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Perspectives on the epizootiology of feline enteric coronavirus and the pathogenesis of feline infectious peritonitis

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ABSTRACT

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This review presents some current thoughts regarding the epizootiology of the feline coronaviruses; feline infectious peritonitis virus (FIPV) and feline coronavirus (FECV), with primary emphasis on the pathogenesis of these viruses in nature. Although the mechanism(s) whereby FIPV causes disease are still incompletely understood, there have been significant contributions to the literature over the past decade which provide a framework upon which plausible explanations can be postulated. Two concepts are presented which attempt to clarify the pathogenesis of FIPV and at the same time may serve as an impetus for further research. The first involves the hypothesis, originally promulgated by Pedersen in 1981, that FIPV is derived from FECV during virus replication in the gastrointestinal tract. The second involves a unique mechanism of the mucosal immune system referred to as oral tolerance, which under normal conditions promotes the production of secretory immunity and suppresses the production of systemic immunity. In the case of FIPV infection, we propose that oral tolerance is important in the control of the virus at the gastrointestinal tract level. Once oral tolerance is disrupted, FIPV is capable of systemic spread resulting in immune-mediated vasculitis and death. Thus, it may be that clinical forms of FIP are due to a combination of two events, the first being the generation of FIPV from FECV, and the second being the capacity of FIPV to circumvent oral tolerance.

INTRODUCTION

Feline coronavirus infections occupy a unique position in the pathogenesis of diseases of cats due to the range of clinical symptoms associated with infection and the lack of preventative measures, i.e. vaccines to assist in controlling the most fatal form, feline infectious peritonitis (FIP) (August, 1989; Barlough and Stoddart, 1990; Pedersen, 1987; Vennema et al., 1990). Due to its severity, FIP was the first clinical entity associated with feline coronavirus infection in 1963 (Holzworth, 1963). It was not until 1981 that the more

mild form of the infection was recognized and subsequently described as feline enteric coronavirus (FECV) (Pedersen, et al. 1981b).

The clinical and pathological features of FIP and FECV have been described in both domestic and exotic felids, and recent reviews are recommended for this resource (Barlough and Stoddart, 1990; Evermann, et al. 1988; Pedersen, 1987, and Saif and Heckert, 1990). This review will focus particularly on the epizootiology of FECV, with emphasis upon the potential for its mutation as the progenitor for eventual fatal mutants, which we recognize as FIPV, and the role of the immune response, specifically circumvention of oral tolerance, in the progression of disease.

Feline enteric coronavirus

Infection/epizootiology. The FECV is generally regarded as a localized infection of the alimentary tract of the cat (Pedersen, 1987; Saif and Heckert, 1990). The virus is a single stranded RNA, which replicates by multiple monomeric RNA and subsequent consolidation into mature virus particles which bud forth from various intracytoplasmic cisterna (DeGroot et al., 1988; Lai. 1988; Lai, et al., 1987; Spaan, et al., 1988). The mature virus particles are enveloped which increases their lability once outside the cell, and even more so once the virus is shed from the cat, usually in fecal matter (DeGroot et al., 1987; Fiscus and Teramoto, 1987b; Marshall et al., 1987; Saif and Heckert, 1990). The virus appears to have a trypsin or host protease dependence, and despite its envelope, a pH resistance, which allows for its retention of infectiousness as it passes through the digestive tract of the cat (McKeirnan, et al., 1987).

The infection is considered to be highly contagious in catteries, especially those which employ common food sources and litter facilities (Pedersen, 1987). Serologic studies have reported from 40% to 85% infection rates in cat populations and the occurrence of clinical signs may vary from asymptomatic to mild enteritis (Barlough and Stoddart, 1990; Pedersen, 1987). The severity of clinical signs has been speculated to be additive depending on other current infections (Evermann, et al., 1988). The infection is generally regarded as not fatal, although one of the few FECV isolates to be grown in cell culture was obtained from a fatal case in a one-year-old cat (McKeirnan, et al., 1981; Pedersen, et al., 1984). The occurrence of a multiple infection with feline panleukopenia could not be ruled out in the aforementioned case.

