Chapter

The Causative Agent of FMD Disease

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Abstract

Foot-and-mouth disease (FMD) is an acute infection of cloven-hoofed animals caused by foot-and-mouth disease virus (FMDV). It is one of the most serious infectious diseases affecting animal husbandry and a major impediment to international trade in livestock and their products. Foot-and-mouth disease virus (FMDV), a member of the *Picornaviridae* family of *Aphthovirus*, is an icosahedral virus without envelope, 25–30 nm in diameter, containing about 8.4 kb of positive-sense single-stranded RNA. The virus exists in seven different serotypes: A, O, C, Asia1, SAT1, SAT2, and SAT3, but a large number of subtypes have evolved in each serotype. This chapter reviews the genome, structure, serotype, and epidemiology of FMDV, which will help people to further explore the mechanism of the interaction between foot-and-mouth disease virus and host and provide reference for scientific prevention and control of FMDV.

Keywords: FMDV, structure, serotypes, epidemiology

1. Introduction

Foot-and-mouth disease (FMD) is an acute and highly contagious disease of cloven-hoofed animals, such as pigs, cattle, sheep, and many wild animals. Disease animals are much show fever, the place such as snout, feet, and breast forms blister and canker. The disease can spread rapidly in many ways. It has broken out many times in the world, causing huge political and economic losses to human beings. The disease was first discovered in 1514 by the Italian monk H. Fracastorius in cattle. In 1897, Loeffler and Frosch demonstrated that a filterable agent caused FMD is the foot-and-mouth disease virus (FMDV) [1]. The causative agent of FMD disease belongs to the family *Picornaviridae*, genus *Aphthovirus*. This chapter describes the status of the genome, structure, serotype, and epidemiology of the virus.

2. The genome of FMDV

The FMDV genome is a positive-sense single-stranded RNA virus with a size of about 8.5 kb [2]. FMDV RNA has a 5′ non-coding region on the left, an open reading frame (ORF) in the middle, and a 3′ non-coding region on the right. At the end of the 5′ non-coding region is a viral coding peptide VPg (or 3B), which is covalently bound to the genome. For FMDV, this 5′ untranslated region (UTR) contains S-fragment (short fragment of the genome), poly(C), pseudoknot, cre structures, and internal ribosome entry site (IRES) [3].

The S fragment can form an over 350 bases stem-ring structure, which is isolated from the genome by a variable length homopolymeric cytidylic acid tract (poly(C)), and there are some differences between the S fragments of different serotypes [4]. Carrillo et al. isolated S fragments with a sequence similarity of 80%, indicating that S fragments are highly conservative [5]. The S fragment can protect the successful replication of daughter RNA and will not be degraded by nucleic acid exonuclease, which greatly ensures the replication process of viral RNA. S fragment was involved in mediating the innate immune system. Kloc et al. found that viral RNA could not survive after deletion of more than 163 nt on stem ring of S fragment [6]. In addition, a short fragment of the G320T mutation prevented rescue of viable virus [7].

Different isolates of FMDV have different lengths of poly(C) tract; Harris and Brown found that the length of poly(C) tract may be related to the virulence of FMDV by comparing a virulent and an avirulent strain of foot-and-mouth disease virus [8]. However, other researchers suggest that the differences in virulence may be due to changes elsewhere in the genome of these strains [3].

The poly (C) tract is followed by three to four tandemly repeated pseudoknots (PKs) [9]. In a recent study, researchers compared the virulence and pathogenic mechanism of different FMDV strains in pigs and cattle by constructing PK recombinant FMDV strains and found that the absence of different sizes of PKs resulted in different pathogeny to the host, indicating that the pseudoknot region was the key to determine the viral tropism and virulence of foot-and-mouth disease virus [10].

In some picornavirus genome coding region, there is a known as cis-acting replicative element (cre) of the basic structure of RNA, cre is a conservative AAACA motif of stem loop structure, its function is to add U residues to the protein primer 3B [11]. Furthermore, Mason et al. found that cre plays an important role in genome replication and that this function is independent of its position at the 5′ end of the genome [12].

