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Theoretical aspects of the immunopathogenesis of coronavirus infection in cats

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Feline Infectious Peritonitis (FIP) is a severe and specific coronavirus infection caused by a mutated feline coronavirus (Feline Infectious Peritonitis Virus (FIPV)). FIP is frequently associated with high mortality rates and a complex multisystem immunopathogenesis. This article provides a comprehensive review of contemporary theoretical knowledge on the pathogenesis of FIP, including the molecular and cellular mechanisms of the immune response underlying disease development. Special attention is given to the analysis of factors determining the virulence of FCoV, mechanisms of viral (FIPV) interaction with macrophages, the role of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) in the progression of the infectious process, and the potential connection of the Arthus reaction to the intricate immunopathological mechanisms involved in FIP. The article discusses the significance of antibody-dependent enhancement (ADE) in stimulating viral replication in target cells and the role of class G immunoglobulins in disease pathogenesis. The article summarises key aspects of FIP pathogenesis, including the immunological mechanisms responsible for the clinical manifestations of the disease. It details the pathogenesis of primary clinical forms of FIP, with an analysis of specific changes occurring in various systems of the body (digestive, respiratory, renal, nervous, and cardiovascular). Additionally, it addresses microcirculatory disturbances and increased vascular wall permeability contributing to systemic inflammation. The text also delves into the cytokine storm induced by hyperactivity of virus-infected immune-competent cells, primarily macrophages. The interplay between pathogen virulence and its ability to modulate the host's immune response by suppressing adaptive immunity is explored. This review synthesises current research, focusing on theoretical insights into the immunopathogenesis of FIP and emphasising the significance of a pathogenetic approach to its diagnosis and prevention.

Keywords: Feline Infectious Peritonitis; Feline Coronavirus; Feline Infectious Peritonitis Virus; immunological mechanisms.

Introduction

Feline Infectious Peritonitis (FIP) is a highly contagious disease caused by a virus belonging to the Coronaviridae family, often resulting in fatal outcomes. The virus spreads easily among cats, especially in settings with high-density populations, such as breeding facilities or multi-cat households with frequent interaction (Drechsler et al., 2011; Felten et al., 2023). The scientific community, led by Dr Jean Holzworth, first identified FIP as a distinct disease in 1963 at the Angell Memorial Animal Hospital in Boston, USA (Holzworth, 1963). While most infected cats are asymptomatic carriers, some develop a fatal form of the disease (Jähne et al., 2022).

FIP is most prevalent in Europe and North America, followed by Asia, where cat cafes are popular (Barker et al., 2013; Černá et al., 2022). Cats worldwide, including those in the United States, Europe, and China, are susceptible to the coronavirus. Prevalence rates range from 80% to 100% in cats from compromised breeding catteries and shelters, compared to 15% to 40% in domestic settings (Ouyang et al., 2022; Chen et al., 2023; Hu et al., 2024). Studies by Kennedy et al. (2024) suggest that at least half of cats in the United States have antibodies against the coronavirus. Research by Thayer et al. (2022) indicates that 0.3% to 1.4% of cats in veterinary clinics die from FIP. The disease primarily affects young cats under two years of age (Riemer et al., 2016) and those recently subjected to stress (Klein-Richers et al., 2020). While FIP predominantly affects domestic cats, it has also been observed in wild feline species (Pedersen, 2012).

Diagnosing FIP is challenging, and treatment is often ineffective (Delaplace et al., 2021). The disease exhibits nonspecific symptoms at its early stages, complicating its detection. The Coronaviridae family is associated with numerous diseases in animals, including infectious bronchitis in chickens, bovine coronavirus enteritis, transmissible gastroenteritis in pigs, and canine coronavirus infections (Vlasova & Saif, 2021; Xing et al., 2022; Zhao et al., 2022; Chen et al., 2023; Falchieri et al., 2024).

Coronaviruses are a diverse group of viruses causing diseases in humans, ranging from mild respiratory infections to severe multisystemic conditions (Sweet et al., 2022). In human medicine, the most notorious coronavirus-related disease, with a high mortality rate and global spread, was COVID-19 (SARS-CoV-2), first identified in China in late 2019 (Paltrinieri et al., 2021; Sweet et al., 2022). Other significant diseases caused by this virus family include Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS-CoV), and seasonal respiratory infections (Lombardi et al., 2021; Chen et al., 2023).

Several theories regarding the origin of FIP exist, including the "mutation theory", viral variant theory, immune hyperactivity theory, environmental factors, and genetic predisposition in certain feline breeds. The "mutation theory" is the most widely accepted. According to this theory, Feline Infectious Peritonitis Virus (FIPV), an RNA virus, arises from mutations in Feline Coronavirus (FCoV), which is typically benign and non-threatening (Baş et al., 2020; Lin et al., 2022; Cao et al., 2023). The mutated FCoV (FIPV) infects macrophages and causes damage to various organs (Gu et al., 2024). The lack of robust experimental evidence supporting existing hypotheses on FIPV pathogenicity acquisition complicates the study of the disease's pathogenesis. Comprehensive studies on the virus's genetic features, host cell interactions, and immune status across different disease stages would be informative. Investigating the aetiological factors influencing the transformation of FCoV into the virulent FIPV remains a priority.

The fundamental mechanisms underlying FIP development remain poorly understood, limiting the development of effective diagnostic and therapeutic approaches. Studying the immunopathogenesis of this viral infection is a critical focus for modern veterinary medicine, as the virus suppresses immune cell function, leading to irreversible damage across multiple organ systems.

Molecular structure and genetic features of Feline Coronavirus (FCoV): Mutations and tropism adaptation

Feline infectious peritonitis is caused by a mutated enteric virus from the Coronaviridae family, genus *Coronavirus*. Coronaviruses

belong to the subfamily Coronavirinae, which is divided into four genera: alpha-, beta-, gamma-, and delta-coronavirus (Kipar & Meli, 2014). Morphologically, virions are polymorphic and spherical, with club-shaped spikes (spike proteins) resembling a solar corona on their surface (Kipar & Meli, 2014). These are enveloped RNA viruses measuring 60–120 nm (Kipar & Meli, 2014). The genome of coronaviruses is represented by positive single-stranded RNA (+ssRNA), which can directly serve as a template for protein synthesis in the cell (Haas, 2022). Two-thirds of the positive single-stranded RNA comprises two open reading frames (ORFs) that encode non-structural polyproteins (Haas, 2022). Coronaviruses also encode accessory proteins involved in viral replication. These proteins enhance viral virulence, trigger inflammatory responses, and interact with the host's immune regulatory mechanisms (Jiao et al., 2024).

