Advances in Foot-and-Mouth Disease Virus Proteins Regulating Host Innate Immunity

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Foot-and-mouth disease (FMD) is a highly contagious disease that affects cloven-hoofed animals such as pigs, cattle, and sheep. The disease is caused by the foot-and-mouth disease virus (FMDV) which has a non-enveloped virion with icosahedral symmetry that encapsulates a positive-sense, single-stranded RNA genome of ~8.4 kb. FMDV infection causes obvious immunosuppressive effects on the host. In recent years, studies on the immunosuppressive mechanism of FMDV have become a popular topic. In addition, studies have shown that many FMDV proteins are involved in the regulation of host innate immunity and have revealed mechanisms by which FMDV proteins mediate host innate immunity. In this review, advances in studies on the mechanisms of interaction between FMDV proteins and host innate immunity are summarized to provide a comprehensive understanding of FMDV pathogenesis and the theoretical basis for FMD prevention and control.

Keywords: innate immunity, interferon, immunosuppression, foot-and-mouth disease virus, virus-host interactions

INTRODUCTION

Foot-and-mouth disease (FMD) is an acute, highly contagious livestock disease that affects cloven-hoofed animals such as pigs, cattle, and sheep, thereby causing severe economic loss. Typical clinical symptoms of FMD include high fever and numerous blisters on the oral mucosa, hoof, and breast, with the disease being both diverse and fast (Thomson et al., 2003). There have been several serious outbreaks of FMD in some countries, across Europe, the Middle East, Africa and Asia, and Taiwan, etc., which have hindered the development of livestock breeding and caused huge losses to the global economy (Sangare et al., 2001; Grubman and Baxt, 2004). The Foot-and-mouth disease virus (FMDV) is the pathogen that causes FMD, belonging to the Aphthovirus genus of Picornaviridae family. There are seven FMDV serotypes in the world, namely, A, O, C, South Africa 1, South Africa 2, South Africa 3, and Asia 1. Each serotype includes multiple subtypes and does not have an antigenic cross-protection reaction (Saiz et al., 2002). FMDV is a single-stranded and positive-sense RNA virus surrounded by an icosahedral capsid. Its genome, comprising of approximately 8,400 nucleotides, has a single open reading frame (ORF) that is translated into a polyprotein, which is then processed by the three viral proteases L\textsuperscript{pro}, 2A, and 3C\textsuperscript{pro} into the polypeptide products P1 (VP1 to VP4), P2 (2A, 2B, and 2C), and P3 (3A, 3B, 3C\textsuperscript{pro}, and 3D\textsuperscript{pol}) and subsequently generated...
four mature structural proteins (VP4, VP2, VP3, and VP1) and eight non-structural proteins (LPro, 2A, 2B, 2C, 3A, 3B, 3CPro, and 3DPpro) (Grubman and Baxt, 2004) (Figure 1). After the host is infected by microbial pathogens, pathogen recognition receptors (PRRs) in the host, recognize conserved molecular structures (i.e., pathogen-associated molecular patterns, PAMPs) from pathogens (Kumar et al., 2011). At present, depending on their different protein domain homologies, PRRs are classified four major families: Toll-like receptors (TLRs), RIG-I (retinoic acid-inducible-gene-I)-like receptors (RLRs), Nod-like receptors (NLRs), and C-type lectin receptors (CLRs) (Kumar et al., 2009). Once PRRs recognize PAMPs in the host cell, various anti-microbial immune responses are rapidly triggered via the induction of inflammatory cytokines, chemokines, and type I interferons (Ye et al., 2019). It has the type I IFNs, type III IFNs can also increase adaptive immune responses in the respiratory mucosa (Ye et al., 2019). Type III IFN (IFN-λ) can inhibit FMDV replication in IBRS-2 cells (Zhang et al., 2019). In addition, VP1 can also act on ribosomal inhibition (Wang et al., 2011b). In addition, innate immune cells are in a constant arms race, such that the virus has evolved multiple strategies to escape the host’s immune surveillance and defense system, which eventually destroys the balance between FMDV replication and host antivirus response (Table 1). In particular, FMDV proteins can directly or indirectly regulate the host’s innate immune response to survive and replicate in the host (Rodriguez Pulido and Saiz, 2017).

In the past two decades, thanks to the improved understanding of FMDV structure, many studies have confirmed that FMDV proteins can inhibit the production of IFNs. Therefore, this article reviews the relationship between FMDV proteins and the host’s innate immune-related proteins and also provides ideas for further studies regarding FMDV inhibiting the host’s innate immune response and regarding effective FMDV vaccines development.

FMDV PROTEINS REGULATE HOST INNATE IMMUNITY
The Role of FMDV Structural Proteins in the Regulation of Host Innate Immunity
Four structural proteins (VP4, VP2, VP3, and VP1) encoded by the P1 region of FMDV, mainly form the icosahedral capsid of virus particles: VP1-3 cooperate to form the capsid surface, while VP4 forms the internal structure of the virus particles. The four structural proteins differ in terms of conservation: VP1 is highly variable, VP2 and VP3 are relatively conserved, and VP4 is highly conserved among all serotypes. VP1 and VP3 play important roles in inhibiting the production of host interferons to weaken the host antiviral response. On the other hand, VP2 is involved in the induction of autophagy (Feng et al., 2018; Li et al., 2019b; Liu et al., 2020).

