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Review

An update on feline infectious peritonitis: Virology and immunopathogenesis

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ABSTRACT

Feline infectious peritonitis (FIP) continues to be one of the most researched infectious diseases of cats. The relatively high mortality of FIP, especially for younger cats from catteries and shelters, should be reason enough to stimulate such intense interest. However, it is the complexity of the disease and the grudging manner in which it yields its secrets that most fascinate researchers. Feline leukemia virus infection was conquered in less than two decades and the mysteries of feline immunodeficiency virus were largely unraveled in several years. After a half century, FIP remains one of the last important infections of cats for which we have no single diagnostic test, no vaccine and no definitive explanations for how virus and host interact to cause disease. How can a ubiquitous and largely non-pathogenic enteric coronavirus transform into a highly lethal pathogen? What are the interactions between host and virus that determine both disease form (wet or dry) and outcome (death or resistance)? Why is it so difficult, and perhaps impossible, to develop a vaccine for FIP? What role do genetics play in disease susceptibility? This review will explore research conducted over the last 5 years that attempts to answer these and other questions. Although much has been learned about FIP in the last 5 years, the ultimate answers remain for yet more studies.

Introduction

Feline infectious peritonitis (FIP) continues to be a major killer of young cats and is one of the most researched infections of the species. Over 100 published articles concerning FIP have appeared in the world's literature since the last extensive review of the disease (Pedersen, 2009). Many of these and earlier publications have been covered in excellent clinical (Addie et al., 2009; Drechsler et al., 2011) and scientific (Myrrha et al., 2011; Kipar and Meli, 2014) reviews. The goal of the present review is not to retrace old tracks, but rather to present old and new discoveries on FIP in a different light.

FIP is a relatively new disease of cats and only became clinically significant in the late 1950s (Pedersen, 2009). It is uncertain where the first FIP virus (FIPV) came from, but one possibility is that feline coronaviruses originated within the century from another host species. Alternatively, it is possible that contemporary feline coronaviruses are genetic variants of a preexisting and somewhat different virus species that was less prone to undergo biotype conversion. Both scenarios are known to occur with coronaviruses. The intestinal form of coronavirus in pigs has been replaced worldwide by a much less pathogenic pneumotropic strain (Rasschaert et al., 1990), while several coronaviruses have entered human beings from other mammalian hosts (Chan et al., 2013).

We also cannot discount the important changes that occurred in the status and husbandry of cats in the period after World War II and how they affect FIP incidence. Cats have grown steadily in numbers as pets, and pedigreed cats and catteries have increased greatly in popularity. The post-war urban and suburban sprawl has greatly increased the numbers of feral and semi-feral (community) cats, and resulted in large numbers of kittens and cats coming into shelters and other foster/rescue organizations. An increasing proportion of our pet cats now come from these types of multicat environments, which can be stressful and favor fecal–oral transmission at a very young age. It should not be surprising that coronaviruses are now the most common pathogen identified in the feces of cats (Sabshin et al., 2012).

Coronaviruses have adapted themselves over thousands of years to virtually every species of mammals and birds, and are a common cause of transient enteritis and respiratory disease. Prior to the last decade, research interest in coronaviruses as pathogens has largely been limited to poultry, pigs, cattle and cats (Hagemeijer et al., 2012). However, with the emergence of severe acute respiratory syndrome (SARS) and Middle Eastern respiratory syndrome (MERS), interest in coronaviruses as pathogens has dramatically increased, along with levels of research funding. There are commonalities between what has been learned with animal coronaviruses and these

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emerging and sometimes fatal human viruses. They are continuously adapting themselves to new hosts, they readily recombine with closely related species to form new viruses, and they even change cell tropisms and virulence within the same host.

Although there is still no cure or sure prevention for FIP, a great deal has been learned about the disease in the last 5 years. The internal mutation theory, whereby a ubiquitous feline enteric coronavirus (FECV) mutates into a FIPV, has been reconfirmed and at least three specific mutations have now been associated with the FECV-to-FIPV biotype conversion. Much more is known about the interaction of enteric and FIP biotypes with their specific and very different host cells, and the radically different host response and clinical outcomes they provoke. A number of new reagents have been developed, allowing researchers to better understand these two biotypes and their diseases, and hopefully more are forthcoming. Nevertheless, FIP remains one of the most complex of all viral infections of cats.

Origin of feline infectious peritonitis viruses

Viral replication

It is not possible to understand the interrelationship of FECVs and FIPVs without understanding how enveloped, positive, single-stranded RNA viruses replicate (Hagemeijer et al., 2012). The genome of feline coronaviruses consists of > 29,000 nucleotides and 11 open reading frames (ORFs) encoding structural, non-structural and accessory genes. Coronaviruses attach to specific cell receptors through a complimentary ligand on the spike or surface (S) protein. Once attachment occurs, fusion with the cell membrane is dependent on a separate fusion domain and a fusion peptide comprising two heptad repeat regions (HR1 and HR2). The virus is then internalized and the single positive strand of RNA is released into the cytosol.

