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Review

Molecular Mechanisms of Feline Cancers

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Abstract

Feline cancers have not been studied as extensively as canine cancers, though they may offer similar advantages, with cats being immunocompetent animals subject to similar conditions as their human counterparts. The most common feline cancers include lymphoma, squamous cell carcinoma, sarcoma, and mammary tumors, though mast cell tumors were also investigated in this review. As the pathogenesis of many feline cancers remains unclear, this study seeks to elucidate some molecular mechanisms behind feline cancers. Feline lymphoma has been commonly associated with feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV), though in recent years it has appeared more as lymphoma of the gastrointestinal tract. Chromosomal alterations (translocations) due to the virus-associated lymphoma, as well as aberrant gene expression (such as in COX-2 and MDR1) have been identified in the past. While feline lymphoma may be divided into many subtypes, feline sarcoma may be divided into two broad classifications of feline injection site associated (FISS) sarcoma and spontaneous sarcoma, with FISS being a potential model for inflammation leading to

tumorigenesis in humans. Previous studies have found multiple chromosomal alterations (including aneuploidy and chromosomal translocations), as well as aberrations in gene expression in feline sarcoma. In the past, oral squamous cell carcinoma has been proposed as a model for human head and neck cancer, and mammary tumors have been proposed as a model for human breast cancers due to similar prognosis and phenotype, as well as higher rate of occurrence in cats than in humans. Mutations have been identified in genes such as TP53, ERBB2, and TWIST1 in feline mammary tumors. c-KIT mutations were commonly located in feline mast cell tumors, though these findings were not particularly significant in terms of correlation to other prognostic indicators. This review seeks to elucidate pathways and treatments for feline cancers for the field of comparative genomics and oncology.

Keywords
Cats; feline; cancer; lymphoma; oral squamous cell carcinoma; sarcoma; mammary gland; mast cell

1. Introduction

While canine cancers have traditionally been used as models for human cancers, studying feline cancers may be advantageous in regards to certain types of cancer. As companion animals, domestic cats are subject to similar environmental risk factors as humans and have shorter life spans, facilitating data collection for disease prognosis and remission rates [1].

Feline lymphoma constitutes approximately one-third of feline tumors, being the most common type of feline cancer [2]. Feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) have been thought to increase risk of developing lymphoma; however, although the mechanism of inducing cancer has not been elucidated, some have hypothesized it to be associated with viral genome insertion and control of gene expression, but this hypothesis has been challenged [3]. While FeLV cases have decreased in the past decades, feline lymphoma cases have increased, in particular cases of feline cancers in the gastrointestinal tract [4]. A study demonstrated alimentary lymphoma as the most common among feline lymphomas, with shorter survival time than other types of lymphoma [5]. Feline lymphoma in the past has been treated with chemotherapy, and some studies have shown chlorambucil treatment led to longer remission times [6].

As a proposed model for human head and neck squamous cell carcinoma (HNSCC), feline oral squamous cell carcinoma (FOSCC) has similar etiopathogenesis, markers, and prognosis. The squamous cell carcinoma (SCC) is the most common feline oral cancer, occurring predominantly in older cats. Similar to HNSCC, FOSCC is an aggressive form of cancer that becomes metastatic late in the disease with high rate of recurrence [7]. Chemotherapy, radiation therapy, and surgical excision by themselves and in combination with each other have yielded few successes, and many cats are euthanized as a result of the progression of cancer [8].

Sarcoma in cats may arise spontaneously or through association with an injection-site. Feline injection site sarcomas (FISS) occur in 1 to 10 of every 10 000 vaccinated cats [9]. Although they may arise from a variety of injections, they are commonly found at vaccination sites, in particular vaccination sites for FeLV and rabies. The association with injection sites is thought to be due to the

presence of adjuvant, which has been observed in biopsies of the tumors [10]. FISS are often treated via radical surgical excision in combination with radiotherapy to reduce chances of recurrence, which are relatively high (70%) without the combination of radiotherapy and surgical excision [9]. FISS are not the only sarcoma associated with chronic inflammation, as feline ocular post-traumatic sarcomas are thought to be associated with chronic inflammation as well [11]. Chromosomal alterations as well as abnormal gene expression and mutations have been investigated in the past [12-18].

Feline mammary carcinoma has been proposed as a model for human breast cancer [19], with the triple negative phenotype occurring more commonly in cats than in humans, enabling it to become a potential model for human triple negative breast cancer (TNBC), which lacks immunolabeling of the ER, PR, and HER2 protein [20]. To treat feline mammary tumors, surgery (radical mastectomy in order to reduce recurrence rate) with chemotherapy may be used, and combination chemotherapy with doxorubicin and cyclophosphamide may also be used for metastatic or unresectable cases [21].

Mast cell tumors (MCT) in cats are often categorized by organ system, split into splenic, intestinal, and cutaneous. Splenic mast cell tumors are commonly removed through a splenectomy, as the role of chemotherapy has not yet been established [22, 23]. In the past, genetic alterations have been identified in the c-KIT gene, closely associated with mast cell tumors [23].

Studying feline cancers could allow for the identification of potential biomarkers and genes associated with cancer development, as well as the identification and development of potential treatments [24]. The purpose of this paper is to elucidate possible molecular mechanisms of feline cancers, in specific, those of lymphoma, squamous cell carcinoma, sarcoma, mammary carcinoma, and mast cell tumors.

2. Lymphoma

Feline lymphoma has been categorized anatomically and cytomorphologically [3, 5]. Among 163 cats with lymphoma, researchers found over half (52%) to have alimentary lymphoma, followed by nasal (15%), mediastinal (12%), and multicentric (9%) lymphoma, with the remaining 12% having lymphoma in other locations [5]. Lymphoma may be categorized histologically, as low, intermediate, or high [3]. The incidence of lymphoma in cats has been found to be higher than in dogs, with Siamese cats generally having higher incidence of lymphoma than other breeds [25]. However, the rate of intermediate grade lymphoma in cats has been found to be similar to the incidence in dogs and humans, at around 30%, while the incidence of high-grade lymphoma is higher in cats (around 50%) than in other animals including humans, but lower than dogs (around 65%) [26]. Lymphoma has numerous subtypes, the more common subtypes including immunoblastic, centroblastic, globule leukocyte, lymphocytic, and lymphoblastic [5, 27]. Cats with high-grade lymphoma have significantly shorter median survival time than low-grade lymphoma, excluding the globule leukocyte subtype, which corresponds to shorter survival times than both other low-grade lymphomas and high-grade lymphomas [5]. Feline lymphoma may also be divided into two immunophenotype categories of B-cell lymphoma and T-cell lymphoma. Lymphoma encompasses a wide range of neoplasms with likely numerous underlying molecular mechanisms; because of the range of lymphoma classifications and prognoses, it is difficult to compare findings across studies, and a wide variety of therapies has been and should be considered in response to each type [26].

