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Immune Evasion Mechanisms of Feline Herpesvirus 1 (FHV-1) and their implications for next-generation vaccine development

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Abstract

Feline Herpesvirus 1 (FHV-1), an alphaherpesvirus belonging to the family *Herpesviridae*, is the primary etiological agent of Feline Viral Rhinotracheitis (FVR), causing severe upper respiratory tract and ocular diseases in felids worldwide. Despite the widespread use of conventional vaccines, FHV-1 remains endemic due to its evolutionary capacity to establish life-long latent infections within the trigeminal ganglia and intermittently reactivate under stressful conditions. This persistence is facilitated by a sophisticated array of immune evasion strategies that neutralize both innate and adaptive host immune responses. Crucial to this process are specific viral envelope glycoproteins (gB, gC, gD, gE, gG, gH, and gL) which mediate attachment, fusion, and direct cell-to-cell spread, thereby minimizing exposure to extracellular neutralizing antibodies. Furthermore, FHV-1 actively interferes with host defense mechanisms by downregulating Major Histocompatibility Complex (MHC) Class I expression to escape CD8+ cytotoxic T lymphocyte surveillance and suppressing innate type I interferon (IFN-α/β) signaling cascades. From a translational perspective, understanding these molecular interactions is vital for upgrading current diagnostic tools and designing next-generation vaccine platforms, including gene-deleted mutants (e.g., thymidine kinase-deficient strains), subunit formulations, and viral-vectored or mRNA technologies. This review comprehensively synthesizes the current knowledge on FHV-1-host immunobiological interactions, structural virulence factors, and latency dynamics, while highlighting critical pathways to overcome the limitations of current vaccinology strategies and achieve sterile immunity.

Keywords: Feline Herpesvirus 1; Immune Evasion; Latency; Viral Glycoproteins; Translational Vaccinology; Next-Generation Vaccines.

1. Introduction

Feline Herpesvirus 1 (FHV-1) is a major, ubiquitous pathogen affecting domestic and wild felids globally [1]. As a member of the *Varicellovirus* genus within the *Alphaherpesvirinae* subfamily, FHV-1 is characterized by a double-stranded DNA genome encased in an icosahedral capsid, surrounded by a proteinaceous tegument and a lipid envelope studded with viral glycoproteins [2]. Transmission occurs predominantly via direct contact with infectious ocular, nasal, or oral secretions [3]. Following exposure, acute infection leads to Feline Viral Rhinotracheitis (FVR), a debilitating syndrome characterized by fever, paroxysmal sneezing, profuse mucopurulent oculonasal discharge, ulcerative

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keratitis, and geographic corneal ulcers [4]. While mortality is generally low in adult cats, severe secondary bacterial infections can lead to fatal pneumonia in kittens and immunocompromised populations [5].

The primary challenge in controlling FHV-1 endemicity lies in the virus's ability to establish a permanent reservoir within the host. Similar to other alphaherpesviruses, acute mucosal replication is rapidly followed by the invasion of local sensory nerve endings, enabling the virus to establish life-long transcriptional quiescence (latency) within the host's nervous system [6]. Periodically, physiological or psychological stressors trigger viral reactivation, leading to recurrent ocular-respiratory shedding and clinical recrudescence [7]. Consequently, infected individuals become chronic, asymptomatic carriers that perpetually fuel transmission dynamics within feline populations.

Current control strategies rely heavily on core feline vaccines, typically formulated as part of the trivalent FVRCP (Feline Viral Rhinotracheitis, Calicivirus, and Panleukopenia) protocol, available as either Modified Live Virus (MLV) or inactivated preparations [8]. While these conventional vaccines provide robust protection against severe clinical pathology and reduce the severity of acute disease, they suffer from a critical limitation: they do not prevent the establishment of latency, nor do they completely halt viral shedding upon reactivation [9]. This vaccinology blind spot allows wild-type strains to circulate unhindered even in highly vaccinated populations.

