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ScienceDirect
Veterinary Immunology and Immunopathology 123 (2008) 138–143
Veterinary immunology and immunopathology
www.elsevier.com/locate/vetimm

Short survey

Molecular pathogenesis of feline leukemia virus-induced malignancies: Insertional mutagenesis

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Abstract

Feline leukemia virus (FeLV), which is subclassified into three subgroups of A, B and C, is a pathogenic retrovirus in cats. FeLV-A is minimally pathogenic, FeLV-C can cause pure red cell aplasia, and FeLV-B is associated with a variety of pathogenic properties such as lymphoma, leukemia and anemia. FeLV-induced neoplasms are caused, at least in part, by somatically acquired insertional mutagenesis in which the integrated provirus may activate a proto-oncogene or disrupt a tumor suppressor gene. The common integration sites for FeLV have been identified in six loci with feline lymphomas: c-*myc*, *flvi*-1, *flvi*-2 (contains *bmi*-1), *fit*-1, *pim*-1 and *flit*-1. Oncogenic association of the loci includes that c-*myc* is known as a proto-oncogene, *bmi*-1 and *pim*-1 have been recognized as *myc*-collaborators, *fit*-1 appears to be closely linked to *myb*, and *flit*-1 insertion is shown to be associated with over-expression of a cellular gene, e.g. *ACVRL1*. Thus, identification of common integration sites for FeLV is a tenable model to clarify oncogenesis. Recent advances in molecular biology and cytogenetics have developed to rapidly detect numbers of retroviral integration sites by genome-wide large-scale analyses. Especially, polymerase chain reaction (PCR)-based strategies and chromosome analyses with fluorescence *in situ* hybridization (FISH) will be applicable for studies on FeLV.
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Keywords: FeLV; Insertional mutagenesis; Retroviral oncogenesis; Oncogene; Feline

Feline leukemia virus (FeLV) is a type-C retrovirus horizontally transmitted among outbred domestic cat populations in natural conditions. FeLV is subclassified into three receptor interference subgroups of A, B and C, which have been defined by genetic sequence variation in the surface glycoprotein unit (SU) of envelope gene (*env*) including the receptor binding domain (RBD) (Neil et al., 1991; Roy-Burman, 1995; Chen et al., 1998; Ramsey et al., 1998). FeLV-B, and probably FeLV-C also, can be formed *in vivo* by recombination of FeLV-A *env* sequences with corresponding, but varied endogenous FeLV-like elements. Due to the variation of *env*, FeLV-B and FeLV-C exhibit a polytropic host range, being able to infect cells of homologous as well as certain heterologous species, whereas FeLV-A is an ecotropic virus, whose host range is practically restricted to cat cells. Recent studies suggest that each subgroup of FeLV uses different kinds of transporter proteins as a receptor (Boomer et al., 1997; Tailor et al., 1999; Quigley et al., 2000; Mendoza et al., 2006). Persistent infection of FeLV is associated with induction of various degenerative and proliferative diseases in the hematopoietic cell lineages in cats (Linenberger and Abkowitz, 1995; Roy-Burman, 1995; Rohn et al., 1996). FeLV-A is minimally pathogenic in the absence of other variants. One of the variants, which is replication defective due to a mutation in the *env*

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0165-2427/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.vetimm.2008.01.019

gene, can induce immunodeficiency syndrome (Mullins et al., 1986; Overbaugh et al., 1988). FeLV-C can be uniquely associated with the development of pure red cell aplasia (PRCA). FeLV-B isolates appear to be associated with a variety of pathogenic properties. The predominant form is thymic form lymphoma, but non-regenerative anemia and varieties of lymphoid neoplasms and acute myeloid leukemias are also recognized in the clinics.

1. The concept of retroviral insertional mutagenesis

To understand the tumorigenesis by retroviruses, insertional mutagenesis can be considered as one of the most tenable models. As depicted in Fig. 1, if the retrovirus has been integrated near (either upstream or downstream) a certain cellular gene (e.g. proto-oncogene), transcription of the gene can be upregulated by the promoter and enhancer function of the retroviral long terminal repeat (LTR). On the other hand, if it has been integrated inside the gene (e.g. tumor suppressor gene), the transcript can be altered or disrupted. And then, the cell acquires growth advantage. From the systems of murine retrovirus-induced tumors, chromosomal regions containing the loci of proto-oncogenes and some other genes have been found as proviral common integration sites (CISs) in the tumor cells. Over a hundred CISs have been identified from murine leukemia virus (MuLV)-induced neoplasms so far, and a number of the affected genes are related with human malignancies (Joosten et al., 2002; Lund et al., 2002; Erkeland et al., 2004; Uren et al., 2005). One of the most representative cellular proto-oncogenes is c-*myc* which has been identified as an insertional target of MuLV (Corcoran et al., 1984) as well as avian leukosis virus (ALV) (Hayward et al., 1981). For transcriptional activation of genes by the proviruses, the U3 portion of LTR contains transcriptional promoter and enhancer elements necessary for viral gene expression, having potentials to regulate the transcription of adjacent cellular genes in the appropriate target cells (Uren et al., 2005).

