

The Pathogenesis of Foot-and-Mouth Disease Virus Infection: How the Virus Escapes from Immune Recognition and Elimination

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Abstract

Foot-and-mouth disease virus (FMDV) is a highly contagious and economically devastating pathogen that affects cloven-hoofed animals worldwide. FMDV infection causes vesicular lesions in the mouth, feet, and mammary glands, as well as severe systemic symptoms such as fever, salivation, and lameness. The pathogenesis of FMDV infection involves complex interactions between the virus and the host immune system, which determine the outcome of the disease. FMDV has evolved several strategies to evade immune recognition and elimination, such as antigenic variation, receptor switching, immune suppression, and subversion of innate and adaptive responses. This review paper summarizes the current knowledge on the pathogenesis of FMDV infection and the mechanisms of immune evasion employed by the virus. It also discusses the challenges and opportunities for developing effective vaccines and therapeutics against this important animal disease.

Keywords

Foot-and-mouth disease virus • Pathogenesis • Immune evasion • Vaccines • Therapeutics

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1. Introduction

Foot-and-mouth disease (FMD) is a highly contagious viral disease that affects domestic and wild animals with cloven hooves, such as cattle, sheep, goats, pigs, and deer (World Organization for Animal Health 2023). FMD is caused by the foot-and-mouth disease virus (FMDV), a positive-sense single-stranded RNA virus belonging to the genus *Aphthovirus* within the family Picornaviridae (Martinez-Salas et al. 2008). FMDV has seven serotypes (O, A, C, Asia 1, SAT 1, SAT 2, and SAT 3) and many subtypes that vary in their antigenic and genetic properties due to frequent mutations and recombination (Ferretti et al. 2018; Aiweisakun et al. 2020). The virus can be transmitted by direct or indirect contact with infected animals or the materials they shed or excrete, such as fomites, aerosols, or vectors. It may also persist in milk and semen for up to 4 days before the animal exhibits clinical signs of disease (World Organization for Animal Health 2023). The clinical signs of FMD include fever;

vesicular lesions in the mouth, feet, and mammary glands; salivation; lameness; reduced milk production; weight loss; and abortion (World Organization for Animal Health 2023). The severity and duration of the disease depend on several factors, such as the virus strain, the host species and breed, the immune status, and the environmental conditions. In fatal cases, death is caused either by dehydration, by ventricular fibrillation during cardiac attacks, or by bacterial complications (Lefebvre et al. 2010; Jamal and Belsham 2013). It is one of the most economically important animal diseases worldwide, as it can cause significant losses in animal productivity, trade restrictions, and control measures (Knight-Jones and Rushton 2013). Some strains of the virus that cause FMD in animals can also infect humans. This poses a potential risk to public health and food security. The most common type of FMDV isolated in humans is type O, followed by type C, and rarely type A. The incubation period in humans ranges from 2 days to 6 days. The symptoms are mostly mild and self-limiting and include uncomfortable tingling blisters on the hands, feet, and mouth, as well as fever and sore throat (Bauer 1997; Prempeh et al. 2001; Grubman and Baxt 2004). Moreover, it also poses a threat to animal welfare and biodiversity, as it can cause pain and suffering to infected animals and endanger rare or endangered wildlife species. Due to its high impact, FMD is classified as a notifiable disease by the World Organisation for Animal Health (OIE), which means that any occurrence of the disease must