Advances in the Suppression of Innate Immunity by FMDV VP1
The FMDV structural proteins VP1, VP2, and VP3 of FMDV are folded into an eight-stranded wedge-shaped-barrel, and compose a major part of capsids; however, most of the antigen sites corresponding to the immune response are mainly found on the G-H loop of VP1 (Abubakar et al., 2018). There is a hypervariable region on the G–H loop which may lead to the high variability of VP1 (Fernandez-Sainz et al., 2019). VP1 plays crucial roles in FMDV infection, such as in inducing neutralizing antibodies, mediating cellular and humoral immunity, inducing host cell apoptosis, and promoting FMDV replication. It has been found that the FMDV structural protein VP1 can interact with soluble resistance-related calcium binding protein (sorcin) to inhibit type I IFN production induced by SeV or TNF-α, and the interaction between FMDV VP1 and sorcin can also disrupt the signal transduction of NF-κB, leading to persistent FMDV infection of the host (Li et al., 2013); however, further study is still required to determine its specific mechanism. Recently, the interaction of the host cell protein DnaJ heat shock protein family (Hsp40) member A3 (DNAJA3) with VP1 was identified through a yeast two-hybrid system. Studies has shown that DNAJA3 can significantly reduce the inhibitory effect of VP1 on SeV-induced IRF3 phosphorylation, dimerization, and nuclear localization through the lysosomal pathway, thus reducing the antagonism on the IFN-β signal pathway and inhibiting FMDV replication (Zhang et al., 2019). In addition, VP1 can also act on ribosomal protein SA (RPSA) to weaken its inhibitory effect on the mitogen-activated protein kinase (MAPK) pathway, which is conducive to the FMDV replication (Zhu et al., 2020). VP2 may indirectly inhibit the host’s type I IFN response pathway by interacting with the host protein heat shock protein family B [small] member 1.
\(\gamma\)-inhibiting IFN-\(\beta\) (JAK1) and degrade it via the lysosomal pathway, thereby rendering transcription 1 dimerization and nuclear accumulation of phosphorylated STAT1, which ultimately leads to the inhibition of the type II IFN signaling pathway to evade the host innate immunity (Li et al., 2016b). Moreover, VP3 depends on its C-terminal (111–220 amino acids) to interact with virus-induced signaling adapter (VISA) and inhibits the expression of VISA by reducing VISA mRNA synthesis, finally inhibiting IFN-\(\beta\) production (Li et al., 2016c). Besides, FMDV VP0 protein interacts with Poly (rC) binding protein 2 (PCBP2) to degrade VISA via apoptotic pathway, thereby increasing FMDV replication (Li et al., 2019c). The latest study has found that the TANK-binding kinase 1 (TBK1) protein can interact with VP3 and degrade VP3 by its kinase and E3 ubiquitin ligase activity to resist FMDV infection (Li et al., 2019b). In addition, microRNA-1307 could enhance the host immune response by promoting VP3 degradation through the proteasome pathway in PK-15 cells to inhibit FMDV replication (Qi et al., 2019). Another structural protein, VP4, interacts with nucleoside diphosphate kinase 1 (NME1) to inhibit p53-induced activation of the IFN pathway (Feng et al., 2018).

**The Role of FMDV Non-structural Proteins in the Regulation of Host Innate Immunity**

Foot-and-mouth disease virus regions P2 and P3 encode partial precursors and eight mature non-structural proteins (L\(^{pro}\), 2A, 2B, 2C, 3A, 3B, 3C\(^{pro}\), and 3D\(^{pol}\)). Moreover, L\(^{pro}\), 3C\(^{pro}\), 2B, 2C, and 3A also regulate host antiviral innate immune responses.

**Advances in the Suppression of Innate Immunity by FMDV VP3**

Though VP3 is more conservative than VP1, it still plays an important role in the process of viral assembly and in suppressing the host innate immunity. For example, study has confirmed that arginine 56 in VP3 is relevant to FMDV virulence (Borca et al., 2012). Subsequent study found that VP3 also plays a vital role in escaping the host’s innate immune response, for example, FMDV VP3 can interact with janus kinase 1 (JAK1) and degrade it via the lysosomal pathway, thereby inhibiting IFN-\(\gamma\)-induced phosphorylation, signal transducer activator of transcription 1 (STAT1) dimerization and nuclear accumulation of phosphorylated STAT1, which ultimately leads to the inhibition of the type II IFN signaling pathway to evade the host innate immunity (Li et al., 2016b). Moreover, VP3 depends on its C-terminal (111–220 amino acids) to interact with virus-induced signaling adapter (VISA) and inhibits the expression of VISA by reducing VISA mRNA synthesis, finally inhibiting IFN-\(\beta\) production (Li et al., 2016c). Besides, FMDV VP0 protein interacts with Poly (rC) binding protein 2 (PCBP2) to degrade VISA via apoptotic pathway, thereby increasing FMDV replication (Li et al., 2019c). The latest study has found that the TANK-binding kinase 1 (TBK1) protein can interact with VP3 and degrade VP3 by its kinase and E3 ubiquitin ligase activity to resist FMDV infection (Li et al., 2019b). In addition, microRNA-1307 could enhance the host immune response by promoting VP3 degradation through the proteasome pathway in PK-15 cells to inhibit FMDV replication (Qi et al., 2019). Another structural protein, VP4, interacts with nucleoside diphosphate kinase 1 (NME1) to inhibit p53-induced activation of the IFN pathway (Feng et al., 2018).