2. Insertional mutagenesis in FeLV

The number of identified CISs in the FeLV systems is much smaller than that in the MuLV systems. So far, six CISs have been identified in FeLV-related feline lymphomas (Table 1). The first discovery of CISs in the FeLV systems is on c-*myc* gene. Insertional mutagenesis of c-*myc* proto-oncogene has been detected in both spontaneously and experimentally induced FeLV associated T-cell lymphomas (Neil et al., 1984; Forrest et al., 1987; Miura et al., 1987; Miura et al., 1989; Levy et al., 1993b; Tsatsanis et al., 1994). The *myc* proto-oncogene is upregulated by the insertional mutagenesis near c-*myc* as well as transduction by *myc*-containing FeLV as v-*myc* (Levy et al., 1984, 1988; Mullins et al., 1984; Neil et al., 1984, 1987; Braun et al., 1985; Stewart et al., 1986; Bonham et al., 1987; Forrest et al., 1987; Fulton et al., 1987, 1996; Miura et al., 1987; Onions et al., 1987; Doggett et al., 1989; Levy and Lobelle-Rich, 1992; Terry et al., 1992; Tsujimoto et al., 1993; Tsatsanis et al., 1994). FeLV proviral insertions at *flvi*-2, which contains a gene encoding feline homolog of *bmi*-1, and *pim*-1 have been observed in spontaneously and experimentally induced T-cell lymphomas (Levy and Lobelle-Rich, 1992; Levy et al., 1993a,b; Tsatsanis et al., 1994). The loci of *bmi*-1

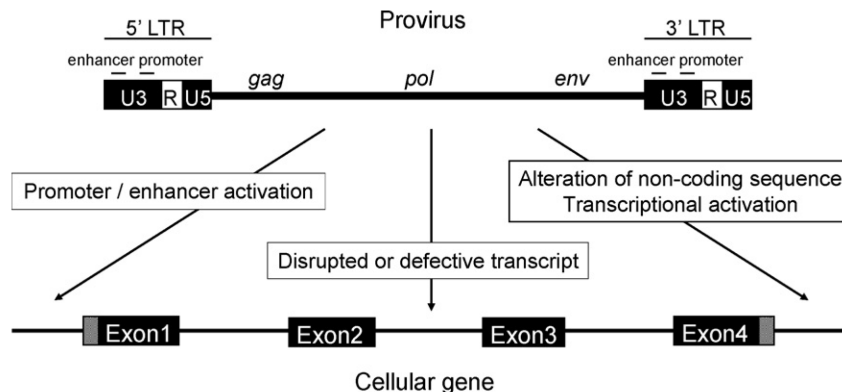

Fig. 1. Concepts of retroviral insertional mutagenesis. The provirus contains long terminal repeats (LTRs) at both ends. LTRs can be subdivided into three regions: U3, R and U5. U3 contains the enhancer and promoter sequences that drive viral as well as cellular gene transcription. Retroviral *gag*, *pol* and *env* encode the viral components required for the assembly of viral particles. The provirus inserted into a certain region of cellular DNA can lead to each event described.

Table 1
Common integration sites identified in FeLV-associated neoplasms

Locus	Tumor type	Frequency	References
c-*myc*	T-cell lymphoid tumor (mainly thymic lymphoma)	34/106 (32%)	Neil et al. (1984), Forrest et al. (1987), Miura et al. (1987). Levy et al. (1993a,b) and Tsatsanis et al. (1994)
flvi-1	Non-T-cell lymphoid tumor (splenic lymphoma)	4/7 (57%)	Levesque et al. (1990)
flvi-2	T-cell lymphoid tumor (mainly thymic lymphoma)	27/95 (28%)	Levy and Lobelle-Rich (1992), Levy et al. (1993a,b) and Tsatsanis et al. (1994)
fit-1	T-cell lymphoid tumor (mainly thymic lymphoma)	13/72 (18%)	Tsujimoto et al. (1993) and Tsatsanis et al. (1994)
pim-1	T-cell lymphoid tumor (mainly thymic lymphoma)	3/63 (5%)	Tsatsanis et al. (1994)
flit-1	T-cell lymphoid tumor (thymic lymphoma)	5/25 (20%)	Fujino et al. (under review)

