficiency syndrome (AIDS), which has recently occurred at increasing rates in homosexual men, intravenous drug users, and others, is characterized by the development of Kaposi's sarcoma and several opportunistic infections including pneumonia caused by* Pneumocystis carinii. *Serum samples from patients with AIDS and from matched and unmatched control subjects were examined for the presence of antibodies to cell membrane antigens associated with human T-cell leukemia virus. Nineteen of 75 of the AIDS patients had antibodies directed to surface antigens of Hut 102, a reference T lymphoid cell line infected with the leukemia virus, as did two of the 336 control subjects.*

The human T-cell leukemia virus (HTLV), initially described in 1980 (*1*), was isolated from an American patient with mycosis fungoides, a form of T-cell lymphoma with extensive skin manifestations. Subsequently, the same virus was found in other individuals with lymphoid malignancies in this country and in various other geographical areas (*2–4*). Two regions of the world where both the virus and T-cell malignancies occur at increased rates are the Caribbean islands (*5–7*) and Southern Japan (*8–10*). In such areas from 4 to 37 percent of the healthy adults have antibodies to HTLV (*6, 7, 10, 11*). This contrasts with less than 1 percent of the healthy adults tested from selected regions of the continental United States, Western Europe, or Northern Japan who have such antibodies (*10–12*).

The acquired immune deficiency syndrome (AIDS) is a newly described disease that has recently been observed in several U.S. cities and in Haiti (*13–15*). The incidence of AIDS has been increasing dramatically. Although the disease was initially seen only in sexually active homosexual men, it has now been recognized in intravenous drug users, patients with hemophilia, Haitian immigrants, and heterosexual contacts of members of other high-risk groups (*15–17*). The syndrome, suspected to be of viral origin (*17*), is characterized by the development of Kaposi's sarcoma (KS), pneumonia caused by *Pneumocystis carinii* (PCP), and infections with various other opportunistic microorganisms. Such infections apparently develop because of an immune dysfunction that is characterized by lymphopenia with an imbalance of the normal ratio of T-helper cells to T-suppressor cells (*14, 16, 18*).

Patients with AIDS have increased titers of antibodies to cytomegalovirus and to the Epstein-Barr virus, and a