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Antigenic variation and host immune response to Foot-and-Mouth disease

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Abstract

Foot-and-mouth disease is caused by a single-stranded RNA virus belonging to the family *Picornaviridae* under the prototypic member of the genus *Aphthovirus*. The most important portal of infection of FMDV is respiratory system. However, the whole genome FMDV serotypes have an average of 86% nucleotide sequence identity to each other across, while the VP1 coding region is more variable with about 50-70% nucleotide sequence identity, to evade a host immune response, an infectious organism changes structure and function of its surface proteins by amino acid substitution, this process is called antigenic variation in which Its genome open reading frame (ORF) that codes for four structural (VP1–4) and 8–10 non-structural proteins form seven immunologically distinct serotypes. These make an organism long-lived in host, repeatedly infect a single host, and are easily transmitted. The virus elicits a rapid humoral response in both infected and vaccinated animals. The response is directed to epitopes on the three external structural proteins and good protective immunity is established between 7 and 14 days after e infection or vaccination. The specific site for binding to neutralizing antibody of FMD capsid is the G-H loop in the VP 1 peptide. FMDV-specific antibody secreting cells (early B-cell response to aerosol infection) are established in the lymphoid tissue of the respiratory tract and spleen after four days of infection. The protective immunity to FMDV is mostly due to neutralizing antibodies and T-cell response. As Foot-and-mouth disease virus (FMDV) has significant socio-economic consequences, antigenic and genotypic characterization of FMDV and the ability of antibody produced by host bound it is required for formulation of appropriate diagnosis tests and vaccine for effective control and eradication of the disease.

Key words*:* *FMDV, immunity, antigen, and antibody*

Introduction

Foot and Mouth Disease (FMD) is the contagious viral disease of mammals and causing severe economic loss in susceptible cloven-hoofed animals. It is categorized as list "A" disease according to OIE disease classifications (2). It is the causative agent of a highly infectious zoonotic vesicular disease that infects lung epithelial cells in respiratory tract of cloven-hoofed livestock including: sheep, goats, cattle and pigs (21, 4). FMDV replication associated viral protein expression induces endoplasmic reticulum (ER) stress and unfolded protein response (UPR), in turn inducing autophagy to restore cellular homeostasis(41). The disease is characterized by fever, vesicular lesions and erosion in the mouth and on the tongue, muzzle, feet and teats and cause great economic losses in the affected countries and they involve an extensive threat for rapid and wide spreads (30, 49). The virus enters a new susceptible animal either orally (especially swine) or via the respiratory tract (especially cattle). Aerosol transmission is the major means of animal-to-animal spread within premises (29).

FMD is caused by a single-stranded RNA virus belonging to the family *Picornaviridae* (51) under the prototypic member of the genus *Aphthovirus* (20). It is a no enveloped virus with a positive-sense, single-stranded RNA genome that is 8.5 kb in length and is immediately translated into a polyprotein upon entry of the virus into a host cell (12). The genome contains a single open reading frame (ORF) that codes for four structural (VP1–4) and 8–10 non-structural proteins (34) in which its Extensive mutational variations result in the differentiation of the virus into seven immunologically distinct serotypes; O, A, C, Asia1, and Southern African territories (SAT) 1–3, but a large number of subtypes have evolved within each serotype (33,45). These serotypes exhibit significant antigenic and hereditary assorted varieties, resulting in several subtypes and genealogies. Accordingly, animals may become resistant to one serotype but still show sensitivity to some other serotype (13). Studies on the antigenicity of FMDV, complemented with crystallographic analysis of the three-dimensional structure of the virus and of virus–antibody complexes, have improved understanding of the interaction between virus and the host immune system, including the mechanism of virus escape from neutralization, which is also responsible for the high antigenic diversification of FMDVs (17).

At early stage of FMDV infection, the innate immune system of the host animal is activated to form an antiviral state. The innate immune response provides the first line of defense, which is crucial for preventing infection (52). The virus elicits a rapid humoral response in both infected

and vaccinated animals. The response is directed to epitopes on the three external structural proteins and good protective immunity is established between 7 and 14 days after e infection or vaccination. Clearing the virus from the infected animal by phagocytosis of opsonized virus carried out by Macrophage (23). The protective immunity to FMDV is mostly due to neutralizing antibodies and T-cell response (10). inactivated FMDV Vaccination within aqueous aluminum hydroxide and saponins or oil-based adjuvants, play an important role in control measure of FMDV (25). Literature review on antigenic variation of FMDV and the immunological response of host animals to the agent is important tools that inspire the people to adopt introduce and apply new diagnostic techniques and vaccine in the controlling and prevention of FMDV. **Therefore,** the objective of this review is to elaborate the current antigenic variation and immunological response of host to the different serotypes of Foot-and-mouth disease from the side of agent and hosts respectively.

