Foot-and-Mouth Disease Virus

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Foot-and-mouth disease (FMD) is an acute and highly contagious disease affecting the cloven-hoofed animals, such as pigs and cattle. The pathogen that causes FMD is known as FMD virus (FMDV), a single-stranded positive-sense RNA virus that is classified into the genus Aphthovirus in the family Picornaviridae.

Keywords: foot-and-mouth disease virus ; immune escape ; innate immune response ; Interferon ; protein interaction ; viral protein

1. Introduction

Foot-and-mouth disease (FMD) is an acute and highly contagious disease affecting thecloven-hoofed animals, such as pigs and cattle. The pathogen that causes FMD is known as FMD virus(FMDV), a single-stranded positive-sense RNA virus that is classified into the genus Aphthovirus inthe family Picornaviridae [1][2]. The pathogen causes vesicular disease of mouth and feet in susceptibleanimals [3]. The high mutation rate of the genome of FMDV and the rapid proliferation has led to therapid evolution of the virus and the formation of seven main serotypes [4][5][6]. The antigenic diversityamong the serotypes poses challenges to the research of efficient and cross-protective vaccines [8].The genome of FMDV contains an open reading frame (ORF) that encodes a polyprotein precursor,and it is cleaved into four structural proteins and 10 non-structural proteins by viral autoproteases andhost protease [7](Figure 1).Upon infection of the host, a virus will face the attack from the host's immune response. In thelong-term battle with the host immune response, the virus has evolved and developed a series ofimmune escape mechanisms to overcome the killing and inhibition from the host immune system.The mechanism of virus immune escape can be divided into three categories: (1) enable the virus toavoid the recognition of humoral immune response; (2) interfere with the function of cellular immuneresponse; (3) interfere with the host's immune response to the virus [8]. All these strategies would beexploited by the virus for replication and spreading to other hosts.As a highly contagious and fast-spreading virus, FMDV has multiple ways to evade the killing bythe immune system [9], which makes it difficult for controlling the virus. Viral capsid protein VP1 and leading protein Lpro can inhibit the production of interferon (IFN) and innate immune responseby interacting with soluble resistance-related calcium-binding protein (sorcin) or host transcriptionfactor ADNP [10][11]. Recently, new mechanisms and functions of FMDV proteins inhibiting innateimmunity have been discovered. DDX56 (a kind of RNA helicase), participate in RNA metabolism andribosome synthesis is reported to involve in this new mechanism. The interaction between FMDV3A and DDX56 suppresses the host innate immunity by reducing the phosphorylation of IRF3 [12].In addition, nucleotide-binding oligomerization domain 2 (NOD2), a member of the nucleotide-bindingoligomerization domain-like receptor (NLR) family [13], activates the NF-κB and IFN-βsignalingpathways during FMDV infection and inhibits the replication of FMDV in infected cells [14]. FMDV 2B,2C, and 3Cproinhibit the expression of NOD2 protein, which antagonizes the antiviral response [14].Reportedly, multiple structural and non-structural proteins of FMDV escape the killing of the hostimmune system. This review summrized the molecular mechanisms of immune evasion caused byFMDV proteins. The present study aimed to fill the gaps of knowledge on FMDV immune evasionmechanism, providing the basis for the prevention and control strategies for FMDV.

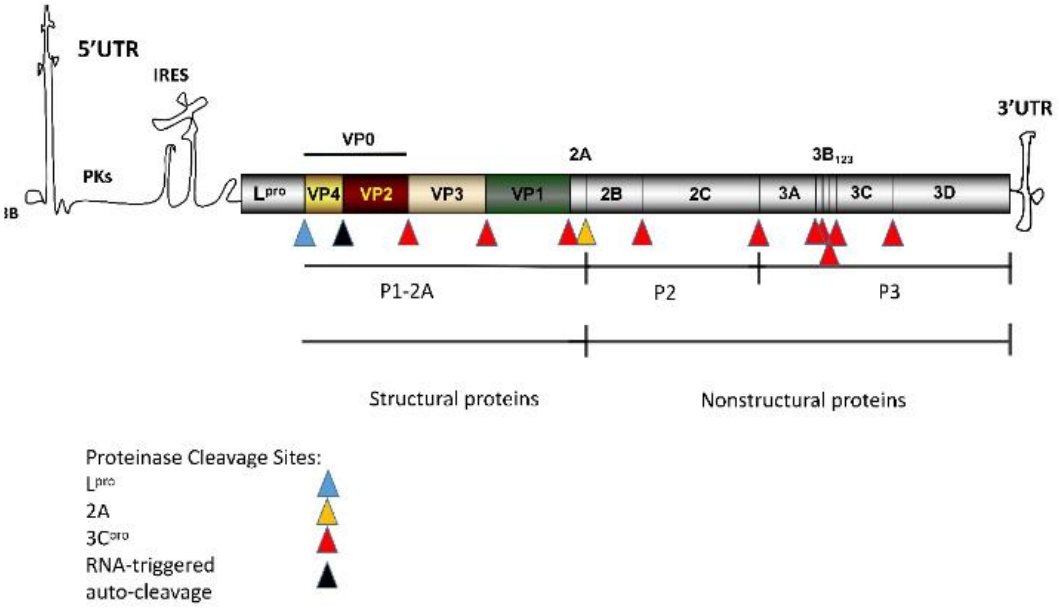

Figure 1.Schematic of the genome and polypeptide processing of FMDV [2][7]. The FMDV genomecontains an ORF of about 7 kbp, indicated by the shaded rectangle. Each region within the ORFrectangle represents a single protein. The flank of ORF is a long 5′untranslated region (5′-UTR) and ashort 3′-UTR. 3B covalently binds to the 5′-end.