Eukaryotes generally begin translation by identifying cap structures at the 5′ end of mRNA; however, the initiation of translation can also occur internally, as has been found in picornavirus RNAs, where a functional element called the internal ribosomal entry site (IRES) at the 5′ end of mRNA also performs this function [13]. The FMDV IRES consists of 462 nucleotides with 5 domains [14]. Earlier studies have found that the interaction between IRES and the translation initiation factor eIF4G, which acts as a linker during translation initiation, is the key to in vivo translation [15]. Later, the researchers found an interaction between the IRES of FMD virus and three other translation initiation factors eIF3, eIF4B, and eIF4GII during translation initiation [16]. Furthermore, IRES trans-acting factor (ITAF) (45) promoted IRES-mediated translation in all cells; however, IRES-mediated translation activity was independent of the host range of FMDV, and only the effects of polypyrimidine tract binding protein (PTB) and eukaryotic initiation factor 4E-binding protein 1 (4E-BP1) were observed in FMDV-sensitive cells [17]. In addition, Ras GTPase SH3 domain binding protein 1 (G3BP1) interacts directly with FMDV IRES to negatively regulate translation [18].

The genome of FMDV contains an open reading frame, and ORF encodes four structural proteins (VP1, VP2, VP3, and VP4) and 10 non-structural proteins (L, 2A, 2B, 2C, 3A, 3B1, 3B2, 3B3, 3C, and 3D), whose functions will be detailed in the following sections [19, 20].

The 3′ -terminal region of FMDV consists of two distinct elements, a 90 nt untranslated region (3′-NCR) and a poly(A) tract, which have been found to stimulate IRES-driven translation [21]. Since the IRES are located at the 5′ UTR, it was assumed that there was a connection between the 3′ and 5′ ends of FMDV,

and Serrano et al. subsequently demonstrated that different 3′ UTR elements are involved in the interaction between the IRES and the S region, suggesting that the 5′-3′ end of the bridge is in direct RNA-RNA contact and plays a role in RNA replication [22]. The absence of SL1 and SL2, two stem-ring structures in the 3′ non-coding region, affects viral infectivity, and the ΔSL1 mutation has been shown in pigs to be harmless to pigs, but to induce an immune response, which is important for the development of FMDV vaccines [23]. In addition, SL2 is an essential component of virus replication [23, 24].

3. Structure of the FMDV

3.1 Structural proteins

FMDV is an icosahedral symmetry non-enveloped virus. It consists of four capsid proteins VP1, VP2, VP3, and VP4, among which VP1, VP2, and VP3 are in the outermost layer of the virus, and VP4 is located in the interior of the virus and contacts with RNA [25]. Malik et al. obtained a high-resolution structure (5.2 Å) of the icosahedron of FMDV using cryo-electron microscopy (cryo-EM), notably, the obtained structure did not contain VP4 [26]. FMDV capsids are susceptible to low pH and high temperature and dissociate into pentamers under acidic conditions and release RNA [27].

In 1982, Barteling et al. proposed that FMDV structural protein (VP1) might be involved in early virus-cell interactions [28]. In the second year, Dawe and King found that the early and late viral virulence obtained by infecting BHK21 cells was different, and the researchers found that the point mutations of the VP1 were the cause of mouse virulence and BHK21 cell pathogenicity [29]. Since most of the VP1 protein is exposed on the surface of the virus, which determines the antigenicity of the virus to a large extent, VP1 protein can induce the body to produce specific neutralizing antibodies and induce anti-infection immunity [30–34]. On the VP1 of FMDV, there is a well-known G-H loop containing a highly conserved Arg-Gly-Asp (RGD) sequence, which is necessary for the virus to adhere to the cell [35, 36]. The researchers used this property of VP1 to make many explorations in the development of a vaccine against FMDV [33, 37–42]. In addition, studies have shown that VP1 N terminal is related to pH stability of FMD virus particles [43]. A recent study showed that VP1 inhibits the beta interferon signaling pathways by inhibiting IRF3 phosphorylation, dimerization, and nuclear translocation. However, the DnaJ heat shock protein family (Hsp40) member A3 (DNAJA3) can attenuate this effect [44].