**Advances in the Suppression of Innate Immunity by FMDV L\(^{pro}\)**

The RNA translation initiation site of FMDV has two AUGs separated by 84 nucleotides. As such, there are two different forms of L\(^{pro}\) after translation, namely, Lab and Lb. It is generally believed that Lb is more powerful and more effective than Lab (Grubman and Baxt, 2004; Liu et al., 2015). L\(^{pro}\) is related to viral virulence and pathogenicity (Wang et al., 2011b; Segundo et al., 2007). L\(^{pro}\) can affect the translation and transcription of IFNs in various ways in order to interrupt antiviral activity mediated by IFN-\(\alpha/\beta\) (de Los Santos et al., 2006, 2007; Hato et al., 2010). L\(^{pro}\) can affect the translation and transcription of IFNs in various ways in order to interrupt antiviral activity mediated by IFN-\(\alpha/\beta\) (de Los Santos et al., 2006). L\(^{pro}\) blocks nuclear translocation of the NF-\(\kappa B\) subunit heterodimer p65/RelA to inhibit the IFN-\(\beta\) expression (de Los Santos et al., 2007). L\(^{pro}\) can also reduce the protein level of IRF3/7 through its catalytic activity to inhibit the transcription of IFN-\(\beta\) mRNA and MDA5-mediated type I IFN (Wang et al., 2010; Medina et al., 2018). L\(^{pro}\) also inhibits poly (I:C)-induced type III IFN (IFN-\(\lambda 1\)) promoter activity through its enzyme activity and the conserved protein domain SAP region, thereby promoting the nuclear localization of L\(^{pro}\), which is related to FMDV virulence and pathogenicity (Wang et al., 2011b; Segundo et al., 2012). As a novel type of viral DUB (deUbiquitinase), L\(^{pro}\) negatively regulates the type I IFN pathway by inhibiting the ubiquitination of innate immune signaling molecules such as as retinoic acid-inducible gene I (RIG-I), tank-binding kinase 1 (TBK1), and TNF receptor-associated factor 3/6 (TRAF3/6) (Wang et al., 2011a). On the contrary, although L\(^{pro}\) also acts as a deISGylase, it is not important for inhibiting type I IFN, and this deISGylation activity is impaired after mutate L\(^{pro}\) W105 (the
FIGURE 2 | Part of the innate immune signaling pathways triggered after the viral RNA is recognized by TLRs and RLRs. After TLR3 and TLR7/8 recognize the ligand in endosome, they recruit and activate TRIF and MyD88, respectively. RLRs member recognizes corresponding ligand and activates the CARD region of MAVS. Activated TRIF, MyD88, MAVS induce TANK, and TRAF3/6. Then one signal pathway activates IKKα/β and NEMO complex, and the other activates TBK1 and IKKe, NEMO complex. Subsequently, the IKKe/IκB and NEMO complex activates NF-κB, while TBK1 and IKKe, NEMO complex phosphorylates and activates IRF3/7 to induce the expression of IFN α/β gene. The produced IFN α/β can bind to receptor IFNAR1/2, recruit STAT1/2 through the JAK1/TYK2 adaptor molecule, and recruit IRF9 through phosphorylated STAT1/2 to form the complex ISGF3 and enter the nucleus, then bind ISRE, and stimulate the expression of ISGs (Rodriguez Pulido and Saiz, 2017; Medina et al., 2018).

only conserved aromatic residue in all FMDV serotypes and can interact with ISG15), then leading to viral attenuation both in tissue culture and in vivo in mice (Medina et al., 2020). Recent study has shown that Lpro can inhibit the expression of IFNs and interferon-stimulated genes (ISGs) by interacting with activity dependent neuroprotective protein, a transcription factor that targets the IFN-α promoter region during early FMDV infection to increase viral replication (Medina et al., 2017); however, its mechanism still requires further study. Lpro can also target the innate immune molecule laboratory of genetics and physiology 2 (LGP2) to reduce the level of IFNs in infected cells, which then promotes the replication of FMDV (Rodriguez Pulido et al., 2018). In addition, Lpro cuts the SG scaffold proteins Ras GTPase SH3 domain binding protein 1 (G3BP1) and G3BP2 through its
catalytic activity to inhibit SG formation, which may be relevant to the inhibition of the type I IFN response pathway (Visser et al., 2019). However, there are some issues about the mechanisms that are still unclear, such as the location of the cleavage site of Lpro into the N-terminal of the histone H3. This cleavage may has an effect on the transcription level of cells infected with FMDV, as H3 is related to the regulatory domain of the transcriptional activity of eukaryotes, eventually almost completely destroying host cell functions (Falk et al., 1990). Based on earlier study, C3Ppro also has the ability to cleave eIF4G, although the cleavage site is different from the Lpro cleavage site, and the effect of C3Ppro is weaker than Lpro. Moreover, C3Ppro also cleaves eIF4A in the late stage of FMDV infection, thus inhibiting the synthesis of host cell proteins (Belsham et al., 2000). Moreover, C3Ppro can specifically cut NF-κB essential modulator (NEMO) at the Gln 383 site due to its proteolytic activity, which inhibits the activity of IRFs and NF-κB, as DUB, inhibiting the ubiquitination of RIG-I, TBK1, TRAF3/6 (Wang et al., 2011a) as delSylase, leading to the attenuation of FMDV (Medina et al., 2020) interacts with ADNP to inhibit the expression of IFNs and ISG (Medina et al., 2017). Targets the LGP2 to reduce the level of IFNs (Rodríguez Pulido et al., 2018) cuts G3BP1 and G3BP2 via catalytic activity (Visser et al., 2019).

