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Short communication

Cross-species infectivity and pathogenesis of the Friend murine leukemia virus complex in Syrian hamsters

Xiaobei Chen [a,c], Rong Da [a], Xiaoming Jin [a], Wuqi Song [a], Xiaoguang Li [a], Yingmei Fu [a], Hong Ling [a], Zhaohua Zhong [a], Kenichi Yamamura [b], Akinori Ishimoto [c], Fengmin Zhang [a,b,c,*]

[a] *Department of Microbiology, Pathology, Harbin Medical University, Bio-Pharmacological Key-Laboratory, Heilongjiang Province 150086, China*
[b] *Department of Developmental Genetics, Institute of Molecular Embryology and Genetics, Kumamoto University, Kumamoto 860-0811, Japan*
[c] *Department of Viral Oncology, Institute for Virus Research, Kyoto University, Kyoto 606-8507, Japan*

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Abstract

To investigate cross-species infectivity and pathogenesis of Friend murine leukemia virus (MuLV) in hamsters, we infected newborn Syrian hamsters with ecotropic Friend MuLV that was passaged in BALB/c mice for approximately 30 years. During acute infection, 39.5% of newborn Syrian hamsters developed severe growth interruption and weight loss, spleen atrophy, severe lymphocyte depletion, and massive viral antigen loads in the spleen. The lymph nodes and thymuses were observed in all diseased hamsters. Ecotropic Friend MuLV was rescued from the sera and spleen and heart extracts of the diseased hamsters, and the same disease was confirmed by induction of erythroleukemia in BALB/c mice. Our results demonstrate that an ecotropic MuLV after extended passage *in vivo* to infect hamster cells that are resistant to infection by wild type MuLV, causing pathologic lesions and a wasting syndrome in newborn hamsters *in vivo*. This may occur with variants of Friend MuLV that have lower infectivity in hamster cells and are not cleared by the immune system of newborn hamsters. These findings suggest the potential danger of the interspecies transmission and pathogenesis of heterologous retroviruses in humans.

Keywords: Murine leukemia virus; Retrovirus; Hamster; Infectivity; Pathogenesis

Friend murine leukemia virus (MuLV) complex containing replication-defective ecotropic spleen focus-forming virus (SFFV) and replication-competent endogenous NB-tropic leukemia-inducing helper virus (LLV), that causes erythroleukemia in sensitive mice and wasting or runting syndrome in rats (Ikawa, 1997; Takeichi and Kobayashi, 1980).It has been previously studied that hamsters cannot be infected with MuLV both *in vivo* and *in vitro* (Heard and Danos, 1991; Miller and Miller, 1992, 1993; Siess et al., 1996; Wilson and Eiden, 1991). Resistance of hamster cells to Friend MuLV complex was demonstrated by treating hamster cells with the tunicamycin of a glycosylation inhibitor (Eiden et al., 1994), or inoculating a variant of ecotropic Friend MuLV that is highly neuropathogenic in sensitive mice (Masuda et al., 1992, 1996). Changes in viral genes encoding core or envelope proteins enhance the infectivity of Friend MuLV complex in hamster cell lines (Jung et al., 2004; Soong et al., 2000). We previously demonstrated limited replication of viral replication in newborn hamsters inoculated with the hamster-adapted ectropic Friend MuLV complex (Ishimoto, 1985), however research investigating MuLV pathogenesis in hamsters has not been shown.

In this report, an ecotropic Friend MuLV complex that was passaged for 30 years by intraperitoneal inoculation of spleen homogenates in BALB/c mice at the Laboratory of Kyoto University in Japan, was used to infect Syrian hamsters. The Friend MuLV stock was prepared from the enlarged spleens of erythroleukemic BALB/c mice, and titrated using the UV-XC test

* Corresponding author at: Department of Microbiology, Pathology, Harbin Medical University, Bio-Pharmacological Key-Laboratory, Heilongjiang Province 150086, China. Tel.: +86 451 86669576; fax: +86 451 86669576.
E-mail address: fengminzhang@yahoo.com.cn (F. Zhang).

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Table 1
Body weight, spleen weight, and viral titer in spleen extracts from Friend MuLV inoculated newborn hamsters at 21 days pi (mean ± S.D.)

Groups[a] of hamster	Numbers	Body weight (g)	Spleen weight (mg)	Viral titers from spleen extracts (log 10 FFU/0.2 ml)
Un-inoculated group	10	55 ± 5	50 ± 5	Negative
Inoculated group I	17	16 ± 4[b]	17 ± 2[b]	1.5 ± 0.3[b]
Inoculated group II	26	50 ± 3	47 ± 4	0.6 ± 0.2

[a] Inoculated groups I and II were divided based on changes in body weight less than 20 g at 21 days pi. Four hamsters from each group were sacrificed at 21 days pi to measure spleen weights and viral titers. Viral titers were detected using the UV-XC test in SC-1 cells.
[b] Compared with un-inoculated group and inoculated group II, $P < 0.01$.