For the structural protein VP2, the researchers believe that VP2 is associated with the persistence of FMDV [45]. Amino acid substitutions in the B-C loop of VP2 protein lead to antigenic differences in different types of FMDV, which indicates that VP2 is related to the antigenic diversity of FMDV [46]. In addition, amino acid substitutions in VP2 also affect the replication ability and virulence of the virus [46]. Interestingly, Vazquez-Calvo et al. found that tyrosine replacement of VP2 histidine enhanced the acid resistance of the FMDV capsid [47]. Further studies have shown that VP2 activates the EIF2S1-ATF4 pathway in cells and induces autophagy via the heat shock protein family B [small] member 1 (HSPB1) [48]. In addition, the researchers found applications for VP2 in vaccine development [49, 50] and detection of viral serotypes [51–53].

VP3 protein is the structural protein of FMDV. An amino acid deficiency of VP3 protein at position 59 of a foot-and-mouth disease virus was found in India, and the presence of this mutant increased the incidence of the epidemic [54–56]. In addition, the substitution of VP3 H142D for FMD virus can enhance the acid resistance

of serotype A [57]. Furthermore, the researchers found that FMDV VP3 inhibited the IFN-beta signaling pathways [58] and the IFN-gamma signal transduction pathways [59]. Interestingly, Qi et al. found that host microRNA miR-1307 promotes the degradation of the viral structural protein VP3 through the proteasome pathway, suggesting that it may be developed for the treatment of foot-and-mouth disease [60].

Regions 20 to 35 of FMDV VP4 may be involved in inducing an immune response in T cells to recognize the T cell epitopes of MHC, a property that could be used to develop peptide vaccines [61, 62].

3.2 Nonstructural proteins of the FMDV

There are two initiation codes AUG in the ORF of FMDV, which can produce two forms of lead proteases, Lab (synthesized by the first AUG) and Lb (synthesized by the second AUG) [63]. Further studies found that the virus could still be produced in transfected cells when the first AUG was deleted, but not when the second AUG was deleted [64]. FMDV inhibits protein synthesis in host cells after infecting the host, which may be related to the cleavage of eukaryotic translation initiation factor 4GII (eIF4GII) induced by leader protease (L-pro) [65]. Further studies by Moral-Lopez et al. found that L-pro can increase the translation driven by IRES [66]. In addition, phylogenetic analysis of nucleotide sequence in L-pro region of FMD type O serum isolates from India revealed that all amino acid residues at the active cleavage site of L-pro sequence were conserved [67].

The P2 portion of FMDV is eventually processed into three mature peptides, 2A, 2B, and 2C [68]. FMDV 2A protein can cleave the site of 2A/2B, and the researchers applied this property to the field of biotechnology and successfully obtained bioactive proteins by expressing multiple proteins in cells [69–76]. It has been shown that the 2A polypeptide can cleaving the 2A/2B junction because it has a conserved c-terminal motif [D(V/I)E(S/T)NPGP], where the last P is the first residue of 2B, which is important for protein processing and virus replication [77, 78]. The researchers produced recombinant antigen of FMDV P1-2A3C in plant species, which can induce humoral immunity in guinea pigs [79]. In addition, the development of a genetically engineered vaccine against FMDV 2A may be an effective means of controlling foot-and-mouth disease [80, 81]. The study of 2B by Zhu et al. showed that, in the study of FMDV, 2B expression reduced the expression of retinoic acid-inducible gene I (RIG-I) through the interaction of residues of 2B carboxyl terminal amino acids 105–114 [82]. Further studies have shown that 2B also interacts with MDA5 and negatively regulates RLR-mediated IFN-beta induction [83]. In addition, Zhi et al. demonstrated that 2B activates NLRP3 inflammasome [84]. Further studies revealed that the non-structural protein 2B of FMDV interacts with eEF1G [85] and CypA [86] and plays a role in the process of virus infection and replication. For 2C, it was used to distinguish between infected and vaccinated animals [87–90]. The researchers identified 2C interacting proteins, including autophagy regulators Beclin1 [91], N-myc, and STAT interactor (Nmi) [92, 93], by yeast two-hybrid system and immunoprecipitation, which are helpful in understanding the mechanism of FMDV.

