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Review

Viral causes of feline lymphoma: Retroviruses and beyond

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ABSTRACT

The most widely recognised cause of feline lymphoma is the gammaretrovirus feline leukaemia virus (FeLV). Research into the mechanisms of cellular transformation employed by FeLV and other oncogenic retroviruses has provided as much information on the regulation of eukaryotic cell growth and differentiation as it has about cancer. The recognition that a cancer has a viral cause opens up the possibility of novel treatments that spare the host from cytotoxic side-effects by specifically targeting the virus, or the host's immune response to it. The ultimate prize for viral-associated cancers is their prevention. Vaccination and changes in management practices have seen the global prevalence of FeLV infection fall and, with it, the incidence of FeLV-related cancers. Remarkably, in the face of this success, the prevalence of feline lymphoma remains high. At least one other virus, the lentivirus feline immunodeficiency virus (FIV), accounts for some of these cases. Transformation by FIV involves incompletely understood mechanisms that are distinct from those employed by FeLV. This review will focus on the current understanding of FeLV-associated and FIV-associated lymphoma and consider whether yet more viral aetiologies could be waiting to be discovered.

Introduction

It is estimated that 20% of human cancers are caused by infectious agents, with over half of these resulting from viral infections (Parkin, 2006). The viruses involved in naturally occurring tumours of humans and animals can be broadly divided into those with DNA genomes, including herpesviruses, papillomaviruses and orthohepadnaviruses, and the RNA tumour viruses found among the retroviruses (Bouvard et al., 2009). To date, cancer-causing viruses in feline patients have been found in the retrovirus and papillomavirus families (Munday et al., 2013).

Cancer results when the normal processes controlling cell growth and proliferation are disrupted. There are many points at which the delicate balance between the initiation and curtailment of cell cycling can be subverted and viruses contribute to cellular transformation through diverse mechanisms. Most involve the products of viral genes. Retroviruses like feline leukaemia virus (FeLV) and feline immunodeficiency virus (FIV) are unusual in this respect in that they have a very simple structure, containing only the genes required for replication.

The recognition that a viral infection represents a risk factor for a particular cancer carries important implications for disease control. Perhaps the most exciting prospect is cancer prevention by screening, education and vaccination to reduce the population at risk. The human papillomavirus (HPV) vaccine program provides a good example of this. Cervical cancer is the second most common cancer of women, resulting in over 300,000 deaths/year worldwide (Thun et al., 2010). Although a measurable impact of HPV vaccine on cervical cancer incidence will not be available for several years, the 5-year outcomes of reduced prevalence of both HPV and genital warts predict a significant reduction in cervical cancer case numbers (Tabrizi et al., 2012; Ali et al., 2013).

Lymphoma (lymphoma/leukaemia) is the most common malignancy of domestic cats and FeLV is its most widely recognised cause (Dorn et al., 1968; Priester and Mantel, 1971). Control of FeLV has been very successful. Changes in management practices involving identification and isolation of progressively infected cats were followed by the development, then refinement, of effective vaccines against FeLV (Hardy et al., 1976b; Weijer et al., 1986; Hoover and Mullins, 1991; Hoover et al., 1991; Poulet et al., 2003). As a result, the global prevalence of FeLV infection has fallen and, with it, the population at risk from FeLV-associated lymphoma (Levy et al., 2006b; Gleich and Hartmann, 2009; Gleich et al., 2009). In the 1970s, 70% of feline lymphoma cases in the USA were attributed to FeLV, compared with <15% in the 20-year period prior to 2003 (Cotter et al., 1975; Louwerens et al., 2005). A similar drop in prevalence, from 59% to 13% between two consecutive 15-year periods up to 2009, was reported in Germany (Meichner et al., 2012). Interestingly, a negative impact on the incidence of feline lymphoma per se is not apparent. In fact, while the relative proportions of the various anatomic subtypes have shifted, the incidence of lymphoma cases could even be increasing (Louwerens et al., 2005).

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This review provides an overview of the roles of FeLV and FIV in lymphomagenesis and considers the possibility that novel infectious agents might play an aetiological role in some cases of feline lymphoma.

Feline leukaemia virus

Since it increases the risk of lymphoma 60-fold in an infected cat, FeLV is by far the most important feline tumour virus known (Shelton et al., 1990; Rezanka et al., 1992). At a time when the concept of virally-induced cancers was starting to be established following descriptions of Rous sarcoma virus in chickens (Rous, 1911), clinical observation of cancer clusters in multicat households fuelled the search for a similar aetiology in cats (Schneide et al., 1967). In 1964, a team led by Professor William Jarrett at the University of Glasgow isolated FeLV from one such household (Jarrett et al., 1964).

FeLV is a gammaretrovirus that infects domestic cats and other Felidae across the globe (Hoover and Mullins, 1991). The virus is transmitted vertically and horizontally. In infected households, there is rapid oronasal spread from contact with virus-containing secretions, principally saliva (Hardy et al., 1976a). Screening tests for infection rely on serological detection of viral antigen, the 27 kDa viral core protein, p27, that is readily detected on point of care tests. Following exposure, cats initially test antigen positive, but a stable outcome, influenced by the age and immune status of the host, as well as the infecting dose of virus, is reached within a few weeks.

Around a third of exposed cats develop progressive infections characterised by persistent antigenaemia (Hardy et al., 1977). Progressively infected cats have high proviral loads, excrete virus in saliva, thereby spreading infection, and succumb to FeLV-related diseases. In the remaining exposed cats, antigenaemia is transient, but residual viral sequences can be detected by quantitative PCR (qPCR) even in cats that develop neutralising antibodies. These cats have regressive infection, where integrated provirus (DNA) and, sometimes also viral RNA, can be detected by qPCR, but at lower levels and with restricted tropism compared with progressively infected cats (Hofmann-Lehmann et al., 2001; Torres et al., 2005; Pepin et al., 2007; Cattori et al., 2008).

