Review Article

Feline Retroviral Infections and Tumour Development: The Oncogenic Roles of Feline Leukaemia Virus and Feline Immunodeficiency Virus

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Abstract

Feline leukaemia virus (FeLV) and feline immunodeficiency virus (FIV) are the two most clinically significant retroviruses of domestic cats, both carrying well-documented oncogenic potential. FeLV, a gammaretrovirus, is the most important feline tumour virus known, increasing the risk of lymphoma development up to 60-fold in progressively infected cats through mechanisms including insertional mutagenesis, proto-oncogene activation, and recombination with host cellular oncogenes. FIV, a lentivirus analogous to human immunodeficiency virus (HIV), increases lymphoma risk approximately 5-6-fold, primarily through chronic immune dysregulation, impaired tumour immunosurveillance, and sustained antigenic stimulation of lymphocytes, although direct insertional oncogenesis has also been demonstrated in rare cases. Co-infection with both viruses synergistically amplifies the risk of lymphoid malignancies up to 77-fold. Despite the marked decline in FeLV prevalence following widespread vaccination programmes, the overall incidence of feline lymphoma has not decreased proportionally, suggesting that FeLV-independent aetiological factors including FIV, environmental carcinogens, and chronic inflammation play increasingly important roles. This review provides a comprehensive overview of the oncogenic mechanisms, epidemiological associations, tumour types, and clinical implications of FeLV and FIV infections in domestic cats, with emphasis on recent advances in the understanding of retroviral oncogenesis.

Keywords: Feline leukaemia virus, Feline immunodeficiency virus, Lymphoma, Oncogenesis, Cats

Introduction

Feline leukaemia virus (FeLV) and feline immunodeficiency virus (FIV) are retroviruses with a global impact on the health of domestic cats (Hartmann, 2012). Both viruses have been associated with the development of neoplasia, particularly lymphoproliferative malignancies, yet they employ fundamentally different oncogenic strategies. FeLV, a gammaretrovirus, is a directly oncogenic virus capable of transforming host cells through insertional mutagenesis, proto-oncogene transduction, and formation of acutely transforming recombinant viruses (Hartmann, 2012; Neil and Onions, 1985). FIV, a lentivirus structurally and functionally analogous to human immunodeficiency virus type 1 (HIV-1), promotes tumourigenesis predominantly through indirect mechanisms involving chronic immune dysfunction and impaired tumour immunosurveillance (Callanan et al., 1996; Beatty et al., 1998).

The landmark retrospective study by Shelton et al. (1990), encompassing sera from 353 FeLV-infected cats collected over two decades (1968–1988), established a strong correlation between FeLV viraemia and lymphoid malignancies and independently demonstrated a significant association between FIV infection and lymphoproliferative disease. Subsequently, Louwerens et al. (2005) reported that the risk of lymphoma was 62-fold higher in FeLV-positive cats, 5.6-fold higher in FIV-positive cats, and 77-fold higher in cats co-infected with both viruses compared to uninfected controls. These findings underscored the critical role of feline retroviruses in the aetiology of feline lymphoma and provided the epidemiological foundation upon which subsequent mechanistic studies were built.

Despite the remarkable success of FeLV vaccination and management programmes in reducing FeLV prevalence globally, the incidence of feline lymphoma has not declined proportionally (Louwerens et al., 2005; Vail et al., 2019). In the 1970s, approximately 70–80% of feline lymphoma cases were attributed to FeLV (Cotter et al., 1975), whereas current data indicate that fewer than 15–25% of lymphoma cases are FeLV-associated (Louwerens et al., 2005; Rolph and Cavanaugh, 2022). This epidemiological shift has prompted renewed interest in FIV-associated oncogenesis, the role of regressive FeLV infections in tumour development, and the potential contribution of novel infectious and non-infectious aetiological factors. This review aims to synthesise the current understanding of FeLV- and FIV-associated neoplasia, covering molecular mechanisms of oncogenesis, tumour types, epidemiological trends, and clinical implications.