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be reported to the OIE (Perry and Rich 2007; Knight-Jones and Rushton 2013). The pathogenesis of FMDV infection involves complex interactions between the virus and the host immune system at different levels: cellular, tissue, organ, and systemic (Jamal and Belsham 2013). The virus enters the host through the respiratory or oral mucosa and replicates in the epithelial cells, causing cell lysis and tissue damage (Grubman and Baxt 2004; Arzt et al. 2014). The virus then spreads through the bloodstream (viremia) to other epithelial sites, where it causes secondary vesicles (Jamal and Belsham 2013; Pacheco et al. 2015). The host immune system responds to the viral infection by activating both innate and adaptive immune mechanisms, such as interferons (IFNs), cytokines, natural killer cells, macrophages, dendritic cells, B cells, and T cells (Grubman and Baxt 2004; Jamal and Belsham 2013). However, FMDV has evolved several strategies to evade immune recognition and elimination by the host. These include antigenic variation, receptor switching, immune suppression, and subversion of innate and adaptive responses (Grubman and Baxt 2004; Jamal and Belsham 2013). Understanding the pathogenesis of FMDV infection and the mechanisms of immune evasion employed by the virus is essential for developing effective vaccines and therapeutics against this important animal disease. In this review paper, we summarize the current knowledge on these topics and discuss the challenges and opportunities for future research.

2. The Structure, Classification, Diversity, and Evolution of FMDV

FMDV, a member of the Picornaviridae family, is characterized by its icosahedral capsid and single-stranded positive sense RNA genome (Domingo et al. 2012). The virus has a genome of about 8.3 kb, which encodes a single long open reading frame (ORF) flanked by a long structured 5'-untranslated region (5'-UTR) and a short 3'-UTR. The ORF is translated into a polypeptide chain and processed into four structural proteins (VP1, VP2, VP3, and VP4), which form the icosahedral capsid, and 8 non-structural proteins (NSPs) (Lpro, 2A, 2B, 2C, 3A, 3B, 3Cpro, 3Dpol), which are involved in RNA replication, protein folding, and virus assembly (Paton et al. 2021). The structural proteins are responsible for the antigenicity and immunogenicity of the virus, as they contain several antigenic sites that are recognized by neutralizing antibodies, while the NSPs are involved in the regulation of viral replication and host cell functions (Li et al. 2021). FMDV exhibits a high degree of genetic and antigenic diversity, which poses a challenge for its control and prevention. The virus has seven major serotypes. These serotypes have some regional variations, and the O serotype is the most common one (Rweyemamu et al. 2008; Naqvi et al. 2022). These serotypes have different geographical distributions and host preferences. The O serotype is the most

common and widespread, whereas the C serotype is the least prevalent and has been eradicated from many regions (Mwine et al. 2019; Ahmed et al. 2020). Within each serotype, there are numerous variants and subtypes that differ in their antigenic properties and virulence. The antigenic diversity of FMDV is mainly determined by the VP1 protein, which is responsible for the virus attachment and entry, protective immunity, and serotype specificity. The VP1 protein contains several antigenic sites that are recognized by neutralizing antibodies. However, these sites are also prone to mutations and recombination events that generate new variants that can escape from immune recognition and elimination (Li et al. 2023). FMDV evolves rapidly due to its high mutation rate, short generation time, large population size, and diverse host range (Orton et al. 2020). FMDV also undergoes frequent genetic exchange by recombination between different strains or serotypes. Viral recombination is the process of genetic exchange between different strains or serotypes of FMDV, a highly contagious and economically important animal pathogen. Recombination can occur within host cells during co-infections by different FMDV strains, and it is a common and key feature of FMDV evolution (Ferretti et al. 2018). It can affect the capsid-coding region, which determines the antigenic properties and host range of the virus (Ferretti et al. 2018). It can also generate mosaic genomes with different genetic blocks that are influenced by positive epistatic interactions between co-evolved variants (Heath et al. 2006). It is one of the factors that contributes to the high genetic diversity and adaptability of FMDV. These evolutionary mechanisms enable FMDV to adapt to changing environmental conditions and host immune responses.

3. Virus–Host Interactions in FMDV Infection

The virus–host interactions during FMDV infection can be divided into three stages: entry, replication, and exit. In each stage, the virus and the host cells engage in a dynamic and complex interplay that determines the outcome of the infection.

