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Diagnosis and Treatment of Feline Infectious Peritonitis

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Abstract: Feline infectious peritonitis (FIP), caused by feline coronavirus (FCoV), remains a devastating disease with high mortality and no universally effective treatment. This research was undertaken to understand FIP pathogenesis and to evaluate emerging solutions, particularly focusing on innovative vaccine designs and antiviral treatments. The growing evidence of successful clinical interventions highlights both the progress made and the critical gaps remaining in FIP management. This research systematically examines FIP's complex pathogenesis, involving viral mutations (particularly in the spike protein) and immune dysregulation mechanisms. It explores four major vaccine approaches, including multi-epitope vaccines targeting immunodominant regions, live-attenuated vaccines with gene deletions, mutation-based spike protein vaccines, and VNAR antibody therapies. For treatment, this research analyzes three key strategies, including antiviral drugs (GS-441524 and GC376), lysosomal pH modulators (CQ/HCQ), and supportive care protocols. Each section presents experimental evidence while noting limitations such as variable efficacy, safety concerns, and the need for further validation. Special attention is given to comparative effectiveness between different treatment modalities and the challenges of clinical translation. This comprehensive analysis provides valuable insights for researchers developing next-generation FIP interventions. The identified promising directions, particularly combination therapies and structure-based vaccine design, may inform future human coronavirus research. Ultimately, this work contributes to the global effort to transform FIP from a fatal diagnosis to a manageable condition, with implications extending beyond feline medicine to broader virology and immunology fields.

Keywords: Feline infectious peritonitis, Feline coronavirus, Vaccine design, Antiviral therapy, Immune response

1. Introduction

Feline infectious peritonitis (FIP) is a fatal disease caused by feline coronavirus (FCoV). FIP primarily consists of two biotypes, including feline enteric coronavirus (FECV) and feline infectious peritonitis virus (FIPV). FECV typically causes mild intestinal infections, whereas FIPV leads to systemic and fatal peritonitis.

The pathogenesis of FIP is complex, involving genetic mutations of the virus, abnormal responses of the host immune system, and interactions between the virus and host cells. Research indicates that mutations in the spike protein may be one of the key factors contributing to the pathogenicity of FIPV. These mutations enable the virus to infect macrophages and further promote viral replication through the antibody-dependent enhancement (ADE) mechanism. Additionally, FIPV infection triggers

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abnormal responses in the host immune system, including programmed cell death of T lymphocytes, suppression of NK cells and regulatory T cells, and the effects of antibody-dependent cellular cytotoxicity (ADCC) [1].

The clinical manifestations of FIP are diverse, including vasculitis, body cavity effusions, and fibrinous and granulomatous inflammatory lesions. These symptoms reflect the severe impact of viral infection on the feline immune system and inflammatory processes. Due to the extremely high fatality rate of FIP and the current lack of effective vaccines or treatments, to investigate its pathogenesis and developing new therapeutic strategies are of paramount importance.

Currently, significant progress has been made in the treatment and research of FIP, yet many challenges remain. In the field of antiviral drugs, GS-441524, a nucleoside analog, has demonstrated potent inhibitory effects against FIP virus in vitro and experimental infections. Studies indicate that GS-441524 shows certain efficacy in treating naturally occurring FIP, particularly when administered in the early stages [2]. However, its long-term efficacy and safety require further investigation. Another antiviral drug, Remdesivir (GS-5734), which has shown potential in treating COVID-19, is also being explored for FIP treatment. In the realm of immunomodulators, polyethylene immunostimulants have been shown to extend the survival time and improve the quality of life in cats with dry-form FIP. Additionally, anti-TNF-alpha monoclonal antibodies, which inhibit inflammatory responses, hold potential value in FIP treatment [3].

Furthermore, multi-component drugs such as Mutian®X and Mutian®Mor have shown some effectiveness in reducing feline coronavirus shedding in cat feces. However, their specific mechanisms and long-term efficacy still require further research [2]. Overall, while these treatment methods have improved the survival time and quality of life for patients to some extent, many unresolved issues remain. Although vaccine development faces challenges, the feasibility of future vaccine development is high. Through further research and technological breakthroughs, more effective prevention and treatment strategies for FIP are anticipated.

This research aims to explore and design a novel vaccine for the prevention and treatment of FIP. There are no effective vaccines or treatments available for this disease. Based on the pathogenesis of FIP, particularly the critical role of the viral spike protein (S protein) in infection and immune evasion, this research will focus on designing a vaccine targeting the antigenic epitopes of the S protein. This research will explore the vaccine's broad-spectrum protection against different FIPV mutant strains and assess its safety and long-term immune effects. This research hopes to provide an innovative vaccine strategy for the prevention and treatment of FIP, contributing to the improvement of feline health.