Feline Leukaemia Virus (FeLV)

Virology and Infection Outcomes

FeLV is an enveloped, single-stranded RNA gammaretrovirus belonging to the family Retroviridae. Following infection, cats may develop one of three outcomes: abortive infection (complete viral clearance), regressive infection (proviral DNA persists in the genome but viraemia resolves), or progressive infection (persistent antigenemia and viraemia) (Hartmann, 2012; Hofmann-Lehmann et al., 2023). Progressively infected cats are at the highest risk of developing FeLV-associated diseases, including lymphoma, leukaemia, bone marrow suppression syndromes, and secondary infections. However, regressively infected cats, despite testing negative on routinely used antigen-based tests, retain proviral DNA integrated into their genome and may also develop lymphoma, albeit at a lower frequency (Hofmann-Lehmann et al., 2023; Hartmann, 2012). This finding has significant clinical implications, as regressive infections may be underdiagnosed using standard screening methods.

FeLV Subgroups and Pathogenesis

FeLV is classified into four subgroups (A, B, C, and T) based on envelope glycoprotein properties and receptor specificity. FeLV-A is the transmissible subgroup present in all naturally infected cats and is weakly pathogenic alone. FeLV-B arises from recombination between FeLV-A and endogenous FeLV (enFeLV) sequences in the host genome and is strongly associated with lymphoma and other lymphoproliferative diseases (Neil and Onions, 1985; Stewart et al., 2013). FeLV-C develops through mutation of the FeLV-A envelope gene and causes pure red cell aplasia. FeLV-T, a variant with tropism for T lymphocytes, causes immunodeficiency through T-cell depletion (Hartmann, 2012). The emergence of these subgroup variants from FeLV-A is a critical step in disease progression, and the presence of FeLV-B in particular is strongly correlated with neoplastic transformation.

Mechanisms of FeLV-Induced Oncogenesis

Insertional Mutagenesis

The primary mechanism by which FeLV induces neoplastic transformation is insertional mutagenesis. FeLV proviral DNA integrates into the host cell genome, and when integration occurs in proximity to cellular proto-oncogenes, it can lead to their transcriptional activation. Six common integration sites have been identified in FeLV-associated feline lymphomas: c-myc, flvi-1, flvi-2 (containing bmi-1), fit-1, pim-1, and flit-1 (Fujino et al., 2009). Activation of c-myc, a well-characterised proto-oncogene involved in cell proliferation, is one of the best-studied consequences of FeLV insertional mutagenesis. The pim-1 and bmi-1 genes are known myc-collaborators in lymphomagenesis, highlighting the cooperative nature of oncogene activation in FeLV-associated tumours (Neil and Onions, 1985; Fujino et al., 2009).

Transduction of Cellular Oncogenes — Feline Sarcoma Virus

In a process distinct from insertional mutagenesis, FeLV can capture cellular oncogenes through genetic recombination, generating acutely transforming feline sarcoma viruses (FeSV). FeSV acquires one of several oncogenes, such as v-fes, v-fms, v-fgr, or v-kit, leading to polyclonal, multicentric fibrosarcomas that typically occur in young cats after a short incubation period (Hartmann, 2012). FeSV is replication-defective and requires co-infection with FeLV-A as a helper virus. With the decline in FeLV prevalence, FeSV-associated fibrosarcomas have become correspondingly rare.

The Epidemiological Shift: Declining FeLV, Persistent Lymphoma

One of the most significant epidemiological observations in feline oncology is the paradoxical persistence — or even increase — in feline lymphoma incidence despite the dramatic decline in FeLV prevalence following the introduction of widespread vaccination and management programmes (Louwerens et al., 2005; Rolph and Cavanaugh, 2022). In the 1970s, up to 70–80% of feline lymphomas were FeLV-positive (Cotter et al., 1975); by 2005, fewer than 15% of lymphoma cases at referral institutions were FeLV-associated (Louwerens et al., 2005). Concurrently, the anatomical distribution of feline lymphoma has shifted from predominantly mediastinal and multicentric forms (typically FeLV-associated) to gastrointestinal (alimentary) lymphoma, which is usually FeLV-negative and occurs in older cats (Vail et al., 2019).