Table 1 FMDV proteins regulate and/or interact with the host’s innate immunity (Medina et al., 2018).

| FMDV proteins | Viral-counter-mechanism |
|---------------|-------------------------|
| **Structural proteins** | | |
| VP1 | Interacts with host protein sorcin to inhibit I IFNs and disrupt the signal transduction of NF-κB (Li et al., 2013) |
| VP3 | Acts on RPSA to conducive to the replication of FMDV (Zhu et al., 2020) |
| Lpro | Cleaves NF-κB to reduce the production of IFN-α/β (de Los Santos et al., 2006, 2007; Hato et al., 2010) Affects the translation and transcription of IFNs (de Los Santos et al., 2006) Blocks nuclear translocation of p65/RelA (de Los Santos et al., 2007) Inhibits the transcription of IFN-β mRNA (Wang et al., 2010; Medina et al., 2018) Inhibits the translation of poly(C)-induced IFN-λ1 promoter activity (Wang et al., 2011b; Segundo et al., 2012) As DUB, inhibiting the ubiquitination of RIG-I, TBK1, TRAF3/6 (Wang et al., 2011a) As delSylase, leading to the attenuation of FMDV (Medina et al., 2020) Targets the LGP2 to reduce the level of IFNs (Rodríguez Pulido et al., 2018) |
| **Non-structural Proteins** | | |
| 3Cpro | Cleaves histone H3 (Falk et al., 1990) Cleaves eIF4G and eIF4A (Belsham et al., 2000) Cuts the NEMO to inhibit the activity of IRFs and NF-κB (Wang et al., 2012a) Degradates KPNA1 and blocks the JAK-STAT pathway (Du et al., 2014) Inhibits the autophagy by degrading ATG5-ATG12 (Fan et al., 2017) Interacts with host protein TBK1 (Li et al., 2016b) |
| 2B | Involves in membrane rearrangement (Moffat et al., 2005; Moffat et al., 2007) Disrupts the Ca2+ balance (Campiglia et al., 2004; de Jong et al., 2008) Regulates LGBP expression level to increase FMDV replication (Zhu et al., 2017) Inhibits of RLRs (MDA5 and RIG-I)-induced IFN-β production (Zhu et al., 2016; Li et al., 2018) Downregulates NOD2 to affect NF-κB and IFN-β (Li et al., 2019b) Interacts with CypA (Li et al., 2018) Activates NLRP3 inflammasomes (Zhi et al., 2020) |
| 3A | Interacts with RLRs (RIG-I/MDA5/VISA) to inhibit the TLRs-mediated IFN-β signaling pathway (Li et al., 2016a) Interacts with DDX56 to reduce phosphorylation of IRF3 (Fu et al., 2019; Li et al., 2019a) Degradates G3BP1 by upregulating LRRC25 (Yang et al., 2020) |
of src-associated protein in mitosis (Sam68), resulting in its redistribution in the cytoplasm, and then binds to the FMDV internal ribosome entry site (IRES), thereby affecting the life cycle of FMDV (Lawrence et al., 2012). Subsequent further study has found that 3CP\textsuperscript{pro} can interact with Sam68 to regulate FMDV replication in vitro (Rai et al., 2015).

Advances in FMDV 2B Suppressing Innate Immunity
Studies have shown that the FMDV non-structural protein precursor 2BC can block endoplasmic reticulum-golgi apparatus transport, and 2B has been found to be closely associated with the endoplasmic reticulum and found to be involved in membrane rearrangement (Moffat et al., 2005, 2007). Further research has proven that 2B is an ion channel protein composed of 154 aa and crosses the endoplasmic reticulum membrane, whereas its C-terminus and N-terminus are exposed to the cytoplasm (Ao et al., 2015). In addition, 2B has the function of increasing the host cell membrane permeability and disrupting Ca\textsuperscript{2+} balance in the host cell, thereby inducing autophagy (Campanella et al., 2004; de Jong et al., 2008). Moreover, 2B amino acid residues (28–147) are related to FMDV replication (Ao et al., 2015; Glade et al., 2018). During FMDV infection, 2B can regulate the LGP2 protein expression level to increase FMDV replication (Zhu et al., 2017). Moreover, 2B can decrease the expression levels of MDA5 and RIG-I followed by disrupting the phosphorylation of key factors TBK1 and IRF3, thereby inhibiting the IFN-β production in the RLRs antiviral signaling pathway (Zhu et al., 2016; Li et al., 2018). Recent studies have demonstrated that 2B affects the NF-kB and IFN-β signaling pathway by downregulating nucleotide-binding oligomerization domain 2 (NOD2) expression to enhance FMDV replication (Liu et al., 2019). In addition, interaction of 2B with the host Cyclophilin A (CypA) reduced CypA-mediated degradation of L\textsuperscript{pro} to promote FMDV replication (Liu et al., 2018). Study has shown that CypA is involved in regulating the HCV-induced type I IFN pathway (Bobardt et al., 2013); however, whether CypA is involved in the FMDV-induced type I IFN pathway is not clear. Additionally, the transmembrane region of 2B promotes IL-1β production by activating NLRP3 inflammasomes to inhibit FMDV replication (Zhi et al., 2020).