2. Vaccine design

2.1. Immunoinformatics-based multi-epitope vaccine

A multi-epitope vaccine targeting the spike (S) protein of FIPV was designed by using computational techniques [4]. The immunoinformatics tools were used to analyze the S protein and identify highly antigenic T-cell epitopes capable of binding to feline MHC-I molecules (Figure 1). After screening thousands of possible epitopes, they selected 11 that were predicted to be antigenic, non-toxic, and non-allergenic. These selected epitopes were then linked together with appropriate adjuvants, such as FimH and CtxB, to enhance the immune response. The researchers used molecular docking and molecular dynamics simulations to evaluate the vaccine’s stability and its ability to bind feline Toll-like receptor 4 (TLR4). The results suggested that the vaccine could strongly interact with TLR4, theoretically triggering an effective immune response. This study's advantage is its ability to quickly identify potential vaccine candidates through computational modeling, saving time compared to traditional vaccine development. A multi-epitope approach could provide broader protection against

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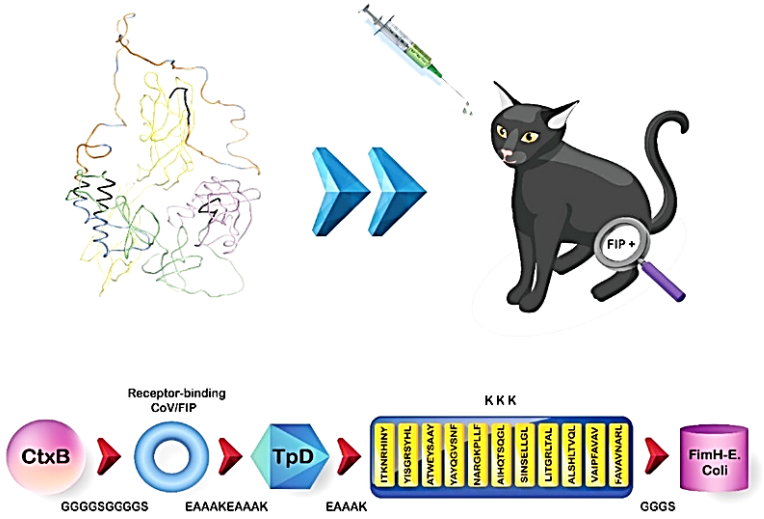
FIPV. However, this study is still in the theoretical phase, and the vaccine has not yet been tested in animal models. Without experimental validation, it remains uncertain whether this approach will be effective in real-world conditions. Further laboratory and clinical testing are needed to confirm its safety and immunogenicity.



Number of Amino acids: 744
Mol. Wt.: 79KDa
pI: 9.44
Instability Index: 27.34 (stable)
Aliphatic index: 89.14
Predicted Probability of Antigenicity: 0.9053
Estimated half-life: 30 hours (mammalian reticulocytes, in vitro) and > 20 hrs in yeast (in vivo), and > 10 hrs in E.Coli (in vivo)
Avg. Hydropathicity: -0.056

TpD adjuvant:
ILMQYIKANSKFIGIPMGLPQSIALSSLMVAQ

Receptor-binding CoV/FIP:
VIYEEGDNIVGVPSDNSGLHDLSVLHLDSCTDYNIYG
RTGVGIIRRTNSTLLSGLYYTSLSGDLLGFKNVSDGVIY
SVTPCDVSAQAAVIDGAIVGAMTSINSELLGLTHWT
TTPNFYYYSIYNYTSERTRGTAIDSNDVDCEPV

CtxB:MIKLKFGVFFTVLLSSAYAHGTPQNITDLCAEYHNTQIYTLNDKIFSYTESLAGKREMAIITFKNGAIFQVEVPGSQHIDSQKKAIERMKDTLRIAYLTEAK
VEKLCVWNNKTPHAIAAISMAN

FimH-E.Coli
FACKTANGTAIPIGGGSANVYVNLAPVVNVGQNLVVDLSTQIFCHNDYPETITDYVTLQRGSAYGGVLSNFSGTVKYSGSSYPFPTTSETPRVVYNSR
TDKPWPVALYLTPVSSAGGVAIKAGSLIAVLILRQTNNYNSDDFQFVWNIYANNDVVVPTGGCDVSARDVTVTLPDYPGSVPIPLTVYCAKSQNLGY
YLSGTTADAGNSIFTNTASFSPAQGVGVQLTRNGTIIPANNTVSLGAVGTSAVSLGLTANYARTGGQVTAGNVQSIIGVTFVYQ

Figure 1: Schematic illustration of the designed FIPV-MEV construct [4]