Coronaviruses contain two primary ORFs, designated ORF1a and ORF1b, occupying the majority of the genome. Proteins encoded by these ORFs (non-structural proteins, NSPs) do not form the physical virus shell but perform crucial functions for its replication. They facilitate genome copying, regulate viral protein translation, and suppress the host's immune response. Consequently, after NSP synthesis in the host cell, a replicase-transcription complex (RTC) is formed, enabling efficient viral replication (Gu et al., 2024). FCoV has five additional genes: 3a, 3b, 3c, 7a, and 7b (Dong et al., 2022). The 3a, 3b, and 3c genes play key roles in virus-host cell interactions and replication processes, while the 7a and 7b genes are crucial for modulating immune responses (Gu et al., 2024). These genes help the virus evade the immune system's effects. In other alpha-coronaviruses, these genes are also located in two distinct genome regions. Comprehensive molecular analyses have shown that mutations in the ORF3c accessory protein genes, S protein, and ORF7b accessory protein result in a shift in the virus's tropism from intestinal epithelial cells to macrophages and peripheral blood monocytes, playing a key role in the systemic infection pathogenesis (Rottier et al., 2005; Ouyang et al., 2022).

Mutations in the FCoV S protein genes enhance its ability to infect and adapt to monocytes and macrophages (Jaimes et al., 2020; Decaro et al., 2021; Gu et al., 2024). Additionally, some researchers note that one of the FIPV genes (ORF7a) plays a significant role in disease development (Jiao et al., 2024). Recombinant strains with deleted ORF7a demonstrated low replication rates in target cells and did not induce systemic inflammatory processes (Jiao et al., 2024). Studies by Balint et al. (2012) focused on examining non-synonymous mutations, frame shifts, and deletions in the ORF3c protein in FIPV virion genomes. Such genetic changes likely increase the replication rate of feline coronavirus in the macrophages of infected animals (Balint et al., 2012). These types of genetic changes in ORF3c do not always affect the development of FIP and its pathogenicity but improve the virus's adaptation to target cells (Chang et al., 2010; Chang et al., 2011; Pedersen et al., 2012). According to Myrrha et al. (2019), the ORF3b gene was once considered a marker of FIPV but is now recognised as inert during the biotransformation between FCoV and FIPV (Myrrha et al., 2019). The detailed mechanism of biotype switching remains poorly understood. Laboratory studies (*in vitro*) often do not correspond to real-life conditions (*in vivo*), complicating hypothesis confirmation. Most contemporary theories suggest that FCoV transformation into the pathogenic FIPV variant results from mutations in specific genes, leading to the acquisition of multi-vector tropism, marking the initial stage of the infectious process (Gu et al., 2024).

Mechanisms of infection by Feline Coronavirus and factors initiating point mutations in the virus genome

The immunopathogenesis of coronavirus infection in cats is complex due to the tropism of Feline Coronavirus (FCoV). Research by Balint et al. (2012) and Chang et al. (2012) explores the role of genetic changes in the virus and their impact on disease pathogenesis, particularly the replication ability of virions in macrophages. This replication is key to the virus's adaptation in the host organism, facilitating the transition of FCoV to Feline Infectious Peritonitis Virus (FIPV) (Takano et al., 2019). The biotransformation from Feline Enteric Coronavirus FCoV to FIPV arises not only from genetic mutations but also through interactions between the coronavirus and the cat's immune system (Gu et al., 2024). Some researchers hypothesise that macrophages serve as reservoirs for FCoV evolution. During the formation of the "virus–cell" complex, the virus actively multiplies, transforming into FIPV (Gu et al., 2024). The synthesis of new genetic material copies in macrophages triggers systemic infection in the host organism. Virus-laden macrophages produce cytokines (TNF-α, IL-1β, and IL-6), exacerbating inflammatory processes (Balint et al., 2012; Chang et al., 2012).

To interpret the pathogenesis of feline coronavirus infection, attention should be given to virus transmission and infection. The virus is transmitted via the faecal-oral route, underscoring its widespread prevalence (Barker & Tasker, 2020). FIP susceptibility is high among young cats (Moyadee et al., 2024), particularly those with rapid metabolic rates, immunodeficiencies, or living in shelters and catteries with overcrowded conditions (Kennedy, 2020). Unscrupulous breeders often neglect essential hygiene, vaccination protocols, and segregation of sick or weak animals, thereby exacerbating viral spread (Tekes & Thiel, 2016; Felten et al., 2023).

Once the virus enters a susceptible cat, it migrates from the tonsils to the intestines. The mechanism by which FIPV Type II attaches to host cells is not fully understood. However, some studies indicate the utilisation of aminopeptidase N as the primary receptor (Tekes & Thiel, 2016). In contrast, FIPV Type I likely employs lectin as a co-receptor, interacting with molecules such as DC-SIGN and CD209 (Regan et al., 2010; Tekes & Thiel, 2016; Takano et al., 2019; Terada et al., 2019). These receptors play a significant role in FIPV binding to enterocytes, where primary replication of FCoV occurs. Normally, the host's immune system responds to this antigen through innate and adaptive immunity, localising the virus. FCoV's ability to undergo point mutations in favourable conditions is a key feature (Gu et al., 2024). Mutations in structural protein-encoding genes shift the virus's tropism from enterocytes to macrophages (FIPV) (Rottier et al., 2005).

Factors contributing to mutations include hypo- or hyper-reactions of the immune system, chronic stress, and comorbidities, which can lead to viral persistence and mutation (Černá et al., 2022; Chen et al., 2024). Genetic predisposition to this pathology is noted in specific cat breeds, such as Maine Coon, Abyssinian, Persian, Birman, Bengal cats, and Devon Rexes, due to hereditary immune system abnormalities facilitating "easy" macrophage or monocyte infection (Tekes & Thiel, 2016; Melnyk et al., 2022). Male cats are reportedly more susceptible to infectious peritonitis (Moyadee et al., 2024). FIP pathogenesis involves the interplay of viral properties, immune system status, stress, and genetic predisposition. Upon infection and FCoV mutation to FIPV, a complex viraemia develops.