The 5' two thirds of the feline coronavirus genome consists of two ORFs, ORF 1a and ORF 1b. Ribosomes initiate translation at the beginning of ORF 1a and a proportion undergo frame shifting at the junction of ORF 1a and 1b, resulting in polyprotein pp1ab. Ribosomes that do not frame shift produce polyprotein pp1a. These polyproteins consist of approximately 16 non-structural proteins involved in proteolytic processing, genome replication and subgenomic mRNA synthesis.

The non-structural proteins of feline coronaviruses interact with components of the endoplasmic reticulum and Golgi apparatus to produce a replication–transcription complex. A RNA-dependent RNA polymerase makes negative sense copies of the genome, as well as subgenomic RNAs, which in turn serve as templates for the production of positive strand mRNAs. Only positive-stranded RNAs are capped and polyadenylated. The 3' polyadenylation and 5' cap structures mimic those of cellular mRNAs, enabling the virus to use the cell's own machinery for viral protein synthesis.

The nucleocapsid (N) protein plays an essential role in viral RNA and protein synthesis, and virion assembly (Verheije et al., 2010). Viruses undergoing assembly make their way to the cell surface within membrane structures, where they are released by exocytosis as mature virions (Almazán et al., 2004). In the process of maturation, the viral envelope also incorporates proteins acquired from various cell compartments. These added host constituents might aid survival in the face of host defenses.

This strategy to produce viral proteins from nested subgenomic mRNAs is highly efficient. However, like any process involving RNA polymerases, an error rate in the order of 1/10,000 nucleotides is expected. To minimize errors, the large genome encodes a number of non-structural proteins that ensure a higher fidelity of replication (Hagemeijer et al., 2012). Nonetheless, mutations do occur with some frequency. Chang et al. (2012) compared whole virus sequencing of 11 FIPV-FECV pairs and observed substitutions in at least 2963 nucleotides, representing 10% of the genome. Of these 2963 nucleotides, 1187 occurred in ORF 1ab, 1246 in ORF S (encoding the S glycoprotein), 248 in ORF 3abc, 22 in ORF E (encoding the small envelope protein), 42 in ORF M (encoding the integral membrane protein), 113 in ORF N (encoding the N protein) and 106 in ORF 7ab. Other types of mutations, leading to insertions, deletions and premature stop codons, as well as recombinants, have also been observed in vivo, both within and between hosts (Pedersen et al., 2009, 2012).

Phillips et al. (2013) studied the mutation rate of FIPV strain WSU-79-1146 in vitro after 1, 8 and 50 passages, followed by whole viral genome sequencing at each passage level. They observed 21 predicted amino acid changes in ORF 1a/1b during this period in culture, one predicted change in the S protein (which reverted back after additional passages), four changes in ORF 3c and one each in ORFs 3a, M, N and 7a, and calculated the mutation rate to be $5–6 \times 10^{-6}$ nucleotides/site/passage. This suggested that the genome was relatively stable in vitro and in the absence of host and environmental selection pressures.

Feline coronavirus mutations that do not have a negative impact on survival accumulate with time and can become dominant within micro- and macro-environments, such as catteries and geographically distinct regions (Pedersen et al., 2009). Such mutations can be used to track a specific coronavirus back to its most likely origin. Recombination also adds to genetic variation between coronaviruses and is common within clades, within the same cat and between cats (Pedersen et al., 2009, 2012). Recombination can even occur between related coronaviruses from different animal species. The type (serotype) II feline coronaviruses are an example of cross-species recombination that has occurred between the S gene region of type I feline coronaviruses and canine coronavirus.

The proportion of types I and II FECVs, and therefore types I and II FIPVs, varies across the world, although type I strains predominate. Duarte et al. (2009) studied the distribution of types I and II FIPVs in a Portuguese cat population using a reverse transcriptase (RT)-PCR assay that amplified the 3' end of the genome encompassing the region of feline/canine coronavirus S gene recombination. In cats with FIP, type I coronavirus was present in 79% and type II coronavirus in 3.5%, whereas the remaining 17.5% could not be typed. These viral sequences were further analyzed using a heteroduplex mobility assay, which detected quasi-species in 17% of samples. Phylogenetic analysis of type I sequences revealed high genetic diversity among Portuguese and previously characterized strains, while the tree for type II strains had higher genetic homogeneity than the tree for type I strains (Duarte et al., 2009).

The internal mutation theory

There is a general consensus that FIPVs arise by internal mutation from FECVs in the same environment (Pedersen et al., 2009, 2012; Harley et al., 2013). Except in unusual circumstances (Wang et al., 2013), the causative mutations occur independently within each cat and each FIPV strain has unique genetic features (Pedersen et al., 2009, 2012; Chang et al., 2012; Barker et al., 2013; Licitra et al., 2013). Currently, three different genes have been associated with the FECV-to-FIPV mutation or biotype conversion. Each mutation is a result of positive selection pressures, initially for a switch from enterocyte to monocyte/macrophage tropism, then ultimately for infection, replication and survival in peritoneal macrophages in the face of host immunity.

Mutations in the ORF 3c accessory gene

The ORF 3c accessory gene was the first gene to be implicated in FECV-to-FIPV conversion (Vennema et al., 1998), and these findings have been corroborated in subsequent studies (Poland et al., 1996; Chang et al., 2010; Pedersen et al., 2012). Two thirds or more