Disease. The FECV may produce an enteritis in cats which resembles the mild form of disease in young pigs caused by transmissible gastroenteritis (TGE) virus, or in dogs by canine coronavirus (CCV) (Barlough and Stoddart, 1990; Pedersen, 1987; Saif and Heckert, 1990). The TGE virus and other porcine coronaviruses, as well as CCV are antigenically related to FECV/FIPV. The

antigenic relationships amongst the coronaviruses affecting pigs, cats and dogs was recognized prior to the actual isolation of feline coronaviruses in cell culture, and has since been expanded to isolates propagated in vitro (Horzinek, et al. 1982; Mochizuiki and Furukawa, 1989; Pedersen et al, 1978; Sanchez et al, 1990). In addition to the serologic cross reactions among this coronavirus group, there have been molecular studies reported on the homology of the viral RNA (DeGroot et al, 1988; Shockley et al, 1987). The antigenic and genomic similarities amongst the porcine, canine and feline coronaviruses have led to speculation on the common origins of the coronaviruses (Barlough and Stoddart, 1990; Yaling, et al., 1988). The potential for interspecies transmission of these coronaviruses whenever these animal species commingle needs to be studied further (McArdle, et al., 1990; Mochizuiki and Furukawa, 1989; Sanchez, et al., 1990; Yaling, et al., 1988). The severity of FECV infection is age-related, with clinical signs most frequently being observed in kittens (Pedersen, 1987). Clinical signs in kittens may include fever, mild to moderate diarrhea of 2 to 5 day duration, and a transient leukopenia. The most severe lesions occur in the mature columnar epithelium of the ileum and jejuenum.

Diagnosis. Diagnosis of FECV infection may be obtained by serologic testing (Barlough, et al., 1986; Fiscus, et al., 1985; Ingersoll and Wylie, 1988b). Serology can also be utilized for surveillance purposes to determine the extent of infection by the virus (Heeney, et al., 1990; Ingersoll and Wylie, 1988a). The majority of serologic assays are regarded as group specific and therefore, they neither distinguish between FECV and FIPV, nor amongst the feline coronaviruses and the coronaviruses of pigs and dogs (TGE and CCV) (Barlough and Stoddart, 1990; Tupper, et al., 1987). However, a history of past contact of the affected cat to other animals would certainly assist in the assessment of the potential of interspecies transmission.

The diagnosis of FECV disease can be assisted by a combination of serology (to determine infection) and electron microscopy on fecal matter (Marshall, et al., 1987). Electron microscopy is valuable in observing coronaviruses in fecal contents from a number of animal species, and is usually correlated with the shedding of a large number of virus particles ($> 10^6$), especially during stressful events such as parturition (Collins, et al., 1987; Crouch, et al., 1985). Cautionary interpretation of electron microscopy results is advisable when assessing the shedding of coronaviruses, since serology does not correlate well with fecal shedding in all cases, and the presence of coronavirus-like particles may serve as a source of diagnostic confusion (Barlough and Stoddart, 1990; Heeney, et al., 1990; Stoddart et al, 1984).

Prevention. The control of FECV disease is based upon minimizing the concentration of FECV in the environment (Pedersen, 1987). It is particularly

important to reduce the amount of FECV to which kittens may be exposed. Therefore, good sanitary conditions and segregation of young cats ($\leqslant 4$ months) from older cats are important management steps. Since the infection is primarily localized to the alimentary tract, good levels of maternal antibody are assumed to limit the pathogen load in the kitten's digestive tract for up to five weeks and as long as five months (Barlough and Stoddart, 1990; Pedersen, 1987). Concurrent infections such as feline panleukopenia, feline leukemia virus and feline lentivirus may predispose cats to feline coronavirus infection and should be monitored closely by testing, and when available, vaccination.

