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Feline Leukemia Virus Nonproducer Lymphosarcomas of Cats as a Model for the Etiology of Human Leukemias

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A. Introduction

It is now thought that most human and animal tumors are caused by environmental factors such as chemical pollutants. However, a small number of animal tumors are known to be caused by viruses. The most common oncogenic viruses are the RNA-containing oncoviruses which are usually contagious and cause lymphoid tumors or sarcomas in young animals. Most of the tumors caused by oncoviruses in animals are viral producers, that is, the causative oncovirus is expressed and can be readily detected in the tumor tissue (Hardy 1978). However, some of the lymphosarcomas (LSA) of pet cats that are caused by the feline leukemia virus (FeLV) exhibit no evidence of FeLV infection even though, as will be clear from the data presented below, FeLV appears to be the etiologic agent for these viral nonproducer (NP) LSAs (Francis et al. 1979; Hardy et al. 1980).

Oncoviruses are found in many vertebrate species and it is thus likely that a human oncovirus exists. There is a high incidence of leukemia among children and, in view of the common occurrence of oncovirus induced lymphoid tumors of young animals, it is probable that some of these childhood leukemias are virally induced. However, at present there is no proof for the existence of a human oncogenic virus and it is possible that, like feline NP LSA, human leukemia is a viral NP tumor. FeLV is spread contagiously among cats and is unique among the mammalian oncoviruses in that it induces a naturally occurring NP LSA (Hardy et al. 1977). FeLV is therefore a potentially valuable model for studying how oncoviruses induce virus negative lymphoid tumors such as human leukemia.

B. Results

I. Immunology of Feline Lymphosarcoma

In order to determine the occurrence of NP feline LSA, we tested 507 cats with LSA for FeLV by the immunofluorescent antibody (IFA) test, which detects FeLV proteins in the cytoplasm of infected cells and indicates persistent infection (Hardy et al. 1973a) In addition, some cats were tested for FeLV by immunodiffusion, tissue culture isolation, and radioimmunoassay (Hardy et al. 1973b; Snyder et al. 1978). We found that 360 (71%) of the cats had FeLV positive LSAs whereas the remaining 147 cats (29%) had NP LSAs. No FeLV proteins nor infectious virus could be detected in the NP LSAs by any of the methods used. However, the FeLV induced tumor specific feline oncornavirus-associated cell membrane antigen (FOCMA) was detected on the surface of both NP and FeLV positive (producer) LSA cells by the viable cell immunofluorescent antibody test (Essex et al. 1971; Hardy et al. 1977). Since no evidence of FeLV expression could be found in feline NP LSA cells, even though they expressed the FeLV induced non-viral antigen FOCMA, it was not certain that FeLV was the etiologic agent for feline NP LSA.

II. Epidemiology of Feline Lymphosarcoma

In an attempt to determine epidemiologically if FeLV was the etiologic agent of feline NP LSA, we observed 1612 FeLV-exposed and -unexposed cats for the development of LSA. All cats were tested for FeLV by the IFA test (Hardy et al. 1973a). The control group of 1074 cats lived in 96 households and had never been exposed to FeLV. These FeLV uninfected

cats were observed for a total of 3225 cat observation years (average: 3 years/cat) and during this period none of these cats developed LSA. The remaining 538 cats lived in 23 households and had been exposed to FeLV at some time in their lives. Of these 538 cats, 389 were found to be FeLV uninfected and 149 were found to be persistently infected. The exposed cats were observed for a total of 2334 cat observation years (average: 4.4 years/cat) and during this period 41 cats developed LSA – 30 cats developed FeLV positive LSA and 11 developed NP LSA. The difference in the occurrence of NP LSA among the FeLV-exposed and -unexposed cats was found to be highly significant ($P<0.001$) by the Chi Square Test. Thus, there appears to be a comparable epidemiologic association in pet cats between FeLV exposure and the occurrence of both FeLV positive and NP LSA. This exposure association, together with the finding that FOCMA is expressed on NP LSA cells, suggests that FeLV is the etiologic agent of feline LSAs regardless of their FeLV status.

C. Discussion

The mechanism by which RNA and DNA containing viruses induce tumors is not fully understood. However, it is known that both classes of viruses are oncogenic by virtue of their ability to integrate their genome into the genome of the host cell. The DNA viruses can insert their DNA directly into the host cell genome, but the oncoviruses must first make a complementary DNA copy of their viral RNA. Little is known about how the integrated viral genome induces cellular transformation and nothing is known about the mechanism by which FeLV induces NP LSA. However, several mechanisms are possible (Gallo et al. 1977). For example, FeLV may recombine with endogenous oncovirus or cellular genes and form a replication-defective leukemogenic virus. Alternatively, the FeLV genome may integrate into the host cell genome in an unstable manner and transform the cell before being lost by deletion. It is also possible that only a fragment of the FeLV genome becomes integrated into the genome of the host cell and that this fragment contains enough information to induce transformation, but not enough for viral production. Yet another possibility is that FeLV infects nonlymphoid cells and causes these cells to produce an abnormal growth factor that results in the uncontrolled proliferation of lymphocytes and, ultimately, in NP LSA.

Feline NP LSA is the only known example of a naturally occurring, virally induced, NP LSA in animals and may therefore be a useful model for elucidating the mechanism of oncovirus transformation. Viruses cause cancer in amphibians, fish, fowl, rodents, cats, cattle, and subhuman primates, and if humans were to be exempt from such a general biological phenomenon, it would be a circumstance unparalleled in the history of parasitism. In fact, evidence is accumulating that some human cancers are virally induced. For example, Burkitt's lymphoma, nasopharyngeal carcinoma, cervical cancer, and Kaposki's sarcoma are thought to be caused by Herpesviruses, which are able to remain latent in their host for many years (De-Thé 1977). Recently, the occurrence of hepatitis B virus antigens have been associated with the development of hepatocellular carcinomas in people. Most of these tumors possess the hepatitis viral antigens, but like the feline NP LSA, about 25% to 30% are antigen negative tumors (Goudeau et al. 1979). Although no oncoviruses have been proven to be associated with human leukemia, an oncovirus with properties quite distinct from those of any animal oncovirus has recently been isolated from the tumor tissue of a human with mycosis fungoides (Poiesz et al., to be published). It is thus also possible that an oncovirus causes human NP leukemias even though no oncogenic virus has been isolated from these tumors. If that is indeed found to be the case, feline NP LSA may be an important model for studying how these NP human leukemias are induced and how they might be prevented.

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