Advances in the Suppression of Innate Immunity by FMDV 3A
Foot-and-mouth disease virus non-structural protein 3A is a conserved protein consisting of 153 amino acids and is much longer than other picornavirus 3A proteins (Medina et al., 2018). FMDV 3A plays a crucial role in viral replication, distinguishing the host range of infection, and virulence. For example, the deletion of 3A residues 87–106 reduces the replication and virulence of FMDV in cattle, but not in pigs (Pacheco et al., 2013). A study has shown that 3A (1–51 amino acids) can interact with RIG-I/MDA5/VISA and inhibit the TLR-mediated IFN-β signaling pathway by downregulating their mRNA expression level, thereby escaping the host innate immunity (Li et al., 2016a). Furthermore, the interaction between FMDV 3A and DEAD-box family protein (DDX56) inhibits type I IFN signaling pathway by reducing IRF3 phosphorylation to increase FMDV replication (Fu et al., 2019; Li et al., 2019a). In addition, recent study has shown that 3A can degrade G3BP1 by upregulating the expression of autophagy-related protein leucine rich repeat-containing 25 (LRRC25) to reduce IFN-β production, thereby facilitating the replication and growth of FMDV (Yang et al., 2020).

The Role of Other FMDV Proteins in the Regulation of Host Innate Immunity
Except for the aforementioned viral proteins that have been widely studied, there are other FMDV proteins involved in the process of regulating the host innate immune response. The non-structural FMDV protein 2C can interact with host protein Nmi (N-myc and STAT interactor), which may be involved in the FMDV 2C-induced apoptosis (Wang et al., 2012b). Further study has indicated that 2C and Nmi induce a type I IFN response, and expression of FMDV 2C or Nmi significantly suppresses VSV replication (Zheng et al., 2014). In addition, 3D\textsuperscript{pol} interacts with DEAD-box RNA helicase 1 (DDX1), which has been identified to inhibit FMDV replication due to its ATPase or helicase activity and induce the production of host IFN-β protein to enhance antiviral innate immunity (Xue et al., 2019). In addition, the non-coding regions (i.e., 5′UTR and 3′UTR) of FMDV also play an important role in FMDV virulence, replication, and inhibition of host antiviral immunity (Grubman and Baxt, 2004). For example, study has shown that the S fragment deletion mutants of the FMDV 5′UTR can increase mRNA levels of IFN-β and ISGs, and weaken FMDV virulence (Kloc et al., 2017). Both 3D\textsuperscript{pol} and ISES can also interact with Sam68 to regulate viral RNA translation (Rai et al., 2015). The host protein G3BP1 can directly interact with the IRES of FMDV 5′UTR, afterward, G3BP1 is cleaved by L\textsuperscript{pro} and 3CP\textsuperscript{pro}, upon which both products, namely, Ct-G3BP1 and Nt-G3BP1, can inhibit FMDV cap- and IRES-dependent translation (Galan et al., 2017). In terms of its function in enhancing IRES activity and determining virulence, the FMDV 3′UTR can bind to S fragment and IRES, and form a 5′–3′ bridge (IRES–3′UTR or S–3′UTR) (Serrano et al., 2006; Gao et al., 2016).

CONCLUDING REMARKS AND FURTHER PERSPECTIVES
In this review, we mainly list the studies on the interaction of FMDV proteins with host proteins to regulate innate immunity. FMDV proteins can act on host proteins through a variety of ways to directly or indirectly block the innate immune signaling pathway in order to enhance its replication ability. For example, FMDV cleaves host proteins by its sub-enzyme activity, and FMDV interacts with key factors in the innate immune pathway to increase its replication (Medina et al., 2018). These mechanisms have shown that FMDV disrupts the dynamic balance between virus and host, thereby providing the direction and theoretical basis for further FMDV research. Given that FMDV has a worldwide spread and seriously affects global economy and trade, FMD is listed as a class A infectious disease
by the World Organization for Animal Health (OIE). Therefore, the aforementioned studies provide a solid theoretical foundation for FMDV vaccine development and technical guidance for FMD control (Aghaei et al., 2019; Dhanesh et al., 2020).

Due to the complexity of the FMDV structure and mutation-prone nature of the FMDV genome, the detailed mechanism of FMDV-mediated host’s innate immune response needs to be further investigated. Several preventive measures are not effective, leading to cross-infection of multiple serotypes, thereby making the diagnosis and prevention of FMDV more difficult. Consequently, there are still some questions that need to be explored: (1) Do the FMDV proteins have other sites to interact with host factors that suppress immune responses? (2) Are there interactions between FMDV proteins that promote FMDV replication? (3) What is the relationship between the inflammatory response and clinical symptoms caused by FMDV infection?

In summary, FMDV proteins interact with host proteins or cytokines to regulate the host’s innate and adaptive immune responses, which subsequently weakens the immunity of the animal and promotes FMDV replication as well as persistent infection. This review provided a theoretical basis for the development of FMDV vaccines and anti-FMDV drugs, as well as novel ideas regarding the diagnosis and control of FMD.

AUTHOR CONTRIBUTIONS

JP and DL conceived and designed the study. JP, JY, WY, JR, YW, HZ, and DL wrote the manuscript. All authors contributed to the article and approved the submitted version.