2.2. Live attenuated vaccine based on gene deletion

A live attenuated vaccine was designed [5]. Using reverse genetics and targeted RNA recombination, they generated mutant viruses that lacked these gene clusters. These mutant viruses showed effective replication in cell cultures while exhibiting an attenuated phenotype in cats. Cats infected with these attenuated viruses did not develop FIP symptoms, but they produced high levels of neutralizing antibodies, indicating an immune response. Challenge experiments showed that the virus lacking the 3abc gene cluster provided strong protection, while the one lacking 7ab had a weaker protective effect. The double-deletion virus (3abc/7ab) was highly attenuated but failed to offer effective immunity. This study demonstrated that deleting specific genes could weaken FIPV while still inducing an immune response. The strength of this study h lies in its experimental validation in cats, proving that a live attenuated vaccine is feasible. However, some mutants had limited immunogenicity, requiring further optimization. The long-term safety and effectiveness of these vaccines in real-world conditions remain uncertain and require further investigation.

2.3. Vaccine design based on mutation of spiny protein

A vaccine was designed by analyzing genetic mutations in systemically disseminated FCoV through experimental infection of healthy cats, exploring its link to FIP [6]. SPF cats were infected with two field-isolated FCoV strains (Zu1 and Zu3), and tissue and fecal samples were collected 14–80 days post-infection. Viral loads were measured via RT-qPCR, and ORF3abc, ORF7b, and the S gene were sequenced, focusing on known FIP-associated mutations. No typical FIP-related mutations (e.g.,

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ORF3c deletions and S gene mutations) were found, but extensive SNPs and some truncating mutations were detected. A novel recombination site in the Zu1 strain suggested viral recombination may influence pathogenicity. The study challenged the view that specific mutations directly cause FIP, emphasizing virus-host interactions. Using molecular cloning and phylogenetic analysis, it revealed FCoV's dynamic mutations in the host. However, the small sample size (7 cats) and lack of natural FIP cases limited generalizability. Some S gene regions couldn't be fully sequenced, possibly missing key mutations. Further studies integrating host immunogenomics and high-throughput sequencing are needed to fully understand FIP mechanisms.

2.4. Antigen-specific VNAR screening and vaccine development

An efficient yeast surface dual-display platform was developed in a study aimed at rapidly screening shark-derived single-domain antibodies, known as Variable Domain of New Antigen Receptor (VNARs) [7]. The platform utilized a semi-synthetic VNAR library with a diversity of 1.97×10^9, as validated by next-generation sequencing (NGS). The CDR3 region of the VNARs in the library was randomized using NNK saturation mutagenesis, and the VNARs were co-expressed with green fluorescent protein (GFP) through yeast surface display technology, enabling the monitoring of antibody expression levels via GFP fluorescence. The researcher screened for VNAR antibodies specific to the feline neonatal Fc receptor (fFeRn) and the nucleocapsid protein of FIPV. NGS analysis of the frequency changes in CDR3 genes before and after screening revealed that biopanning significantly enhanced the enrichment of high-affinity sequences, ultimately validating the antigen-binding capacity of four candidate VNARs. This method does not rely on shark immunization or long-term animal breeding but allows for the rapid acquisition of functional antibodies through in vitro synthesis and screening. The incorporation of the GFP tag simplified the detection process for expression levels, while the application of NGS enabled a systematic analysis of library diversity and screening outcomes. The study successfully isolated VNARs specific to fFeRn and the FIPV nucleocapsid protein, and their binding specificity was confirmed through cellular fluorescence experiments. Although the library exhibited high diversity, the number of effectively screened antibodies was limited, possibly due to yeast transformation efficiency or random biases in library design. Tthe affinity and stability of the candidate antibodies require further optimization, and their therapeutic efficacy has yet to be validated in animal models.

Overall, recent studies on the design of vaccines for FIP have focused on multi-epitope vaccines, live attenuated vaccines, vaccines with spiked protein mutations, and VNAR screening techniques. These studies provide an important scientific basis and technical support for the development of more efficient and safer FIP vaccines, but further experimental validation and optimization are still needed for clinical application.

3. Treatment methods

3.1. Antiviral drugs: protease inhibitors and nucleoside analogs

Among protease inhibitors, GC376 has emerged as a particularly effective option by targeting the viral 3C-like protease, which is essential for viral replication [8]. In vitro studies demonstrated its potent activity with IC50 values ranging from 0.04 to 0.4 μM, and clinical trials showed remission in 7 out of 20 naturally infected cats, although relapses were observed in some cases. Resistance to GC376 was rare, with only minor mutations detected in viral protease sequences. Another protease inhibitor, nelfinavir, originally developed for HIV, also exhibited inhibitory effects against FCoV-II, albeit with lower efficacy (IC50: 8.19 μM) compared to its activity against SARS-CoV.

