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Review Article

Foot and Mouth Disease Virus, Its Structure and Functional Characterization

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Abstract

Foot and mouth disease is an infectious and highly contagious viral disease of domestic and wild cloven-hoofed animals causing a huge loss to the agricultural economy worldwide. It is caused by FMD virus that belongs to the genus Aphthovirus of family Picornaviridae. Understanding the genome and structure of FMD virus can give the insight to control the disease. In this review, we discussed in brief about the genome of FMD virus, structure and assembly, functions of the non-structural protein that can help to increase our understanding of FMD.

Key words: FMD, Virus Assembly, Virus Structure

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Introduction

Foot and mouth disease is an infectious and highly contagious viral disease of domestic and wild cloven-hoofed animals causing a huge economic loss in agriculture worldwide (Kandeil *et al.*, 2013). As per the latest ICTV virus taxonomy release the etiological agent, FMD virus is grouped under the genus *Aphthovirus* of family *Picornaviridae* (ICTV, 2015). FMDV consists of a single molecule of single stranded positive sense RNA within a non-enveloped icosahedral particle (Mahy, 2005) of about 30nm in diameter (Wild *et al.*, 1969) with a molecular weight of approximately 6.9 million daltons of which 69% is protein and 31% RNA (Bachrach, 1964). The buoyant density of the virus is 1.43-1.45 g/cm^3 in CsCl with a sedimentation coefficient of 146s. The transmission of the virus is mainly through air, blood, tissues, secretions and excretions of the infected animals. The carrier state persists for 15 months in cattle and 4 months in sheep (Bachrach, 1968). The entry of the virus occurs through a receptor-mediated endocytosis followed by acid pH dependent release and translocation of RNA across the endosomal membrane (Carrillo *et al.,* 1985). The investigations on FMD outbreak of Bulandsahar, Uttar Pradesh, India revealed that the market place of cattle as the common source for spread of infection where the infected cattle and buffalo from neighboring areas have been introduced (Verma *et al.,* 2017). This press the importance of having a regulation in common market areas to control the disease.

Genome Organisation

The FMDV genome is about 8400 nucleotide long and encodes a large polyprotein from a single open reading frame of about 7000 nucleotides (Belsham and Botner, 2015). The 5′ end of RNA is covalently linked to virus-encoded protein 3B (VPg) (Diaz-San Segundo *et al.,* 2014). The open reading frame of FMDV genome is flanked by highly conserved and structured untranslated regions *viz.,* 5′ UTR and 3′ UTR. The 5′ UTR is approximately 1300 bases containing 5 specific regions including S fragment, poly (C) tract, pseudoknots, cre, internal ribosomal entry site (IRES) that are required for efficient replication and translation (Grubman and Baxt, 2004). The 3′ UTR is a poly (A) tract separated from $3D^{pol}$ coding sequence by a short RNA segment that can fold into specific structure (Pilipenko *et al.,* 1992). Replication and translation of RNA occurs in the cytoplasm of the infected cell (Sobrino *et al.,* 2001). Translation of the viral polyprotein begins after the IRES, at two alternative AUG codons and yields a large polyprotein of approximately 2300 amino acids that is co- and post-translationally processed by virus-encoded enzymatic activities into many precursor and mature products (Clarke and Sangar, 1988). The L protein, a papain-like protease (L^{pro}) autocatalytically cleaves itself from the growing polypeptide chain *via* cleavage between its own C-terminus and the N-terminus of VP4 at the sequence RKLK ↓ GAGS during viral maturation (Guarne *et al.,* 1998). L^{pro} also plays a critical role in viral pathogenesis by inhibiting host protein synthesis and has been identified as a viral virulence factor (Falk *et al.,* 1990). The P1 region codes for structural polypeptides VP4, VP2, VP3, VP1 and the P2 region codes for three viral proteins 2A, 2B, 2C whereas the P3 region codes for four viral proteins 3A, 3B, $3C^{pro}$, $3D^{pol}$, of which 3C is a viral protease and 3D is an RNA dependent RNA polymerase (Klump *et al.,* 1984).