Feline infectious peritonitis

Infection/epizootiology. Recognition of FIP has occurred in various stages over the past three decades. The disease was well described on the basis of pathological lesions in 1963 (Holzworth, 1963). It was not until 1970 (Ward, 1970) that a viral etiology was considered, and then it was not until 1979 that the FIPV was isolated (Black, 1980; Evermann, et al., 1981; McKeirnan, et al., 1981; O'Reilly, et al., 1979). The exact virus etiology was preceeded by several years of serology studies utilizing heterologous, cross-reacting coronaviruses, such as TGE and CCV. These studies revealed that coronavirus infection was quite common especially in catteries in which the population of seropositive cats approaches 85%. Although FIP was, and still is, considered to be 100% fatal once clinical signs developed, there is a lack of correlation between the incidence of coronavirus seropositive cats and those that succumb to FIP. It was during this same time frame that FECV was reported (McKeirnan, et al., 1981; Pedersen, et al., 1981b). These observations are consistent with the interpretation that the feline coronaviruses are comprised of divergent strains of virus that are closely related antigenically and genomically, but vary in their pathogenicity for cats (Barlough and Stoddart, 1990; DeGroot et al, 1988; Horzinek et al, 1982; Pedersen et al, 1978).

In 1981, Pedersen suggested that FIP may be the result of mutation of the more common FECV (Pedersen, et al., 1981b). This hypothesis would account for several observations. First, that FIP may occur in a low percentage of cats that are housed in catteries that are closed to outside cats; and second, that the FIPV strains isolated in cell culture outnumber the more avirulent FECV strains (one may interpret this observation that FECV is host-cell dependent, whereas FIPV has "escaped" host-cell dependence and is, hence, less fastidious).

The occurrence of host-range mutants has precedent amongst the coronavirus and includes: Mouse hepatitis virus (MHV); infectious bronchitis virus (IBV) of birds; and TGE virus (Aynaud, et al., 1985; Bernard, et al., 1989; Chen, 1985; Chen and Kahn, 1985; Gallagher, et al., 1990; Spaan, et al., 1988).

Although there may be several mechanisms whereby a mutation may occur, the coronaviruses are known to have a recombination frequency that may account for the generation of escape mutants, and in the case of parental FECV, the occurrence of FIPV (Goldbach and Wellink, 1988; Lai, 1988; Lai, et al., 1987; Spaan, et al., 1988; Steinhauer and Holland, 1987).

Disease. The generation of FIPV may not in itself result in disease of the cat in which the mutation occurred. The FIPV may be shed and transmitted to other susceptible cats. The mechanism of spread may be by either direct inoculation (via cat bite, licking open wounds, etc.), or by ingestion (Pedersen, 1987). Experimental infection with FIPV has been reported by the oronasal route of inoculation (Evermann, et al., 1981; Fiscus, et al., 1987; Pedersen and Black, 1983; Pedersen, et al., 1981a; Stoddart, et al., 1988a, b, c). Also, some FIPV strains have been reported to cause an enteritis only upon oral inoculation (Hayashi, et al., 1982; Hayashi, et al., 1983). This observation would support the contention that there are other variables in the pathogenesis of FIPV to consider.

One important variable, although not defined in cats yet, may be the circumvention of oral tolerance. Oral tolerance is defined as the decreased systemic immune response to antigens previously encountered in the gastrointestinal tract (Brantzaeg, 1989; Emancipator and Lamm, 1988; Kagnoff, 1988; Nicklin and Miller, 1983). This form of tolerance is one feature of the mucosal immune response which involves a mechanism for *promoting* the production of secretory IgA antibody while at the same time *suppressing* the production of systematic humoral and cell mediated immunity. The protection of the host from harmful systemic types of immune reactions generated by IgG, IgE and T cell-mediated delayed-type hypersensitivity (DTH) probably involves multiple immunoregulatory events which may be different from humoral immunity and DTH (Brandtzaeg, 1989). The presentation of antigens to the intact gut epithelium and subsequent antigen processing appear to be critical features in the suppression of systemic DTH. However the nature of such antigen presentation and processing and the cells involved remains to be elucidated. Brandtzaeg (1989) has speculated that special mucosal macrophages may be one of the cellular elements involved in the processing of antigens for induction of oral tolerance. The proposed role of macrophages in the preservation of oral tolerance is compatible with a recent study which reported on the pathogenicity of feline coronaviruses in macrophages in vitro and its correlation with the virulence of the viruses in cats (Stoddart and Scott, 1989).