To bridge this therapeutic gap, it is essential to reframe FHV-1 not merely as a transient mucosal pathogen, but as an active molecular architect of host immunosuppression. Rather than passively evading immune recognition, FHV-1 utilizes specialized structural proteins and metabolic interference pathways to reprogram host local microenvironments, dampening cellular activation and disrupting antigen presentation [10, 11]. Therefore, this review aims to comprehensively elucidate the structural and molecular mechanisms utilized by FHV-1 to achieve immune evasion and latency. Furthermore, we evaluate how these mechanistic insights can be leveraged to optimize molecular diagnostics and guide the development of next-generation vaccine platforms capable of inducing sterile immunity.

2. Viral Glycoproteins and Structural Components

The envelope of FHV-1 contains at least eleven distinct glycoproteins that serve as the primary interface between the virus and the host immune system. These surface molecules are not only essential for viral attachment, penetration, and cell-to-cell spread, but also act as prominent virulence factors that modulate host immune responses.

2.1. Attachment and Receptor Binding (gC and gD)

The initial cascade of FHV-1 infection begins with low-affinity tethering to the host cell surface. This step is largely mediated by glycoprotein C (gC), which binds to heparin sulfate proteoglycans ubiquitously expressed on feline epithelial cell membranes [12]. Following this initial attachment, glycoprotein D (gD) executes high-affinity binding to specific cellular receptors [13]. In alphaherpesviruses, gD interacts with receptors such as nectin-1 or herpesvirus entry mediator (HVEM); however, the exact primary functional receptor configuration in felids continues to be a subject of intense molecular mapping [14]. This binding induces conformational shifts that trigger the downstream fusion machinery.

2.2. Membrane Fusion Complex (gB and gH/gL)

Once gD is engaged, the signal is transduced to a highly conserved core fusion machinery consisting of glycoprotein B (gB) and the heterodimer glycoprotein H/glycoprotein L (gH/gL) [15]. Glycoprotein B acts as the primary viral fusogen, inserting its hydrophobic fusion loops into the host plasma membrane [16]. This process is stabilized and regulated by the gH/gL complex, which acts as a molecular switch converting receptor-binding energy into membrane fusion, allowing the viral capsid and tegument proteins to enter the host cytoplasm [17]. Due to their structural necessity, gB and gD represent the most highly immunogenic targets for neutralizing antibodies and are critical markers for vaccine design.

2.3. Cell-to-Cell Spread and Antibody Evasion (gE/gI and gG)

To avoid exposing newly synthesized virions to neutralizing antibodies circulating in the extracellular mucosal fluid, FHV-1 utilizes a mechanism of direct cell-to-cell spread. This process is mediated by the heterodimeric complex of glycoprotein E (gE) and glycoprotein I (gI) [18]. The gE/gI complex localizes to cell-to-cell junctions, facilitating the lateral transfer of viral capsids between adjacent epithelial cells without viral egress into the extracellular space [19]. Additionally, FHV-1 encodes glycoprotein G (gG), a secreted and membrane-bound molecule that functions as a chemokine-binding protein [20]. By binding host chemokines with high affinity, gG disrupts normal chemotactic

gradients, preventing the recruitment of neutrophils, macrophages, and natural killer (NK) cells to the site of infection, thereby weakening the localized innate immune response.

3. Mechanisms of Immune Evasion and Latency

The capacity of FHV-1 to establish life-long persistence relies on a sophisticated dual strategy: actively suppressing host immune surveillance during lytic replication, and retreating into an immunologically privileged latent state.

3.1. Downregulation of MHC Class I and Cell-Mediated Immune Evasion

To survive the acute phase of infection, FHV-1 must evade detection by the host's adaptive immune system, particularly cell-mediated immunity. A primary mechanism employed by this alphaherpesvirus is the severe downregulation of Major Histocompatibility Complex Class I (MHC-I) surface expression on infected epithelial cells and macrophages [21]. By disrupting the intracellular transport or promoting the degradation of MHC-I molecules, FHV-1 effectively prevents the presentation of viral antigens to CD8+ cytotoxic T lymphocytes (CTLs) [21]. Consequently, infected cells escape CTL-mediated apoptosis, allowing the virus to complete its replication cycle and spread to adjacent tissues before cell clearance can occur. Furthermore, FHV-1 utilizes direct cell-to-cell spread mediated by specific surface glycoproteins, minimizing its exposure to extracellular neutralizing antibodies circulating in the mucosal environment [22].