Beyond the higher incidence of lymphoma in Siamese breeds, a recent UK study found that older, unvaccinated, male cats were at in increased risk of being diagnosed with lymphoma [28]; the higher rate of lymphoma diagnosis in male cats has been observed in previous studies [2]. The UK study also found alimentary lymphoma as the most common anatomical location. Another study found that an increased duration and quantity of environmental tobacco smoke exposure increased the risk of cats developing malignant lymphoma [29].

Feline cutaneous lymphoma has developed at injection sites. Roccabianca and colleagues' study determined that chronic inflammation and reactivation of FeLV may have led to the development of feline injection-site lymphoma [30]. A previous study analyzing lymphoma that developed after treatment of FISS suggested that the lymphoma development could potentially be due to the mutagenic activity from chemotherapy or radiotherapy treatment [31].

Development of alimentary lymphoma in cats has been associated with retroviruses FeLV and FIV, though lymphoma may also develop in cats without FeLV and FIV infections, associated with risk factors such as secondhand tobacco smoke and chronic inflammation [32]. Cats diagnosed with FIV and FeLV are 5.6 and 62.1 times respectively more likely to develop lymphoma than cats that have tested FIV and FeLV negative [33]. Cases of virus-induced lymphoma have decreased with investigations in the 1970s and vaccination development in the 1980s; with this decrease came also a shift in the predominant anatomical location and form of feline lymphoma, and increased importance of non-viral lymphoma. FeLV associated lymphoma was generally of T-cell lineage and multicentric or thymic, FIV of B-cell lineage and nasopharyngeal, and non-retrovirus associated lymphoma of either B- or T-cell lineage and abdominal (with renal and intestinal lymphoma most common) [25, 34, 35].

Although the specific mechanisms of FeLV induced lymphomagenesis are unknown, gene rearrangement via FeLV and its correlation to lymphoma has been studied in the past, especially in regards to the c-MYC gene [36, 37]. Forrest and colleagues, in their study investigating c-MYC expression, rearrangement, and viral transduction in T-cell lymphoma, proposed that observed absence of normal c-MYC allele expression could signify the presence of an oncogenic form of the MYC gene, such as rearranged c-MYC or transduced v-MYC [37].

Chromosomal translocations, t(A2;D3)(p-;p+) and t(A2;B2)(p-;p+), were identified in two FeLV-induced T-cell lymphoma lines [30]. The feline A2 chromosome involved in both identified translocations contains genes including MDR1, EGFR, RAF-1, and MET. The D3 chromosome includes the YES oncogene and BCL-2, an apoptosis inhibitor. The B2 chromosome includes MYB (proto-oncogene, transcription factor) and PIM-1 (proto-oncogene, serine-threonine protein kinase), along with FIT-1, a common proviral integration site for FeLV [38]. Proviral insertion at the FIT-1 integration region was thought to occur in later stages of the development of feline lymphoma [36]. Chromosomal rearrangement (as a result of viruses or in general) and effects of these chromosomal changes (whether that be alterations in gene function or expression) in regions involving proto-oncogenes, oncogenes, and tumor suppressor genes may be further studied to understand lymphomagenesis.

Although FeLV infections have declined, feline lymphoma rates have increased, in particular feline lymphoma of the gastrointestinal tract [4]. In the study of 163 cats, the median survival time for alimentary lymphoma (48 days) was significantly lower (p = 0.0311) than the median survival time for nasal lymphoma (135 days) [5]. A study found mucosal T-cell lymphomas predominate in the feline GI tract [4]. The median survival time for cats with mucosal T-cell lymphoma,

predominantly small-cell lymphoma with median survival of 28 months, was 29 months, in contrast to the 1.5 months of those with transmural T-cell lymphoma, predominantly of large-cell lymphoma with median survival of 1.5 months. For both mucosal and transmural T-cell lymphoma, the jejunum of the small intestine was the most affected region [4].

The immunophenotype of lymphoma is closely linked to its location in the gastrointestinal tract. A study of 50 feline gastrointestinal lymphomas revealed that tumors present in the stomach and the large intestine were predominantly B-cell tumors, while tumors in the small intestine were predominantly T-cell tumors [27].

MDR1 and COX-2 in feline low-grade alimentary lymphoma (LGAL) both had significant increased expression in comparison to expression in inflammatory bowel disease (IBD), and cats with LGAL and IBD generally had higher expression of these genes than the control group [39]. MDR1 encodes protein P-gp, an efflux pump that may allow cancer cells to continue proliferating with resistance to drugs, an issue that has been examined and addressed in human cancers as well [40]. The COX-2 gene and the prostaglandin cascade are related to integral stages of cancer development, and upregulation of the gene has been shown to transform normal cells into cancerous, metastatic cells in other domestic animals [41]. Results from these studies suggest MDR1 and COX-2 are suitable targets to consider in prevention and therapy development.

Reduced expression of tumor suppressor gene CDKN1B (p27kip1), which controls the G1-S cell cycle checkpoint through inhibition of cyclin complexes, may correspond with acceleration of feline lymphoma development [42]. BCL-2 had high expression in T-cell lymphoma cell lines FL-74-UDC-1 and FT-1, in contrast to the low expression in healthy cell line FeTJ-1, though cells freshly isolated from a healthy cat did not have low BCL-2 expression [43]. BCL-2 was found in one study to be expressed in 11 of 21 feline lymphoma tumors (as opposed to no BCL-2 expression in SCC tumors), and expression of the gene was higher in T-cells than B-cells [44]. However, another study showed lack of BCL-2 expression in follicular lymphomas [45]. Because the BCL-2 family of genes regulates apoptosis, with BCL-2 (along with BCL-XL and BCL-W) acting as an apoptosis inhibitor through inhibition of cytochrome C and AIF release, which would then activate caspases leading to apoptosis [46], dysregulated BCL-2 may lead to extended cell survival and resistance to lymphoma therapies seeking to initiate apoptosis [44].