3.1. Entry

The entry of FMDV into host cells is mediated by the interaction between the viral capsid proteins and the cellular receptors. FMDV can use different receptors, depending on the host species and the virus strain. The main receptors for FMDV are integrins, which are heterodimeric transmembrane glycoproteins that mediate cell–cell and cell–matrix adhesion (Xin et al. 2018). Integrins are composed of two subunits, α and β , and FMDV can bind to several integrin subtypes, such as $\alpha\beta1$, $\alpha\beta3$, $\alpha\beta6$, and $\alpha\beta8$ (Kotecha et al. 2017). The binding of FMDV to integrins is facilitated by a highly conserved arginine–glycine–aspartic acid motif located in the

GH loop of VP1 (Mason et al. 1994). However, some FMDV strains can also use alternative receptors, such as heparan sulfate proteoglycans (HSPGs), which are ubiquitous molecules on the cell surface that have a core protein and one or more heparan sulfate chains (Biswal et al. 2015). HSPGs can bind to FMDV through electrostatic interactions between the negatively charged heparan sulfate chains and the positively charged residues in VP1 and VP3 (Li et al. 2021). The use of HSPGs as receptors may enhance the attachment and entry of FMDV into cells that express low levels of integrins or have different integrin subtypes (Kotecha et al. 2018). The binding of FMDV to receptors triggers a series of events that lead to the internalization of the virus into endosomes. FMDV can enter cells by different endocytic pathways, such as clathrin-mediated endocytosis, caveolae-mediated endocytosis, macropinocytosis, or lipid raft-dependent endocytosis (Han et al. 2016; Haseeb et al. 2018). The choice of the endocytic pathway may depend on the cell type, the virus strain, and the receptor used (Ye et al. 2018). Once inside the endosomes, FMDV undergoes a conformational change that exposes a hydrophobic pocket in VP1. This pocket binds to a small molecule called pocket factor, which is usually a fatty acid derived from the host cell membrane (Burman et al. 2006). The displacement of the pocket factor by low pH or receptor binding induces further structural changes in the capsid that result in the release of VP4 and the N-terminus of VP1. These regions form a pore in the endosomal membrane that allows the viral RNA to escape into the cytoplasm (Martín-Acebes et al. 2007; Han et al. 2016). After escaping from the endosomes, FMDV initiates its replication cycle in the cytoplasm. The viral RNA is translated by host ribosomes into a single polyprotein that is subsequently cleaved by viral proteases into structural NSPs (O'Donnell et al. 2008). The NSPs are involved in various aspects of viral replication, such as RNA synthesis, polyprotein processing, and modulation of the host-immune response (Ye et al. 2018). The structural proteins form new viral capsids that encapsidate newly synthesized viral RNA molecules. The assembly of viral particles occurs at specific sites on the surface of intracellular membranes, such as the endoplasmic reticulum (ER) or the Golgi apparatus (He et al. 2021a). The mature virions are then released from the infected cells by exocytosis or cell lysis (He et al. 2021b).

3.2. Replication

The replication of FMDV takes place in the cytoplasm of infected cells. The viral RNA serves as both mRNA and template for RNA synthesis (Belsham and Martinez-Salas 2019). The viral RNA has a 5'-terminal covalently linked protein called VPg, which acts as a primer for RNA polymerase (Wu et al. 2022). The viral RNA also has a 3'-poly(A) tail that is generated by a poly(C) tract in the 5'UTR and a