3.2. Interference with Innate Interferon (IFN) Signaling

Beyond evading adaptive immunity, FHV-1 actively dampens the host's first line of defense: the innate antiviral response. Type I Interferons (IFN-α/β) are essential for establishing an antiviral state in neighboring uninfected cells. FHV-1 encodes specific regulatory proteins that interfere with the production and signaling cascades of these cytokines [23]. Viral components have been shown to block the phosphorylation and nuclear translocation of transcription factors required for IFN expression, or directly target the downstream JAK-STAT signaling pathway [24]. By neutralizing these signaling mechanisms, FHV-1 diminishes the expression of Interferon-Stimulated Genes (ISGs), thereby disabling the host's localized antiviral environment during early mucosal colonization.

3.3. Retrograde Transport and Establishment of Latency in the Trigeminal Ganglia

The hallmark of FHV-1 chronicity is its ability to transition from a lytic cycle to a silent, latent state. Following initial replication in the ocular and upper respiratory tract mucosa, viral capsids enter the sensory nerve endings of the trigeminal nerve [3]. Utilizing host dynein motors, the virus undergoes retrograde axonal transport along the axons until it reaches the neuronal cell bodies within the trigeminal ganglia (TG) [25].

Within the nucleus of these sensory neurons, a profound transcriptional shift occurs. The expression of viral lytic genes that responsible for replication and structural assembly is stringently repressed [6]. Instead, the viral genome enters a transcriptionally quiescent state, where the only heavily transcribed region belongs to the Latency-Associated Transcripts (LATs) [6]. These LATs serve an essential survival function by maintaining heterochromatin structures over lytic promoters and inhibiting neuronal apoptosis, ensuring that the host cell remains viable while harboring the viral DNA [1]. Because latent neurons express minimal viral proteins and low baseline levels of MHC-I, the latent viral reservoir remains completely invisible to host immune surveillance.

3.4. Stress-Induced Reactivation and Viral Shedding

This balance of latency is disrupted when the host experiences physiological or psychological stressors, such as overcrowding, parturition, concurrent infections, or systemic corticosteroid administration [7]. Stress triggers a hormonal cascade that reactivates the lytic cycle within the trigeminal ganglia. Newly synthesized viral particles undergo anterograde axonal transport back to the peripheral nerve endings, leading to recurrent viral shedding at mucosal surfaces [3]. This reactivation often induces clinical relapse (Feline Viral Rhinotracheitis) and provides a continuous mechanism for transmission within feline populations, even in environments with high vaccine coverage [26].

Collectively, these viral components and latency-associated mechanisms illustrate the multifaceted strategies employed by FHV-1 to evade host immune surveillance and establish persistent infection. The major viral genes and glycoproteins involved in immune modulation, together with their functional roles and potential applications in diagnostics and vaccine development, are summarized in Table 1.

Table 1 Key Viral Components of FHV-1, Mechanisms of Immune Modulation, and Translational Applications

No.	Viral Gene/ Component	Primary Functional Role in Lytic Cycle	Mechanism of Host Immune Evasion	Translational Potential (Vaccine/ Diagnostics)	Reference
1	Glycoprotein B (gB)	Core component of the viral fusion machinery; mediates capsid entry.	Promotes direct cell-to-cell spread, shielding virions from neutralizing antibodies.	Primary target for neutralizing antibody induction; key antigen in subunit vaccines and qPCR detection.	[15]
2	Glycoprotein D (gD)	Executes high-affinity binding to host cellular receptors (e.g., nectin-1).	Initiates cellular entry and triggers structural changes in the fusion complex.	Major immunogen for next-gen vaccines; frequently used in molecular diagnostics and subunit design.	[13]
3	Glycoprotein E / I (gE/gI)	Heterodimeric complex localizing to lateral cell junctions.	Facilitates direct lateral transport between epithelial cells, avoiding extracellular fluid exposure.	Target for gene-deletion marker vaccines; serves as a vital DIVA diagnostic marker.	[19]
4	Glycoprotein G (gG)	Secreted and membrane-bound surface structural envelope protein.	Functions as a chemokine-binding protein; disrupts localized leukocyte chemotactic gradients.	Potential target for attenuation; deletion enhances host leukocyte recruitment to vaccination sites.	[20]
5	Thymidine Kinase (TK)	Enzyme facilitating viral DNA synthesis in non-dividing host cells.	Enables viral replication within specialized host environments like sensory neurons.	Gold standard target for conventional PCR; primary deletion site for creating live-attenuated strains.	[27]
6	Latency-Associated Transcripts (LATs)	Non-coding RNAs heavily transcribed within the neuronal nuclei.	Epigenetically represses viral lytic promoters and blocks host cell neuronal apoptosis.	Diagnostic marker for identifying latent carriers within tissues; key target for latency-reversal studies.	[6]