2. Prospects and Future Directions

FMDV is a highly contagious virus that infects almost all cloven-hoofed animals, showingvesicles on the foot and mouth, skin erosion on the mucous membranes, fever, weight loss, pacing,and salivation, severely threatening the development of animal husbandry. However, in additionto causing acute infections and diseases, FMDV can be asymptomatic carriers in some cases, whichmight lead to another outbreak of FMD, making prevention and control challenging and costly. Highinfectivity, wide geographical distribution, wide host range, short-term immunity without serotypecross-protection, multiple modes of transmission, and persistent infection render the control and eradication of this disease rather difficult. Therefore, study the molecular mechanism underlyingFMDV evading immunity is imperative for the control of an epidemic situation.The immune system includes innate immunity and acquired immunity, which is a major protectivesystem against the invasion of pathogenic microorganisms, surveillance, and removal of foreign bodies.FMDV suppresses the function of the immune system at the initial stage of infection, such that thevirus can proliferate rapidly in the respiratory system and spread to its natural infection site [15].In terms of evading the humoral immune system, each serotype of FMDV is prone to antigenicvariation, which makes the virus escape from the neutralizing antibodies [16]. In the aspect ofinhibiting cellular immune response, FMDV infection can cause the decrease of host lymphocytes andis accompanied by severe viremia, which will eventually lead to the destruction of T cells and FMDVinfection inhibits the function of dendritic cells and weakens the ability of dendritic cells to processthem into antigens [143,144]. Previous studies have shown that, MHC class I molecule expression onthe surface of cells was suppressed at 30 min after FMDV infection, indicating that the cells infectedwith FMDV will immediately lose the ability to present MHC-I-related viral peptides to T lymphocytes.This mechanism would facilitate the virus escape from the host's cytotoxic immune response. Limitingthe killing effect mediated by NK cells is also an important mechanism for FMDV to evade the cellularimmune response. Some studies have shown that the responsiveness of porcine NK cells decreasessignificantly 2–3 days after FMDV infection, and then returns to normal [17]. Strikingly, NK cellsisolated from infected pigs could not secrete IFN-γ [18]. The research on FMDV interference withimmune effect and suppression of innate immunity has been widely studied. Some proteins of FMDV(Lpro,2B, 3A, 3B, 3C) can directly or indirectly act on retinoic acid-induced gene I-like receptor (RLR) toinhibit innate immunity [19][20][21][22][23]. FMDV VP0, VP3, 3A, and 3B reduce the expression of junctionprotein VISA at the transcriptional or protein level [23][24][25]. FMDV Lpro, VP0, VP1, 2B, and 3A candirectly or indirectly target IRF3 to inhibit interferon production [21][23][26]. VP3 and 3C proteinsinhibit JAK-STAT signaling pathway, thus inhibiting ISGs production [27][28]. FMDV proteins Lproand 3C inhibit the synthesis of antiviral molecules by cutting related factors of host transcriptionand translation [11][29][30][31][32] . In addition, it is interesting that Lproprotein can not only induceapoptosis, but also inhibit host cell apoptosis and promote virus replication, which is achieved byblocking the translation ofα-IFN and inhibiting PKR synthesis [33]. FMDV protein VP2 and 2C canpromote virus replication by regulating autophagy [34][35]. These mechanisms provide opportunitiesfor rapid transcription and translation of FMDV.In the previous studies on FMDV, HEK293 cells have been widely used inin vitroexperimentsbecause of its highly transfected efficiency. However, HEK293 cells are not FMDV susceptible cells andthere are species differences between HEK293 cells and FMDV susceptible cells. Therefore, the use ofHEK293 cells for FMDV-related research has some limitations.

3. Conclusions

In summary, FMDV has evolved a variety of ways to evade the immune response in the long-termcombat with the host immune system. Although there are many breakthroughs in the research on theimmune escape of FMDV, many mechanisms underlying the FMDV-affected host immunity have notyet been elucidated, and the interaction between FMDV protein and host protein need to be exploredfurther. In addition to the interaction between the virus and host protein, exploring the mechanismof synergistic inhibition of immune response by multiple viral proteins is of great significance forthe development of specific drugs and new vaccines. Previous studies mainly focused on the effectof FMDV with respect to innate immunity. However, there are a few studies on acquired immunity,and these need to be supplemented further. Also, persistent infection of FMDV needs to be investigatedintensively in the future.

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