Pathogenetic mechanisms of FCoV entry into target cells: Role of immunoglobulins in antibody-dependent enhancement of infection and participation of pro-inflammatory mediators TNF-α, IL-1β, and IL-6 in the infectious process

The entry process of mutated feline coronavirus into target cells is complex and not fully elucidated. It likely involves cellular endocytosis (Takano et al., 2019). The virus evades immune detection by suppressing macrophage activity and interferon activation processes (Takano et al., 2019). Within two weeks, the virus spreads to the colon, lymph nodes, and liver, eventually affecting other organs, leading to multisystemic disease.

Coronavirus replication in monocytes and macrophages results in immune system dysfunction. Infected macrophages act as "transport vehicles", disseminating infection while evading immunological responses since macrophages are crucial for cellular immunity (Drechsler et al., 2020; Mangiaterra et al., 2024). Cellular and humoral immune functions are interconnected. Plasma cell activation triggers antibody synthesis, forming antigen-antibody complexes that deposit on blood vessel walls, causing vasculitis. Immunoglobulins (IgA, IgG, IgM) interact with FCoV, with IgG playing a pivotal role in antibody-dependent enhancement (ADE) of infection (Hohdatsu et al., 1998). This interaction promotes viral replication in macrophages (Dewer-

chin et al., 2005; Jaimes et al., 2018). High antibody titres against FCoV often correlate with increased susceptibility to FIP (Ehmann et al., 2018). The interaction between the virus and the immune system activates inflammatory responses, impairing microcirculation and increasing vascular permeability due to cytokines and mediators such as TNF-α, IL-1β, and IL-6. These pro-inflammatory mediators, released by infected macrophages, accumulate in various organs, including the liver, spleen, intestines, lungs, kidneys, heart, and central nervous system (Malbon et al., 2019), exacerbating inflammation, exudate accumulation, and granuloma formation.

Immunological mechanisms in the development of key clinical forms of FIP. Pathogenetic role of immune response in clinical symptom formation

Feline infectious peritonitis (FIP) manifests in several clinical forms: wet (effusive), dry (non-effusive), and occasionally, a distinct neurological form. Abdominal manifestations of the disease are generally more common than thoracic ones (Slaviero et al., 2024). The clinical manifestations of feline coronavirus infection vary and are closely tied to the immune system of the affected animal. The dry form is associated with cell-mediated immunity (dominated by cellular immunity, particularly CD4+ T-lymphocytes), leading to granuloma formation (nodules) in organs such as the liver, brain, kidneys, spleen, and brain. This occurs due to granulomatous inflammation. Gene expression analysis in the lymph nodes of infected cats indicates increased activity of pro-inflammatory pathways and reduced T-cell activity compared to clinically healthy cats (Pedersen, 2014). Clinically, affected animals present with vomiting, depression, anorexia, diarrhoea, and fever (Thayer et al., 2022).

The wet form is hypothesised to be associated with Type III immune response (Arthus reaction) (Hartmann, 2005). The Arthus reaction is characterised by local inflammation and necrosis due to the deposition of immune complexes on blood vessel walls. This accumulation of antigen-antibody complexes activates the complement system, promoting macrophage recruitment and subsequent viral replication. Animals with the wet (effusive) form often exhibit weight loss, rapid abdominal distension, poor appetite, and lethargy (Gülersoy et al., 2023).

Occasionally, a neurological form is recognised, where the mutated feline coronavirus infects the central nervous system. Some researchers categorise the neurological form as part of the dry (non-effusive) form (Tekes & Thiel, 2016). The virus crosses the blood-brain barrier, potentially due to microcirculation damage, increased vascular permeability, or through infected inflammatory cells, leading to vasculitis in the brain's blood vessels. Granulomas form in brain tissue, and perivascular infiltration by immune cells is observed in the brain's vasculature and meninges, resulting in encephalitis, meningitis, and behavioural changes (Ramezanpour Eshkevari et al., 2024).

FIP involves multi-system organ damage that is pathogenetically dependent on the disease form. For example, kidney damage in cats is characterised by renal failure (effusive form). Renal dysfunction arises due to oedema caused by disrupted microcirculation and increased vascular permeability mediated by inflammatory mediators (Gülersoy et al., 2023). In the dry form, granulomatous inflammation consisting of lymphocytes, plasma cells, and macrophages is observed in kidney tissue (Gülersoy et al., 2023). The kidneys are among the most affected organs in FIP, especially in the non-effusive form. Ultrasonographic examination of the kidneys in cats with non-effusive FIP reveals morphological and parenchymal changes, including cortical echogenicity, renomegaly, pyelonephritis, distortion of internal structures, loss of corticomedullary differentiation, and cortical nodules (Gülersoy et al., 2023; Müller et al., 2023).

Feline infectious peritonitis induces pathophysiological changes in the gastrointestinal system, including epithelial barrier dysfunction, Peyer's patch damage, and impaired erythrocyte transport. Feline coronavirus replicates in macrophages within the large intestine and directly affects mucosal cells. Inflammatory exudate leads to mucosal oedema and ulcer formation. Absorption dysfunction in the large intestine results in gastrointestinal symptoms such as diarrhoea, abdominal pain, bloating, and anorexia. In some cases, abscess formation in the intestines complicates the disease, leading to lymph node enlargement, infection progression, and sepsis. Ultrasonographic examination of the abdominal cavity in cats with FIP reveals asymmetrical intestinal wall thickening and loss of stratification, with the most significant lesions occurring in the large intestine (Müller et al., 2023). Borisevich et al. (2023) identified small, protruding white spots in the mesentery of the small intestine in FIP-affected cats, consistent across dry and mixed forms. Mesothelial and submesothelial collagen fibre layers on the mesentery surface are necrotic or absent, with fragmented collagen fibres in some areas. Lymphocyte, monocyte, and macrophage infiltrates present in loose connective tissue and mesenteric adipose tissue, along with necrosis and vascular wall destruction (Borisevich et al., 2023).

The liver, heart, and spleen play critical roles in systemic inflammation due to pro-inflammatory cytokine activation and immune system stimulation (Felten & Hartmann, 2019). Researchers have investigated the potential role of hepatocytes in cytokine production. Cats with FIP exhibit elevated acute-phase proteins (CRP, AGP) produced by hepatocytes (Malbon et al., 2019; Rossi, 2023). Histological liver lesions in FIP-affected cats include multifocal or coalescent caseous necrosis, with viral antigens detected in macrophages surrounding necrotic areas (Cony et al., 2024). Ultrasonographic findings include hepatomegaly and hypoechogenicity (Müller et al., 2023). Coronavirus-induced cardiac vasculopathy in cats leads to myocarditis and endocarditis, mediated by IL-1, IL-6, and TNF-α activation (Guarnieri et al., 2024). The inflammatory mediators of the cardiovascular system activate the coagulation cascade, resulting in thrombosis (Guarnieri et al., 2024).

