Humoral Immune Response to T Cell Dependent and Independent Antigens in Cats Infected with Feline Immunodeficiency Virus

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(Received 2 August 1990/Accepted 21 November 1990)

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KEY WORDS: cat, feline immunodeficiency virus, humoral immunity.

The causal relationship between feline immunodeficiency virus (FIV) and immunosuppressive disorders has been suggested by a number of observations that there is an increased risk of acquired immunodeficiency (AIDS)-like illnesses in infected cats and that the infection rate in cats with various chronic diseases is significantly higher than that in healthy cats [5]. Furthermore, in our previous study, we demonstrated that proliferative response of peripheral blood lymphocytes to concanavalin A was significantly decreased in FIV-infected cats, and that the decrease paralleled progression of FIV-related diseases [8]. The evidence, however, of helper T cell impairment as demonstrated in human immunodeficiency virus (HIV) infection [2, 3, 4] is still lacking in feline system. In the present study, we investigated humoral response to T cell dependent and independent antigens in FIV-infected cats as a part of studies pertaining to the helper T cell function.

Seven naturally infected asymptomatic carrier cats [6] and an equal number of age- and sex-matched, uninfected healthy control cats were used. Sheep red blood cells (SRBC) was used as a T cell dependent antigen. To see the primary response, each animal, seronegative for SRBC, was injected intravenously (iv) with 1.5 x 10^8 SRBC. One month later those animals were boostered with the same antigen for the secondary response. Blood samples were taken daily after each immunization. The serum antibody against SRBC was measured by means of hemolytic reaction. An equal volume (100 µl) of heat-inactivated serum sample and 4% SRBC suspension were mixed in a 96 well plate and incubated for 30 min at room temperature. After removal of the supernatant, rabbit complement preabsorbed with SRBC was added and incubated at 37°C for 1 hr. The supernatant was collected by centrifugation at 1,500 rpm for 5 min, and release of hemoglobin was measured by optical density analysis at 540 nm.

In the primary response to SRBC, the mean antibody titers of FIV-infected group increased till day 4 and subsequently decreased. The uninfected group showed a biphasic antibody response; the first peak was detectable at day 3, and the titer increased to reach the second peak at day 7. There were significant differences in anti-SRBC hemolytic titers between two groups at days 5, 6 and 7 (P<0.05) (Fig. 1). Next, the non-IgM hemolytic titers were determined after heat treatment at 63°C for 30 min to denature IgM [7]. The remaining antibody activity in uninfected group started to rise after day 4 and reached a plateau at day 6, while FIV-infected group only showed a slight increase after day 7. The mean antibody titers were significantly lower than those of uninfected group (P<0.05) at days 5, 6 and 7 (Fig. 2). The major anti-SRBC antibody class remaining in the IgM depleted samples was confirmed to be IgG by an indirect hemagglutination test using specific anti-cat IgG or IgM sera.

In the secondary anti-SRBC response, no significant difference was observed between FIV-infected and uninfected groups, although the mean antibody activity of FIV-infected cats, consisted of IgM and IgG or mainly IgG, was lower than that of uninfected cats (Figs. 3 and 4).

In the next experiment, the same cats were injected...
subcutaneously with a T cell independent antigen, tri-nitrophenyl-LPS conjugate (TNP-LPS conjugate) (10 µg/head), 3 months after the SRBC study. Serum samples were collected every 5th day until day 55. The antibody titer against TNP-LPS was measured by an indirect hemolytic reaction using TNP-bound SRBC. The binding of TNP with SRBC was carried out by incubating 0.2 ml 2, 4, 6-trinitrobenzene-sulfonic acid sodium salt dihydrate (TNBS) (10 mg/ml), 0.1 ml SRBC, 3.8 ml saline and 0.2 ml CrC13 (1 mg/ml) for 60 min at 37°C. The serum samples were first heat-inactivated and absorbed with SRBC. The lack of hemolytic activity against SRBC was visually confirmed. An equal volume (50 µl) of serum sample and 2% TNP-bound SRBC suspension were mixed, and incubated for 1 hr at room temperature. After removal of the supernatant, rabbit complement preab- sorbed with SRBC was added and incubated at 37°C for 1.5 hr. Released hemoglobin of the supernatant due to hemolysis was determined as in the SRBC study, with unbound SRBC as the background control. As shown in Fig. 5, there was no significant difference in the antibody response to TNP between FIV-infected and uninfected groups.

The present study demonstrates suppression of primary antibody response to a T cell dependent antigen in FIV-infected asymptomatic carrier cats. This suppression is considered to be due to impairment of IgM-IgG switching which might lead a delay in IgG production. The same phenomenon has been demonstrated in HIV-infected children [1]. With a T cell independent antigen, however, there was no significant difference in antibody response between FIV-infected and uninfected cats. These results indicate that the lack of proper antibody response may be related to impairment of helper T cell function that is necessary for immunoglobulin production by B cells. Although FIV-infected cats showed the initial IgM response that is comparable to control cats, the IgM production may not necessarily require the full range of helper T cell function.

In the secondary response to T cell dependent antigen, no significant difference was observed between the two groups, although the antibody activity of FIV-infected cats was lower than that of FIV uninfected cats. The FIV carriers who were unable to produce a significant amount of anti-SRBC antibody by the time control animals have a maximum level seem to produce IgG later, and thus could respond to the antigen in the secondary response. It may be possible to speculate that once the B cells are triggered, antibody production can be achieved to some degree.

Inadequate immune response to a specific antigen including viral, fungal and bacterial pathogens, due to the lack of T cell function, may result in devastating morbidity and mortality in FIV-infected cats. The decline of humoral immune response may indicate a progressive reduction in the baseline activity of the immune system. When this reduction reaches a critical level, other qualitative changes related to the onset of AIDS related complex (ARC) [6] may occur.

REFERENCES