4. Diagnostic Targets and Molecular Detection

Accurate detection of FHV-1 during both acute and chronic phases is essential for effective clinical management and epidemiological monitoring. However, the unique biology of alphaherpesviruses introduces significant challenges into molecular diagnostics, particularly concerning target gene selection and primer design.

4.1. Conventional Molecular Targets: TK, gB, gD

Polymerase Chain Reaction (PCR) assays represent the gold standard for diagnosing active FHV-1 infections due to their high sensitivity and specificity. The most frequently utilized molecular targets include:

- **Thymidine Kinase (TK) Gen:** Highly conserved among alphaherpesviruses, the TK gene is indispensable for viral DNA replication in non-dividing cells like neurons [27]. Its genetic stability makes it an excellent diagnostic target for identifying wild-type virus strains [28].
- **Glycoprotein B (gB) and Glycoprotein D (gD) Gen:** These structural genes are chosen for real-time quantitative PCR (qPCR) assays because of their high copy numbers during active lytic replication, enabling accurate quantification of viral loads from clinical swabs [29].

4.2. Pitfalls in Primer Selection and Laboratory Implementation

The development and selection of diagnostic primers for FHV-1 require strict bioinformatic and experimental validation. A primary obstacle is **cross-reactivity** or false-negative results arising from genetic drift within field strains or sequence variations between domestic and wild felid isolates [2]. Furthermore, conventional PCR assays often fail to differentiate between wild-type infectious strains and vaccine strains (such as those derived from MLV FVRCP formulations) shedding post-vaccination [30].

To overcome these limitations, contemporary vaccinology and diagnostics require the development of Differentiating Infected from Vaccinated Animals (DIVA) assays [31]. For instance, designing primers that target specific deleted virulence regions in marker vaccines (e.g., TK-deleted or gE-deleted strains) allows laboratories to selectively identify natural exposures, ensuring diagnostic precision in highly vaccinated populations.

5. Translational Vaccinology: Overcoming the Pitfalls of Current Vaccines

The ultimate goal of studying FHV-1 immunobiology is the development of advanced vaccine platforms that transcend the clinical limitations of current commercial options. To achieve sterile immunity, wherein the host is protected against both disease and subclinical viral colonization/latency, vaccinology must adopt novel recombinant design strategies.

5.1. Evaluating Modified Live vs. Inactivated Vaccines

Current commercial vaccines generally rely on two traditional approaches:

- **Inactivated (Killed) Vaccines:** These formulations provide a high safety profile, making them ideal for pregnant queens or immunocompromised animals [26]. However, they are poor inducers of mucosal IgA and cell-mediated immunity (CTL responses), necessitating frequent booster regimens and providing weaker protection against environmental shedding [8].
- **Modified Live Virus (MLV) Vaccines:** MLV formulations mimic natural infections more closely, stimulating both systemic IgG and local mucosal IgA antibodies, alongside robust T-cell responses [9]. Despite their superior efficacy, MLVs retain safety risks, including the potential to induce mild clinical symptoms post-vaccination, revert to virulence, or establish their own latent vaccine infections within the trigeminal ganglia [32].