A recent study from the Netherlands by Sanchez Salguero et al. (2023) evaluated 174 cats with large cell lymphoma over a 10-year period and found that only 1 of 90 screened cats was FeLV-positive and 3 were FIV-positive, confirming the diminished role of retroviruses in feline lymphoma in regions with low retroviral prevalence. The study also demonstrated a shift toward older age at diagnosis (median 8.7 years) and predominance of alimentary and nasopharyngeal subtypes, consistent with the broader epidemiological trend. These findings suggest that non-retroviral aetiological factors — including chronic intestinal inflammation (inflammatory bowel disease), environmental tobacco smoke exposure, and possibly other infectious agents such as Helicobacter species — may play increasingly important roles in feline lymphomagenesis (Rolph and Cavanaugh, 2022; Bertone et al., 2002).

Regressive FeLV Infection and Occult Oncogenesis

An important emerging concept is the potential role of regressive (latent) FeLV infections in tumour development. Regressively infected cats harbour FeLV proviral DNA integrated into their genome despite the absence of detectable viraemia or antigenemia on standard diagnostic tests. Hofmann-Lehmann et al. (2023) emphasised that the clinical significance of regressive FeLV infections may be underestimated, as proviral DNA can be reactivated under immunosuppressive conditions, and insertional mutagenesis can occur regardless of active viral replication. Hartmann (2012) noted that regressively infected cats can develop FeLV-associated diseases including lymphoma, underscoring the need for proviral PCR-based testing in cats with unexplained lymphoproliferative disease, even when standard antigen tests are negative.

Long Terminal Repeat (LTR) Determinants

The FeLV long terminal repeat (LTR) region contains transcriptional regulatory elements that influence both viral tropism and oncogenic potential. Studies of FeLV isolates from naturally occurring lymphomas have demonstrated that specific LTR structures are associated with distinct tumour types: thymic lymphoma-derived LTRs contain transcription factor binding sites adapted for T-cell recognition, while non-T-cell disease-associated LTRs contain unique sequence motifs

(Stewart et al., 2013). These LTR variations serve as genetic determinants of tumour phenotype and contribute to the diversity of FeLV-associated neoplasms.

Tumour Types Associated with FeLV

Lymphoma is the most common neoplasm associated with FeLV infection and was historically the most frequent malignancy in domestic cats overall (Vail et al., 2019). FeLV-associated lymphomas are predominantly of T-cell origin and most commonly present as mediastinal (thymic) or multicentric forms, particularly in young cats (Vail et al., 2019; Cotter et al., 1975). With the decline in FeLV prevalence, the anatomical distribution of feline lymphoma has shifted, with gastrointestinal (alimentary) lymphoma — which is predominantly FeLV-negative — becoming the most common form in many populations (Louwerens et al., 2005; Rolph and Cavanaugh, 2022).

Beyond lymphoma, FeLV is associated with various forms of leukaemia, including lymphoid, myeloid, erythroid, and megakaryocytic leukaemias (Hartmann, 2012). Myeloproliferative diseases and myelodysplastic syndrome (MDS) are also well-documented complications of progressive FeLV infection. FeSV-induced multicentric fibrosarcomas, although rare today, represent another important FeLV-associated neoplasm. Hodgkin's-like lymphoma, olfactory neuroblastoma, and osteochondromatosis have also been sporadically associated with FeLV infection (Hartmann, 2012; Rolph and Cavanaugh, 2022).

Feline Immunodeficiency Virus (FIV)

Virology and Pathogenesis

FIV, first isolated by Pedersen et al. (1987) from a group of cats in Petaluma, California, is a lentivirus classified within the family Retroviridae. FIV infection follows a clinical course analogous to HIV infection in humans, progressing through acute, asymptomatic, and terminal (AIDS-like) phases characterised by progressive CD4+ T lymphocyte depletion, immunodeficiency, and susceptibility to opportunistic infections and neoplasia (Hartmann, 2012; Bęczkowski et al., 2025). FIV prevalence in healthy cats is approximately 2–4% in most countries, while in sick or high-risk cats it may reach 15–30% (Hartmann, 2012). Risk factors for FIV infection include male sex, outdoor access, and aggressive behaviour (bite wounds being the primary route of transmission).

