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Role of Integrin Proteins as Receptors for Foot and Mouth Disease Virus

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Abstract | Foot-and-mouth disease (FMD) is an infectious, highly contagious and acute disease of cloven-hoofed animals. The morbidity after infection may reaches to 100% however mortality in adults is relatively low. For FMDV infection to establish host cell adsorption is required and it depends on the cell surface receptors. This review highlights the critical role of integrin proteins as receptors for FMDV. An effective understanding of virus internalization may open new horizon to study virus pathobiology and for establishment of an effective antivirals.

Keywords | Integrin protein, Foot and mouth disease virus, FMD infection, Host cell receptors, Pathogenesis

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Foot-and-mouth disease (FMD) is an infectious, highly contagious and acute disease of cloven-hoofed animals that include cattle, buffalo, swine, sheep and goats and around 70 species of wild animals (Brehm et al., 2009). FMD virus that belongs to the *Aphthovirus* genus of the *Picornaviridae* family causes the disease. The virus initially infects the upper respiratory tract and exhibits a tropism for epithelial cells (Alexandersen et al., 2003). Initial viral replication takes place in epithelial cell (Grubman and Baxt, 2004). FMD is prevalent worldwide and is endemic in Asia, Africa, Middle East and South America (Thomson et al., 2003). The incidence of FMD results in heavy economic losses due to reduction in milk yield, decreased growth rate of meat animals, decreased fertility and death in young infected animals (Grubman and Baxt, 2004; Doel, 2004).

There are seven serotypes of FMDV that includes A, O, C, Asia-1, South African territories 1 (SAT1), SAT2 and SAT3 and every serotype contains many subtypes (Manson et al., 2003; Domingo et al., 2003). FMDV is a single-stranded, non-enveloped, positive-sense RNA genome of 8.4 Kb (Jackson et al., 2003; Mittal et al., 2005). Four structural and eight non-structural proteins are encoded in viral genome *i.e.* VP1-VP4. VP1-VP3 constitutes the outer capsid shell while VP4 forms the internal surface (Manson et al., 2003; Burman et al., 2006). VP1 contains an outer flexible loop called G-H loop that is a major antigenic site on virus. Moreover, it also contains an Arg-Gly-Asp (RGD) motif that is important in host receptor binding process (Fry et al., 2005; Alcala et al., 2001).

FMDV initially attaches with the host cell-surface receptors that is followed by entry into the cells by receptor-mediated endocytosis (O'Donnell et al., 2005). The low pH of endosome facilitates the un-coating of the viral genome (Berryman et al., 2005). Many receptors of FMD have been reported including integrins (Jackson et al., 2003) and heparan sulfate proteoglycans (HSPGs) (Jackson et al., 1996). It has been described that virus enters into the cells after binding to the integrins via clathrin-mediated endocytosis. Moreover, virus can also take another route i.e. binding to heparan sulfate that helps the FMDV to enter into the cells via caveola-mediated endocytosis pathway (Ruiz-Saenz et al., 2009). In this review, we will focus on role on integrins that are critically important in the pathogenesis of FMD.

INTEGRINS

Integrins are critical proteins utilized by the cells to bind and communicate with extracellular matrix (Springer, 2002). Integrins can be divided into two transmembrane

glycoprotein subunits known as alpha (α) and beta (β) (Springer, 2002). It has been reported that there are 19α and 8β subunits (Grundstorm, 2003). The role on integrins have been explained by different techniques including monoclonal antibodies, chromatography and cell adhesion assays. Integrins play a role in adhesion between cells as well as with extracellular matrix. They are also involved in cell proliferation, apoptosis and cell migration. They regulate many physiological processes including inflammation, morphogenesis, embryogenesis, wound-repair and tumor cell migration, by interacting with different extracellular ligands. They have ligands such as intracellular adhesion molecules (ICAM) and vascular cell adhesion molecule (VCAM), collagen, fibronectin, laminin and fibrinogen (Dedhar and Hannigan, 1996; O'Donnell et al., 2005). The physiological processes where integrins are involved include platelet aggregation (O'Donnell et al., 2005; Jackson et al., 2004). The concentration of integrins on the cell surface is ten to hundred folds higher than other cell surface receptors but they show low affinity of binding with their ligands (Burman et al., 2006). Many integrins have been shown to serve as FMDV receptors. Cell culture studies have described that at least four integrins *i.e.* αvβ3, αvβ6, αvβ1, αvβ8 and α5β1 are being used by FMDV (Berinstein et al., 1995; Jackson et al., 2003, 2004).

Integrin αvβ3

It has been demonstrated that integrin αvβ3 bind to all serotypes of FMDV through RGD tripeptide (Berinstein et al., 1995; Mould et al., 1995; Mateu et al., 1996). Mg2+ facilitates binding of integrin αvβ3 to the ligands while Mn^{2+} can increase the binding. Ca^{2+} has a dual role as on one side it assists fibronectin and vitronectin to bind to integrin αvβ3 but on the other side it blocks binding of fibronectin (Neff and Baxt, 2001). Studies have shown that integrin αvβ3 serves as internalization receptor for FMDV serotype A12 (Berinstein et al., 1995). In another study, Chinese hamster ovary (CHO) cells that do not express αvβ3 but heparan sulfate were used. This CHO cell line was transfected with human αvβ3. It has been described that the replication of FMDV was dependent on expression of αvβ3 (Neff et al., 1998). FMDV has been shown to bind to human and simian αvβ3 for entry into the cells but efficient replication of virus occur in the presence of bovine αvβ3 (Green et al., 2003). So, this could be a reason that FMDV developed as a disease of cloven-hoofed animals because they have such structure of integrin αvβ3 that fits well with viral surface resulting in enhanced viral replication and spread of disease among these species (Xiong et al., 2002, Monaghan et al., 2005, Du et al., 2010).