and *pim*-1, which have been recognized as *myc*-collaborating genes, have been also identified as common proviral insertion sites in lymphomas induced by MuLV (Haupt et al., 1991; van Lohuizen et al., 1991; Uren et al., 2005). Additional unique common integration sites for FeLV have been identified as *flvi*-1 in non-T-cell lymphomas (Levesque et al., 1990, 1991) and *fit*-1 in T-cell lymphomas, and the latter has been shown to be closely linked to *myb* (Tsujimoto et al., 1993; Tsatsanis et al., 1994; Barr et al., 1999; Hanlon et al., 2003). Recently, a novel common proviral integration site for FeLV in T-cell lymphomas has been discovered as *flit*-1 (Fujino et al., under review), and the insertion has been shown to be associated with over-expression of a cellular gene, e.g. activin A receptor type II-like 1 (*ACVRL1*) gene which encodes a cell-surface receptor for the transforming growth factor (TGF)-beta superfamily.

As shown in the other retroviruses, the U3 region of FeLV-LTR has potentials to enhance the transcription of adjacent cellular genes (Ghosh and Faller, 1999; Ghosh et al., 2000). Moreover, tandem repeats of enhancer motifs in the U3 region have been found in the FeLV proviruses integrated in the genomes of feline lymphoid neoplasms and myeloid leukemias (Miura et al., 1989; Matsumoto et al., 1992; Athas et al., 1995a,b; Rohn and Overbaugh, 1995; Nishigaki et al., 1997; Starkey et al., 1998; Prabhu et al., 1999; Nishigaki et al., 2002; Chandhasin et al., 2004). So that, the enhanced expression of the genes adjacent to the integrated proviral genome is considered to be associated with the oncogenesis.

3. Advances to hunt up retroviral insertions

Until lately, the screening of retroviral integration sites has been a laborious procedure. Recent advances in molecular biology and molecular cytogenetics have developed to rapidly detect numbers of retroviral integration sites by genome-wide large-scale analyses. In the technique of molecular biology, strategies of polymerase chain reaction (PCR)-based genome walking have been applied to detect integration sites for kinds of retroviruses such as MuLV, ALV and human immunodeficiency virus (HIV) (Bushman et al., 2005; Uren et al., 2005). One of them, inverse PCR, has been established early. A lot of different insertions can be amplified within the same reaction, however, the products of the inverse PCR are limited because the size of fragments should be short enough to be efficiently amplified but long enough to efficiently circularize. Although dilution of the template before ligation to circularize is required for the inverse PCR, it can also result in inefficient amplification. Another strategy, linker-mediated PCRs, can avoid the use of diluted and circularized template DNA by instead using linkers ligated to the ends of digested DNA. Recently, numbers of variants on this method have been developed using different linkers to raise specificity of amplification. Once the sequences of retroviral integration regions have been obtained by the PCRs, chromosome loci and surrounding genes will be found by searching application to the genome database of mouse as well as human. Though the PCR-based strategies will be applicable to the analysis of FeLV insertions, it will be difficult to identify the chromosome loci and adjacent genes until the sequencing project of the whole cat genome is completed (O'Brien et al., 2002).

Recent advances in molecular cytogenetics have made it possible to detect chromosomal proviral insertions of retroviruses such as MuLV (Acar et al., 2000), human T-cell lymphotropic virus (HTLV), HIV (Deichmann et al., 1997; Uemura et al., 1997; Ohshima et al., 1998; Glukhova et al., 1999; Richardson et al., 2001; Zucker-Franklin et al., 2003) as well as FeLV (Fujino et al., 2003) by using fluorescence *in situ* hybridization (FISH). It can be enumerated the integrated proviruses, mapped the loci of the retroviral insertions, and also detected chromosomal aberrations

at the same time. Progresses on feline cytogenetics have established the high-resolution G- and Q-band karyotyping (Cho et al., 1997d), regional chromosome assignment of some tumor-associated genes by FISH (Cho et al., 1997a,b,c, 1998; Okuda et al., 1997; Lee and Cho, 1999; Fujino et al., 2001a,b), and extensive radiation hybrid chromosome map (Murphy et al., 2000). Considering about extensive conserved synteny among human, mouse and cat chromosomes (O'Brien et al., 1999; Murphy et al., 2000; O'Brien et al., 2002), the chromosomal FeLV integration sites can be compared with the map positions in human and mouse chromosomes, and can apply to predict the related adjacent genes. Moreover, some reports have also showed chromosomal aberrations in cats with hematopoietic and lymphoid malignancies (Grindem and Buoen, 1989; Gulino, 1992; Wu et al., 1995; Mayr et al., 1996; Fujino et al., 2004). The analyses of chromosomal FeLV insertions and abnormalities in feline neoplasms can provide valuable information on oncogenesis.