FIV and Neoplasia

The association between FIV infection and neoplasia, particularly lymphoma, has been consistently demonstrated in epidemiological studies. Shelton et al. (1990) identified a significant independent correlation between FIV infection and lymphoproliferative malignancies. Louwerens et al. (2005) quantified the risk, reporting a 5.6-fold increased likelihood of lymphoma development in FIV-positive cats. In one Australian cohort study, lymphoma was the most common condition diagnosed at post-mortem examination, affecting 56% of FIV-infected cats that died (Bęczkowski et al., 2014). The prevalence of FIV infection in one cohort of cats with lymphoma was 50%, substantially higher than the FIV prevalence in the general population, providing further support for a causal relationship (Gabor et al., 2001). In a survey of 826 naturally FIV-infected cats examined at North American Veterinary Teaching Hospitals, neoplasia — especially lymphoma and cutaneous squamous cell carcinoma — was among the most common disease syndromes (Hartmann, 2012).

Mechanisms of FIV-Associated Oncogenesis

Indirect Mechanisms: Immune Dysregulation

The predominant mechanism by which FIV promotes tumourigenesis is considered indirect, involving chronic immune dysregulation and impaired tumour immunosurveillance. Progressive CD4+ T-cell depletion leads to a diminished capacity for immune-mediated elimination of transformed cells. Concurrently, chronic antigenic stimulation of B lymphocytes by persistent viral replication promotes polyclonal B-cell activation and hyperactivity, creating a permissive environment for the emergence of clonal malignancies (Callanan et al., 1996; Beatty et al., 1998). This mechanism parallels the pathogenesis of HIV-associated lymphomas in humans, where chronic immune activation and B-cell stimulation are well-established oncogenic factors.

Callanan et al. (1996) characterised the immunological deficits in FIV-infected cats that developed lymphoma and identified impaired cell-mediated immunity combined with B-cell hyperactivity as potential indirect mechanisms in FIV-associated lymphomagenesis. FIV-associated lymphomas are predominantly high-grade B-cell neoplasms of the centroblastic or immunoblastic subtypes, frequently presenting at extranodal sites — features that closely mirror HIV-associated lymphomas in humans (Callanan et al., 1996;

Beatty et al., 1998).

Direct Mechanisms: Insertional Mutagenesis

Although FIV is primarily considered an indirect oncogenic agent, evidence for occasional direct insertional oncogenesis exists. Beatty et al. (1998) demonstrated clonally integrated FIV proviral DNA in lymphoma cells from an experimentally infected cat, providing the first evidence that FIV could directly contribute to malignant transformation through insertional mutagenesis in rare cases. This finding suggests that while indirect immune-mediated mechanisms predominate, FIV may occasionally act as a direct oncogene, particularly in cases of long-standing infection (Beatty et al., 1998; Hartmann, 2012).

Tumour Types Associated with FIV

Lymphoma is the most common neoplasm associated with FIV infection. Unlike FeLV-associated lymphomas, which are predominantly T-cell-derived and mediastinal, FIV-associated lymphomas are most commonly B-cell-origin, high-grade, and arise at extranodal sites including the kidneys, liver, central nervous system, and nasal cavity (Callanan et al., 1996; Beatty et al., 1998; Hartmann, 2012). Myeloproliferative disease and cutaneous squamous cell carcinoma have also been reported in association with FIV infection. Shelton et al. (1990) described two co-infected (FIV+FeLV+FeSV) cats with multicentric fibrosarcomas. Although squamous cell carcinoma has been observed in FIV-infected cats, the causal relationship remains less clearly defined, as this tumour is common in older cats regardless of retroviral status and may involve feline papillomavirus co-infection (Rolph and Cavanaugh, 2022).

FeLV-FIV Co-infection and Synergistic Oncogenic Risk

Co-infection with FeLV and FIV represents a particularly high-risk scenario for neoplastic disease. Louwerens et al. (2005) demonstrated that the risk of lymphoma in co-infected cats was increased 77-fold compared to uninfected controls — far exceeding the additive risk of either infection alone. Pedersen et al. (1990) demonstrated experimentally that pre-existing FeLV infection greatly potentiated the severity of FIV infection, with enhanced FIV proviral DNA expression in both lymphoid and non-lymphoid tissues and more severe CD4+/CD8+ ratio inversion. Shelton et al. (1990) reported that illnesses in co-infected cats were similar to those of cats infected with FeLV alone, suggesting that FeLV-associated pathogenesis may dominate in the dual-infection context, but with accelerated immunodeficiency contributed by FIV.