Histological changes in the spleen in cats that succumbed to dry and mixed forms of FIP show no differentiation by disease form, age, or sex, but they correlate with disease duration (Lisova & Kotliarov, 2022). At three weeks of illness, the red pulp of the spleen appears unevenly oedematous and infiltrated by lymphocytes and monocytes, while the white pulp exhibits hyperplasia of lymphoid nodules of varying sizes (Lisova & Kotliarov, 2022). Fibrinous necrotic layers are noted on the organ's capsule, infiltrated by lymphocytes and monocytes (Lisova & Kotliarov, 2022). Beyond three weeks of illness, researchers observe red pulp oedema with sparse nodules (Lisova & Kotliarov, 2022). Ultrasonographic evaluation of the spleen in cats with FIP reveals splenomegaly, hypoechoic nodules, and a mottled parenchyma (Müller et al., 2023).

The liver, heart, and spleen are pivotal in systemic inflammation during FIP, as elevated pro-inflammatory cytokine levels disrupt vascular microcirculation and organ function.

Systemic manifestations of feline infectious peritonitis: Immune-mediated inflammation with the release of pro-inflammatory mediators

The non-specificity of symptoms associated with feline infectious peritonitis complicates its diagnosis. According to research by Solikhah et al. (2024), FIP is a viral infectious disease characterised by non-specific laboratory changes and clinical symptoms (Solikhah et al., 2024). The virulence of the causative agent is difficult to determine solely through clinical signs and a limited number of laboratory tests. Felten & Hartmann (2019) have described the clinical features of FIP in detail. Key symptoms include fever, anorexia, weight loss, yellowish fluid excretions instead of formed faeces, and neurological signs (Felten & Hartmann, 2019). Other researchers note that non-effusive forms exhibit fever, weight loss, and neurological symptoms, whereas effusive forms of FIP commonly involve abdominal distension due to fluid accumulation (Moyadee et al., 2024). Cytological analysis of effusions reveals high protein content and the presence of cells indicative of inflammatory processes (Moyadee et al., 2024).

Biochemical analysis in cats with FIP confirms disruptions in albumin-to-globulin ratios, characterised by hyperglobulinaemia (60%) and hypoalbuminaemia (91%) (Melnyk et al., 2022; Moyadee et al., 2024). In addition to hallmark clinical signs, respiratory symptoms are also observed (Slaviero et al., 2024). The pathogenicity of the virus is

influenced by molecular mechanisms of viral mutation. Mutated FIP virus (FIPV) infects macrophages and infiltrates the interstitial lung tissue, triggering inflammation (Murphy et al., 2024). This leads to interstitial pneumonia, presenting as fluid accumulation in alveoli and interstitial spaces. Respiratory tract involvement manifests with symptoms such as tachypnoea, hypoxia, and dyspnoea (Murphy et al., 2024). Slaviero et al. (2024) highlight that although FIP is a systemic disease, some cats exhibit significant thoracic cavity involvement (Slaviero et al., 2024). Histologically, cats with FIP show lesions in the visceral pleura and pulmonary parenchyma, with diffuse and multifocal patterns. Viral antigen is detected in perivascular and peribronchial macrophages, as well as in macrophages of bronchus-associated lymphoid tissue (Slaviero et al., 2024). In cases of systemic FIPV, pronounced ophthalmic issues may develop. For instance, a case report titled "Feline Infectious Peritonitis with Distinct Ocular Involvement in a Cat in Turkey" describes a fatal case involving severe ocular lesions (Baydar et al., 2014). Clinical signs included absence of pupillary reflex, coordination disturbances, opisthotonus, circling, anisocoria, and the accumulation of dense proteinaceous exudate in the vitreous body of both eyes (Baydar et al., 2014). Pedersen et al. (2019) emphasise that vasculitis and uveitis, including iridocyclitis and chorioretinitis, are key pathological features in the ophthalmic system during FIP (Pedersen et al., 2019; Ergin et al., 2024; Pineda et al., 2024). The pathogenesis of ocular lesions, involving all ocular structures, is mediated by immune-driven inflammation linked to cytokine release: IL-1, IL-6, and TNF-α (Wronski et al., 2023). The hyper-reactive immune response includes the synthesis of immunoglobulins, which subsequently form immune complexes that intensify inflammation by depositing in ocular tissues (Pedersen et al., 2019).

Key immunopathogenetic factors in the development of FIP

Understanding the immunopathogenesis of FIP, including its clinical manifestations, is crucial for developing diagnostic, therapeutic, and preventative approaches to this disease. The immunopathogenesis of FIP is a complex interaction between the mutated feline coronavirus and immune cells, including components of the mononuclear phagocyte system, gut-associated lymphoid tissue (GALT), and other organs such as the liver, intestines, kidneys, spleen, lungs, heart, and central nervous system (ocular system). This interaction leads to systemic inflammatory responses.

Key immunopathogenetic factors include:

Cytokine storm: Activation of FIPV-infected macrophages releasing inflammatory mediators.

Inflammatory vasculitis: Disruption of microcirculation and increased vascular permeability.

Immune complex-mediated damage: Injury to organs caused by antigen-antibody complexes deposited in tissues.

Cellular immune dysfunction: Depressive effects of the virus on T-lymphocytes, leading to persistent infection.

Research prospects for feline infectious peritonitis (FIP) based on pathogenesis data

A comprehensive understanding of the pathogenesis of feline infectious peritonitis (FIP) unveils new opportunities for scientific research aimed at improving existing approaches and developing novel strategies for the prevention, diagnosis, and treatment of FIP (Fig. 1).