The importance of restricting the systemic immune response to feline coronaviruses is vital, especially when one considers the enhancement of disease states by antibody. Previous studies have shown that FIPV will induce an immune-mediated vasculitis, which is characterized by elevated levels of
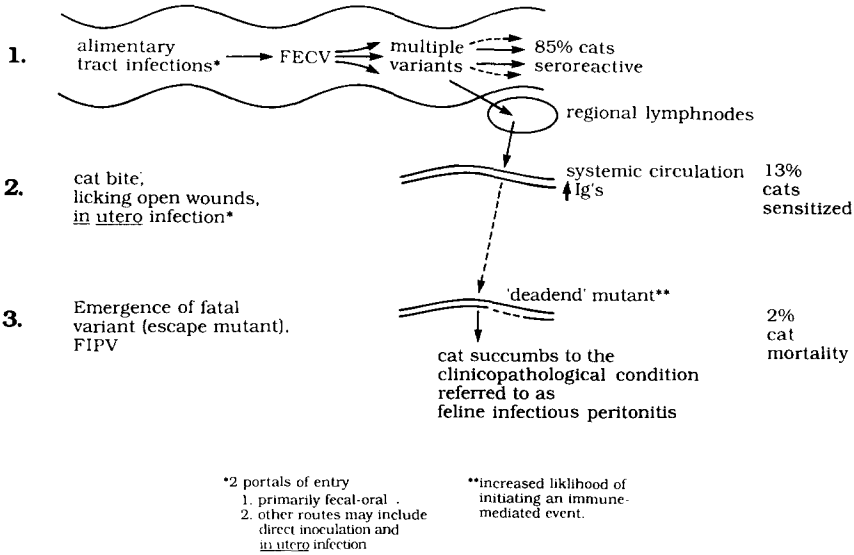
Fig. 1. Proposed pathogenesis of the emergence of feline infectious peritonitis virus (FIPV) from feline enteric coronavirus (FECV). (1) Alimentary tract infection with FECV results in multiple variants, one of which may be an escape mutant which infects and replicates in regional lymph nodes. (2) The mutant virus (FIPV) circumvents oral tolerance and spreads systemically. The FIPV may also be introduced into systemic circulation by inoculation and/or in utero infections. (3) The resulting systemic infection results in the onset of an immune-mediated vasculitis.

serum proteins, in particular, viral antibodies of non-neutralizing type (Pedersen, 1987; Pedersen, 1989; Shelly, et al., 1988; Stoddart, et al., 1988a, b, c). Passive acquisition of serum from sensitized cats has also been demonstrated to enhance the progression of FIPV-induced disease (Pedersen, 1987). Although cell-mediated immunity is generally regarded as being important in protection against FIPV-induced disease, there have been studies which suggest that the vasculitis associated with FIP may be due in part to cellular rather than humoral mechanisms (Pedersen, 1985; Weiss and Cox, 1989).

The disease attributable to FIPV may well be a combination of two events. The first being the generation of an escape mutant (FECV→FIPV), and the second, the capacity of the escape mutant to circumvent oral tolerance, thereby resulting in sensitization of the systemic immune response, and eventually immune-mediated disease and death. The proposed sequence of events leading to FIP is presented in Fig. 1.

Diagnosis. The diagnosis of FIP is made by a combination of tests including clinical pathology and histopathology (Pedersen, 1987; Shelly, et al., 1988). Serology may be useful in assisting with the diagnosis, but should not be the