The synergistic mechanisms likely involve: (1) FIV-mediated acceleration of CD4+ T-cell depletion, weakening antiviral and antitumour immunity; (2) FeLV-mediated insertional mutagenesis operating in a permissive immunological environment created by FIV; and (3) enhanced replication and dissemination of both viruses within shared target cell populations. Clinically, co-infected cats present earlier, with more severe disease manifestations and shorter survival times than cats infected with either virus alone (Pedersen et al., 1990).

Clinical Implications and Future Perspectives

The recognition of retroviral oncogenesis in cats has profound implications for clinical practice. Routine screening of all cats for FeLV and FIV is recommended, particularly in animals presenting with neoplasia. The 2020 American Association of Feline Practitioners (AAFP) retrovirus management guidelines advocate for universal testing, identification of retroviral status prior to vaccination, and appropriate isolation or management of infected individuals (Little et al., 2020). FeLV vaccination remains the cornerstone of prevention; however, awareness of the continued oncogenic potential of regressive FeLV infections and FIV-associated neoplasia is essential for comprehensive clinical management.

The prognosis for cats with retrovirus-associated lymphoma is generally poorer than for retrovirus-negative cats. FeLV-positive cats with lymphoma exhibit shorter remission and survival times following chemotherapy, partly due to concurrent immunosuppression and increased susceptibility to secondary infections during treatment (Vail et al., 2019). Nevertheless, even progressively FeLV-infected cats with lymphoma can respond favourably to chemotherapy, and treatment should be offered when appropriate.

Future research directions include the development of more sensitive diagnostic tools for detecting regressive FeLV infections, further elucidation of FIV-associated oncogenic mechanisms at the molecular level, investigation of the potential oncogenic role of endogenous FeLV sequences, exploration of novel infectious agents (e.g., feline papillomaviruses, Helicobacter spp.) in

feline tumourigenesis, and the development of immunotherapeutic strategies targeting virus-associated tumour antigens. The feline model continues to provide valuable comparative insights into human retroviral oncology, with FIV-associated lymphoma serving as a natural analogue of HIV-associated non-Hodgkin lymphoma (Beatty et al., 1998; Callanan et al., 1996).

Conclusion

FeLV and FIV remain the most clinically significant oncogenic agents in domestic cats, despite the declining prevalence of FeLV in many populations. FeLV-induced oncogenesis, operating through insertional mutagenesis, proto-oncogene transduction, and LTR-mediated transcriptional activation, represents one of the best-characterised models of retroviral tumourigenesis in veterinary medicine. FIV-associated oncogenesis, predominantly driven by chronic immune dysregulation and impaired tumour immunosurveillance, parallels the mechanisms observed in HIV-associated malignancies in humans. The synergistic oncogenic risk of co-infection underscores the importance of screening for both viruses in feline patients.

The epidemiological shift from predominantly FeLV-associated mediastinal lymphoma to FeLV-negative gastrointestinal lymphoma in ageing cat populations highlights the evolving landscape of feline oncology and suggests that non-retroviral aetiological factors require further investigation. Comprehensive retroviral testing, appropriate vaccination strategies, and awareness of the oncogenic potential of both progressive and regressive infections are essential components of feline healthcare. Continued research into the molecular mechanisms of retroviral oncogenesis will not only benefit feline patients but also contribute to the broader understanding of virus-associated cancers across species.