5.2. Next-Generation Vaccine Platforms

To synthesize the efficacy of live vaccines with the safety profiles of inactivated formulations, next-generation platforms are actively being engineered:

- **Gene-Deleted Marker Vaccines (TK, gE):** By deleting specific virulence genes, such as the Thymidine Kinase (TK) gene or the gE/gI complex, researchers can produce attenuated strains that retain replication competence in mucosal epithelial tissues but are incapable of establishing neurolatency or retrograde axonal transport [33]. These deletions also serve as DIVA markers, allowing serological separation of vaccinated versus naturally infected animals.
- **Subunit Recombinant Vaccines:** Utilizing purified immunogenic proteins, primarily recombinant gD and gB expressed in baculovirus or mammalian systems, completely eliminates the risk of viral replication [31]. When paired with advanced adjuvant delivery systems (such as nano-emulsions or immune-stimulating complexes), subunit vaccines can drive targeted Th1/Th2 balanced immune responses without pathology.
- **Viral-Vectored and mRNA Technology:** Utilizing non-replicating viral vectors (e.g., canarypox virus) or lipid nanoparticle (LNP)-encapsulated mRNA encoding target FHV-1 glycoproteins represents the vanguard of feline vaccinology [34]. These platforms force host cells to synthesize specific viral antigens intracellularly, effectively stimulating endogenous antigen presentation through MHC Class I pathways, thereby activating potent CD8+ cytotoxic T lymphocytes capable of eliminating wild-type virus before it accesses neural networks.

6. Conclusion and Future Perspectives

Feline Herpesvirus 1 remains a formidable veterinary pathogen due to its complex evolutionary adaptations for immune evasion and lifelong neurolatency. As highlighted in this review, the virus employs structural glycoproteins to navigate tissue boundaries and avoid extracellular neutralizing antibodies via cell-to-cell spread, while simultaneously downregulating host cellular defenses and silencing its own replication within the trigeminal ganglia. Traditional

vaccination strategies, though effective at reducing severe clinical pathology, fail to halt the transmission cycle because they do not prevent latency or subclinical mucosal shedding.

To dismantle the endemic nature of FHV-1, future research must capitalize on structural vaccinology and precision molecular engineering. Priority must be given to mapping the precise cellular receptors involved in feline mucosal entry and further characterization of the regulatory mechanisms governing LAT-mediated gene silencing. Standardizing advanced molecular diagnostics, specifically quantitative DIVA-PCR assays will be vital to differentiate wild-type field strains from next-generation gene-deleted marker vaccines. By translating these basic immunobiological insights into targetable platforms, such as mRNA and gene-deleted attenuated vaccines, veterinary medicine can move closer to achieving sterile immunity, ultimately safeguarding feline health from the chronic burden of alphaherpesvirus infections.

Limitations of Current Vaccination

Despite the widespread use of feline herpesvirus type 1 (FHV-1) vaccines and their proven ability to reduce disease severity, several biological and immunological challenges continue to limit vaccine effectiveness. Unlike many acute viral infections in which vaccination can induce sterilizing immunity, FHV-1 possesses unique characteristics that enable persistent infection, immune evasion, and recurrent transmission. Consequently, vaccinated cats may still become infected, establish latency, reactivate infection, and shed virus throughout their lifetime.

Understanding these limitations is essential for interpreting vaccine performance, improving vaccination protocols, and guiding the development of next-generation vaccines aimed at enhancing mucosal immunity and reducing viral persistence.

- **Maternal Antibody Interference**

Maternal-derived antibodies (MDA) represent one of the most important factors influencing vaccine efficacy in young kittens [35]. During the first weeks of life, kittens acquire passive immunity through the ingestion of colostrum containing maternally derived immunoglobulins. These antibodies provide essential protection against infectious diseases during early life when the neonatal immune system remains immature [36].

Although beneficial, maternal antibodies may interfere with vaccine-induced immune responses. Vaccine antigens can be neutralized by circulating maternal antibodies before sufficient stimulation of the kitten's immune system occurs. As a result, vaccination performed during periods of high maternal antibody titers may fail to induce adequate active immunity [37].

The decline of maternal antibodies varies considerably among individuals and is influenced by factors such as maternal immune status, colostrum intake, and litter characteristics. Consequently, a period known as the "window of susceptibility" may occur when maternal antibodies are insufficient to protect against natural infection but still high enough to interfere with vaccination [38].

This phenomenon explains why multiple vaccine doses are recommended during kittenhood. Repeated vaccination increases the likelihood that at least one dose will be administered after maternal antibody levels have declined sufficiently to permit effective immune priming.