2.1 Etiology

Foot and mouth disease (FMDV) are classified within the *Aphtho* virus genus as a member of Picornaviridae family and exists in seven serologically distinct serotypes: O, A, C, SAT 1, SAT 2, SAT 3 and Asia 1. based on the sequence of the viral structural protein gene (VP1), which reflects genetic, antigenic and geographical relationships among the strains, each serotype is further delineated into clades (topo type) (27). within each serotype, there are a large number of strains with their own antigenic characteristics, so there may be only partial cross-immunity between strains of the same serotype (44).

2.1.1 Structure of FMDV

Foot and mouth disease virus is a small, non-enveloped and single standard positive sense RNA virus (7), which serves as both mRNA and the template for negative-stranded RNA. The FMDV particle is roughly spherical (Icosahedral) in shape and about 25–30 nm in diameter. It consists of the RNA genome surrounded by a protein shell or capsid. The capsid is composed of 60 copies of the capsomers. Each capsomer consists of four structural polypeptides, VP1, VP2, VP3 and VP4. The VP1, VP2 and VP3 are exposed on the surface of the virus while VP4 is located internally (24, 9). The genomic size of virus varies according to the serotype, but it is estimated at about 8.5Kb and as the following 3 components: a 5′-untranslated region (5′- UTR), an open reading fragment (ORF), and a 3′-UTR. The ORF encodes a polyprotein that forms four fragments after the primary cleavage: The L fragment, the P1/2A fragment, the P2BC fragment, and the P3 fragment. After the secondary cleavage and the maturation cleavage, 4 structural proteins (VP4, VP2, VP3, and VP1) and 8–9 non-structural proteins (Lab/Lb, 2A, 2B, 2C, 3A, 3B1, 3B2, 3B3, 3C, and 3D) are formed (47).

The 5' UTR contain 1300 nucleotides while 3' UTR have 100 nucleotides. The viral genome replication is mainly occurred under 5' UTR and it also initiates the viral polyprotein by using cap independent translation. The 3' UTR have 90 nucleotides in length and also involved in genome replication through its cis-acting elements (36). Also, secondary structural element of 5'UTR consist of: the short fragment (S-fragment), poly-c tract, RNA pseudoknots, the cis-acting replication element (cre) and internal ribosome entry site (IRES). From 5'UTR secondary structure elements, the cre and IRES play an important for translation and replication. The 3'UTR also contains secondary structure elements. There are two stem loops directly following the ORF called stem loop 1 (SL1) and stem loop 2 (SL2) which are involved in viral replication. The 3' end of the genome consists of a poly-A tail (33). Primary co-translational processing of

P1-2A, P2, and P3 precursors are formed by the cleavage of the leader protease (Lpro), 3Cpro and a translational recoding event mediated by 2A. Lpro, a papain-like cysteine proteinase, is formed in two unique forms: Labpro and Lbpro, which generated by translation initiation at two in-frame AUG codons separated by 84 nt on the viral RNA and subsequent intra-molecular self-processing (40). Two virus-encoded proteinases (leader (Lpro) and 3Cpro) form structural and NSPs protein by cleavage of polyprotein of about 250 kDa which formed from translation of viral ORF. Maturation of polypeptides have different functions which form four functional regions of ORF in FMDV genome as (**Figure 1**): L region, which is located at 5′ end and codes for Lpro. P1 region, encoding a precursor for capsid polypeptide (VP4, VP2, VP3, and VP1). P2 region encodes (2A, 2B, and 2C) And P3 region (3A, 3B, 3Cpro and 3Dpol, in which, 3C is a viral protease and 3D an RNA-dependent RNA polymerase) (15).