sole criterion used (Barlough and Stoddart, 1990). Once clinical signs are manifested, FIP is generally regarded as 100% fatal (Pedersen, 1987). The definitive diagnosis is based upon histopathological examination. The typical lesions include disseminated pyogranulomatous and fibrinonecrotic reactions around veins, necrotizing phlebitis and thrombosis, and lymphoreticular and mesothelial cell hyperplasia. Due to the high fatality rate of cats with clinical signs, there is an immediate need for a prognostic test which would be of predictive value for cats prone to develop FIP. This test may be directed at either the occurrence of FIPV nucleic acids or antigens in circulation, or the formation of immune complexes in circulation, and/or a combination of several techniques (Fiscus, et al., 1985; Fiscus and Teramoto, 1987a; Shockley, et al., 1987; Ingersoll and Wylie, 1988a; Weiss and Cox, 1989). Prophylactic anti-viral therapy should be directed at pre-clinical high risk cats. Support for this concept has come from several reports on the effectiveness of anti-viral substances in the course of FIPV infection in vitro and in vivo (Barlough and Scott, 1990; Weiss and Toivio-Kinnucan, 1988; Weiss and Oostrom-Ram, 1989; Weiss, 1989).

Prevention. On the basis of the aforementioned pathogenesis of FIP, the prevention of FIP may revolve around the intervention of two independent events. The first would be to minimize the occurrence of high frequency FECV recombinants in the GI tract and the second would be the maintenance of oral tolerance (Ahmed and Oldstone, 1985; Emancipator and Lamm, 1988). In reality, this may be occurring in nature, since constant coronavirus oral exposure may be stimulating levels of mucosal IgA thereby minimizing the escape of mutants, such as FIPV (Childers, et al., 1989; Christianson, et al., 1989; Crouch, 1985; Fitzgerald and Welter, 1990; Gerber, 1989; Moxley and Olson, 1989, Moxley, et al., 1989; Mestecky, 1987; Vellenga, et al., 1988). In order to minimize the occurrence of FIP and prevent recombination of FECV it may be important to utilize strains of FECV that are trypsin dependent (survive in the GI environment, but not in systemic circulation) and resistant to recombination (genetically stable). These trypsin-dependent, genetically stable mutants would then be capable of inducing and sustaining a level of gut immunity, and the integrity of oral tolerance to prevent FIPV from being generated, and thereby, FIP from being manifested (Whitaker-Dowling and Youngner, 1987).

CONCLUSION

This past decade has seen a tremendous interest develop in understanding the pathogenesis of FIP of cats. The impetus for this concern has been motivated by several independent lines of investigation, which have included; successful in vitro culture of FIPV and FECV; and the occurrence of FIP in an

endangered felid, the cheetah; and the difficulty in prevention of FIP by conventional and unconventional vaccines (Black, 1980; Evermann, et al., 1988; McKeirnan, et al., 1987; O'Reilly, et al., 1979; Pedersen, 1989; Vennema, et al., 1990). The recognition of high recombination frequencies amongst members of the mouse coronaviruses may offer a plausible explanation as to how FIPV evolves from FECV in nature, and how fatal forms of FIPV emerge in closed catteries (Goldbach and Wellink, 1988; Lai, 1988; Pedersen, et al., 1981b).

While the feline immune response has historically been known to be ineffectual toward controlling FIPV once clinical signs are manifested, the mechanisms for this breakdown have not been adequately explained. It is conceivable that a virus-restrictive form of intestinal immunity is required for control of FIPV, and that oral tolerance is maintained to minimize systemic spread of the virus and also reduce the occurrence of a systemic immune response represented by high levels of humoral antibody and certain forms of cell-mediated immune responsiveness (Emancipator and Lamm, 1988; Kagnoff, 1988; Nicklin and Miller, 1983). Once oral tolerance is disrupted, the virus is capable of systemic spread and the well-recognized immune-mediated vasculitis results (Stoddart, et al., 1988b, 1988c; Stoddart and Scott, 1989). Thus, it may be that clinical forms of FIP are due to a combination of two events, one being the generation of an escape mutant we recognize as FIPV, and the other being the capacity of the FIPV to overcome oral tolerance. Additional studies are necessary to assist in unraveling the pathogenesis of FECV–FIPV, since this understanding is critical to our successful control of this fatal disease of domestic and exotic cats.

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ADDENDUM, APRIL, 1991

Since the completion of the manuscript there have been additional articles which have been published which pertain to the discussion on feline coronaviral infections, disease amd control. The key articles are as follows:

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