TP53 has been extensively studied in human cancers, and genetic aberrations in this gene have been observed in feline lymphoma cell lines as well. MDM2–p53 interactions lead to regulation and degradation of p53 protein, contributing to carcinogenesis, and inhibition of this interaction via nutlin-3 has been shown to increase production of wild-type p53 (as opposed to mutant-type) and induce apoptosis in these cell lines, serving as a potential cancer therapy [47]. In another study, centrosome amplification was observed in three of five feline lymphoma cell lines and was found to be strongly correlated with chromosomal instability, associated with malignant lymphomas. One of the three cell lines with centrosome amplification contained p53 with an alternate amino-acid sequence, suggesting aberrant p53 function may lead to centrosome amplification and chromosomal instability. However, no significant difference in MDM2 expression between the feline lymphoma cell lines and those of a healthy cat were found, leading researchers to suggest that other mechanisms (beyond p53–MDM2 interactions) may be involved [48].

Inhibition of DNA methylation via 5-aza in feline lymphoma cell lines FT-1, MS4, and 3281 and their effects on certain genes (BCL family, SOX-11, EZH2, CDKN1B) have been analyzed, with varying gene expression in each cell line, though cellular proliferation was ultimately inhibited [49].

Epigenetic alterations, with hypermethylation at the promoter region of the CDKN2A gene encoding the p16 protein, have also been found in feline lymphoid tumors [50]. CDKN2A is a tumor suppressor gene encoding products of p16 and $p19^{ARF}$. In humans, while p16 has been implicated in the Rb pathway of tumorigenesis via CDK4/6, $p19^{ARF}$ has been implicated in the p53 pathway, mediating degradation of MDM2, which then inhibits MDM2 degradation of p53, as previously stated [51]. In a study of human diffuse large B-cell lymphoma, increased expression of CDKN2A correlated with decreased cellular proliferation [52].

Table 1 Gene expression in feline lymphoma.

Chromosome	Gene	Expression	Location / Type	Function	Reference
F1	COX2	increased expression	alimentary	inflammation	[39]
A2	MDR1	increased expression	alimentary	efflux pump	[39]
B4	CDKN1B	reduced protein expression	lymph nodes and tissues from other sites	inhibits control of cellular proliferation	[42]
D4	CDKN2A	association between promoter methylation and decreased mRNA expression	lymphoma cell lines	tumor suppressor (p16 controls G_1 to S)	[50]

3. Squamous Cell Carcinoma

Feline oral squamous cell carcinoma (FOSCC) has been studied as a model for human head and neck squamous cell carcinoma (HNSCC) due to similar etiopathogenesis and prognosis, being an aggressive and invasive form of carcinoma that can become metastatic in later stages. Because of its nature, a multimodal treatment is often adopted, though there has been limited success using combinations of surgery, radiotherapy, and chemotherapy. FOSCC is the most common type of oral cancer in cats [8]. As an oral cancer, FOSCC tends to affect the sublingual area more than the mandible and the maxilla regions [53].

While HNSCC is often associated with human papillomavirus (HPV), being divided into HPV-positive and HPV-negative categories, there seems to be no consistent association between FOSCC and the virus, with FOSCC being more similar to the HPV-negative category of HNSCC [54]. However, another study suggests that *Felis catus* papillomavirus type 2 (FcaPV-2), which has already been implicated as a causative agent in feline cutaneous SCC via E6 and E7 oncogenes inhibiting pro-apoptotic processes (binding to tumor suppressor proteins p53 and pRb, leading to downstream effects) [55], may be implicated as a causative agent in FOSCC as well [56].

Immunostaining results for p16, p53, and pRb in 43 FOSCC xenografts were analyzed and contrasted against the immunostaining results in HNSCC and feline cutaneous SCC. 43% of the FOSCC had low-intensity p16 staining, while 14% had high-intensity; the differing staining intensities could support different paths of oncogenesis, with inhibition/underexpression of CDKN2A or with overexpression of the gene [57]. In contrast, Munday's study (on papillomavirus DNA and oral squamous cell carcinomas (OSCCs)) yielded results that a small percentage of FOSCCs had loss of p16 immunoreactivity and a small percentage of FOSCCs had an increase in p16 immunoreactivity; this contrasts against what is observed in human non-PV-induced OSCCs, suggesting alternative

underlying molecular mechanisms [58]. In HPV-associated HNSCC, the E7 oncogene inactivates pRb, which leads to upregulation of CDKN2A [59].

p53 dysregulations were found in FOSCC, with mutated TP53 in exons 5–8 in FOSCC as opposed to wild type TP53 found in non-FOSCC cells. According to this study, TP53 mutations and aberrant p53 expression were not associated with exposure to environmental secondhand tobacco smoke, though different observations were found in previous studies [60, 61]. Another study found TP53 mutations in 68% of FOSCC in contrast to 3% in normal cells, and DNA methylation was found in genes FLI1, MiR124-1, MAGEC2, and KIF1A [62]. A prior study found a one base-pair deletion in codon 97 leading to a predicted premature stop codon 103 in exon 4 of TP53 in a SCC [63].

Splicing has also been studied in FOSCC. Full-length and Del-e10 variants of fTERT were observed alongside increased telomerase activity in FOSCC cell lines and tumors, warranting further study on whether this relationship is causal [64].

A study evaluating the protein expression of COX-1 and COX-2 found that they were overexpressed in FOSCC, which may play roles in tumorigenesis, as both COX enzymes produce prostaglandins associated with inflammation [65]. Another study on COX-1 expression in FOSCC hypothesized that the distribution of COX-1 in tumor cells may be a prognostic indicator, as diffuse distribution in immunohistochemical (IHC) staining of COX-1 seemed to increase hazard. The same study found that NSAID therapy administration after FOSCC diagnosis seemed to reduce hazard [66]. In humans, the COX-2 enzyme seems to play a more significant role than COX-1, which generates prostanoids primarily promoting housekeeping functions, in prostanoid formation for inflammation and tumor formation [67].