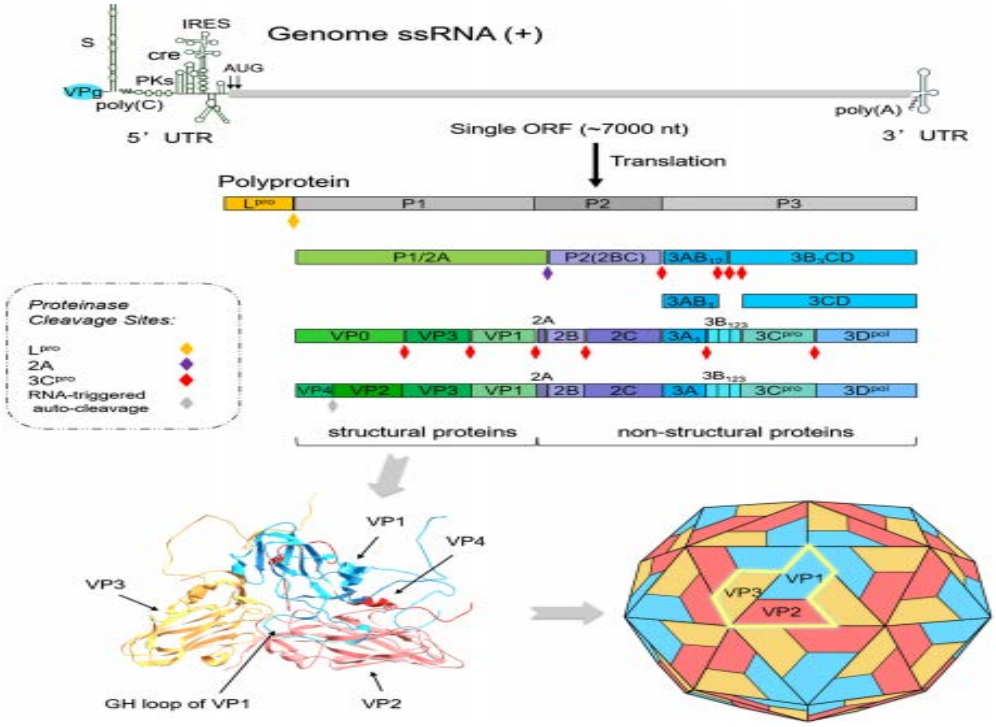

Figure 1: Schematic diagram of FMDV genome, processing of viral polypeptide and conformations of the structural proteins (15).

2.1.2 Antigenic Variation

To evade a host immune response, an infectious organism change's structure and function of its surface proteins by amino acid substitution, this process is called Antigenic variation. These make an organism long-lived in host, repeatedly infect a single host, and are easily transmitted. One main character of RNA viruses is an error-prone RNA replication, which results variation of

an organism (38). Such like Antigenic and genetic diversity hinder eradication of FMDV through vaccination. Antigenicity is mainly expressed by the surface coating proteins (capsid). This antigenic variability classified FMDV in to Seven immunologically distinct serological types of FMDV namely: serotypes O, A, C, Asia 1 and SAT (Southern African Territories) 1-3 (Chakraborty *et al.*,2014).

The whole genome FMDV serotypes have an average of 86% nucleotide sequence identity to each other across, while the VP1 coding region is more variable with about 50-70% nucleotide sequence identity (24). Antigenic variation in FMDV serotypes is caused by VP4. The binding of the Arg-Gly-Asp motif with recogVP1, VP2, and VP3 that have structural and sequence similarity results the viral antigenicity. Most serotypes of FMDV share high variable sites of VP1 with 135-155 amino acid residue. High sequence variability in Beta-cell epitopes cause low cross-reactivity between the serotypes of FMDV. These regions also contain antigenic site “A” in which the high mutation in RNA replication occur (37). To determining the antigenic properties of the virus, the surface-exposed capsid proteins of FMDV are also critical for binding of the virus to cells (20).

2.2 Epidemiology

Currently, in Asia, Africa, and Venezuela in South America, FMDV is endemic (23). Host species, population density, animal movements within and transboundary and indirect contacts between domestic and wild host species are the main factor for the multiplication and transmission of FMDV. The environment become the geographical barriers to virus dissemination. this multi factorial scenario, results FMDV variation and adaptation has been modeled as a complex evolutionary pattern that can revealed by molecular epidemiology analyses or nucleotide sequencing of capsid protein genes (33). VP1 coding nucleotide sequences can indicate a tendency for same viruses to re-emerge in the same geographical area or another new virus to the given geographical area. There is a genetically and antigenically distinguishable, seven FMDV regional pools, however some countries share viruses belonging to two different pools (**Figure 2**) (Jamal *et al*., 2013).