On the other hand, nucleoside analogues like GS-441524, an adenosine analogue, have shown remarkable promise in treating FIP [8]. With IC50 values between 0.78 and 3.5 μM, GS-441524

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achieved remission in approximately 80% of cats with non-neurological FIP in clinical trials, and higher doses (5-10 mg/kg) were effective in some neurological cases. Its parent compound, remdesivir, has also been explored, while ribavirin, another nucleoside analogue, proved too toxic for feline use. Despite their efficacy, challenges such as viral resistance and uneven tissue distribution persist, prompting researchers to investigate combination therapies to enhance outcomes. The success of GS-441524 and GC376 not only offers hope for FIP treatment but also provides valuable insights for developing therapies against other coronaviruses.

3.2. Lysosomal pH regulators: chloroquine and hydroxychloroquine

Chloroquine (CQ) and its derivative hydroxychloroquine (HCQ) function as lysosomal pH modulators by inhibiting endosomal acidification, thereby disrupting the fusion of viral and cellular membranes during FCoV entry [8]. In vitro studies demonstrated that CQ exhibited potent antiviral activity against FIPV-II strain 79-1146, with an IC50 of 0.38 μM at 24 hours post-infection (p.i.) and a high selectivity index (SI) of 216 (CC50: 82.31 μM). HCQ, while less cytotoxic (CC50: 515.7 μM), showed slightly reduced efficacy against FIPV-I (IC50: 48.7 μM) and FIPV-II (IC50: 30.3 μM). Both compounds were most effective when administered prior to or during viral entry, losing potency if delayed by 1-hour post-infection. In vivo, CQ (10 mg/kg subcutaneously) extended survival in experimentally infected cats by approximately 10-13 days compared to controls, though all eventually succumbed to FIP. Notably, CQ-treated cats exhibited elevated alanine aminotransferase (ALT) levels, indicating potential hepatotoxicity. HCQ, while safer, has not been tested in vivo for FIP. Despite their limitations—including incomplete efficacy and side effects—CQ and HCQ highlight the therapeutic potential of targeting host cell pathways, particularly for combination therapies. Their broader anti-coronavirus activity (e.g., against SARS-CoV-2) further underscores their relevance in antiviral research.

3.3. Supportive care and symptomatic management

In cases of effusive FIP, characterized by golden-yellow gelatinous ascites, therapeutic drainage may alleviate discomfort, though it is palliative and does not address the underlying viral pathology. Concurrently, nutritional support is critical [9], as affected cats often present with weight loss and anorexia. High-calorie, easily digestible diets and appetite stimulants are recommended to combat malnutrition and support immune function. For anti-inflammatory and immunomodulatory adjuncts, corticosteroids (e.g., prednisolone) are frequently employed to mitigate granulomatous inflammation and systemic immune hyperactivation, particularly in the proliferative form of FIP [9]. However, their use remains controversial due to potential immunosuppression. The study notes the presence of lymphoid hyperplasia and fibrinoid-necrotic granulomas, suggesting a dysregulated immune response. While immunosuppressants like cyclosporine have been explored, their efficacy is limited, and they may exacerbate concurrent infections (e.g., FeLV). Immunostimulants such as feline interferon-omega (IFN-ω) have shown anecdotal benefits in reducing viral load and modulating Th1 responses, though evidence from controlled studies is lacking.

4. Conclusion

FIP is a complex and fatal disease caused by FCoV, which exists in two primary biotypes, including the relatively benign FECV and the highly pathogenic FIPV. The pathogenesis of FIP involves critical viral mutations, particularly in the S protein, which enable macrophage infection and trigger immune dysregulation through mechanisms such as ADE. Clinically, FIP manifests as severe systemic inflammation, vasculitis, and effusions, with a near-100% fatality rate in untreated cases.

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Recent research has focused on developing innovative vaccines and treatments to combat FIP. Here are some vaccine strategies. A multi-epitope vaccine can be designed using immunoinformatics to target antigenic regions of the S protein, which showed strong theoretical binding to feline TLR4. Live attenuated vaccines can be created through targeted gene deletions (e.g., 3abc and 7ab), some of which induced protective immunity in cats. VNAR-based therapies can be developed, where shark-derived single-domain antibodies were screened for targeting FIPV nucleocapsid proteins. However, these approaches remain in experimental stages, requiring further validation for safety and efficacy.
In treatment, antiviral drugs such as the nucleoside analog GS-441524 and protease inhibitor GC376 have demonstrated significant success, achieving remission in many cases, though challenges like viral resistance and tissue distribution persist. Lysosomal pH regulators (e.g., chloroquine) showed limited efficacy in delaying disease progression, while supportive care (e.g., effusion drainage and immunomodulators) remains palliative but critical for managing symptoms.
Despite these advancements, major hurdles remain, including the need for more effective vaccines, optimized drug regimens, and a deeper understanding of FIPV-host interactions. Future research should prioritize large-scale clinical trials, combination therapies, and novel immunomodulatory strategies to improve outcomes for this devastating disease.

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