Despite current vaccination protocols, maternal antibody interference remains a significant challenge in preventing early-life FHV-1 infection, particularly in shelters and breeding facilities where exposure risk is high.

- **Latent Infection**

The ability of FHV-1 to establish lifelong latency represents perhaps the greatest limitation of current vaccination strategies. Following primary infection, the virus migrates from mucosal epithelial tissues to sensory neurons within the trigeminal ganglia, where it persists in a dormant state [39].

During latency, viral replication is largely absent, and only limited viral gene expression occurs. Consequently, infected neurons become largely invisible to immune surveillance mechanisms. Neither vaccine-induced antibodies nor cytotoxic T lymphocytes can completely eliminate latent viral genomes from neuronal tissues [4].

Current vaccines are highly effective at reducing clinical disease severity and viral replication during acute infection; however, they do not prevent the establishment of latency following exposure. Therefore, vaccinated cats may still become lifelong carriers.

The persistence of latent infection creates several important consequences:

- Long-term maintenance of viral reservoirs.
- Periodic viral reactivation.
- Intermittent viral shedding.
- Continued transmission risk.
- Difficulty achieving disease eradication.

Because latent infection is a defining characteristic of alphaherpesviruses, complete control of FHV-1 will likely require novel vaccine technologies capable of preventing neuronal invasion or enhancing immune control of latent reservoirs.

- **Immune Escape**

FHV-1 possesses several mechanisms that enable partial evasion of host immune responses. Although genetic variability among FHV-1 isolates is relatively limited compared with rapidly mutating RNA viruses, the virus has evolved sophisticated strategies that allow persistence despite host immunity [40].

One important mechanism involves the intracellular nature of viral replication. Once FHV-1 enters host cells, it becomes less accessible to circulating antibodies. Viral spread can also occur directly between adjacent cells, reducing exposure to extracellular immune effectors.

Additionally, herpesviruses can modulate host immune responses through interference with antigen presentation pathways, cytokine signaling, and apoptosis regulation. Such mechanisms may reduce the efficiency of immune recognition and prolong viral survival within infected tissues.

Another challenge arises from the distinction between protection against disease and protection against infection. Vaccine-induced immunity may successfully reduce clinical signs while allowing limited viral replication at mucosal surfaces. Consequently, vaccinated animals can remain susceptible to infection and may continue to shed virus under certain circumstances.

The capacity of FHV-1 to persist despite robust immune responses highlights the need for vaccine strategies that enhance mucosal immunity, tissue-resident memory T-cell responses, and local antiviral defenses.

- **Stress-Associated Reactivation**

A major obstacle to long-term FHV-1 control is the ability of latent virus to reactivate in response to stress. Reactivation occurs when physiological or environmental stressors compromise immune surveillance mechanisms that normally suppress viral activity within sensory ganglia.

Numerous factors have been associated with viral reactivation, including:

- Transportation and relocation.
- Shelter admission.
- Overcrowding.
- Surgical procedures.
- Pregnancy and lactation.
- Corticosteroid administration.
- Concurrent illness.
- Nutritional stress.
- Social disruption and environmental changes.

Stress-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis results in increased glucocorticoid production, which can suppress cellular immune responses and facilitate viral reactivation [41]. Once reactivated, FHV-1 travels from neuronal tissues back to peripheral mucosal sites, where active replication resumes.

Importantly, reactivation may occur with or without clinical signs. Asymptomatic carrier cats can therefore shed infectious virus while appearing completely healthy [1]. This phenomenon contributes substantially to viral persistence in shelters, catteries, and multicat households.

Although vaccination may reduce the severity of disease following reactivation, it generally does not prevent reactivation itself. Consequently, stress management has become an essential complementary strategy to vaccination in FHV-1 control programs.

Environmental enrichment, reduction of overcrowding, maintenance of stable social groups, appropriate nutrition, and minimization of stressful procedures may help decrease the frequency of reactivation episodes and reduce viral transmission within feline populations.

In summary, maternal antibody interference, latent infection, immune evasion mechanisms, and stress-induced reactivation collectively limit the effectiveness of current FHV-1 vaccines. These challenges explain why complete prevention of infection and viral shedding remains difficult despite widespread vaccination. Addressing these limitations will require innovative approaches that integrate improved vaccine technologies, enhanced mucosal immunity, and comprehensive management strategies aimed at controlling both viral replication and latency.