Studies on the retroviral insertional mutagenesis including the analyses of CISs can be very powerful tools for identifying candidate genes involved in oncogenesis as well as normal development. Although the number of identified CISs for FeLV has been smaller than that for MuLV or ALV, the analysis of insertional mutagenesis in FeLV-associated neoplasms has potential for contribution to clarify oncogenesis in cats as well as in humans. Recently developed techniques for detection of CISs will be applicable to analyses on FeLV, and hold promise on the theme.

Conflict of interest statement

None of the authors has a financial or personal relationship with other people or organizations that could inappropriately influence or bias the paper entitled "Molecular pathogenesis of feline leukemia virus: Insertional mutagenesis".

Acknowledgements

The authors were grateful to Mrs. Akane Fujino for providing helpful suggestions. This work was supported by grants from the Ministry of Education, Science, Sports and Culture in Japan.

References

Acar, H., Copeland, N.G., Gilbert, D.J., Jenkins, N.A., Largaespada, D.A., 2000. Detection of integrated murine leukemia viruses in a mouse model of acute myeloid leukemia by fluorescence in situ hybridization combined with tyramide signal amplification. Cancer Genet. Cytogenet. 121, 44–51.

Athas, G.B., Choi, B., Prabhu, S., Lobelle-Rich, P.A., Levy, L.S., 1995a. Genetic determinants of feline leukemia virus-induced multicentric lymphomas. Virology 214, 431–438.

Athas, G.B., Lobelle-Rich, P., Levy, L.S., 1995b. Function of a unique sequence motif in the long terminal repeat of feline leukemia virus isolated from an unusual set of naturally occurring tumors. J. Virol. 69, 3324–3332.

Barr, N.I., Stewart, M., Tsatsanis, C., Fulton, R., Hu, M., Tsujimoto, H., Neil, J.C., 1999. The fit-1 common integration locus in human and mouse is closely linked to MYB. Mamm. Genome 10, 556–559.

Bonham, L., Lobelle-Rich, P.A., Henderson, L.A., Levy, L.S., 1987. Transforming potential of a myc-containing variant of feline leukemia virus in vitro in early-passage feline cells. J. Virol. 61, 3072–3081.

Boomer, S., Eiden, M., Burns, C.C., Overbaugh, J., 1997. Three distinct envelope domains, variably present in subgroup B feline leukemia virus recombinants, mediate Pit1 and Pit2 receptor recognition. J. Virol. 71, 8116–8123.

Braun, M.J., Deininger, P.L., Casey, J.W., 1985. Nucleotide sequence of a transduced myc gene from a defective feline leukemia provirus. J. Virol. 55, 177–183.

Bushman, F., Lewinski, M., Ciuffi, A., Barr, S., Leipzig, J., Hannenhalli, S., Hoffmann, C., 2005. Genome-wide analysis of retroviral DNA integration. Nat. Rev. Microbiol. 3, 848–858.

Chandhasin, C., Lobelle-Rich, P., Levy, L.S., 2004. Feline leukaemia virus LTR variation and disease association in a geographical and temporal cluster. J. Gen. Virol. 85, 2937–2942.

Chen, H., Bechtel, M.K., Shi, Y., Phipps, A., Mathes, L.E., Hayes, K.A., Roy-Burman, P., 1998. Pathogenicity induced by feline leukemia virus, Rickard strain, subgroup A plasmid DNA (pFRA). J. Virol. 72, 7048–7056.

Cho, K.W., Okuda, M., Endo, Y., Satoh, H., Kang, C.B., Watari, T., Tsujimoto, H., Hasegawa, A., 1997a. Assignment of the cat p53 tumor suppressor gene (TP53) to cat chromosome E1p14→p13 by fluorescence in situ hybridization. Cytogenet. Cell Genet. 79, 145–146.

Cho, K.W., Satoh, H., Youn, H.Y., Watari, T., Tsujimoto, H., Hasegawa, A., 1997b. Assignment of the feline c-myc gene (MYC) to cat chromosome F2q21.2 by fluorescence in situ hybridization. Cytogenet. Cell Genet. 78, 135–136.