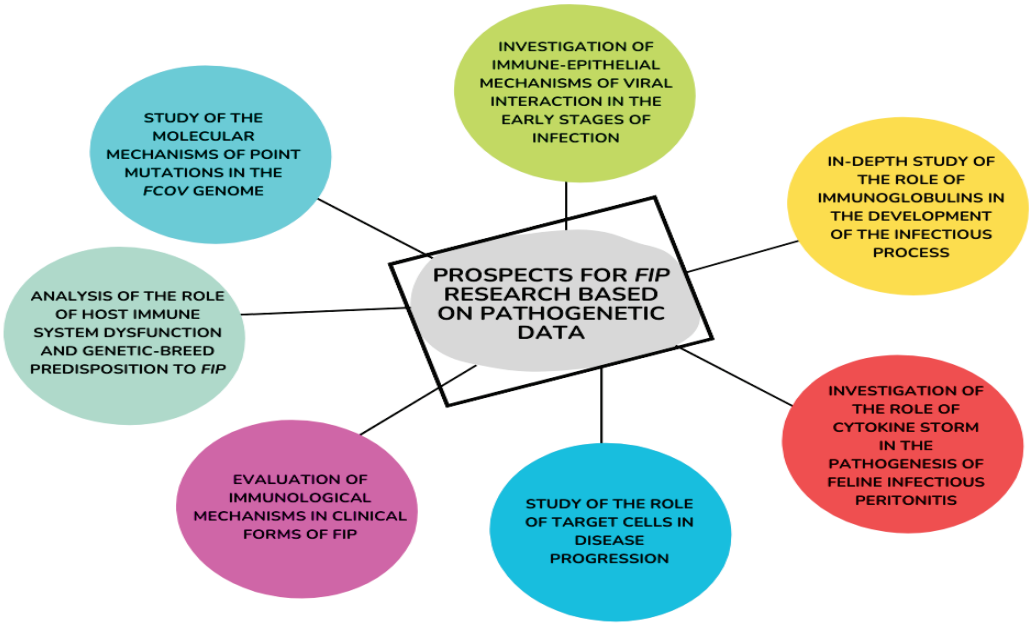

Fig. 1. Prospects for FIP research based on pathogenetic data

The research prospects can be oriented in several directions: Study of the molecular mechanisms of point mutations in the FCoV genome. Such studies will enhance understanding of the reasons behind changes in FCoV virulence, facilitating the development of new diagnostic tools and markers.

Investigation of immune-epithelial mechanisms of viral investigation in the early stages of infection. In-depth analysis of FCoV interactions with epithelial cells will expand knowledge and aid in identifying new therapeutic targets for the pathology.

In-depth study of the role of immunoglobulins in the development of the infection process. Detailed research into antibody-dependent enhancement (ADE) in the pathogenesis of FIP may form the basis for creating immunobiological preparations that prevent or do not provoke ADE.

Investigation of the role of cytokine storms in the pathogenesis of FIP. Investigating the contribution of pro-inflammatory mediators (TNF-α, IL-1β, and IL-6) to systemic inflammation will enhance the understanding of microcirculation disturbances and vascular permeability.

Study of the role of target cells in disease progression. Macrophages play a central role in viral replication, secretion of inflammatory mediators, and the virus's systemic dissemination. Further research into the signalling mechanisms regulating macrophage activation could provide promising therapeutic approaches for FIP.

Evaluationof the immunological mechanisms in clinical forms of FIP. Detailed analysis of immunological heterogeneity in the context of cellular and molecular mechanisms of exudative and non-exudative clinical forms of FIP will enable the identification of specific markers and improvements in early disease diagnosis.

Analysis of the role of host immune system dysfunction and genetic-breed predisposition to FIP. Identifying the mechanisms by which FIPV suppresses adaptive immune responses will allow identi-

fication of risk factors for disease development, potentially linked to the genetic predisposition of certain cat breeds and immune dysfunctions. These approaches will aid in identifying genetic markers that can be used for early disease diagnosis or the selective breeding of animals resistant to this pathology.

Conclusions

Feline infectious peritonitis is a complex infectious disease caused by a mutated feline coronavirus from the Coronaviridae family. The immunopathogenesis of this disease involves a unique interaction between the virus and macrophages, which play a central role in the infection process. FIPV utilises specific receptors to infiltrate macrophages, enabling it to evade immune defences at various levels. Viral persistence and the development of systemic inflammatory processes are facilitated by the inhibition of interferon-mediated immune responses and antibody-dependent enhancement of infection.

The clinical manifestations of FIP result from immune-mediated reactions in various organ systems. Symptom expression depends on the disease form and stage of pathogenesis. Immunopathogenesis demonstrates a complex interplay between viral properties and immune system functionality. Target cells not only facilitate virion replication but also activate systemic inflammatory processes by releasing mediators such as cytokines. The pathogenic potential of FCoV is determined by mutations in its genome for FIPV, while disease progression is exacerbated by impaired adaptive immune responses. Further research into the immunopathogenesis of FIP will be critical in developing and implementing new strategies to combat the disease effectively.

References

Bálint, Á., Farsang, A., Zádori, Z., Hornyák, Á., Dencső, L., Almazán, F., Enjuanes, L., & Belák, S. (2012). Molecular characterization of feline infectious peritonitis virus strain DF-2 and studies of the role of ORF3abc in viral cell tropism. Journal of Virology, 86(11), 6258–6267.

Barker, E. N., Tasker, S., Gruffydd-Jones, T. J., Tuplin, C. K., Burton, K., Porter, E., Day, M. J., Harley, R., Fews, D., Helps, C. R., & Siddell, S. G. (2013). Phylogenetic analysis of feline coronavirus strains in an outbreak of feline infectious peritonitis. Journal of Veterinary Internal Medicine, 27(2), 445–450.

Barker, E., & Tasker, S. (2020). Update on feline infectious peritonitis. In Practice, 42(7), 372–383.

Baş, T. M., Sevinç, M., & Ok, M. (2020). Coronavirus infection in cats. Eurasian Journal of Veterinary Sciences, 36, 106–117.

Baydar, E., Eröksüz, Y., Mö, T., & Eröksüz, H. (2014). Feline infectious peritonitis with distinct ocular involvement in a cat in Turkey. Kafkas Üniversitesi Veteriner Fakültesi Dergisi, 20(6), 961–965.

Borisevich, B., Dzimira, S., Lisova, V., & Kotlyarov, E. (2023). Morphological changes in the small intestine mesentery of cats with infectious peritonitis. Ukrainian Journal of Veterinary Sciences, 14(4), 23–39.

Černá, P., Lobová, D., Bubeníková, J., Vrábelová, J., Molínková, D., & Hořín, P. (2022). Shedding persistency and intensity patterns of feline coronavirus (FCoV) in feces of cats living in breeding catteries in the Czech Republic. Research in Veterinary Science, 152, 524–529.

Chang, H. W., de Groot, R. J., Egberink, H. F., & Rottier, P. J. (2010). Feline infectious peritonitis: Insights into feline coronavirus pathobiogenesis and epidemiology based on genetic analysis of the viral 3c gene. Journal of General Virology, 91(2), 415–420.