Future Perspectives

Despite significant advances in feline herpesvirus type 1 (FHV-1) vaccination, current immunization strategies remain unable to provide sterilizing immunity or completely prevent viral latency and reactivation. As a result, substantial efforts are being directed toward the development of next-generation vaccines capable of inducing stronger mucosal immunity, enhancing cellular immune responses, and reducing viral shedding. Recent progress in molecular virology, immunology, and vaccine biotechnology has created new opportunities to overcome many of the limitations associated with conventional modified-live and inactivated vaccines.

Future vaccine development is expected to focus on improving protection at mucosal surfaces, strengthening tissue-resident immune responses, and targeting viral persistence mechanisms. Several innovative approaches have emerged as promising candidates for achieving these goals.

- **Recombinant Vaccines**

Recombinant vaccine technology allows specific viral antigens to be expressed using genetically engineered systems without requiring administration of the entire pathogen [42]. Recombinant FHV-1 vaccines are designed to stimulate protective immunity while minimizing the risks associated with viral replication [43].

Several FHV-1 glycoproteins, particularly glycoproteins B (gB), C (gC), and D (gD), have been identified as important immunogenic targets because they play critical roles in viral attachment and entry into host cells. Recombinant expression of these antigens can induce both antibody-mediated and cellular immune responses.

Potential advantages of recombinant vaccines include:

- Improved safety profiles.
- Reduced risk of vaccine-associated disease.
- Targeted immune stimulation.
- Compatibility with advanced delivery systems.
- Potential differentiation of infected from vaccinated animals (DIVA).

Future studies should investigate the ability of recombinant vaccines to induce durable mucosal immunity and reduce viral shedding under field conditions.

- **Gene-Deleted Vaccines**

Gene-deleted vaccines represent a promising strategy for balancing vaccine safety and immunogenicity. These vaccines are generated by removing specific virulence genes while retaining the ability of the virus to replicate sufficiently to stimulate protective immunity [44].

Deletion of genes associated with neuroinvasion, immune evasion, or virulence may produce attenuated strains that generate strong immune responses without establishing efficient latent infections [45]. Such approaches have been successfully applied in several veterinary herpesvirus vaccines and may offer significant advantages for FHV-1 control.

Potential benefits include:

- Strong cellular immunity.
- Enhanced mucosal immune responses.
- Reduced pathogenicity.
- Improved safety compared with conventional modified-live vaccines.
- Potential reduction of latency establishment.

If successful, gene-deleted vaccines may help address one of the most important limitations of current FHV-1 vaccination strategies: the persistence of latent viral reservoirs.

- **Viral-Vectored Vaccines**

Viral-vectored vaccines utilize harmless carrier viruses to deliver FHV-1 antigens directly to host cells. This strategy allows efficient antigen expression while stimulating both innate and adaptive immune responses [46].

Common viral vectors under investigation include adenoviruses, poxviruses, and other replication-defective viral platforms [46]. These vectors can mimic natural infection processes and effectively activate cytotoxic T lymphocyte responses, which are critical for controlling intracellular pathogens such as herpesviruses.

Advantages of viral-vectored vaccines include:

- Strong induction of cellular immunity.
- Efficient antigen presentation.
- Potential for mucosal administration.
- Long-lasting immune memory.
- Reduced need for multiple booster doses.

Because T-cell-mediated immunity plays an essential role in controlling herpesvirus infections, viral-vectored vaccines may provide improved protection against viral reactivation and shedding.

- **Nanovaccines and Advanced Delivery Systems**

Nanotechnology has emerged as an innovative approach for enhancing vaccine delivery and immunogenicity. Nanoparticle-based vaccine platforms can protect antigens from degradation, improve antigen uptake by antigen-presenting cells, and facilitate targeted delivery to mucosal tissues [47].

Several nanoparticle systems have been investigated in veterinary vaccinology, including:

- Lipid nanoparticles.
- Polymeric nanoparticles.
- Chitosan-based nanoparticles.
- Virus-like particles (VLPs).
- These delivery systems offer several advantages:
- Enhanced antigen stability.
- Controlled antigen release.
- Improved mucosal uptake.
- Increased stimulation of local immune responses.
- Reduced vaccine dosage requirements.