Cho, K.W., Satoh, H., Youn, H.Y., Watari, T., Tsujimoto, H., O'Brien, S.J., Hasegawa, A., 1997c. Assignment of the cat immunoglobulin heavy chain genes IGHM and IGHG to chromosome B3q26 and T cell receptor chain gene TCRG to A2q12→q13 by fluorescence in situ hybridization. Cytogenet. Cell Genet. 79, 118–120.

Cho, K.W., Youn, H.Y., Watari, T., Tsujimoto, H., Hasegawa, A., Satoh, H., 1997d. A proposed nomenclature of the domestic cat karyotype. Cytogenet. Cell Genet. 79, 71–78.

Cho, K.W., Tsujimoto, H., Hasegawa, A., Satoh, H., 1998. The cat immunoglobulin lambda light chain gene maps to chromosome D3p12-p11. Mamm. Genome 9, 178–179.

Corcoran, L.M., Adams, J.M., Dunn, A.R., Cory, S., 1984. Murine T lymphomas in which the cellular myc oncogene has been activated by retroviral insertion. Cell 37, 113–122.

Deichmann, M., Bentz, M., Haas, R., 1997. Ultra-sensitive FISH is a useful tool for studying chronic HIV-1 infection. J. Virol. Methods 65, 19–25.

Doggett, D.L., Drake, A.L., Hirsch, V., Rowe, M.E., Stallard, V., Mullins, J.I., 1989. Structure, origin, and transforming activity of

feline leukemia virus-myc recombinant provirus FTT. J. Virol. 63, 2108–2117.

Erkeland, S.J., Valkhof, M., Heijmans-Antonissen, C., van Hoven-Beijen, A., Delwel, R., Hermans, M.H., Touw, I.P., 2004. Large-scale identification of disease genes involved in acute myeloid leukemia. J. Virol. 78, 1971–1980.

Forrest, D., Onions, D., Lees, G., Neil, J.C., 1987. Altered structure and expression of c-myc in feline T-cell tumours. Virology 158, 194–205.

Fujino, Y., Mizuno, T., Masuda, K., Ohno, K., Satoh, H., Tsujimoto, H., 2001a. Assignment of the feline Fas (TNFRSF6) gene to chromosome D2p13→p12.2 by fluorescence in situ hybridization. Cytogenet. Cell Genet. 95, 122–124.

Fujino, Y., Mizuno, T., Masuda, K., Ohno, K., Satoh, H., Tsujimoto, H., 2001b. Assignment of the feline Fas ligand gene (TNFSF6) to chromosome F1q12→q13 by fluorescence in situ hybridization. Cytogenet. Cell Genet. 94, 92–93.

Fujino, Y., Satoh, H., Hisasue, M., Masuda, K., Ohno, K., Tsujimoto, H., 2003. Detection of the integrated feline leukemia viruses in a cat lymphoid tumor cell line by fluorescence in situ hybridization. J. Hered. 94, 251–255.

Fujino, Y., Ma, Z., Satoh, H., Mizuno, T., Hisasue, M., Baba, K., Masuda, K., Ohno, K., Onishi, T., Tsujimoto, H., 2004. Characterization of a newly established nonproducer lymphoma cell line for feline leukemia virus. Vet. Immunol. Immunopathol. 102, 429–439.

Fulton, R., Forrest, D., McFarlane, R., Onions, D., Neil, J.C., 1987. Retroviral transduction of T-cell antigen receptor beta-chain and myc genes. Nature 326, 190–194.

Fulton, R., Gallagher, R., Crouch, D., Neil, J.C., 1996. Apparent uncoupling of oncogenicity from fibroblast transformation and apoptosis in a mutant myc gene transduced by feline leukemia virus. J. Virol. 70, 1154–1162.

Ghosh, S.K., Faller, D.V., 1999. Feline leukemia virus long terminal repeat activates collagenase IV gene expression through AP-1. J. Virol. 73, 4931–4940.

Ghosh, S.K., Roy-Burman, P., Faller, D.V., 2000. Long terminal repeat regions from exogenous but not endogenous feline leukemia viruses transactivate cellular gene expression. J. Virol. 74, 9742–9748.

Glukhova, L.A., Zoubak, S.V., Rynditch, A.V., Miller, G.G., Titova, I.V., Vorobyeva, N., Lazurkevitch, Z.V., Graphodatskii, A.S., Kushch, A.A., Bernardi, G., 1999. Localization of HTLV-1 and HIV-1 proviral sequences in chromosomes of persistently infected cells. Chromosome Res. 7, 177–183.