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REFERENCES

Abubakar, M., Manzoor, S., and Ahmed, A. (2018). Interplay of foot and mouth disease virus with cell-mediated and humoral immunity of host. Rev. Med. Virol. 28:e1966. doi: 10.1002/rmv.1966

Aghaei, A., Moghbeli, M., Kargar, M., Nazarian, S., and Kafizadeh, F. (2019). Cloning and expression of a novel synthetic gene containing VP1 and 3A in Bacillus subtilis as a vaccine candidate against foot-and-mouth disease virus. Biotechnol. 60, 55–59. doi: 10.1016/j.biotec.2019.05.003

Ao, D., Guo, H. C., Sun, S. Q., Sun, D. H., Fung, T. S., Wei, Y. Q., et al. (2015). Viroporin activity of the foot-and-mouth disease virus non-structural 2B protein. PLoS One 10:e0125828. doi: 10.1371/journal.pone.0125828

Belsham, G. J., Mclnerney, G. M., and Ross-Smith, N. (2000). Foot-and-mouth disease virus 3C protease induces cleavage of translation initiation factors eIF4A and eIF4G within infected cells. J. Virol. 74, 272–280. doi: 10.1128/jvi.74.1.272–280.2000

Birtley, J. R., Knox, S. R., Jaulent, A. M., Brick, P., Leatherbarrow, R. J., and Curry, S. (2005). Crystal structure of foot-and-mouth disease virus 3C protease: new insights into catalytic mechanism and cleavage specificity. J. Biol. Chem. 280, 11520–11527. doi: 10.1074/jbc.m413254200

Bobardt, M., Hopkins, S., Baugh, J., Chatterji, U., Hernandez, F., Hiscott, J., et al. (2013). HCV NS5A and IRF9 compete for CypA binding. J. Hepatol. 58, 16–23. doi: 10.1016/j.jhep.2012.08.007

Borca, M. V., Pacheco, J. M., Holinka, L. G., Carrillo, C., Hartwig, E., Garriga, D., et al. (2012). Role of arginine-56 within the structural protein VP3 of foot-and-mouth disease virus (FMDV) O1 Camps in virus virulence. Virology 422, 37–45. doi: 10.1016/j.virol.2011.09.031

Campanella, M., de Jong, A. S., Lanke, K. W., Melchers, W. J., Willems, P. H., Pinton, P., et al. (2004). The coxsackievirus 2B protein suppresses apoptotic host cell responses by manipulating intracellular Ca2+ homeostasis. J. Biol. Chem. 279, 18440–18450. doi: 10.1074/jbc.m309494200

Curry, S., Roque-Rosell, N., Zunszain, P. A., and Leatherbarrow, R. J. (2007). Foot-and-mouth disease virus 3C protease: recent structural and functional insights into an antiviral target. Int. J. Biochem. Cell Biol. 39, 1–6. doi: 10.1016/j.biocel.2006.07.006

de Jong, A. S., de Mattia, F., Van Dommelen, M. M., Lanke, K., Melchers, W. J., Willems, P. H., et al. (2008). Functional analysis of picornavirus 2B proteins: effects on calcium homeostasis and intracellular protein trafficking. J. Virol. 82, 3782–3790. doi: 10.1128/jvi.02076-07

de Los Santos, T., de Avila Botton, S., Weiblen, R., and Grubman, M. J. (2006). The leader proteasein of foot-and-mouth disease virus inhibits the induction of beta interferon mRNA and blocks the host innate immune response. J. Virol. 80, 1906–1914. doi: 10.1128/jvi.80.4.1906-1914.2006

de Los Santos, T., Diaz-San Segundo, F., and Grubman, M. J. (2007). Degradation of nuclear factor kappa B during foot-and-mouth disease virus infection. J. Virol. 81, 12803–12815. doi: 10.1128/jvi.01467-07

Deretic, V., and Levine, B. (2018). Autophagy balances inflammation in innate immunity. Autophagy 14, 243–251. doi: 10.1080/15548627.2017.1402992

Dhanesh, V. V., Hosamani, M., Basagoudanavar, S. H., Saravanam, P., Biswal, J. K., Tamil Selvan, R. P., et al. (2020). Immunogenicity and protective efficacy of 3A truncated negative marker foot-and-mouth disease virus serotype A vaccine. Appl. Microbiol. Biotechnol. 104, 2589–2602. doi: 10.1007/s00253-020-10370-z

Du, Y., Bi, J., Liu, J., Liu, X., Wu, X., Jiang, P., et al. (2014). 3Cpro of foot-and-mouth disease virus antagonizes the interferon signaling pathway by blocking STAT1/STAT2 nuclear translocation. J. Virol. 88, 4908–4920. doi: 10.1128/jvi.03668-13

Falk, M. M., Grigera, P. R., Bergmann, L. E., Zibert, A., Multhaup, G., and Beck, E. (1990). Foot-and-mouth disease virus protease 3C induces specific proteolytic cleavage of host cell histone H3. J. Virol. 64, 748–756. doi: 10.1128/jvi.64.2.748-756.1990

Fan, X., Han, S., Yan, D., Gao, Y., Wei, Y., Liu, X., et al. (2017). Foot-and-mouth disease virus infection suppresses autophagy and NF-κB activation via degradation of ATG5–ATG12 by 3C(pro). Cell Death Dis. 8:e2561. doi: 10.1038/cddis.2016.489

Feng, H. H., Zhu, Z. X., Cao, W. J., Yang, F., Zhang, X. L., Du, X. L., et al. (2018). Foot-and-mouth disease virus induces lysosomal degradation of NME1 to impair p53-regulated interferon-inducible antiviral genes expression. Cell Death Disc. 9:885.