In HNSCC, EGFR, a receptor tyrosine kinase, has been implicated in tumorigenesis through its activation of downstream pathways, and high EGFR expression has been found in FOSCC as well, though its correlation to prognosis is unclear [7]. One study found that there was a negative correlation between EGFR expression and survival time, similar to the case in HNSCC [68]. Further studies on EGFR expression and pathways are needed to determine the role of EGFR in FOSCC. Antigen KI-67 proliferation index (high KI-67 expression) has been shown in some cases to correlate with poor prognosis in FOSCC [7, 53]. A study on FOSCC for cats, who underwent stereotactic radiotherapy, observed BMI-1 as a negative prognostic indicator, with tumor cells with high telomerase activity correlating to higher BMI-1, EGFR, and KI-67 levels. The study indicates combination therapy with stereotactic radiotherapy and inhibition of these molecules could be evaluated in the future [69].

Another study found strong expression of BCL11B in FOSCC, concurrently analyzing expression of EGFR, the VEGF family, and the effect of dasatinib on FOSCC. The study found that all the samples of FOSCC expressed VEGF-D, and a majority of samples variably expressed EGFR. The study analyzed the SRC pathway, hypothesizing that the inhibition of the SRC pathway leads to the hyperphosphorylation of EGFR as a compensatory mechanism. Dasatinib was found to decrease BCL11B phosphorylation and VEGF formation, reducing angiogenesis, while EGF stimulation promoted EGFR, ERK, and BCL11B phosphorylation as well as VEGF production. Because of the crosstalk occurring between these molecules and their contribution to resistance to inhibition, Harris articulates that a combined therapy approach may be more suitable [70]. In cases of HNSCC, studies have shown c-SRC and EGFR inhibition have had some success [71].

Protein kinase CK2 downregulation via RNA interference allowed for apoptosis and lowered cell viability in one FOSCC cell line, and further studies may be done to evaluate CK2 as a potential

therapeutic target for FOSCC [72]. Past analyses have suggested that CK2, an important molecule in cell viability, hinders apoptosis through protecting proteins from caspase degradation, indicating its downregulation would allow for apoptosis, a process necessary for regulation of tumor growth [73].

4. Sarcoma

Feline sarcoma are mesenchymal in origin and can be classified as injection-site associated (feline injection-site sarcoma, FISS) or as spontaneous. Injection sites leading to development of feline sarcoma may be vaccine related (vaccines commonly for rabies or for FeLV), termed vaccine-associated sarcoma (VAS), but they may also arise from other injections of antibiotics, corticoids, microchips, and non-absorbable suture. The sarcoma may be of various types, most commonly fibrosarcoma, but liposarcoma, rhabdomyosarcoma, and myxosarcoma, among others, have also been diagnosed [74]. The etiopathogenesis of FISS is unclear, but the inflammation following the injection may play a role in tumorigenesis, serving as a potential model for inflammation leading to tumor development in humans [1].

TP53 expression has been examined in 40 FISS using IHC staining, with 17/40 sarcomas having darkly stained nuclei, 8/40 having palely stained nuclei, and 15/40 having unstained nuclei. IHC staining has been correlated with mutations in the TP53 gene, though mutations were not examined in this particular study [75].

Upregulation of 53 genes (including those involved with the immune system, ECM, cellular proliferation, gene regulation, signaling, among others) and downregulation of 38 genes (including those involved with membrane transport and metabolism, among others) in FISS cell lines were found in a 2019 study. The study involved comparing gene expression of soft-tissue sarcomas in cats, dogs, and humans, and multiple common genes amongst the three species were identified. In the study, researchers articulate three upregulated genes in particular, including fibroblast activation protein alpha (FAP-alpha), a cell surface serine protease, Wilms tumor 1 (WT1), a tumor suppressor and transcription factor, and preferentially expressed antigen in melanoma (PRAME), as well as downregulated tumor suppressors TP63, EPHA1, and DUSP26. In the study, GSK-1059615, an inhibitor of PI3K and mTOR in humans, was found to lower FISS cell growth, indicating PI3K and mTOR pathways could potentially be considered in new therapies [12].

FISS is often more aggressive than spontaneous sarcoma (non-injection site associated), with a high recurrence rate, being locally invasive and potentially metastatic. As such, FISS requires a multimodal treatment and is often treated through radical surgical excision, as well as radiotherapy and chemotherapy [74]. Several drugs have been studied using sarcoma cell lines as possible treatments to the cancer. Metformin was found to induce apoptosis in an FISS cell line, though the mechanism was not through mTOR inhibition (the drug was thought to inhibit proliferation via upregulation of AMPK or inhibition of mTOR) [76]. In another study, strong nuclear expression of NF-κB p65 (subunit of NF-κB complex that manages transcription, cytokines, and other processes) was found in FISS; DHMEQ inhibited cellular proliferation and growth and promoted apoptosis, suggesting DHMEQ as a potential treatment to consider for inhibition of the NF-κB p65 target in FISS [77].

Studies on spontaneous feline sarcoma demonstrated genetic alterations, including chromosome number instability (with monosomies to heptasomies, and polyploidy), as well as centrosome hyperamplification [78]. Proto-oncogene loci have been mapped to some of these

chromosomes, such as N-RAS to C1 [18]. In 2012, a spontaneous feline fibrosarcoma cell line, Cocca-6A, was established, and the study found a deletion of an E1 chromosome, the chromosome to which feline tumor suppressor TP53 maps; the study found reduction in TP53 expression when compared to FSkMC cells [79].

The tables below display genetic aberrations in feline sarcoma. Table 2 shows the chromosomal alterations in feline sarcoma, while Table 3 displays specific mutations.

Table 2 Chromosomal alterations in feline sarcoma (unspecified whether spontaneous or ISS).