template-dependent uridylylation of VPg by 3D pol (Loundras 2017). The viral RNA is translated into a polyprotein by host ribosomes in a cap-independent manner (Mason et al. 2002). The translation is mediated by an internal ribosome entry site located in the 5'-UTR, which interacts with several host factors, such as eukaryotic initiation factors (eIFs), poly(A)-binding protein, and La autoantigen (Stassinopoulos and Belsham 2001; Sonenberg and Hinnebusch 2009; Abdullah et al. 2023). The polyprotein is then processed by viral proteases Lpro, 2A, and 3C pro into structural and non-structural proteins. The structural proteins form pentamers that assemble into empty capsids or progeny virions in association with viral RNA. The NSPs are involved in various functions, such as RNA replication, protein folding, virus assembly, and immune evasion (Grubman et al. 2008; Agudo Torres 2009). The RNA replication of FMDV occurs in membrane-associated complexes that are derived from host organelles, such as the ER, the Golgi apparatus, or lysosomes (Knox et al. 2005; Li et al. 2021). The RNA replication complex consists of viral proteins 2B, 2C, 3A, 3B (VPg), 3C pro, and 3D pol, as well as host factors, such as phosphatidylinositol-4-kinase III β (PI4KB), the oxysterol-binding protein, and GBF1 (Howes 2018). The RNA replication complex synthesizes positive-sense RNA from negative-sense RNA templates and vice versa. The positive-sense RNA can be used for translation, encapsidation, or further replication. The negative-sense RNA can also serve as an intermediate for the production of double-stranded RNA (dsRNA), which is a potent inducer of innate immune responses (Lin et al. 2009).

3.3. Exit

The exit of FMDV from infected cells can occur by two mechanisms: cell lysis or cell-to-cell transmission. Cell lysis is the result of the cytopathic effect of FMDV, which causes the disruption of the plasma membrane and the release of viral particles into the extracellular space (Midgley et al. 2013). Cell lysis is influenced by several factors, such as the virus strain, the host cell type, and the multiplicity of infection (Li et al. 2021). Cell-to-cell transmission is a more efficient and rapid way of spreading FMDV within a tissue or an organism. Cell-to-cell transmission involves the formation of intercellular junctions between infected and noninfected cells, which allow the direct transfer of viral RNA or virions (Naghavi and Walsh 2017). Cell-to-cell transmission is mediated by viral proteins 2B, 2C, and 3A, which modulate the expression and function of host proteins involved in cell junction formation, such as claudins, occludins, and E-cadherins (Xin et al. 2018; Li et al. 2021). Cell-to-cell transmission may also facilitate the evasion of FMDV by neutralizing antibodies and innate immune responses (Lei et al. 2015). The exit of FMDV from infected cells is also influenced by the genetic diversity of the virus, which results from its high mutation rate and recombination

events. FMDV belongs to the genus *Aphthovirus* within the family Picornaviridae, which comprises single-stranded positive-sense RNA viruses with a genome size of about 8.3 kb (Yang et al. 2020). FMDV has seven serotypes: O, A, C, Asia 1, SAT 1, SAT 2, and SAT 3, which differ in their antigenic properties and geographic distribution (Brito et al. 2017). Within each serotype, there are multiple subtypes or topotypes that can be further classified into lineages or strains based on their genetic and phylogenetic relationships (Li et al. 2021). The genetic diversity of FMDV is mainly generated by two mechanisms: point mutations and recombination. Point mutations occur during viral RNA replication due to the lack of proofreading activity of the viral RNA-dependent RNA polymerase (Sanjuán 2012). The mutation rate of FMDV has been estimated to be about 10^{-3} to 10^{-4} substitutions per nucleotide per replication cycle (Haydon et al. 2001), which means that every progeny virus may have one or more mutations compared to its parent virus. Recombination occurs when two or more different FMDV genomes co-infect the same cell and exchange genetic segments during RNA synthesis (Li et al. 2021). Recombination can occur between different serotypes, subtypes, or strains of FMDV, resulting in novel variants with new antigenic or biological characteristics (Xu and Yang 2021). The genetic diversity of FMDV has important implications for its exit from infected cells and its transmission among hosts (Tekleghiorghis et al. 2016). First, genetic diversity allows FMDV to adapt to different environmental conditions, such as temperature, pH, or salinity, which may affect its stability and infectivity. Second, genetic diversity enables the FMDV to escape from host immune responses, such as neutralizing antibodies or innate immune effectors, by generating antigenic variants that can evade recognition or elimination. Third, genetic diversity increases the fitness and virulence of FMDV by generating beneficial mutations that enhance its replication efficiency, tissue tropism, or transmission potential. Finally, genetic diversity facilitates the emergence and spread of new FMDV strains that can cause outbreaks in previously unaffected regions or hosts (Li et al. 2021).