The prevalence of regressive infection in the field ranges from <1% to 10 % and generally mirrors the prevalence of progressive infection in the population (Hofmann-Lehmann et al., 2001; Pinches et al., 2007; Beatty et al., 2011; Englert et al., 2012). Regressively infected cats pose minimal risk to other cats, although disease outcomes are still under investigation, as discussed below (Gomes-Keller et al., 2006). Loss of immunological containment of regressive infection has been documented, but seems to be rare (Helfer-Hungerbuehler et al., 2010). Abortive infection, only detectable by seroconversion, is apparently also rare and of no consequence to the cat or other cats in contact with it (Major et al., 2010).

Cats with progressive FeLV infection have a poor prognosis, with only 20–50% expected to survive for 3 years after diagnosis (McClelland et al., 1980; Levy et al., 2006a). FeLV is pancytotropic and results in degenerative or proliferative pathologies, with bone marrow and lymphoid organs being major targets. Clinically, infection manifests as a spectrum of disease including cytopenias, opportunistic infections, myeloproliferative disorders, immune-mediated diseases, enteritis and reproductive problems (Hardy, 1982; Hoover and Mullins, 1991). Although not implicit from the virus's name, haematopoietic malignancies are not the most common outcome; lymphoid malignancies occur in only 10–20% of progressive FeLV infections (Hardy et al., 1980; Reinacher, 1989; Shelton et al., 1990). FeLV-associated lymphomas are typically high-grade, of T-cell or null cell origin and affect young cats (Rojko et al., 1989; Rezanka et al., 1992). The strongest association is found with thymic, multicentric and spinal locations (Francis et al., 1979; Hardy, 1981b; Spodnick et al., 1992; Tsatsanis et al., 1994).

Progressive FeLV infection and lymphomagenesis

The lethal transformational capability of FeLV is mediated by a relatively simple structure. The single-stranded (ss)RNA genome bears three genes essential for the production of new virions, namely, *gag, pol* and *env* encoding the viral core proteins, enzymes and envelope glycoproteins, respectively. Infection of the host cell is initiated by recognition of the cellular receptor by the envelope glycoprotein spikes. The viral core is internalised and the two copies of the ssRNA genome are released. The viral RNA-dependent DNA polymerase, reverse transcriptase, makes a DNA copy of the viral genome, the provirus, which becomes integrated into the host genome, flanked by long terminal repeats (LTR). Within the U3 region of the LTR are promoter and enhancer sequences that control viral gene transcription. Provirus forms the template for the production of new virions.

FeLV describes a group of closely related viruses. Inherent in its life cycle are opportunities for the generation of genetic variants. The process of reverse transcription is error-prone, resulting in frequent mutation because the enzyme lacks a proof-reading function (Svarovskaia et al., 2003). Recombination can occur with host genomic sequences and with other FeLV sequences, including endogenous sequences. There are three major FeLV subgroups, A, B and C, which differ in their envelope sequence, receptor usage and cell tropism. Subgroup A is found in all isolates transmitted between cats, while B and C are generated from subgroup A viruses by recombination and mutation respectively. Subgroup C viruses cause fatal non-regenerative anaemia. They arise rarely and are not transmitted further. Subgroup B infection, which can be transmitted with subgroup A, has been associated with a poorer prognosis and a higher lymphoma risk than infection with subgroup A alone (Jarrett et al., 1978; Sheets et al., 1993). However, examination of tumour DNA has shown that variants within subgroup A are often associated with lymphoma (Rohn et al., 1994; Tsatsanis et al., 1994; Bolin and Levy, 2011). A fourth subgroup, FeLV-T, is associated with wasting and immunosuppressive disease (Donahue et al., 1991).

Key features of FeLV that influence cellular transformation are its LTRs, integration of provirus and its propensity to generate variants that increase its transformational potential. Each interplay between viral variants and cellular genes (principally proto-oncogenes) that confers a survival advantage to the cell is a step towards transformation. Proto-oncogenes encode a variety of products such as growth factors, growth factor receptors and protein kinases, whose inappropriate activation favours cell proliferation. The *myc* proto-oncogene, which is commonly dysregulated in FeLV-associated lymphomas (Tsatsanis et al., 1994), encodes a family of transcription factors (Dang, 1999). Proto-oncogene activation is a consequence of viral promoters gaining control of transcription, either because of their proximity in the case of insertional mutagenesis, or by transduction, where the virus acquires a copy of, for example, cellular *myc* (*c-myc*) during replication and transduces it as viral-*myc* (*v-myc*) into another cell where it is removed from its normal transcription unit. Conversely, examples of virally mediated loss of function of tumour suppressor genes are uncommon, because of the requirement for inactivation of both alleles.

FeLV variants transducing powerful oncogenes, including *fes, fms, fgr, abl* and *kit*, result in the rapid induction of polyclonal, multifocal, fibrosarcomas (Hardy, 1981a; Bonham et al., 1987). Referred to as feline sarcoma viruses (FeSFV), these viruses arise de novo in FeLV-infected cats but are rendered replication-incompetent by the replacement of a large part of their genome by a cellular oncogene. Such dramatic examples of oncogenesis are very rare in the field where transduction of an oncogene alone is rarely sufficient for transformation. Ten to fifteen percent of naturally occurring FeLV-associated lymphomas contain *myc*-transducing viruses, rising to 30% among thymic lymphomas (Rezanka et al., 1992). However, when