Sarcoma	Chromosomal Alteration	Notes	Reference
Fibrosarcoma	t(A1q;B4p)	female, 4 years	[15]
Fibrosarcoma	t(A2q;E3q)	female, 6 years	[15]
Fibrosarcoma	B2 (q-arm) deletion	male, 14 years	[15]
Fibrosarcoma	F1 large marker	male, 12 years, 13 years	[14, 15]
Fibrosarcoma	D1 trisomy (in 20% of tumor cells)	female, 11 years	[14]
Sarcoma	hyperdiploidy (40-46) extra chromosomes C1, C2, B4, D4, E3 monosomy in A1, F2, E3	male, 8 years	[18]
Subcutaneous fibrosarcoma	near triploidy (69.2% of cells with 51--64 chromosomes) (from monosomies to heptasomies) multiple copies of C2, E2, E3 single copies of A1, B1, C1	male, 7 years	[13]
Fibrous histiocytoma	38,XY,t(E1q:B2q) 38,XY,t(E1p;C2q) deleted short arm of D1	male, 8 years	[16]
Fibrous histiocytoma	38,XY,t(E1p;derB3) E1, C2 chromosome fusion A3 homologues chromosome fusion D3 trisomy	male, 9 years	[16]
Fibrosarcoma	38,XY,t(E1p;A1p)	male, 8 years	[16]

Table 3 Genetic mutations in feline sarcoma (unspecified whether spontaneous or ISS).

Type	Gene	Exon	Position	Aberration	Reference
Fibrosarcoma	TP53	5	146	G>A (TGG → TGA) p. W to Stop	[63]

Fibrosarcoma	TP53	7	244	G>T (GGG → GTG) p. G to V	[63]
Malignant fibrous histiocytoma	TP53	7	249	G>A (AGG → AAG) p. R to K	[63]
Osteosarcoma	TP53	8	273	G>A (CGA → CAA) p. R to Q	[17]
Fibrosarcoma	TP53	8	282	C>G (CGG → GGG) p. R to G	[63]
Non-lymphoid fibrosarcoma	CDKN2A	1	c.23	C>A p. A to E	[50]

Several treatments have been explored in spontaneous feline fibrosarcoma. Zimmermann and colleagues treated advanced feline soft-tissue sarcoma using doxorubicin-loaded phosphatidyldiglycerol-based thermosensitive liposomes (DPPG2-TSL-DOX) in combination with local hyperthermia; this treatment proved promising, warranting further study in regards to drug efficacy and potential side effects [80]. The use of local hyperthermia in addition to chemotherapy in humans has proved more effective in terms of survival rates than chemotherapy by itself [81], potentially due to modulation of immune regulation and synergistic effects between hyperthermia and chemotherapeutic drugs, where hyperthermia increases their cytotoxicity [82]. Hyperthermia may induce cell death pathways of apoptosis and necrosis, and increase sensitization to both chemotherapy and radiotherapy [83].

Interleukins, a group of cytokines involved in regulating the immune response, have been investigated in spontaneous feline sarcomas. Recombinant poxviruses expressing IL-2 (ALVAC expressing feline IL-2, NYVAC expressing human IL-2) have been studied in spontaneous feline fibrosarcomas as a potential immunotherapy. Tumor recurrence rates were 61% for a treatment combining surgery and radiotherapy, while those with ALVAC and NYVAC treatments had much lower recurrence rates, at 39% and 28% respectively [84]. Hyperthermia-induced gene immunotherapy with adenoviral feline IL-12 has been studied in spontaneous feline fibrosarcoma: intratumoral expression of the gene with limited systemic toxicity was achieved [85]. Enrichment of genes associated with IL-2 and IL-12 was also found in FISS cell lines [12].

Electrochemotherapy uses electric pulses to temporarily increase cell permeability and allow chemotherapeutic drugs (such as bleomycin) to reach the interior of the cell. A clinical trial of twelve cats with sarcoma demonstrated longer survival times for those treated with electrochemotherapy (6.1 months) when compared to the control (0.8 months) [86]. Another study compared recurrence times for spontaneous feline sarcoma treated with surgery or with surgery and adjuvant electrochemotherapy found that tumors treated using the combination of surgery and electrochemotherapy (both intraoperative and postoperative) had a larger time of recurrence: spontaneous feline sarcoma treated with only surgery had a 4 month recurrence time, while the intraoperative group had a 12 month recurrence time, and the postoperative group had a 19 month recurrence time [87]. While the 2006 study used bleomycin, a 2011 study using cisplatin had similar results with minimal toxicities, increasing local control of the sarcoma [88]. More recently, electrochemotherapy with bleomycin and cisplatin as an adjuvant therapy has also been shown to improve control of sarcoma in canines [89].

5. Mammary Tumors

Feline mammary cancers are most often seen as tubular, papillary, or solid adenocarcinoma, though there have been anaplastic and scirrhous carcinoma observed as well [90]. Feline mammary cancers (and carcinomas in particular) have been studied as models of different classifications of human breast cancer.

Feline mammary carcinoma (FMC) is an aggressive form of cancer with rapid growth and metastasis to regional lymph nodes and lungs in some cases, a proposed model of hormone-independent human breast carcinomas. A 2005 study found overexpression of the feline HER2 orthologue and a 92% similarity between feline HER2 and HER2 exons 17 and 23 in humans [19]. While in human breast cancers, HER2 gene amplification is common, the increased mRNA expression in feline HER2 was found not associated with gene amplification, but led to higher protein expression, suggesting a mechanism for HER2 regulation in felines distinct from that in humans [19]. Similar results were observed in the study of Soares and colleagues, where feline HER2 was overexpressed in 33% of FMC without gene amplification [91]. Another study suggested FMC as a model of human breast carcinoma with HER2 protein expression without gene amplification, finding only 16% having HER2 gene amplification [92]. However, a more recent study found a significant positive correlation between HER2 gene amplification and protein expression [93]. Mechanisms of HER2 expression regulation are unclear with regards to gene amplification, warranting further study, potentially with higher specificity of carcinoma type, as multiple mechanisms may be involved.

In humans, TOP2α aberrations have been found in HER2-amplified cancers. TOP2α has been proposed as a potential biomarker due to its promising value as a predictor for response to anthracycline-based chemotherapy [94, 95]. TOP2α is a nuclear enzyme involved in DNA transcription and replication, among other cell cycle processes. Ferreira and colleagues' study found HER2 and TOP2α were both overexpressed in a majority of feline mammary tumors, and that their expression levels were highly correlated. In their study, authors concluded that the co-amplification of the two genes was not relevant to their overexpression, and that there were likely other regulatory, transcriptional and post-transcriptional, mechanisms at play [96]. However, Soares and colleagues' study discovered that TOP2α gene amplification was not found in FMC HER2-positive samples [91].