FMDV infection and vaccination elicit both humoral and cellular immune responses in the host, which are essential for the protection against the disease (Wu et al. 2021). The humoral immune response is mediated by the production of neutralizing antibodies that bind to the viral capsid and prevent the attachment and entry of the virus into host cells. The cellular immune response is mediated by the activation of cytotoxic T lymphocytes (CTLs) that recognize and kill infected cells, and helper T lymphocytes (Th) that provide cytokines and costimulatory signals for B cells and CTLs (Xiao et al. 2021). The humoral immune response to FMDV infection is characterized by the rapid induction of high levels of neutralizing antibodies, which can be detected as early as 4 days post-infection in cattle (Li et al. 2021). The neutralizing antibodies

are mainly directed against the immunodominant epitopes located in the GH loop of VP1, which are also involved in receptor binding. However, these epitopes are highly variable among different FMDV serotypes and subtypes, and even within the same strain during infection. Therefore, the neutralizing antibodies induced by one FMDV strain may not be effective against another strain, resulting in antigenic mismatch and vaccine failure (Li et al. 2021). To overcome this challenge, several strategies have been developed to improve the cross-reactivity and breadth of neutralizing antibodies, such as using multiple-valent vaccines, chimeric viruses, consensus sequences, or mosaic antigens (Xiao et al. 2021). The cellular immune response to FMDV infection is less well understood than the humoral immune response, but it is also important for the clearance of the virus and the generation of immunological memory (Li et al. 2023). The cellular immune response to FMDV infection involves both CD4⁺ and CD8⁺ T cells, which can recognize viral peptides presented by the major histocompatibility complex (MHC) class II and class I molecules, respectively. CD4⁺ T cells can differentiate into different subsets, such as Th1, Th2, Th17, or T follicular helper (Tfh) cells, depending on the cytokine environment and the costimulatory signals. Th1 cells produce IFN- γ and tumor necrosis factor (TNF)- α , which activate macrophages and enhance the expression of MHC class II molecules. Th2 cells produce interleukin (IL)-4 and IL-10, which promote B cell differentiation and antibody production. Th17 cells produce IL-17 and IL-22, which recruit neutrophils and induce inflammation. Tfh cells produce IL-21 and CXCL13, which help B cell migration and germinal center formation. CD8⁺ T cells can exert cytotoxic effects by releasing perforin and granzymes, or by expressing Fas ligand, which induce apoptosis of the infected cells. CD8⁺ T cells can also produce IFN- γ and TNF- α , which have antiviral and immunomodulatory functions (Li et al. 2021). The immune responses to FMDV vaccination are similar to those induced by natural infection, but they are usually weaker and shorter-lived (Xiao et al. 2021). The conventional vaccines for FMD are based on inactivated whole-virus particles, which can induce neutralizing antibodies but not CTLs. The inactivated vaccines require multiple doses and adjuvants to achieve sufficient protection, and they may also carry residual infectivity or NSPs that can interfere with the serological diagnosis. Therefore, alternative vaccines based on subunit antigens, virus-like particles, DNA plasmids, or viral vectors have been developed to overcome these limitations. These vaccines can induce both humoral and cellular immune responses, as well as mucosal immunity, which may provide better protection against FMDV infection (Xiao et al. 2021). The infection and vaccination induce both humoral and cellular immune responses in the host, which are essential for the protection against the disease. However, these immune responses are not sufficient to eradicate FMDV from the host, as the virus has evolved various