Grindem, C.B., Buoen, L.C., 1989. Cytogenetic analysis in nine leukaemic cats. J. Comp. Pathol. 101, 21–30.

Gulino, S.E., 1992. Chromosome abnormalities and oncogenesis in cat leukemias. Cancer Genet. Cytogenet. 64, 149–157.

Hanlon, L., Barr, N.I., Blyth, K., Stewart, M., Haviernik, P., Wolff, L., Weston, K., Cameron, E.R., Neil, J.C., 2003. Long-range effects of retroviral insertion on c-myb: overexpression may be obscured by silencing during tumor growth in vitro. J. Virol. 77, 1059–1068.

Haupt, Y., Alexander, W.S., Barri, G., Klinken, S.P., Adams, J.M., 1991. Novel zinc finger gene implicated as myc collaborator by retrovirally accelerated lymphomagenesis in E mu-myc transgenic mice. Cell 65, 753–763.

Hayward, W.S., Neel, B.G., Astrin, S.M., 1981. Activation of a cellular onc gene by promoter insertion in ALV-induced lymphoid leukosis. Nature 290, 475–480.

Joosten, M., Vankan-Berkhoudt, Y., Tas, M., Lunghi, M., Jenniskens, Y., Parganas, E., Valk, P.J., Lowenberg, B., van den Akker, E., Delwel, R., 2002. Large-scale identification of novel potential disease loci in mouse leukemia applying an improved strategy for cloning common virus integration sites. Oncogene 21, 7247–7255.

Lee, J.H., Cho, K.W., 1999. Assignment of TCRB encoding the T-cell receptor beta chain gene to cat chromosome A2q25-q26 by fluorescence in situ hybridization. Cytogenet. Cell Genet. 84, 109–110.

Levesque, K.S., Bonham, L., Levy, L.S., 1990. flvi-1, a common integration domain of feline leukemia virus in naturally occurring lymphomas of a particular type. J. Virol. 64, 3455–3462.

Levesque, K.S., Mattei, M.G., Levy, L.S., 1991. Evolutionary conservation and chromosomal localization of flvi-1. Oncogene 6, 1377–1379.

Levy, L.S., Lobelle-Rich, P.A., 1992. Insertional mutagenesis of flvi-2 in tumors induced by infection with LC-FeLV, a myc-containing strain of feline leukemia virus. J. Virol. 66, 2885–2892.

Levy, L.S., Gardner, M.B., Casey, J.W., 1984. Isolation of a feline leukaemia provirus containing the oncogene myc from a feline lymphosarcoma. Nature 308, 853–856.

Levy, L.S., Fish, R.E., Baskin, G.B., 1988. Tumorigenic potential of a myc-containing strain of feline leukemia virus in vivo in domestic cats. J. Virol. 62, 4770–4773.

Levy, L.S., Lobelle-Rich, P.A., Overbaugh, J., 1993a. flvi-2, a target of retroviral insertional mutagenesis in feline thymic lymphosarcomas, encodes bmi-1. Oncogene 8, 1833–1838.

Levy, L.S., Lobelle-Rich, P.A., Overbaugh, J., Abkowitz, J.L., Fulton, R., Roy-Burman, P., 1993b. Coincident involvement of flvi-2, c-myc, and novel env genes in natural and experimental lymphosarcomas induced by feline leukemia virus. Virology 196, 892–895.

Linenberger, M.L., Abkowitz, J.L., 1995. Haematological disorders associated with feline retrovirus infections. Bailliere's Clin. Haematol. 8, 73–112.

Lund, A.H., Turner, G., Trubetskoy, A., Verhoeven, E., Wientjens, E., Hulsman, D., Russell, R., DePinho, R.A., Lenz, J., van Lohuizen, M., 2002. Genome-wide retroviral insertional tagging of genes involved in cancer in Cdkn2a-deficient mice. Nat. Genet. 32, 160–165.

Matsumoto, Y., Momoi, Y., Watari, T., Goitsuka, R., Tsujimoto, H., Hasegawa, A., 1992. Detection of enhancer repeats in the long terminal repeats of feline leukemia viruses from cats with spontaneous neoplastic and nonneoplastic diseases. Virology 189, 745–749.

Mayr, B., Wegscheider, H., Loupal, G., Reifinger, M., 1996. Cytogenetic findings in two cases of feline histiocytoma. J. Small Anim. Pract. 37, 239–240.