Fernandez-Sainz, I., Gavitt, T. D., Koster, M., Ramirez-Medina, E., Rodriguez, Y. Y., Wu, P., et al. (2019). The VP1 G-H loop hypervariable epitope contributes to protective immunity against foot and mouth disease virus in swine. Vaccine 37, 3435–3442. doi: 10.1016/j.vaccine.2019.05.019

Fu, S. Z., Yang, W. P., Ru, Y., Zhang, K. S., Wang, Y., Liu, X. T., et al. (2019). DDX56 cooperates with FMDV 3A to enhance FMDV replication by inhibiting the phosphorylation of IRF3. Cell Signal 64:109393. doi: 10.1016/j.cellsig.2019.109393

Galan, A., Lozano, G., Pineiro, D., and Martinez-Salas, E. (2017). G3BP1 interacts directly with the FMDV IRES and negatively regulates translation. FEBS J. 284, 3202–3217. doi: 10.1111/febs.14184

Gao, Y., Sun, S. Q., and Guo, H. C. (2016). Biological function of Foot-and-mouth disease virus non-structural proteins and non-coding elements. Virol. J. 13:107.
Li, D., Fu, S., Wu, Z., Yang, W., Ru, Y., Shu, H., et al. (2019a). DDX56 inhibits type I interferon induction. J. Virol. 93:e01360-19. doi: 10.1128/JVI.01360-18

Gold, S. J., Sánchez-Arciga, C., and Taka, D. T. (2009). Vaccine efficacy in foot-and-mouth disease virus infected swine. Immunol. Rev. 225, 85–95. doi: 10.1111/j.1600-065x.2008.00672.x

Grubman, M. J., and Baxt, B. (2004). Foot-and-mouth disease. Clin. Microbiol. Rev. 17, 465–493.

Guan, S. H., and Belsham, G. J. (2017). Separation of foot-and-mouth disease virus leader protein activities; identification of mutants that retain efficient self-processing activity but poorly induce eIF4G cleavage. J. Gen. Virol. 98, 671–680. doi: 10.1099/jgv.0.000747

Hato, S. V., Sorellos, F., Ricour, C., Zoll, J., Melchers, W. J., Michiels, T., et al. (2010). Differential IFN-alpha/beta production suppressing capacities of the leader proteins of mengovirus and foot-and-mouth disease virus. Cell Microbiol. 12, 310–317. doi: 10.1111/j.1462-5822.2009.01395.x

Kloc, A., Díaz-San Segundo, F., Schafer, E. A., Rai, D. K., Kenney, M., de Los Santos, T., et al. (2017). Foot-and-mouth disease virus 5’-terminal S fragment is required for replication and modulation of the innate immune response in host cells. Virology 512, 132–143. doi: 10.1016/j.virol.2017.08.036

Kumar, H., Kawai, T., and Akira, S. (2009). Pathogen recognition in the innate immune system. Annu. Rev. Immunol. 27, 203–232. doi: 10.1146/annurev.immunol.031208.134121

Lawrence, P., Schafer, E. A., and Rieder, E. (2012). The nuclear protein Sam68 is required for replication and modulation of the innate immune response in host cells. J. Virol. 86, 10561–10573. doi: 10.1128/JVI.00636-12

Liu, H., Xue, Q., Cao, W., Yang, F., Ma, L., Liu, W., et al. (2018). Foot-and-mouth disease virus nonstructural protein 2B interacts with cyclophilin A, modulating virus replication. FASEB J. 32, 6706–6723. doi: 10.1096/fj.201701351

Liu, Y., Zhu, Z., Zhang, W., and Zheng, H. (2015). Multifunctional roles of leader protein of foot-and-mouth disease viruses in suppressing host antiviral responses. Vet. Res. 46:127

Liu, H., Zhu, Z., Xue, Q., Yang, F., Cao, W., Zhang, K., et al. (2019). Foot-and-mouth disease virus antagonizes NOD2-mediated antiviral effects by inhibiting NOD2 protein expression. J. Virol. 93:e0124-19. doi: 10.1128/JVI.0124-19

Ma, X., Ma, L. N., Chang, Y. Q., Ma, P., Li, L. J., Wang, Y. Y., et al. (2018). Type I interferon induced and antagonized by foot-and-mouth disease virus. Front. Microbiol. 9:1862. doi: 10.3389/fmicb.2018.01862

Mason, P. W., Grubman, M. J., and Baxt, B. (2003a). Molecular basis of pathogenesis of FMDV. Virus Res. 91, 9–32. doi: 10.1016/s0168-1702(02)00257-5

Mason, P. W., Marvin, J., Grubman, and Baxt, B. (2003b). Molecular basis of pathogenesis of FMDV. Virus Res. 91, 9–32.

Medina, G. N., Knudsen, G. M., Greiner, A. L., Kloc, A., Diaz-San Segundo, F., Rieder, E., et al. (2017). Interaction between FMDV L(pro) and transcription factor ADNP is required for optimal viral replication. Virology 505, 12–22. doi: 10.1016/j.virol.2017.02.010

Medina, G. N., Segundo, F. D., Stenfeldt, C., Arzt, J., and de Los Santos, T. (2018). The different tactics of foot-and-mouth disease virus to evade innate immunity. Front. Microbiol. 9:2644. doi: 10.3389/fmicb.2018.02644

Moftak, K., Howell, G., Knox, C., Belsham, G. J., Monaghan, P., Ryan, M. D., et al. (2005). Effects of foot-and-mouth disease virus nonstructural proteins on the structure and function of the early secretory pathway: 2BC but not 3A blocks endoplasmic reticulum-to-Golgi transport. J. Virol. 79, 4382–4395. doi: 10.1128/JVI.79.11.4382-4395.2005