Feline mammary adenocarcinoma (FMA) have been observed as a model for human triple-negative breast cancer (TNBC), a type of breast cancer negative for estrogen receptor (ER), progesterone receptor (PR), and epidermal growth factor receptor 2 (HER2). Although in humans, TNBC with basal-like morphology is associated with genetic abnormalities in the BRCA genes, a study found that FMAs (14 of 24 triple-negative and 11 of the 14 basal-like subtype) did not have these genetic abnormalities [20]. Even though such genetic abnormalities were not found in the BRCA genes specifically, the use of FMAs as a model for human TNBC could prove useful due to similar morphology and triple-negative phenotype.

In one study, expression of COX-2 in varying degrees from low to high under IHC analysis was found in a majority (35/40) of feline mammary carcinomas. The feline COX-2 gene and amino acid sequence were found similar to COX-2 homologs in other mammalian species and identical in length [97]. Studying conserved genes could contribute to advances in comparative oncology.

The cadherins are a group of transmembrane proteins involved in Ca^{2+} dependent cellular adhesion. Epithelial cadherin (E-cadherin) is a tumor suppressor gene involved in the E-cadherin/β-catenin complex, which stabilizes cellular contact, regulates epithelial to mesenchymal transition (EMT) and mesenchymal to epithelial transition (MET), and participates in the Wnt signaling pathway [98]. E-cadherin aberrations have been reported in feline mammary carcinoma, with one study observing loss or reduced expression of E-cadherin in 11/14 carcinomas [99]. Another study found preservation of E-cadherin and β-catenin was significantly higher in grade 1 tumors, while metastasizing tumors had the greatest reduction in E-cadherin [100].

In addition to sequence and expression similarities demonstrating high evolutionary conservation, exon-splicing mRNA variants have been observed in both human and feline ER-α. While the study proposed feline ER-α as a model for human ER-α over murine models (though expression of ER-α in felines was lower than in normal tissues in contrast to higher expression in humans), it concluded that alternative splicing of ER mRNA was not involved in feline mammary cancer development, suggesting further analysis on wild-type ER [101].

A study found lower expression of TWIST1 mRNA, a transcription factor and oncogene, in FMC compared to benign mammary tumors. The germline mutation c.309C>G found in humans was not identified in feline TWIST1. Sequence alterations in the introns were germline and not associated with mRNA levels [102]. In contrast to FMC, in human cancers, TWIST1 expression has been implicated in carcinogenesis, metastasis, and EMT, with studies demonstrating repression and silencing of E-cadherin (via TWIST1 recruitment of the NuRD complex), ERα (via TWIST1 recruitment of the NuRD complex or DNMT3B), and FOXA1 (a transcription factor), as well as upregulation of AKT2 (an oncogene), BMI1 (an oncogene), Wnt5a (member of Wnt pathway), PDGFRα (cell surface tyrosine kinase receptor for PDGF family), and JAG1 (ligand for Notch receptors) [103]. However, another study concerning repression of E-cadherin demonstrated that TWIST1 downregulation was associated with the triple-negative phenotype (p = 0.022) and correlated to poorer prognosis in humans. No statistically significant correlation between TWIST1 expression (along with ZEB1 and SNAIL) and E-cadherin inhibition was found [104]. Further studies are thus needed to determine the mechanistic pathways behind FMC with aberrant TWIST1 expression and their relation to E-cadherin expression.

In humans, STAT3 promotes cellular proliferation and survival, being involved with anti-apoptotic proteins, as well as chemoresistance and immunosuppression. STAT3 dysregulation may promote oncogenesis, as it regulates downstream targets involved in cellular proliferation, angiogenesis, and EMT, ultimately enabling tumor progression and metastasis [105]. The IL-6/JAK/STAT3 pathway in the past has been shown to upregulate Cyclin D1, BCL-2, c-MYC, and BAX to inhibit apoptosis in human breast cancer [106]. Nuclear positivity of STAT3 in feline malignant mammary lesions was found, as well as correlation between STAT3, histologic grade, and mitotic count [107]. However, in another study of feline mammary lesions, nuclear staining of Cyclin D1 was not observed [108]. Nuclear staining of Cyclin A was present in 41.9% (18/43) of feline mammary lesions, with moderate to intense speckled nuclear staining in 48.6% (18/37) of feline mammary carcinomas, in contrast to the weak or no staining in the epithelium of benign tumors/ordinary tissue. p53 nuclear staining was found in 16.3% (7/43) of mammary lesions, all belonging to the 18.9% (7/37) of mammary carcinomas, and weak or no staining was found in benign tumors/ordinary tissue as well [108]. In human breast cancers, deregulation of Cyclin E has led to p53 dysfunction/loss of the tumor suppressor gene [109]. This could suggest multiple mechanisms for tumorigenesis in feline

mammary glands; expression of the cyclins may be further investigated to elucidate their role in feline mammary tumors (and in the context of known signaling pathways).

A study found the f-STK gene, a gene homologous to the overexpressed RON gene (part of the MET family of tyrosine kinases) in human breast cancers, was consistently expressed in feline mammary cancers [90]. In FMC, p-AKT activation and HER2 expression were found to have a positive association (though in FNNm and FMCp cell lines, HER2 likely does not regulate AKT activation), while p-AKT and PTEN were found to have a negative association, with 89% of FMCs in the study (comparative to a 76% in a previous study [110]) having loss of PTEN expression [111]. Loss of PTEN expression is significantly correlated to lymphatic vessel invasion in FMC [110]. Therapies targeting and inhibiting the PI3K/AKT/PTEN pathway may prove useful in treating FMC, and investigating the underlying mechanisms behind PTEN loss may lead to development of new therapies. In human breast cancer, miRNAs have been investigated as part of the mechanism in suppressing tumor suppressor PTEN [112].

A study analyzing mutations in feline mammary tumors found overall upregulation of TP53 and HSPB1, which plays a role in cell differentiation, cellular regulation, and apoptosis [113]. Table 4 below displays cases of genetic changes in different types of feline mammary tumors.

Table 4 Genetic alterations in feline mammary tumors.