Nanovaccine platforms may be particularly valuable for intranasal immunization strategies because they facilitate prolonged interaction with mucosal tissues and promote stronger secretory IgA responses.

- **Mucosal Adjuvants and Precision Immunomodulation**

The effectiveness of mucosal vaccines can be significantly enhanced through the use of specialized adjuvants that stimulate local immune responses without inducing excessive inflammation.

Modern mucosal adjuvants aim to:

- Enhance antigen uptake.
- Promote secretory IgA production.
- Activate tissue-resident memory T cells.
- Strengthen innate antiviral responses.
- Improve long-term immune memory.

Potential candidates include Toll-like receptor agonists, cytokine-based adjuvants, bacterial-derived immunostimulants, and nanoparticle-associated immunomodulators.

Future vaccine formulations may combine multiple adjuvant systems to generate balanced humoral and cellular immunity tailored specifically for respiratory herpesvirus infections.

- **mRNA Vaccine Platforms**

The success of messenger RNA (mRNA) vaccine technology in human medicine has stimulated interest in its application to veterinary infectious diseases. mRNA vaccines provide genetic instructions that enable host cells to produce selected viral antigens, thereby inducing both antibody and T-cell responses [48].

Several characteristics make mRNA vaccines attractive candidates for future FHV-1 control:

- Rapid vaccine development.
- High antigen specificity.
- Strong humoral and cellular immunity.
- Flexible antigen design.
- Potential adaptation to emerging viral variants.

Furthermore, mRNA platforms may be combined with lipid nanoparticles and mucosal delivery technologies to enhance local respiratory immunity. Although research on feline mRNA vaccines remains limited, this technology represents one of the most promising areas for future investigation.

- **Toward Sterilizing Immunity and Transmission Control**

The ultimate objective of future FHV-1 vaccine development is not merely the reduction of clinical disease but the achievement of sterilizing immunity capable of preventing infection, latency establishment, viral reactivation, and transmission.

To accomplish this goal, future vaccines will likely need to:

- Induce robust secretory IgA responses.
- Generate durable tissue-resident memory T-cell populations.
- Enhance antiviral innate immunity.
- Reduce neuronal invasion and latency.
- Minimize viral shedding following exposure.

A comprehensive understanding of feline mucosal immunology, viral pathogenesis, and host–pathogen interactions will be essential for achieving these objectives.

In conclusion, next-generation FHV-1 vaccines are expected to move beyond traditional protection against clinical disease and toward comprehensive control of viral transmission. Advances in recombinant technologies, gene editing, viral vectors, nanotechnology, mucosal adjuvants, and mRNA platforms provide exciting opportunities for the

development of safer and more effective vaccines. Such innovations may ultimately transform the management of FHV-1 infections and significantly reduce the burden of disease in both individual cats and feline populations.

7. Conclusions

Feline herpesvirus type 1 (FHV-1) remains a major cause of feline upper respiratory and ocular disease worldwide. Although current vaccines effectively reduce clinical severity, they do not completely prevent infection, latency, reactivation, or viral shedding. Consequently, vaccinated cats may continue to serve as reservoirs of infection and contribute to disease transmission.

Mucosal immunity plays a crucial role in controlling FHV-1 because the virus initially infects the nasal and conjunctival mucosa. Protective mechanisms such as secretory IgA, tissue-resident memory T cells, and innate immune responses can limit viral replication at the site of entry and reduce viral shedding. Evidence suggests that vaccines capable of inducing strong mucosal immune responses, particularly intranasal vaccines, may provide additional benefits in controlling transmission.

However, several challenges remain, including maternal antibody interference, latent infection, immune evasion, and stress-associated reactivation. These limitations highlight the need for improved vaccination strategies that target both disease prevention and transmission control.

Future advances in recombinant vaccines, viral-vectored platforms, nanovaccines, mucosal adjuvants, and mRNA technologies offer promising opportunities to enhance mucosal immunity and reduce viral persistence. A better understanding of feline mucosal immunology will be essential for developing next-generation vaccines capable of limiting viral shedding and improving long-term control of FHV-1 in feline populations.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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