Chang, H. W., Egberink, H. F., Halpin, R., Spiro, D. J., & Rottier, P. J. (2012). Spike protein fusion peptide and feline coronavirus virulence. Emerging infectious diseases, 18(7), 1089.

Chen, C. H., Chang, C. C., Chen, W. C., & Lee, Y. J. (2024). Evaluation of chronic stress status and quality of life in cats suffering from chronic kidney disease and suspected feline infectious peritonitis based on hair cortisol concentration analysis and a questionnaire. Veterinary Quarterly, 44(1), 1–9.

Chen, D., López-Pérez, A. M., Vernau, K. M., Maggs, D. J., Kim, S., & Foley, J. (2023). Prevalence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and feline enteric coronavirus (FECV) in shelter-housed cats in the Central Valley of California, USA. Veterinary Record Open, 10(2), e73.

Chen, Y., Zhang, Y., Wang, X., Zhou, J., Ma, L., Li, J., Yang, L., Ouyang, H., Yuan, H., & Pang, D. (2023). Transmissible gastroenteritis virus: An update review and perspective. Viruses, 15(2), 359.

Cony, F. G., Pereira, V. C., Slaviero, M., Lima, R. P., de Castro, L. T., de Moraes, J. T., Aliardi, J. M. G., Driemeier, D., Sonne, L., Panziera, W., & Pavarini, S. P. (2024). Anatomopathological characterization of hepatic lesions of feline infectious peritonitis in cats. Journal of Comparative Pathology, 215, 59–65.

Decaro, N., Mari, V., Lanave, G., Lorusso, E., Lucente, M. S., Desario, C., Colaianni, M. L., Elia, G., Ferringo, F., Alfano F., & Buonavoglia, C. (2021). Mutation analysis of the spike protein in Italian feline infectious peritonitis virus and feline enteric coronavirus sequences. Research in Veterinary Science, 135, 15–19.

Delaplace, M., Huet, H., Gambino, A., & Le Poder, S. (2021). Feline coronavirus antivirals: A review. Pathogens, 10(9), 1150.

Dewerchin, H. L., Cornelissen, E., & Nauwynck, H. J. (2005). Replication of feline coronaviruses in peripheral blood monocytes. Archives of Virology, 150, 2483–2500.

Dong, B., Zhang, X., Song, Y., Li, C., Zhang, G., & Lin, W. (2022). Genomic and phylogenetic analysis of the ORF7b gene from a Chinese feline infectious peritonitis virus isolate. The Thai Journal of Veterinary Medicine, 52(2), 303–309.

Drechsler, Y., Alcaraz, A., Bossong, F. J., Collisson, E. W., & Diniz, P. P. V. (2011). Feline coronavirus in multicat environments. Veterinary Clinics of North America: Small Animal Practice, 41(6), 1133–1169.

Drechsler, Y., Vasconcelos, E. J., Griggs, L. M., Diniz, P. P., & Collisson, E. (2020). Host gene expression of macrophages in response to feline coronavirus infection. Cells, 9(6), 1431.

Ehmann, R., Kristen-Burmann, C., Bank-Wolf, B., König, M., Herden, C., Hain, T., Thiel, H., Ziebuhr, J., & Tekes, G. (2018). Reverse genetics for type I feline coronavirus field isolate to study the molecular pathogenesis of feline infectious peritonitis. MBio, 9(4), 01422-18.

Ergin, İ. R. E. M., Sainkaplan, S., Sayim, A. A., & Şenel, O. O. (2024). Suspicion of feline infectious peritonitis in cats with uveitis: Diagnostic value of coronavirus antibodies and blood parameters. Kafkas Üniversitesi Veteriner Fakültesi Dergisi, 30(6), 769–777.

Falchieri, M., Coward, V. J., Reid, S. M., Lewis, T., & Banyard, A. C. (2024). Infectious bronchitis virus: An overview of the "chicken coronavirus". Journal of Medical Microbiology, 73(5), 001828.

Felten, S., & Hartmann, K. (2019). Diagnosis of feline infectious peritonitis: A review of the current literature. Viruses, 11(11), 1068.

Felten, S., Klein-Richers, U., Unterer, S., Bergmann, M., Zablotski, Y., Hofmann-Lehmann, R., & Hartmann, K. (2023). Patterns of feline coronavirus shedding and associated factors in cats from breeding catteries. Viruses, 15(6), 1279.

Gu, G., Fung, T. S., Hung, W. T., Osterrieder, N., & Go, Y. Y. (2024). Development and characterization of reverse genetics systems of feline infectious peritonitis virus for antiviral research. Veterinary Research, 55, 124.

Guarnieri, C., Bertola, L., Ferrari, L., Quintavalla, C., Corradi, A., & Di Lecce, R. (2024). Myocarditis in an FIP-diseased cat with FCoV M1058L mutation: Clinical and pathological changes. Animals, 14(11), 1673.

Gülersoy, E., Balıkçı, C., Kısmet, E., Günal, İ., Şahan, A., Güçlü, M. A., & Ok, M. (2023). Renal ultrasonography findings in cats with feline infectious peritonitis. Van Veterinary Journal, 34(1), 63–69.

Gülersoy, E., Ok, M., Üney, K., Durgut, M. K., Parlak, T. M., & Ekici, Y. E. (2023). Intestinal injury and vasculitis biomarkers in cats with feline enteric coronavirus and effusive feline infectious peritonitis. Veterinary Medicine and Science, 9(6), 2420–2429.

Hartmann, K. (2005). Feline infectious peritonitis. Veterinary Clinics of North America: Small Animal Practice, 35(1), 39–79.

Hohdatsu, T., Yamada, M., Tominaga, R., Makino, K., Kida, K., & Koyama, H. (1998). Antibody-dependent enhancement of feline infectious peritonitis virus infection in feline alveolar macrophages and human monocyte cell line U937 by serum of cats experimentally or naturally infected with feline coronavirus. Journal of Veterinary Medical Science, 60(1), 49–55.

Holzworth J. E. (1963). Some important disorders of cats. Cornell Veterinarian, 53, 157–160.

Hu, T., Zhang, H., Zhang, X., Hong, X., & Zhang, T. (2024). Prevalence and risk factors associated with feline infectious peritonitis (FIP) in Mainland China between 2008 and 2023: A systematic review and meta-analysis. Animals, 14(8), 1220.