strategies to evade or suppress them. For example, FMDV can modulate the expression of cellular receptors, interfere with IFN signaling pathways, inhibit antigen presentation, and induce immunological tolerance or exhaustion (Cacciabue et al. 2020; Li et al. 2021). Therefore, understanding the virus–host interactions and the mechanisms of immune evasion is critical for designing more effective vaccines and antiviral therapies for FMD. In this review, we have summarized the current knowledge on how FMDV infects different host cells, modulates the innate and adaptive immune responses, and exploits various cellular pathways to enhance its replication and survival. We have also discussed the challenges and opportunities for developing novel vaccines and antivirals that can target the viral and host factors involved in FMDV pathogenesis. However, there are still many gaps and unanswered questions in this field that require further investigation. For example, what are the molecular determinants of FMDV tropism and virulence? How does FMDV interact with the mucosal immune system and induce local immunity? How does FMDV affect the function and differentiation of dendritic cells, T cells, and B cells *in vivo*? How does FMDV induce lymphopenia and immunosuppression in swine? How does FMDV modulate autophagy and apoptosis in different cell types? How does FMDV interfere with the Golgi-ER network and affect protein trafficking and secretion? How can we overcome the antigenic diversity and variability of FMDV and induce broad-spectrum and long-lasting immunity? How can we improve the safety and efficacy of FMD vaccines and antivirals? These are some of the important questions that need to be addressed in future research to better understand the complex virus–host interactions in FMDV infection and to develop more effective strategies for the prevention and control of this devastating disease.

4. Immune Evasion Strategies of FMDV

FMDV has to face the host immune system, which consists of innate and adaptive components that work together to eliminate the viral infection. The innate immune system is the first line of defense and involves the recognition of viral components by pattern recognition receptors (PRRs), such as Toll-like receptors, retinoic acid-inducible gene I-like receptors, and nucleotide-binding oligomerization domain-like receptors. The activation of PRRs leads to the production and secretion of type I and type III IFNs, which are cytokines that induce the expression of hundreds of interferon-stimulated genes (ISGs) that have antiviral, immunomodulatory, and pro-inflammatory functions. The adaptive immune system is the second line of defense and involves the activation of B cells and T cells, which produce antibodies and cytotoxic or helper effector molecules, respectively. The adaptive immune system is more specific and generates immunological memory that confers long-term protection against

reinfection. FMDV has indeed developed numerous strategies to evade the immune response, especially the type I IFN response. Viral proteins target this innate antiviral response at different levels, ranging from blocking the detection of viral RNAs to inhibiting the expression of ISGs. For example, the viral leader proteinase (Lpro) cleaves the transcription factors NF- κ B and IRF3, which are essential for the induction of IFN- β mRNA (Medina et al. 2018). Lpro also inhibits the translation of host proteins by inducing the cleavage of eIF4G, a component of the eIF4F complex (Medina et al. 2018). Another viral proteinase, 3Cpro, interferes with the transcription of host genes by cleaving histone H3, a component of the chromatin structure (Li et al. 2016). Moreover, FMDV can use alternative receptors, such as HSPGs, that do not trigger endosomal acidification and thus prevent the exposure of dsRNA in the cytoplasm (Ye et al. 2018). FMDV also modulates the expression and function of ISGs, such as PKR, OAS, RNase L, MxA, viperin, and tetherin (Medina et al. 2018). Additionally, FMDV can affect the adaptive immune response by reducing the surface expression of MHC class I molecules on infected cells, causing transient lymphopenia in swine (Stenfeldt et al. 2016), and impairing the maturation and function of dendritic cells. In summary, FMDV has evolved multiple mechanisms to escape from immune recognition and elimination by exploiting its small RNA genome. These mechanisms contribute to the virulence and persistence of FMDV in its natural hosts. A better understanding of these mechanisms may provide new insights for the development of novel vaccines and therapeutics against FMD.