on SC-1 cells at approximately 5.3 log focus-forming units (FFU)/0.2 ml in 5% spleen homogenates with minimum essential medium (MEM), then confirmed to be hamster adaptive with lower replication in the Syrian hamster embryo cells (data not shown). Forty-three newborn Syrian hamsters within 3 days of birth and 20 4-week-old adult Syrian hamsters were intraperitoneally inoculated with 0.2 or 0.5 ml Friend MuLV stock, respectively, and 39.5% (17/43) of the inoculated newborn Syrian hamsters developed severe growth interruption and weight loss during acute infection. Abnormal growth interruption and weight loss were first observed between approximately 7 and 10 days post-viral inoculation (pi) and the body weights of the diseased hamsters were significantly lower than those of the remaining hamsters by between 15 and 20 days pi (Table 1). The diseased hamsters had diarrhea, ruffled hair, hunched posture, and early mortality, but did not have anemia, leukemia, or neurological symptoms by between 25 and 30 days pi. In contrast, the remaining inoculated newborn hamsters and adult Syrian hamsters showed no symptoms of growth interruption, leukemia, or neurological disorders, and survived for at least 150 days pi.

At least four hamsters in each group were sacrificed at day 21 pi for pathological observation and viral antigen detection. Marked spleen atrophy and severe lymphocyte depletion was observed in the spleens, lymph nodes, and thymuses of the diseased hamsters (Table 1 and Fig. 1). The spleens of the diseased hamsters had atrophic white and red pulp, unclear germinal centers, and a fibrotic appearance (Fig. 1A–C). Friend MuLV antigen was detected on the spleen sections by immunohistochemistry with monoclonal antibody 720 that recognizes the C-terminal one-third of the Friend MuLV gp70 envelope protein, and distinguishes Friend MuLV and Rauscher MuLV from other mouse retroviruses (Robertson et al., 1991). Viral antigen was present on the spleen tissue sections of the diseased hamsters in significant quantities, coinciding with the pathological lesions on the diseased hamster organs (Fig. 1D). Tissue from the asymptomatic hamsters, in contrast, had no pathological lesions or viral antigen. Moreover, infectious Friend MuLV complex was rescued from the sera and organic extracts of the diseased hamsters at 21 days pi, and examined using the UV-XC test on SC-1 cells. Viral titers were lower than observed in a sensitive BALB/c mouse (Table 1). The erythroleukemia tumorigenesis of the Friend MuLV complex was confirmed by inoculation of 0.5 ml spleen homogenate extracts from the diseased hamsters into 10 adult BALB/c mice. Characteristic splenomegaly was observed and high viral titers were detected in the inoculated BALB/c mice by day 14 pi (Table 2). This suggested that Friend MuLV virus complex rescued from the diseased hamsters was able to induce erythroleukemia in BALB/c mice.

The pathogenesis of main components of Friend MuLV complex in mice has been well analyzed to be fully leukemogenic, the replication defective spleen-focus-forming virus (SFFV) is for the induction of erythroleukemia in mice, and the replication competent ecotropic Friend lymphatic leukemia inducing helper virus (LLV) could helps SFFV replication and induces lymphatic leukemia when isolate free of SFFV and inoculated into susceptible newborn BALB/c mice (Ishimoto et al., 1978; Li et al., 1987). However the transmission and induction of

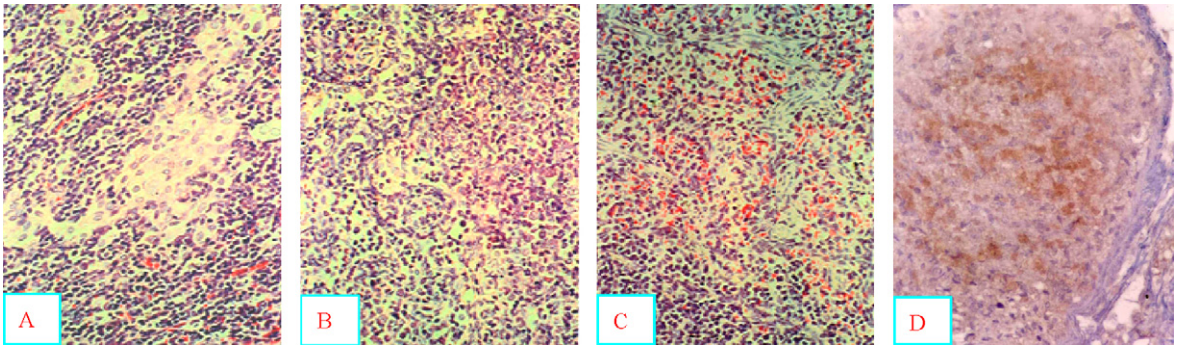

Fig. 1. Histopathological and immunohistochemical examination of lymphatic tissuse from diseased hamsters inoculated with Friend MuLV at 21 days pi. An almost depleted cortex in the thymus (A), decreased lymphoid cells in the lymph nodes (B), atrophy of both the white and red pulp, unclear germinal center, and fibrotic appearance of the red pulp in the spleen (C), and massive Friend MuLV antigen expressed in the spleen (orange color) (D) were observed in the lymphatic tissuse of at least four hamsters after HE staining (A–C) or immumohistochemistric staining with monoclonal antibody 720 against Friend MuLV gp70 evelope antigen (original magnification 10 × 20).