Jähne, S., Felten, S., Bergmann, M., Erber, K., Matiasek, K., Meli, M. L., Hofmann-Lehmann, R., & Hartmann, K. (2022). Detection of feline coronavirus variants in cats without feline infectious peritonitis. Viruses, 14(8), 1671.

Jaimes, J. A., & Whittaker, G. R. (2018). Feline coronavirus: Insights into viral pathogenesis based on the spike protein structure and function. Virology, 517, 108–121.

Jaimes, J. A., Millet, J. K., Stout, A. E., André, N. M., & Whittaker, G. R. (2020). A tale of two viruses: The distinct spike glycoproteins of feline coronaviruses. Viruses, 12(1), 83.

Jiao, Z., Wang, P., Hu, X., Chen, Y., Xu, J., Zhang, J., Benyuan, W., Ruxu, L., Yuejun, S., & Peng, G. (2024). Feline infectious peritonitis virus ORF7a is

a virulence factor involved in inflammatory pathology in cats. Antiviral Research, 222, 105794.
Kennedy, M. A. (2020). Feline infectious peritonitis: Update on pathogenesis, diagnostics, and treatment. Veterinary Clinics of North America: Small Animal Practice, 50(5), 1001–1011.
Kennedy, M. A., Abd-Eldaim, M., Zika, S. E., Mankin, J. M., & Kania, S. A. (2008). Evaluation of antibodies against feline coronavirus 7b protein for diagnosis of feline infectious peritonitis in cats. American Journal of Veterinary Research, 69(9), 1179–1182.
Kennedy, U., Paterson, M. B. A., Magalhaes, R. S., Callaghan, T., & Clark, N. (2024). A scoping review of the evidence on prevalence of feline upper respiratory tract infections and associated risk factors. Veterinary Sciences, 11(6), 232.
Kipar, A., & Meli, M. L. (2014). Feline infectious peritonitis: still an enigma? Veterinary Pathology, 51(2), 505–526.
Klein-Richers, U., Hartmann, K., Hofmann-Lehmann, R., Unterer, S., Bergmann, M., Rieger, A., Leutenegger, C., Pantchev, N., Balzer, J., & Felten, S. (2020). Prevalence of feline coronavirus shedding in German catteries and associated risk factors. Viruses, 12(9), 1000.
Lin, L., Yao, D., Wu, L., Fan, R., Liu, Y., & Zhou, Z. (2022). Molecular epidemiology of type I and II feline coronavirus from cats with suspected feline infectious peritonitis in China between 2019 and 2021. Archives of Virology, 167(1), 189–194.
Lisova, V., & Kotliarov, E. (2022). Microscopic changes in the spleen due to feline infectious peritonitis. Ukrainian Journal of Veterinary Sciences, 13(4), 35–41.
Lombardi, A. F., Afsahi, A. M., Gupta, A., & Gholamrezanezhad, A. (2021). Severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), influenza, and COVID-19, beyond the lungs: A review article. La Radiologia Medica, 126, 561–569.
Malbon, A. J., Fonfara, S., Meli, M. L., Hahn, S., Egberink, H., & Kipar, A. (2019). Feline infectious peritonitis as a systemic inflammatory disease: Contribution of liver and heart to the pathogenesis.Viruses, 11(12), 1144.
Mangiaterra, S., Gavazza, A., Biagini, L., & Rossi, G. (2024). Study of macrophage activity in cats with FIP and naturally FCoV-shedding healthy cats. Pathogens, 13(6), 437.
Melnyk, V., Martyniuk, O., Bodnar, A., & Bodnar, M. (2022). Epizootological features of coronavirus infection in cats. Ukrainian Journal of Veterinary Sciences, 13(1), 52–60.
Melnyk, V., Mickiewicz, M., Martyniuk, O., Bodnar, A., & Bodnar, M. (2022). Morphological and biochemical changes in blood parameters in cats with infectious peritonitis. Ukrainian Journal of Veterinary Sciences, 13(3), 42–49.
Moyadee, W., Sunpongsri, S., Choowongkomon, K., Roytrakul, S., Rattanasrisomporn, A., Tansakul, N., & Rattanasrisomporn, J. (2024). Feline infectious peritonitis: A comprehensive evaluation of clinical manifestations, laboratory diagnosis, and therapeutic approaches. Journal of Advanced Veterinary and Animal Research, 11(1), 19–26.
Müller, T. R., Penninck, D. G., Webster, C. R., & Conrado, F. O. (2023). Abdominal ultrasonographic findings of cats with feline infectious peritonitis: An update. Journal of Feline Medicine and Surgery, 25(12), 1098612X231216000.
Murphy, B. G., Castillo, D., Neely, N. E., Kol, A., Brostoff, T., Grant, C. K., & Reagan, K. L. (2024). Serologic, virologic and pathologic features of cats with naturally occurring feline infectious peritonitis enrolled in antiviral clinical trials. Viruses, 16(3), 462.
Myrrha, L. W., Silva, F. M. F., Vidigal, P. M. P., Resende, M., Bressan, G. C., Fietto, J. L. R., Santos, M. R., Silva, L. M. N, Assao, V. S., Silva Junior, A., & de Almeida, M. R. (2019). Feline coronavirus isolates from a part of Brazil: Insights into molecular epidemiology and phylogeny inferred from the 7b gene. Journal of Veterinary Medical Science, 81(10), 1455–1460.
Ouyang, H., Liu, J., Yin, Y., Cao, S., Yan, R., Ren, Y., Zhou, D., Li, Q., Li, J., Liao, X., Ji, W., Du, B., Si, Y., & Hu, C. (2022). Epidemiology and comparative analyses of the S gene on feline coronavirus in Central China. Pathogens, 11(4), 460.
Paltrinieri, S., Giordano, A., Stranieri, A., & Lauzi, S. (2021). Feline infectious peritonitis (FIP) and coronavirus disease 19 (COVID-19): Are they similar? Transboundary and Emerging Diseases, 68(4), 1786–1799.
Pedersen, N. C. (2014). An update on feline infectious peritonitis: Virology and immunopathogenesis. The Veterinary Journal, 201(2), 123–132.
Pedersen, N. C., Liu, H., Scarlett, J., Leutenegger, C. M., Golovko, L., Kennedy, H., & Kamal, F. M. (2012). Feline infectious peritonitis: Role of the feline coronavirus 3c gene in intestinal tropism and pathogenicity based upon isolates from resident and adopted shelter cats. Virus Research, 165(1), 17–28.