5. Challenges and Opportunities for FMD Vaccines and Immunotherapies

FMD is a serious threat to the health and productivity of cloven-hoofed animals worldwide. The causative agent, FMDV, belongs to the family Picornaviridae and has seven serotypes (O, A, C, Asia 1, SAT 1, SAT 2, and SAT 3) and numerous subtypes that exhibit high antigenic and genetic variability (Knight-Jones and Rushton 2013). This diversity poses a major challenge for the development and implementation of effective vaccines and immunotherapies, as it requires the selection and matching of appropriate vaccine strains for each region and outbreak situation. Another challenge is the limited cross-protection and short duration of immunity conferred by conventional inactivated vaccines, which require frequent revaccination and cold chain maintenance. Moreover, these vaccines do not allow the differentiation of infected from vaccinated animals (DIVA) using serological tests, which hampers the surveillance and control of FMD in endemic and free areas. Furthermore, the production of these vaccines involves the use of large quantities of infectious, virulent FMDV, which poses a potential risk of accidental or intentional

release of live FMDV from vaccine production facilities that could cause outbreaks in FMD-free countries or regions. Additionally, there is a lack of effective antiviral drugs or immunomodulators that can prevent or treat FMD in emergency situations, which limits the options for disease management. Despite these challenges, there are also many opportunities for the improvement and innovation of FMD vaccines and immunotherapies. For instance, the advances in molecular biology, biotechnology, and bioinformatics enable the design and production of novel vaccine candidates, such as subunit antigens, virus-like particles, DNA plasmids, or viral vectors, that can induce broader and longer-lasting immunity, facilitate DIVA, and reduce biosafety concerns (Grubman and Baxt 2004; Lawrence et al. 2016; Hardham et al. 2020). In addition, the development of new adjuvants, delivery systems, and formulations, such as nanoparticles, microneedles, or spray-drying, can enhance the immunogenicity and stability of vaccines, as well as enable alternative routes of administration, such as mucosal or transdermal vaccination (Biswal et al. 2015; Li et al. 2016). Moreover, the discovery of new biomarkers, correlates, and predictors of protection, such as T cell responses, mucosal antibodies, or neutralizing epitopes, can facilitate the evaluation and optimization of vaccine efficacy and quality (Golde et al. 2005; Stenfeldt et al. 2016; Zhu et al. 2020). Furthermore, the application of new diagnostic tools and platforms, such as lateral flow devices, microfluidics, or biosensors, can enable rapid, sensitive, and specific detection of FMDV infection or vaccination status in the field or at the point-of-care (Madi et al. 2015; Wang et al. 2020; Zhang et al. 2020). Additionally, the exploration of new immunotherapeutic strategies, such as monoclonal antibodies, IFNs, or cytokines, can provide passive or active protection against FMDV infection or enhance the host immune response (Zhang et al. 2004; Diaz-San Segundo et al. 2010; Mahapatra et al. 2016). In summary, FMD is a challenging disease that requires continuous research and development efforts to improve the existing vaccines and immunotherapies and to discover new ones. A better understanding of the virus–host

interactions and the immune mechanisms involved in FMD will provide the basis for the design and evaluation of novel vaccines and immunotherapies. A close collaboration among researchers, policy makers, industry partners, and stakeholders will facilitate the translation and implementation of these innovations into effective tools for the prevention and control of FMD.

6. Conclusion

FMD is a major threat to animal health and food security worldwide. The current vaccines based on inactivated FMDV have limitations in terms of safety, efficacy, and DIVA compatibility. Therefore, there is a need for novel vaccines and immunotherapies that can overcome these challenges and provide better protection against FMD. Several promising candidates have been developed, such as subunit antigens, virus-like particles, DNA plasmids, or viral vectors, that can induce broader and longer-lasting immunity, facilitate DIVA, and reduce biosafety concerns. However, these candidates still face technical and regulatory hurdles that need to be addressed before they can be applied in the field. Moreover, new immunotherapeutic strategies, such as monoclonal antibodies, IFNs, or cytokines, could provide passive or active protection against FMDV infection or enhance the host immune response. A better understanding of the virus–host interactions and the immune mechanisms involved in FMD will provide the basis for the design and evaluation of novel vaccines and immunotherapies. A close collaboration among researchers, policy makers, industry partners, and stakeholders will facilitate the translation and implementation of these innovations into effective tools for the prevention and control of FMD.

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