Coronavirus genomes possess a high level of genetic variation owing to the high error rate of RNA polymerase, and are, thus, prone to genetic mutations. Mutations in an individual cat leading to a switch in cellular tropism (gastrointestinal epithelium to monocytes/macrophages) and infection of monocytes/macrophages are crucial for systemic spread of FCoV (1–3). Monocyte/macrophage entry alone is not sufficient for the development of FIP; likely, mutations leading to persistence and efficient replication within and activation of monocytes/macrophages are required (see 'prerequisites' box on page 908 of the Guidelines)(4,5). FCoV strains from different cats with FIP in the same household show mostly unique genetic characteristics, demonstrating that these viruses develop independently in individual cats (5–8).

Viral proteins and genes

To date, specific viral mutations leading to the biotype switch remain undetermined. Two single nucleotide polymorphisms in genes encoding the fusion peptide of the (S) protein, leading to amino acid changes (M1058L and S1060A), were initially shown to be linked to the conversion of the biotype (9,10); however, they were later suggested to only indicate systemic spread of FCoV irrespective of the development of FIP (ie, identified in healthy cats as well; see supplemental 6) (11,12).

Intact open reading frame (ORF) 3c gene appears to be essential for effective FCoV replication in gastrointestinal epithelium, but it is dispensable for systemic spread and/or replication within monocytes/macrophages (13–19). Indeed, most isolates of cats with FIP contain mutations in the ORF 3c gene, limiting its associated protein expression. An interplay between S protein mutations and ORF 3c seems to be involved in alteration of FCoV tropism, allowing enhanced internalization within monocytes/macrophages and facilitating cell-associated systemic spread of the virus (13,20). Mutations within other FCoV genome protein-encoding regions, including non-structural proteins ORFs 3a, b and ORFs 7a, b domains, and structural membrane (M) protein, have also been investigated regarding biotype switching; however, the importance of mutations in these other regions is largely unknown (13). At one point, it was proposed that ORF 7a protein could interfere with the function of the antiviral cytokine, interferon (21). However, mutations in ORF 7b gene have since been shown to cause virulence loss and can be found in both biotypes (18,22–27).

Immunological response

Monocytes'/macrophages' main functions within the immune system include phagocytosis of foreign material, antigen presentation and cytokine production. Monocytes/macrophages usually respond to FCoV infection by presenting viral antigens on their surface, leading to antibody-dependent, complement-mediated lysis and cell death (5,28,29); however, FIP immune system evasion can occur whereby some FIP-infected macrophages lack surface expression of viral antigens, thus allowing the infected macrophages to persist (28). Once infected by FCoV, macrophages become activated leading to the production of a variety of inflammatory mediators (30). These cytokines include IL-1β, IL-6, IL-15, TNF-α, the interferons α, β, and γ, and the chemokines CXCL10 and CCL8 (see supplemental 5b) (30). In addition, upregulation of macrophage adhesion molecules leads to interaction with the endothelial cells of smaller veins (30,31). The expression of enzymes, such as matrix metalloproteinase 9, is also increased (32). Compromise to the endothelial barrier leads to vasculitis, perivascular necrosis and monocyte extravasation. Leukocytes that remain uninfected, such as neutrophils, also become activated and likely contribute to endothelial cell damage. Increased expression of vascular endothelial growth factor by activated macrophages is also believed to enhance vascular permeability (33).

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Pathogenesis of FIP (continued)

Immunological response (*continued*)

Inflammation provoked by replicating virus leads to a characteristic vasculitis and FIP lesions centered around small venules in target tissues, which in many cats can cause edema and effusions. The characteristic inflammatory cells are neutrophils, monocyte/macrophages, and mature virus-laden macrophages with sparse numbers of lymphocytes (23,34). Collections of these cells around small vessels are referred to as pyogranulomatous vasculitis (see 'd' in supplemental 4). If effusion is not present, lesions are usually less diffuse, localized deeper below the surface of organs, less edematous or effusive, and often appear as more characteristic granulomas with a predominance of lymphocytes, plasma cells, mature and immature macrophages and sparser neutrophils (23,35). Transitional forms often occur in which cats with predominantly effusion (eg, ascites, pleural effusion) develop organ serosal-associated granulomas and vice versa (35).

The extent of the FIP lesions depends on the cat's cell-mediated immune (CMI) response (see supplemental 6) (23). It has been suggested that effusions dominate when a zealous humoral response to virus infection occurs and induces a type III (immune complex disease) hypersensitivity reaction (23). Within the lesions themselves, a type IV (delayed) hypersensitivity response dominates, resulting in granuloma formation (23,36). In large part, FIP lesion types depend on host immune-mediated response and are contingent on which hypersensitivity reactions dominate (23).

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