Structural Proteins and Capsid Assembly

Structural Proteins and Its Role (P1 Region)

FMDV structural proteins assemble into capsid, virus binding to target cells and antigenic specificity, influencing significant aspects of virus infection and immunity (Jackson *et al.,* 2003). The structural proteins are encoded by P1 region of the genome and the P12A is processed by $3C^{pro}$ to form three major structural proteins VP0, VP1, VP3 (Fry *et al.,* 2005(a)). VP0 is an intermediate protein later gets cleaved to VP2 and VP4 upon encapsidation of RNA to form a mature virus (Knipe *et al.,* 1997). Electron

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microscopic studies showed FMD virions about 30 nm in diameter with a smooth round surface (Bachrach, 1968). Crystallographic studies have shown fine structures of the viral capsids at atomic resolution 3-dimensional structure of several FMDV isolates and antigenic variants (Curry *et al.*, 1996). Viral particles are composed of 60 copies of each of four capsid proteins termed VP1, VP2, VP3, VP4 assembled into an icosahedral structure (Fry *et al.*, 2005(b)). The P1 region undergoes cleavage by $3C^{pro}$ and assembles into a sixty-copy empty capsid particle (Han *et al.*, 2015). The VP1 protein comprises of 213 amino acid residues (Acharya *et al.*, 1989) is concerned in formation of neutralizing antibodies and attachment to susceptible cells (Wild *et al.*, 1969). The major cellular receptor of FMDV is integrin $\alpha_v\beta_6$ expressed on epithelial cells seems to bind with the RGD motif of VP1 protein (Jackson *et al.*, 2000; Monaghan *et al.*, 2005). VP2 is a 218 amino acid protein plays a critical role in virion structural stability and maturation (Curry *et al.*, 1997). A disulphide bond link between VP1 and VP2 noticed very close to the major antigenic loop on VP1 is considered to influence structure of antigenic site. This combination of cysteine residues at position 130 on VP2 and 134 on VP1 has found only in serotype O (Acharya *et al.*, 1989). VP3 contain 219 to 221 amino acids with an important conformational neutralizing epitope and contribute significantly to capsid stability (Logan *et al.*, 1993). VP4 is the most conserved FMDV protein with an N- terminal myristylation site and swine and bovine T-cell epitope at positions 20 to 35 (Blanco *et al.*, 2001). The antigenic site of VP4 appears to be located internally (Talbot *et al.*, 1973).

Capsid Structure and Assembly

The protein cores of VP1, VP2, VP3 consists of highly conserved eight stranded wedge shaped β barrel, which fit to form a majority of the capsid structure. The VP4 is buried within the capsid and has myristyl group covalently attached to its N- terminus (Belsham *et al.*, 1991). The $3C^{pro}$ protease process the structural polypeptide P1 to major structural proteins VP1, VP3, VP0. Three major structural proteins associate with each other to form a protomer, 5 protomers associate to form pentamers, and 12 of these self-assemble into empty capsids. At later stage of infection, the empty capsid with VP1, VP3, VP0 undergo encapsidation of viral genome to form a mature virus particle (Gulberg *et al.*, 2013). After viral encapsidation, myristylation of VP0 is necessary for efficient assembly of capsid structures (Ansardi *et al.*, 1992). Myristylation is thought to help in autocatalytic cleavage of VP0 to yield capsid proteins VP4 and VP2 (Rossmann *et al.*, 1985). There is considerable controversy concerning the role of empty capsids and provirions in the assembly process. Though the Pulse chase experiments are consistent with a pathway in which protomers assemble into pentamers, which subsequently assemble into intact shells such as empty capsids, provirions and virions (Jacobson *et al.*, 1970; Oppermann and Koch, 1973) but the exact kinetic roles of the empty capsids and provirions have not been established. Thus, it is unclear whether the viral RNA is inserted into empty capsids or encapsidated by the condensation of pentamers around it (Ghendon *et al.*, 1972). A

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number of intermediate particles are identified in *Picornavirus* infected cells including protomers, pentamers, empty capsid, and provirion and mature virus (Lee *et al.*, 1993). The naturally occurring empty capsid contains all polypeptides as that of complete virus but VP2 and VP4 are seen as an uncleaved VP0 molecule (Rowlands *et al.*, 1975). Particles in which VP0 is uncleaved are much less stable than mature virions to a variety of conditions, including elevated temperature, detergents, high salt and extremes of pH (Guttman and Baltimore, 1977). Based on structural studies of poliovirus and rhinovirus, the existence of hydrogen bond between C-terminal carboxylate group of VP4 and the side chain hydroxyl group of Ser 10 of VP2 is observed. This provoked a thought that serine protease type mechanism of the cleavage, in which the hydroxyl group of Ser 10 of VP2 served as the nucleophile and one of the nucleotide bases of the viral RNA served as the base in the now-classic catalytic triad (Arnold *et al.,* 1987). However, when mutated Ser 10 of VP2 by Ala does not interfere with VP0 cleavage (Harber *et al.*, 1991). This suggests that VP0 cleavage may be required for the production of stable particles (Basavappa *et al.*, 1994). VP0 cleavage is thought to be autocatalytic and resulted from the conserved His residue in VP2 which activates local water molecules, leading to nucleophilic attack on sessile bond and cleavage (Hindiyeh *et al.,* 1999).