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References

1. Beatty JA, Callanan JJ, Terry A, Jarrett O, Neil JC. Molecular and immunophenotypical characterization of a feline immunodeficiency virus (FIV)-associated lymphoma: a direct role for FIV in B-lymphocyte transformation? Journal of Virology. 1998;72(1):767-771.
2. Bęczkowski PM, Norris JM, Keller SM, Ratcliffe N, Scase TJ, Jarrett O, Hosie MJ. Contrasting clinical outcomes in two cohorts of cats naturally infected with feline immunodeficiency virus (FIV). Veterinary Microbiology. 2014;176(1-2):50-60.
3. Bęczkowski PM, El-Hage C, Gill H, Hosie MJ. Feline immunodeficiency virus: current insights into pathogenesis, clinical impact, and advances in treatment and vaccine development. Frontiers in Veterinary Science. 2025;12:1665999.
4. Bertone ER, Snyder LA, Moore AS. Environmental tobacco smoke and risk of malignant lymphoma in pet cats. American Journal of Epidemiology. 2002;156(3):268-273.
5. Callanan JJ, Jones BA, Irvine J, Willett BJ, McCandlish IAP, Jarrett O. Feline immunodeficiency virus (FIV)-associated lymphoma: an indirect role for immune dysfunction in tumourigenesis. Veterinary Immunology and Immunopathology. 1996;55(1-3):143-158.
6. Cotter SM, Hardy WD Jr, Essex M. Association of feline leukemia virus with lymphosarcoma and other disorders in the cat. Journal of the American Veterinary Medical Association. 1975;166(5):449-454.
7. Fujino Y, Ohno K, Tsujimoto H. Molecular pathogenesis of feline leukemia virus-induced malignancies: insertional mutagenesis. Veterinary Immunology and Immunopathology. 2009;123(1-2):138-143.
8. Gabor LJ, Love DN, Malik R, Canfield PJ. Feline immunodeficiency virus status of Australian cats with lymphosarcoma. Australian Veterinary Journal. 2001;79(8):540-545.
9. Hartmann K. Clinical aspects of feline retroviruses: a review. Viruses. 2012;4(11):2684-2710.
10. Hofmann-Lehmann R, Hartmann K, Bae Y, Möstl K, Addie DD, Belák S, et al. Feline leukaemia virus infection: ABCD guidelines on prevention and management. Journal of Feline Medicine and Surgery. 2023;25(9):1098612X231183237.
11. Little S, Levy J, Hartmann K, Hofmann-Lehmann R, Hosie M, Olah G, Denis K. 2020 AAFP feline retrovirus testing and management guidelines. Journal of Feline Medicine and Surgery. 2020;22(1):5-30.
12. Louwerens M, London CA, Pedersen NC, Lyons LA. Feline lymphoma in the post-feline

leukemia virus era. Journal of Veterinary Internal Medicine. 2005;19(3):329-335.
13. Neil JC, Onions DE. Feline leukaemia viruses: molecular biology and pathogenesis. Anticancer Research. 1985;5(1):49-63.
14. Pedersen NC, Yamamoto JK, Ishida T, Hansen H. Feline immunodeficiency virus infection. Veterinary Immunology and Immunopathology. 1989;21(1):111-129.
15. Pedersen NC, Torten M, Rideout B, Sparger E, Tonachini T, Luciw PA, et al. Feline leukemia virus infection as a potentiating cofactor for the primary and secondary stages of experimentally induced feline immunodeficiency virus infection. Journal of Virology. 1990;64(2):598-606.
16. Rolph KE, Cavanaugh RP. Infectious causes of neoplasia in the domestic cat. Veterinary Sciences. 2022;9(9):467.
17. Sanchez Salguero X, van Straten G, Meij BP, Fieten H, van Rijn S, Teske E. Feline lymphoma: patient characteristics and response outcome of the COP-protocol in cats with malignant lymphoma in the Netherlands. Animals. 2023;13(16):2602.
18. Shelton GH, Grant CK, Cotter SM, Gardner MB, Hardy WD Jr, DiGiacomo RF. Feline immunodeficiency virus and feline leukemia virus infections and their relationships to lymphoid malignancies in cats: a retrospective study (1968-1988). Journal of Acquired Immune Deficiency Syndromes. 1990;3(6):623-630.
19. Stewart H, Jarrett O, Hosie MJ, Willett BJ. Are endogenous feline leukemia viruses really endogenous? Veterinary Immunology and Immunopathology. 2013;153(3-4):352-357.
20. Vail DM, Thamm DH, Liptak JM. Hematopoietic tumors. In: Withrow SJ, Vail DM, Page RL, eds. Withrow and MacEwen's Small Animal Clinical Oncology, 6th ed. Elsevier, St. Louis; 2019:688-772.