Moftak, K., Knox, C., Howell, G., Clark, S. J., Yang, H., Belsham, G. J., et al. (2007). Inhibition of the secretory pathway by foot-and-mouth disease virus 2BC protein is reproduced by coexpression of 2B with 2C, and the site of inhibition is determined by the subcellular location of 2C. J. Virol. 81, 1129–1139. doi: 10.1128/JVI.00393-06

Pacheco, J. M., Gladue, D. P., Holinka, L. G., Arzt, J., Bishop, E., Smoliga, G., et al. (2013). A partial deletion in non-structural protein 3A can attenuate foot-and-mouth disease virus in cattle. Virology 446, 260–267. doi: 10.1016/j.virol.2013.08.003

Parida, S., Oh, Y., Reid, S. M., Cox, S. J., Statham, R. J., Mahapatra, M., et al. (2006). Interferon-gamma production in vitro from whole blood of foot-and-mouth disease virus (FMDV) vaccinated and infected cattle after incubation with inactivated FMDV. Vaccine 24, 964–969. doi: 10.1016/j.vaccine.2005.08.108

Qi, L., Wang, K., Chen, H., Liu, X., Lv, J., Hou, S., et al. (2019). Host microRNA miR-1307 suppresses foot-and-mouth disease virus replication by promoting VP3 degradation and enhancing innate immune response. Virology 535, 162–170. doi: 10.1016/j.virol.2019.07.009

Rai, D. K., Lawrence, P., Kloc, A., Schafer, E., and Rieder, E. (2015). Analysis of the interaction between host factor Sam68 and viral elements during foot-and-mouth disease virus infections. J. Virol. 12:224.

Randall, R. E., and Goodbourn, S. (2008). Interferons and viruses: an interplay between induction, signalling, antiviral responses and virus countermeasures. J. Gen. Virol. 89, 1–47. doi: 10.1099/vir.0.83391-0

Richter, C., and Faure, M. (2015). Autophagy in antiviral innate immunity. Cell Microbiol. 17, 368–376. doi: 10.1111/cmi.12043

Rodriguez Pulido, M., and Saiz, M. (2017). Molecular mechanisms of foot-and-mouth disease virus targeting the host antiviral response. Front. Cell Infect. Microbiol. 7:252. doi: 10.3389/fcimb.2017.00252

Rodriguez Pulido, M., Sanchez-Aparicio, M. T., Martinez-Salas, E., Garcia-Sastre, A., Sobrino, F., and Saiz, M. (2018). Innate immune sensor LGP2 is cleared by the Leader protease of foot-and-mouth disease virus. PLoS Pathog. 14:e1007135.

Saiz, M., Nunez, J. I., Jimenez-Clavero, M. A., Baranowski, E., and Sobrino, F. (2002). Foot-and-mouth disease virus: biology and prospects for disease control. Microbes Infect. 4, 1183–1192. doi: 10.1016/s1286-4579(02)01644-1
Sangare, O., Bastos, A. D., Marquardt, O., Venter, E. H., Vosloo, W., and Thomson, G. R. (2001). Molecular epidemiology of serotype O foot-and-mouth disease virus with emphasis on West and South Africa. *Virus Genes* 22, 345–351.

Segundo, F. D., Weiss, M., Perez-Martin, E., Dias, C. C., Grubman, M. J., and Santos Tde, L. (2012). Inoculation of swine with foot-and-mouth disease SAP-mutant virus induces early protection against disease. *J. Virol.* 86, 1316–1327. doi: 10.1128/jvi.05941-11

Serrano, P., Pulido, M. R., Saiz, M., and Martinez-Salas, E. (2006). The 3′ end of the foot-and-mouth disease virus genome establishes two distinct long-range RNA-RNA interactions with the 5′ end region. *J. Gen. Virol.* 87, 3013–3022. doi: 10.1099/vir.0.82059-0

Stetson, D. B., and Medzhitov, R. (2006). Type I interferons in host defense. *Immunity* 25, 373–381. doi: 10.1016/j.immuni.2006.08.007

Sun, P., Zhang, S., Qin, X., Chang, X., Cui, X., Li, H., et al. (2018). Foot-and-mouth disease virus with emphasis on West and South Africa. *Virus Genes* 22, 345–351.

Wang, J., Wang, Y., Liu, J., Ding, L., Zhang, Q., Li, X., et al. (2012b). A critical role of interferon-induced protein IFP35 in the type I interferon response in cells induced by foot-and-mouth disease virus (FMDV) protein 2C. *Arch. Virol.* 159, 2925–2935. doi: 10.1007/s00705-014-2147-7

Zhi, X., Zhang, Y., Sun, S., Zhang, Z., Dong, H., Luo, X., et al. (2020). NLRP3 inflammasome activation by Foot-and-mouth disease virus infection mainly induced by viral RNA and non-structural protein 2B. *RNA Biol.* 17, 335–349. doi: 10.1080/15476286.2019.1700058

Zhang, B., Wang, Y. Y., and Shu, H. B. (2010). Regulation of virus-triggered type I interferon signaling by cellular and viral proteins. *Front. Biol. (Beijing)* 5, 312–321. doi: 10.1007/s12250-2010-0013-x

Zheng, W., Li, X., Wang, J., Li, X., Cao, W., Yang, F., et al. (2014). A critical role of interferon-induced protein IFP35 in the type I interferon response in cells induced by foot-and-mouth disease virus (FMDV) protein 2C. *Arch. Virol.* 159, 2925–2935. doi: 10.1007/s00705-014-2147-7