Similarly, the researchers were able to identify infected and vaccinated animals using non-structural protein 3A [94], which was more specific and sensitive than other non-structural proteins 3B and 3AB [95]. By means of yeast double hybridization, Gladue et al. identified that the interaction between 3A and host protein DCTN3 affected viral virulence [96]. In 2013, a study found that a

partial deletion of 3A attenuated the foot-and-mouth disease virus in cattle [97], after 5 years, further research found that the deletion did not prevent subclinical infection [98]. The genome of FMDV contains three copies of the 3B protein (or VPg). In addition, 3A was found to inhibit interferon-beta signaling to evade the host immune system [99]. The study indicates that the 3B copy number is closely related to the virulence of the virus, and the virus containing a single 3B is less virulent, producing only mild disease [100]. By acting on the FMDV capsid precursor, P2-2A, 3C protease cleaved it into VPO, VP3, VP1, and 2A, and these three cleaved independently of each other [101]. Birtley et al. obtained a crystal structure with a resolution of 1.9 Å of 3C protease, which was folded like chymotrypsin and had a cys-his-asp catalytic triad [102]. It has been shown that 3C also attacks the host cytoskeleton during FMDV attack on the host [103]. Further studies showed that 3C protease could inhibit autophagy by degrading the autophagy-related protein ATG5-ATG12 [104]. The last non-structural protein is RNA-dependent RNA polymerase, 3D polymerase. Studies have shown that the synthesis of microRNA targeting 3D polymerase can effectively inhibit the replication of FMD virus in vitro [105, 106]. Therefore, 3D polymerase is one of the effective targets for the development of antiviral drugs targeting FMDV. 5D9, a 3D polymerase inhibitor, can effectively inhibit the replication of FMDV in host cells [107]. There are still many problems to be solved, and the specific function and mechanism of FMD virus non-structural proteins need to be further explored by researchers.

4. Serotypes of the FMDV

There are seven serotypes of foot-and-mouth disease virus divided into A, O, C, Asia-1, SAT 1, SAT 2, and SAT 3, and there are many subtypes of each serotype. Most of the world has had outbreaks of foot-and-mouth disease, the most common of which is serotype O. Six of the seven serotypes (A, O, C, SAT1, SAT2, and SAT3) have occurred in Africa, while four serotypes (O, A, C, Asia1) in Asia and only three serotypes (O, A, C) in South America [108]. However, there are also SAT 1 and SAT 2 viruses from as well as from Africa entering the Middle East [108]. In addition, the most recent outbreak of foot-and-mouth disease caused by serotype C virus occurred in 2004 and is now probably extinct [109].

5. Epidemiology of the FMDV

The epidemiology of FMDV includes the source of infection and the route of transmission. Foot-and-mouth disease (FMD) has the epidemiological characteristics of rapid epidemic, wide spread, and acute onset. The main source of infection is sick animals and the incubation period of animals, the incubation period 1–7 days, the average 2-4 days. Foot-and-mouth disease mainly affects artiodactyls, mainly cattle, especially calves, followed by pigs, camels, sheep, goats, and wild animals. In addition, the virus was found in blisters, milk, urine, saliva, tears, and feces of sick animals. The transmission route is extensive, which can be transmitted to susceptible animals either by direct contact or by indirect contact (e.g., secretions, feces, animal products, contaminated air, feed, etc.). Foot-and-mouth disease occurs frequently in the spring and fall. Clinical features are blister rash in the oral mucosa, hoof, and breast skin. This disease has broken out in the world several times, causing huge political and economic losses.

6. Conclusions

Foot-and-mouth disease will reduce the milk production of sick animals; severe cases will cause acute death; animal husbandry production caused a great loss, so many countries in the world to foot-and-mouth disease as the most important animal quarantine object. In the world, the United States and other developed countries have completely eliminated foot-and-mouth disease; however, in the developing countries, foot-and-mouth disease still exists. There are seven serotypes of FMD virus, which cannot be immune to each other due to their different antigens. Vaccination is a reliable and effective method for specific prevention of FMD, and a safe and effective vaccine is a prerequisite for the successful prevention, control, and eventual elimination of FMD. Therefore, in order to effectively prevent and control foot-and-mouth disease, it is necessary to thoroughly study the mechanism of action of the virus and develop more effective prevention and control methods to ensure the healthy development of animal husbandry.

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