Pedersen, N. C., Perron, M., Bannasch, M., Montgomery, E., Murakami, E., Liepnieks, M., & Liu, H. (2019). Efficacy and safety of the nucleoside analog GS-441524 for treatment of cats with naturally occurring feline infectious peritonitis. Journal of Feline Medicine and Surgery, 21(4), 271–281.
Pineda, A. M., Lavergne, E., Brauge, C., Laveran, E., Bertagnoli, S., Boucraut-Baralon, C., & Bessière, P. (2024). Feline coronavirus-associated uveitis: The eye as a gateway to systemic spread and feline infectious peritonitis? Veterinary Microbiology, 301, 110355.
Prince, T., Smith, S. L., Radford, A. D., Solomon, T., Hughes, G. L., Patterson, E. I. (2021). SARS-CoV-2 infections in animals: Reservoirs for reverse zoonosis and models for study. Viruses, 13, 494.
Ramezanpour Eshkevari, S., Sasani, F., Shokrpoor, S., Mardjanmehr, S. H., Akbarein, H., & Ashrafi, I. (2024). A histopathological study on the changes in the central nervous system of dead cats with neurological symptoms. Iranian Journal of Veterinary Medicine, 18(4), 545–554.
Regan, A. D., Ousterout, D. G., & Whittaker, G. R. (2010). Feline lectin activity is critical for the cellular entry of feline infectious peritonitis virus. Journal of Virology, 84(15), 7917–7921.
Riemer, F., Kuehner, K. A., Ritz, S., Sauter-Louis, C., & Hartmann, K. (2016). Clinical and laboratory features of cats with feline infectious peritonitis – a retrospective study of 231 confirmed cases (2000–2010). Journal of Feline Medicine and Surgery, 18(4), 348–356.
Rossi, G. (2023). Acute phase proteins in cats: Diagnostic and prognostic role, future directions, and analytical challenges. Veterinary Clinical Pathology, 52, 37–49.
Rottier, P. J., Nakamura, K., Schellen, P., Volders, H., & Haijema, B. J. (2005). Acquisition of macrophage tropism during the pathogenesis of feline infectious peritonitis is determined by mutations in the feline coronavirus spike protein. Journal of Virology, 79(22), 14122–14130.
Shi, J., Wen, Z., Zhong, G., Yang, H., Wang, C., Liu, R., He, X,. Shuai, L., Sun, Z., Zhao, Y., Liang, L., Cui, P., Wang, J., Zhang, X., Guan, Y., Chen, H., Bu, Z., & Chen, H. (2020). Susceptibility of ferrets, cats, dogs, and different domestic animals to SARS-coronavirus-2. Science, 368(6469), 1016–1020.
Slaviero, M., Cony, F. G., da Silva, R. C., De Lorenzo, C., de Almeida, B. A., Bertolini, M., Driemeier, D., Pavarini, S., & Sonne, L. (2024). Pathological findings and patterns of feline infectious peritonitis in the respiratory tract of cats. Journal of Comparative Pathology, 210, 15–24.
Solikhah, T. I., Dwi Agustin, Q. A., Damaratri, R. A., Fika Siwi, D. A., Rafi'uttaqi, G. N., Hartadi, V. A., & Solikhah, G. P. (2024). A review of feline infectious peritonitis virus infection. Veterinary World, 17(11), 2417–2432.
Sweet, A. N., André, N. M., Stout, A. E., Licitra, B. N., & Whittaker, G. R. (2022). Clinical and molecular relationships between COVID-19 and feline infectious peritonitis (FIP). Viruses, 14(3), 481.
Takano, T., Nakaguchi, M., Doki, T., & Hohdatsu, T. (2017). Antibody-dependent enhancement of serotype II feline enteric coronavirus infection in primary feline monocytes. Archives of Virology, 162, 3339–3345.
Takano, T., Wakayama, Y., & Doki, T. (2019). Endocytic pathway of feline coronavirus for cell entry: Differences in serotype-dependent viral entry pathway. Pathogens, 8(4), 300.
Takano, T., Yamada, S., Doki, T., & Hohdatsu, T. (2019). Pathogenesis of oral type I feline infectious peritonitis virus (FIPV) infection: Antibody-dependent enhancement infection of cats with type I FIPV via the oral route. Journal of Veterinary Medical Science, 81(6), 911–915.
Tekes, G., & Thiel, H. J. (2016). Feline coronaviruses: Pathogenesis of feline infectious peritonitis. Advances in Virus Research, 96, 193–218.
Terada, Y., Kuroda, Y., Morikawa, S., Matsuura, Y., Maeda, K., & Kamitani, W. (2019). Establishment of a virulent full-length cDNA clone for type I feline coronavirus strain C3663. Journal of Virology, 93(21), 01208-19.
Thayer, V., Gogolski, S., Felten, S., Hartmann, K., Kennedy, M., & Olah, G. A. (2022). 2022 AAFP/EveryCat feline infectious peritonitis diagnosis guidelines. Journal of Feline Medicine and Surgery, 24(9), 905–933.
Vlasova, A. N., & Saif, L. J. (2021). Bovine coronavirus and the associated diseases. Frontiers in Veterinary Science, 8, 643220.
Wronski, J. G., de Cecco, B. S., Raiter, J., Henker, L. C., de Lorenzo, C., Bandinelli, M. B., Driemeier, D., Pavarini, S., & Sonne, L. (2023). Ophthalmic and immunopathological characterization of systemic infectious diseases in cats. Veterinary Pathology, 60(3), 352–359.
Xing, N., Wang, Z., Wang, J., Nascimento, M., Jongkaewwattana, A., Trimpert, J., Osterrieder, N., & Kunec, D. (2022). Engineering and characterization of avian coronavirus mutants expressing fluorescent reporter proteins from the replicase gene. Journal of Virology, 96(14), e00653-22.
Yang, H., Peng, Q., Lang, Y., Du, S., Cao, S., Wu, R., Zhao, Q., Huang, X., Wen, Y., Lin., J., Zhao, S., & Yan, Q. (2022). Phylogeny, evolution, and transmission dynamics of canine and feline coronaviruses: A retro-prospective study. Frontiers in Microbiology, 13, 850516.
Zhao, Y., Yang, Y., Gao, J., Huang, K., Hu, C., Hui, X., & Jin, M. (2022). A serological survey of severe acute respiratory syndrome coronavirus 2 in dogs in Wuhan. Transboundary and Emerging Diseases, 69(2), 591–597.