Mendoza, R., Anderson, M.M., Overbaugh, J., 2006. A putative thiamine transport protein is a receptor for feline leukemia virus subgroup A. J. Virol. 80, 3378–3385.

Miura, T., Tsujimoto, H., Fukasawa, M., Kodama, T., Shibuya, M., Hasegawa, A., Hayami, M., 1987. Structural abnormality and over-expression of the myc gene in feline leukemias. Int. J. Cancer 40, 564–569.

Miura, T., Shibuya, M., Tsujimoto, H., Fukasawa, M., Hayami, M., 1989. Molecular cloning of a feline leukemia provirus integrated adjacent to the c-myc gene in a feline T-cell leukemia cell line and the unique structure of its long terminal repeat. Virology 169, 458–461.

Mullins, J.I., Brody, D.S., Binari Jr., R.C., Cotter, S.M., 1984. Viral transduction of c-myc gene in naturally occurring feline leukaemias. Nature 308, 856–858.

Mullins, J.I., Chen, C.S., Hoover, E.A., 1986. Disease-specific and tissue-specific production of unintegrated feline leukaemia virus variant DNA in feline AIDS. Nature 319, 333–336.

Murphy, W.J., Sun, S., Chen, Z., Yuhki, N., Hirschmann, D., Menotti-Raymond, M., O'Brien, S.J., 2000. A radiation hybrid map of the cat genome: implications for comparative mapping. Genome Res. 10, 691–702.

Neil, J.C., Hughes, D., McFarlane, R., Wilkie, N.M., Onions, D.E., Lees, G., Jarrett, O., 1984. Transduction and rearrangement of the myc gene by feline leukaemia virus in naturally occurring T-cell leukaemias. Nature 308, 814–820.

Neil, J.C., Fulton, R., Tzavaras, T., Forrest, D., McFarlane, R., Onions, D., 1987. Viral transduction of host genes in naturally occurring feline T-cell leukaemias: transduction of myc and a T-cell antigen receptor beta-chain gene. Haematol. Blood Transfus. 31, 372–376.

Neil, J.C., Fulton, R., Rigby, M., Stewart, M., 1991. Feline leukaemia virus: generation of pathogenic and oncogenic variants. Curr. Top. Microbiol. Immunol. 171, 67–93.

Nishigaki, K., Okuda, M., Endo, Y., Watari, T., Tsujimoto, H., Hasegawa, A., 1997. Structure and function of the long terminal repeats of feline leukemia viruses derived from naturally occurring acute myeloid leukemias in cats. J. Virol. 71, 9823–9827.

Nishigaki, K., Hanson, C., Thompson, D., Yugawa, T., Hisasue, M., Tsujimoto, H., Ruscetti, S., 2002. Analysis of the disease potential of a recombinant retrovirus containing Friend murine leukemia virus sequences and a unique long terminal repeat from feline leukemia virus. J. Virol. 76, 1527–1532.

O'Brien, S.J., Menotti-Raymond, M., Murphy, W.J., Nash, W.G., Wienberg, J., Stanyon, R., Copeland, N.G., Jenkins, N.A., Womack, J.E., Marshall Graves, J.A., 1999. The promise of comparative genomics in mammals. Science 286 pp. 458–462, 479–481.

O'Brien, S.J., Menotti-Raymond, M., Murphy, W.J., Yuhki, N., 2002. The feline genome project. Annu. Rev. Genet. 36, 657–686.

Ohshima, K., Ohgami, A., Matsuoka, M., Etoh, K., Utsunomiya, A., Makino, T., Ishiguro, M., Suzumiya, J., Kikuchi, M., 1998. Random integration of HTLV-1 provirus: increasing chromosomal instability. Cancer Lett. 132, 203–212.

Okuda, M., Minehata, K., Setoguchi, A., Cho, K.W., Nakamura, N., Nishigaki, K., Watari, T., Cevario, S., O'Brien, S.J., Tsujimoto, H., Hasegawa, A., 1997. Cloning and chromosome mapping of the feline genes p21WAF1 and p27Kip1. Gene 198, 141–147.

Onions, D., Lees, G., Forrest, D., Neil, J., 1987. Recombinant feline viruses containing the myc gene rapidly produce clonal tumours expressing T-cell antigen receptor gene transcripts. Int. J. Cancer 40, 40–45.

Overbaugh, J., Donahue, P.R., Quackenbush, S.L., Hoover, E.A., Mullins, J.I., 1988. Molecular cloning of a feline leukemia virus that induces fatal immunodeficiency disease in cats. Science 239, 906–910.