Type	Gene	Exon	Position	Aberration	Reference
Unspecified	TP53	7	c.859	G>T	[113]
Adenocarcinoma	TP53	5	158	C>T (CGC → TGC) p. R to C	[63]
Adenocarcinoma	TP53	7	254-256	9 bp deletion: ATC.ATC.ACC	[63]
Solid carcinoma	TP53	8	282	C>T (CGG → TGG) p. R to W	[114]
Unspecified	ERBB2	11	g.229	T>A p. V47E	[115]
Unspecified	ERBB2	15	g.2041	A>C p. H206P	[115]
Unspecified	ERBB2	15	g.2065	T>C p. V214A	[115]
Unspecified	HSPB1	1	c.34	C>C/A	[113]
Unspecified	HSPB1	Intron 1	1326	T>T/C	[113]
Unspecified	HSPB1	Intron 2	1490	C>C/G	[113]
Unspecified	HSPB1	Intron 2	1514-1517	GTCT Deletion	[113]
Unspecified	HSPB1	3	c.773	A>A/T	[113]
Carcinoma	TWIST 1	Intron	g.535 (GQ167299)	G deletion	[102]
Carcinoma	TWIST 1	Intron	g.460 (GQ167299)	C>T	[102]

6. Mast Cell Tumors

Feline mast cell tumors (MCTs) are common neoplasia in cats, often classified by location: cutaneous, splenic, and intestinal [22]. Feline cutaneous MCTs are one of the most common types of cutaneous tumors [116], and feline splenic MCTs constitute around 15-26% of splenic diseases in cats [23]. In contrast to canine MCTs, feline MCTs are less well understood, with prognostic markers generally having weaker association with survival [117].

Feline splenic MCTs generally occur in older cats with mean age of 9 to 13 years. Anemia is common in feline splenic MCTs, occurring in around 14–70% of these cats [22]. Another study reported anemia in one third of cats with splenic MCTs [23]. While anemia, anorexia, mastocytemia, and liver metastases among other conditions have been considered negative prognostic factors of feline splenic MCTs for splenectomy, Evans and colleagues' study found that these were not statistically significant, and that splenectomy may still yield good prognosis for such cats: among the recorded conditions of anemia, mastocytemia, liver metastases, cutaneous masses, weight loss, anorexia, age, weight, and splenectomy, only splenectomy yielded a statistically significant (p = 0.008) difference in median survival time, with splenectomy having a median survival of 856 days, while no splenectomy with median survival of 342 days [22]. Other studies report that splenectomy as the treatment for MCTs may allow for survival of up to 38 months [118]. Kraus and colleagues had shown that blood transfusions ($p < 0.0001$) and lymph node metastases (p = 0.022) were statistically significant negative prognostic factors, but liver metastasis correlated with improved survival time (p = 0.0004). There was a statistically significant correlation between positive response to post-operative chemotherapy and survival time (p = 0.0008), though there was no statistically significant association found between administration of chemotherapy and survival time [119].

Feline splenic MCTs are commonly treated with a splenectomy, and though adjuvant chemotherapy has been used, it has not been found to increase survival time and has unestablished effects [22, 23]. However, another study found tyrosine kinase inhibitors (including imatinib, dasatinib, midostaurin, and nilotinib) to inhibit MCT growth, where tumors had KIT (proto-oncogene and receptor tyrosine kinase) mutations [120]. Tyrosine kinase inhibitors have in the past been used to treat human cancers.

c-KIT mutations are commonly found in feline MCTs, occurring mainly in exons 8–11 (see Table 5). Sabattini and colleagues studied feline splenic MCT and elucidated mutations in exons 8–9, which constitute the IgD5 domain of the KIT receptor. However, the study demonstrated no significant correlation between mutations and survival time, mitotic activity, or degree of differentiation, though poor cell differentiation (based on morphologic appearance) generally indicated higher mitotic activity, consistent with prior studies in cutaneous and intestinal MCTs [23]. The relationship between mutations in the c-KIT gene and tumorigenesis for mast cells appears to remain unclear. Another study on feline splenic MCTs found no mutations in the juxtamembrane and catalytic domains and suggests targeting KIT may not be the best course of treatment [121]. A study found that some cats with multiple nodules of mast cell tumors had different c-KIT mutations across the different tumors [122].

While extensive grading systems have been put into place on canine MCTs, no such grading system has yet been widely implemented for feline cutaneous MCTs [123]. In humans, mastocytosis is commonly divided into cutaneous mastocytosis and systemic mastocytosis [124]. The Patnaik and Kiupel grading systems used to classify canine cutaneous MCTs are not used for feline MCTs, as they

are poor predictors of malignancy [125]. Feline MCTs have been generally grouped into mastocytic (including both well-differentiated and pleomorphic subtypes) and histiocytic (atypical) types, and may be benign or malignant [123]. While most cutaneous MCTs are clinically benign, Sabattini and colleagues' study considered an aggressive subgroup of cutaneous MCTs that were metastatic and had visceral involvement [126]. A study on 15 feline cats with pleomorphic feline cutaneous MCTs found that a majority of the cats were behaviorally benign, but that one cat had a behaviorally aggressive tumor; mitotic rate was identified as a potential prognostic indicator [127]. However, another study determined pleomorphic MCTs were more aggressive than well-differentiated and atypical MCTs [123]. In 2018, Sabattini and Bettini proposed a grading system for feline cutaneous MCTs, whereby they were split into two groups depending on disease condition post-surgery and further classified into high or low grade, with high-grade tumors significantly correlated to shorter survival times [126].

Immunohistochemistry analyses for KIT were done on cutaneous MCTs. Atypical, pleomorphic, and well-differentiated MCTs all had diffuse cytoplasmic KIT staining, with well-differentiated MCTs also including membranous KIT stain. However, no association was found between MCT type and KIT staining [128]. Another study on feline cutaneous MCTs found significant correlation between cytoplasmic KIT labeling and survival (p = 0.045), where cytoplasmic labeling was associated with increased risk of death, and cytoplasmic KIT and mitotic activity (p = 0.01), where cytoplasmic expression was associated with increased mitotic activity. However, no significant correlation was found between KIT protein expression and mutations [122]. A prior study demonstrated that pleomorphic cutaneous MCTs (in contrast to well-differentiated and atypical cutaneous MCTs) had higher mitotic and KI-67 indices, leading to poorer outcome. This study also found TERT expression in 68% of the cutaneous MCTs, suggesting further study concerning telomerase activity in MCTs [123].