Role of Non-Structural Proteins

P2 Region

The P2 portion in the genome encodes three mature viral proteins namely 2A, 2B, 2C (Gao *et al.*, 2016). 2A is a small peptide of 18 amino acids with a conserved cleavage site of Gly/ Pro between 2A and 2B respectively (Gao *et al.*, 2014). 2A gets cleaved autocatalytic from other non-structural proteins (Ryan *et al.*, 1991), separated as P12A, later gets cleaved from P1 by $3C^{pro}$ or $3CD^{pro}$ (Ryan and Drew, 1994). 2B, is 154 amino acid a viroporin peptide that induces dispersion in phospholipid, increasing membrane permeability and promotes release of viral particles (Ao *et al.*, 2014). FMDV 2B induces damage to the integrity of the host cell's membrane and causes Ca^{2+} abnormalities, activating autophagy (Ao *et al.*, 2015). 2C is a 318 amino acid polyprotein, highly conserved molecule among viral proteins (Gorbalenya and Koonin, 1989) with a predicted amphipathic helix in N-terminus (Teterina *et al.*, 2006). 2C plays a role in membrane rearrangement, formation of virus replication complex and implicated in virus induced cytopathic effect (Bolten *et al.*, 1998). It is also involved in FMDV induced autophagy (O'Donnell *et al.*, 2011). This protein reduces the cellular killing effect against viruses and promotes virus survival and proliferation, thereby facilitating viral proliferation and release of virus particles (Gao *et al.*, 2016).

P3 Region

The P3 portion in the genome encodes for proteins 3A, 3 copies of 3B, $3C^{pro}$, $3D^{pol}$ (Diaz-San Segundo *et al.*, 2014). 3A protein is a 153 amino acid peptide in which half coding region in N- terminus encoding hydrophilic and hydrophobic domain capable of binding to membranes, is highly conserved whereas many

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mutations and deletions occur in C-terminus. Protein 3B (VPg) bound covalently to genome and antigenome at 5′ terminus primes RNA synthesis (Mason *et al.*, 2003). The 3B protein of FMD is unique existing in three similar but non-identical copies *viz.*, $3B_1$, $3B_2$, $3B_3$ of 24 amino acids long (Pacheco *et al.*, 2003) but viruses can be obtained with only one copy of VPg for full infectivity (Arias *et al.*, 2010). Of the three isoforms of 3B, $3B_3$ is likely the most efficient substrate for $3D^{pol}$ activity (Nayak *et al.*, 2005). $3C^{pro}$ is a chymotrypsin like cysteine protease responsible for most of the viral polypeptide cleavage (Birtley *et al.*, 2005). FMDV $3C^{pro}$ cleavage sites show great heterogeneity, with cleavage occurring between multiple dipeptides, including Gln-Gly, Glu-Gly, Gln-Leu, and Glu-Ser (Palmenberg, 1990). FMDV $3C^{pro}$ is also responsible for inhibition of host cell transcription (Tesar and Marquardt, 1990). $3D^{pol}$ is a highly conserved (Manju *et al.*, 2001) viral encoded RNA dependent RNA polymerase (Robertson *et al.*, 1983). The overall structure of $3D^{pol}$ is similar to cupped 'right hand' consisting of 'palm', 'fingers' and 'thumb' subdomains. The active site of the polymerase consists of a conserved YGDD sequence and a highly conserved D residue that are also found in palm subdomain (Hansen *et al.*, 1997). This domain is involved in structural integrity, nucleotide recognition and binding, phosphoryl transfer, and priming nucleotide binding (Ferrer-Orta *et al.*, 2006(a)). In FMDV, VPg binds to the residues in the active site cleft of the polymerase in the uridylylation reaction (Ferrer-Orta *et al.*, 2006(b)). $3D^{pol}$ is the catalytic component of RNA replication to synthesize positive and negative sense genome and plays an important role in the life cycle of RNA viruses (Gao *et al.*, 2016).

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