Integrin αvβ6

Jackson et al. (2000) have revealed that integrin αvβ6 acts as a receptor for FMDV. Integrin αvβ6 is expressed on the epithelial cells. In a study, FMDV binding was inhibited using anti- αvβ6 monoclonal antibody (10D5) that exhibits the specificity of αvβ6 for FMDV (Jackson et al., 2000). It has been shown that after transfection with integrin β6 and expressing αvβ6, human colon carcinoma cell line became permissive for FMDV infection. Viral entry enhanced after binding to αvβ6 in these cells (Jackson et al., 2004). Another study has revealed that deletion of β6 cytoplasmic domain slightly reduced the virus binding but this domain is critical for virus infection suggesting an essential function of this domain in post-binding events during FMDV infection (Miller et al., 2001). Initially, only integrin αvβ3 was considered as FMDV receptor but αvβ6 has more diverse expression on epithelial cells especially where early stages of viral replication occur (Brown et al., 2006; Jackson et al., 2000; Du et al., 2010). It has been reported that αvβ6 plays a role to transport the virus to early endosomes (O'Donnell et al., 2005). Monaghan and colleagues studied the expression of αvβ3 and αvβ6 within epithelial cells of cattle, which are aimed by the FMDV during infection. Data using confocal microscopy, immunofluorescence and RT-PCR described that integrin αvβ6 is mainly expressed on the surface of these epithelial cells that are the site of viral replication during FMDV infection (Monaghan et al., 2005)

Integrin αvβ1

In another studies, it has been demonstrated that αvβ1 also serves as FMDV when expressed on CHO cells (Jackson et al., 2002). Amino acid residues close to RGD can reveal the binding specificity between αvβ1 and αvβ6 (Neff et al., 1998; Jackson et al., 2002). Integrin αvβ1 does not efficiently support viral binding and infection at physiological concentrations of Mg^{2+} and Ca^{2+}. However, when αvβ1 expressing cells were treated with Mn^{2+}, there was a radical increase in FMDV infection (Berryman et al., 2005; Jackson et al., 2002). The role of αvβ1 was further detected using monoclonal antibodies against human αv that inhibited the virus binding as well as infection (Jackson et al., 2002). Binding efficiencies between αvβ1 and αvβ6 can be differentiated on the basis of amino acid residues close to RGD motif (Du et al., 2010; Jackson et al., 2000). The specificity of αvβ1, αvβ3 and αvβ6 during FMDV infection was studied for two strains of FMDV serotype O and three strains of serotype A. It has been shown that cells expressing these integrins mediated viral infection for all strains of both FMDV serotypes. Although there were some differences in usage of these integrins by different viral strains such as both strains of serotype O used αvβ1 and αvβ6 with same efficiency but more efficiently than αvβ3. While there was moderate usage of αvβ1 by strains of FMDV serotypes A as compare to αvβ3 and αvβ6 (Duque and Baxt, 2003). This data suggest an expected interplay between efficiency of integrin usage and FMDV pathogenesis.

Integrin αvβ8

It has been shown that another integrin *i.e.* integrin αvβ8 can serve as a host cellular receptor for FMDV (Fjellbirkeland et al., 2003; Jackson et al., 2004). It has been shown that transfecting human β8 with SW480 cell line and expressing αvβ8 made these non-permissive cells susceptible to FMDV infection. Moreover, role of αvβ8 was further established by monoclonal antibodies inhibiting function of αvβ8. Integrin αvβ8 has been detected in the basal cells of the epithelial airway, which could show their role in the tropism of FMDV during the early stages of viral infection (Jackson et al., 2004; Fjellbirkeland et al., 2003; Cambier et al., 2000).

Integrin α5β1

Integrins α5β1 are expressed on epithelial and lymphoid cells and bind to the ligands through RGD motif which is important for serving FMDV as a cellular receptor. Although they have this important RGD motif but they are not used by FMDV for initiating viral infection (Baranowski et al., 2000; Duque and Baxt, 2003). Moreover, studies have shown that the ability of FMDV to bind to α5β1 and αvβ3 depends on the presence of certain amino acid residues following the G-H loop RGD motif (Jackson et al., 2000).

CONCLUSIONS

FMDV is a major issue for meat and milk producers. It is important to understand the mechanism of viral entry and replication and the factors involved in FMDV infection. Receptors are the main factors responsible for viral pathogenesis and tropism. The aim of this review was to highlight the role of integrin proteins in the FMDV infection and its transmission to other animals. FMDV interacts with different host cell factors at different phases of pathogenesis. It utilizes different integrins such as αvβ3, αvβ6, αvβ1, αvβ8 and α5β1 to initiate viral infection. However, the role of each receptor and how it supports FMDV infection is not completely characterized yet. Moreover, Heparan sulfate is also considered as FMDV receptor but with reduced virulence and there may be some unknown host cell factors associated with viral pathogenesis. The interaction of different FMDV strains with host receptors has different efficiencies. Therefore, study of FMDV receptors explains the mechanism of pathogenesis involving different serotypes and subtypes. Finally, the characterization of these receptors and their functions in FMDV pathogenesis provides the opportunity to design drugs against the receptors that will help in the prevention and control of FMD.

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CONFLICT OF INTERESTS

There exists no conflict of interests

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