Stem cell factor (SCF), a cytokine binding to c-KIT, was investigated in feline cutaneous MCTs: SCF-positive cells were found in marginal regions of the tumor, near KIT-positive cells (with some cells being both SCF- and KIT-positive), but away from KI-67-positive cells; the study suggests that SCF signaling mechanisms may contribute to cutaneous MCT expansion, as SCF-positive cells may have migrated to the marginal regions, but no clear relationship was defined between SCF expression and proliferation [129].

The table below shows mutations found in the c-KIT gene in feline mast cell tumors.

Table 5 Mutations in the c-KIT gene for mast cell tumors.

Type	Exon	Position	Aberration	Reference
Mast cell	6	c.957_966	delinsT deletion: G.ATG.AAT.ACC	[116]
Cutaneous mast cell	8	c.1243	G>A, p. E415K	[122]
Mast cell	8	c.1244_1255	Duplication AA.ATC.CTG.ACT.C	[116]
Splenic mast cell	8	c.1245_1256	Duplication A.ATC.CTG.ACT.CA,	[23]
Splenic mast cell	8	c.1246_1257	Duplication ATC.CTG.ACT.CAT	[23]
Splenic mast cell	8	c.1247_1261	Duplication TC.CTG.ACT.CAT.GAA.A	[23]

Splenic mast cell	8	c.1254_1263	T.CAT.GAA.AGT deletion G.TAA insertion	[23]
Cutaneous mast cell	8	c.1256_1263	delinsTG premature stop codon	[122]
Mast cell	8	c.1256_1264	delinsTCA deletion: AT.GAA.AGT.C	[116]
Mast cell	8	c.1256_1262	delinsT deletion: AT.GAA.AG	[116]
Splenic mast cell	9	c.1426	C>A p. Q476K	[23]
Splenic mast cell	9	c.1430	G>T p. S477I	[122, 130]
Cutaneous mast cell	9	c.1471	del21 premature stop codon	[122]
Mast cell	9	c.1517_1518	delinsTT deletion: AC p. N506I	[116]
Cutaneous mast cell	9	c.1487	G>A p. R493K	[122]
Mast cell	11	c.1661_1663	delinsGC.AAG.TGC.ACC.C deletion: ATG	[116]
Cutaneous mast cell	11	c.1663	G>A p. E555K	[122]
Cutaneous mast cell	11	c.1687	G>A p. E563K	[122]

7. Conclusion

In the present paper, the molecular mechanisms behind feline lymphoma, squamous cell carcinoma, sarcoma, mammary tumors, and mast cell tumors are described.

Feline lymphoma have been associated with FeLV and FIV infections in the past. Chromosomal translocations have been found in FeLV lymphoma lines. Although FeLV infections have decreased, feline gastrointestinal lymphoma rates have increased. Increased expression has been found in MDR1 and COX-2, while reduced expression has been found in CDKN1B. p53–MDM2 interactions have been observed in multiple studies, though alternate mechanisms involving p53 or excluding p53 entirely may be involved in centrosome amplification and chromosomal instability.

FOSCC has been proposed as a model for HNSCC, though varying gene expression and association with papillomavirus may suggest alternative molecular mechanisms. p53 dysregulations and overexpression of COX-1 and COX-2 were observed in FOSCC. The relationship between EGFR and prognosis remains unclear, warranting further study. Combined therapy and multimodal treatments may be adopted to better treat FOSCC.

Feline sarcoma has been classified as injection-site associated or spontaneous. Aberrant gene expression was found in FISS cell lines; researchers identified upregulated genes including FAP, WT1, and PRAME, and downregulated genes including TP63, EPHA1, and DUSP26, among many others. Genetic alterations have been identified in feline sarcoma, including chromosomal translocations and number instability, as well as mutations in TP53 and CDKN2A. A number of treatments have been explored for feline sarcoma, including chemotherapy and electrochemotherapy. Multimodal treatment is often used for FISS, the more aggressive of the two.

Feline mammary tumors have been proposed as models for human breast cancer, with FMA considered as a model for TNBC due to morphology and triple-negative phenotype. Mechanisms of HER2 expression regulation and gene amplification remain unclear. Aberrant E-cadherin expression has been reported, as well as lowered expression of TWIST1 mRNA. Multiple mechanisms may be

responsible for tumorigenesis in feline mammary glands, and cyclins may be further investigated in this context. Numerous genetic mutations have been found in TP53, ERBB2, HSPB1, and TWIST1.

Feline mast cell tumors are commonly treated with a splenectomy and adjuvant chemotherapy. c-KIT mutations are common in MCTs, though the relationship between mutations in the gene and tumorigenesis warrants further study.

As the field of medicine rapidly progresses with both a greater understanding of health and the development of new technologies in the modern world, therapies for a multitude of diseases may be created or improved, whether for acute or chronic health conditions. Better treatments may be developed to specifically target desired molecular markers and other underlying causes of cancer across all species, and comparative genomics may be used to build upon each of these new developments. The present study seeks to illuminate molecular mechanisms behind feline cancers, specifically lymphoma, squamous cell carcinoma, sarcoma, mammary tumors, and mast cell tumors. With a greater understanding of feline cancers, therapies for human cancers may improve through the use of comparative genomics.

Author Contributions

VK suggested the project topic, participated in discussions regarding several parts of the article, and edited the article. IT suggested the general article structure, format, and specific topics addressed, and participated in discussions regarding several parts of the article. JL conducted selection of sources of scientific information, analysed them, and wrote the article.

Competing Interests

The authors have declared that no competing interests exist.

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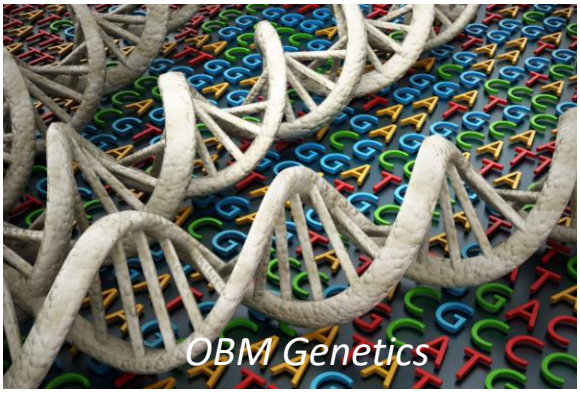

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