Prabhu, S., Lobelle-Rich, P.A., Levy, L.S., 1999. The FeLV-945 LTR confers a replicative advantage dependent on the presence of a tandem triplication. Virology 263, 460–470.

Quigley, J.G., Burns, C.C., Anderson, M.M., Lynch, E.D., Sabo, K.M., Overbaugh, J., Abkowitz, J.L., 2000. Cloning of the cellular receptor for feline leukemia virus subgroup C (FeLV-C), a retrovirus that induces red cell aplasia. Blood 95, 1093–1099.

Ramsey, I.K., Spibey, N., Jarrett, O., 1998. The receptor binding site of feline leukemia virus surface glycoprotein is distinct from the site involved in virus neutralization. J. Virol. 72, 3268–3277.

Richardson, J.H., Rose, N.J., Mann, S., Ferguson-Smith, M., Lever, A.M., 2001. Chromosomal positioning of human T-lymphotropic type 1 proviruses by fluorescence in situ hybridisation. J. Virol. Methods 93, 65–74.

Rohn, J.L., Overbaugh, J., 1995. In vivo selection of long terminal repeat alterations in feline leukemia virus-induced thymic lymphomas. Virology 206, 661–665.

Rohn, J.L., Gwynn, S.R., Lauring, A.S., Linenberger, M.L., Overbaugh, J., 1996. Viral genetic variation, AIDS, and the multistep nature of carcinogenesis: the feline leukemia virus model. Leukemia 10, 1867–1869.

Roy-Burman, P., 1995. Endogenous env elements: partners in generation of pathogenic feline leukemia viruses. Virus Genes 11, 147–161.

Starkey, C.R., Lobelle-Rich, P.A., Granger, S., Brightman, B.K., Fan, H., Levy, L.S., 1998. Tumorigenic potential of a recombinant retrovirus containing sequences from Moloney murine leukemia virus and feline leukemia virus. J. Virol. 72, 1078–1084.

Stewart, M.A., Forrest, D., McFarlane, R., Onions, D., Wilkie, N., Neil, J.C., 1986. Conservation of the c-myc coding sequence in transduced feline v-myc genes. Virology 154, 121–134.

Tailor, C.S., Willett, B.J., Kabat, D., 1999. A putative cell surface receptor for anemia-inducing feline leukemia virus subgroup C is a member of a transporter superfamily. J. Virol. 73, 6500–6505.

Terry, A., Fulton, R., Stewart, M., Onions, D.E., Neil, J.C., 1992. Pathogenesis of feline leukemia virus T17: contrasting fates of helper, v-myc, and v-tcr proviruses in secondary tumors. J. Virol. 66, 3538–3549.

Tsatsanis, C., Fulton, R., Nishigaki, K., Tsujimoto, H., Levy, L., Terry, A., Spandidos, D., Onions, D., Neil, J.C., 1994. Genetic determinants of feline leukemia virus-induced lymphoid tumors: patterns of proviral insertion and gene rearrangement. J. Virol. 68, 8296–8303.

Tsujimoto, H., Fulton, R., Nishigaki, K., Matsumoto, Y., Hasegawa, A., Tsujimoto, A., Cevario, S., O'Brien, S.J., Terry, A., Onions, D., Neil, J.C., 1993. A common proviral integration region, fit-1, in T-cell tumors induced by myc-containing feline leukemia viruses. Virology 196, 845–848.

Uemura, Y., Kubota, T., Miyagi, T., Imamura, J., Kubonishi, I., Taguchi, H., Miyoshi, I., Shimizu, K., 1997. Detection of HTLV-I proviral DNA by fluorescence in situ hybridization. Am. J. Hematol. 54, 86–88.

Uren, A.G., Kool, J., Berns, A., van Lohuizen, M., 2005. Retroviral insertional mutagenesis: past, present and future. Oncogene 24, 7656–7672.

van Lohuizen, M., Verbeek, S., Scheijen, B., Wientjens, E., van der Gulden, H., Berns, A., 1991. Identification of cooperating oncogenes in E mu-myc transgenic mice by provirus tagging. Cell 65, 737–752.

Wu, F.Y., Iijima, K., Tsujimoto, H., Tamura, Y., Higurashi, M., 1995. Chromosomal translocations in two feline T-cell lymphomas. Leuk. Res. 19, 857–860.

Zucker-Franklin, D., Pancake, B.A., Najfeld, V., 2003. Localization of HTLV-I tax proviral DNA in mononuclear cells. Blood Cells Mol. Dis. 31, 1–6.