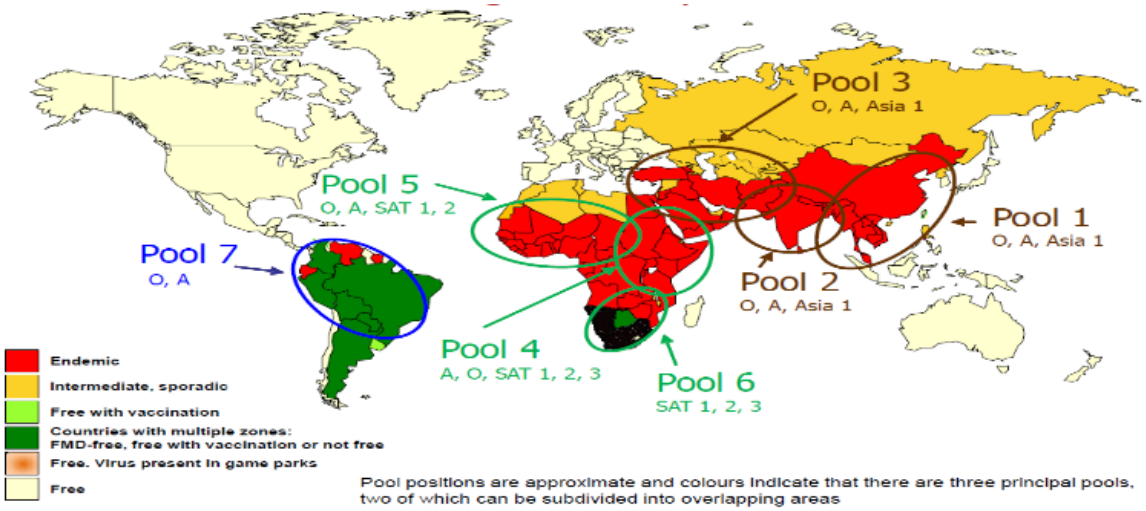

Figure 2: *Geographical pools of FMDV (source: Robinson* et al.*, 2014).*

Six serotypes of FMDV (O, A, C, SAT-1, SAT-2 and SAT-3) have been known in African countries, while four serotypes in Asia (O, A, C, Asia-1) and three in South America (O, A, C). Even if FMDV classified in seven pool, SAT-1 and SAT-2 serotype spread from Africa to the Middle East. Globalization make the spread of FMDV worldwide (3).

2.3 Pathogenesis

All cloven-hoofed domestic and wild animal can be infected by the FMD virus; however, the development of the disease is depending the host and virus (2). The most important portal of infection of FMDV is respiratory system. The virus can affect the pharynx and primary multiplication of the virus is occurring on the mucous membrane and by lymphatic and blood circulation transported to the sites of secondary multiplication in the lymphatic glands, epithelial tissues in and around the mouth, feet and in the mammary glands. Before the appearance of clinical signs of FMD following secondary replication in other glandular tissues, the FMDV can be detected in body fluids such as: milk, urine, respiratory secretions and semen, the virus can also persist for long periods after the acute infection. In cattle, virus may be detectable up to 2 years' periods after exposure to infection and up to 6 months in sheep. Gross lesions develop only in areas exposed to mechanical trauma or unusual physiological conditions such as the epithelium of the mouth, feet to a less extent, the teats (2). The dorsal surface of the soft palate and the roof of the pharynx, just above the soft palate, are sites of particular significance. Viral symptoms occur subsequently within the cornified stratified squamous epithelia of the skin (including the feet and mammary gland) and mouth (including the tongue) and myocardium of young animals (5). The severity of FMDV clinical signs on cattle and pigs is highly sever, while

that of sheep and goat is discrete (25). The replication of the virus is rapid after entry through the upper respiratory tract or lung, viremia seeding infection into the epithelium where secondary virus multiplication results in vesicles and shedding from the udder in milk (7).

The severity of FMD is high in young animals, with a higher mortality rate due to myocardium degeneration, whereas adult animals generally clear infection within two weeks. The virulence determinants in FMDV is the viral leader protease, which inhibits induction of beta interferon mRNA and blocks the innate immunity of the host animal (26). FMD pathogenesis are variably species-specific (6).

2.3.1 Genome Penetration

Integrin are heterodimer proteins composed of two differing subunit, type 1 trans membrane subunits, a and b, with large extracellular domains and usually a cell entry determinants short cytoplasmic tail of FMDV (Stuart *et al.*,2005). Many evidences show that conformational changes result in the insertion of VP4 and the N-terminus of VP1 into the cellular membranes to form the channels through which the genomic RNA might traverse the membrane. An acid condition of host cell results the dissociation of the virus into pentameric subunits, VP4 and the genome. Then after the RNA enter into the cytoplasm, while the capsid proteins left in cell endosomes. It is possible that VP4 may associate with the endosomal membrane to produce channels into the cytoplasm (Stuart *et al.,2005).* The following figure (3) shows the viral genome (A), replication cycle(B) of virus in to the host cells.

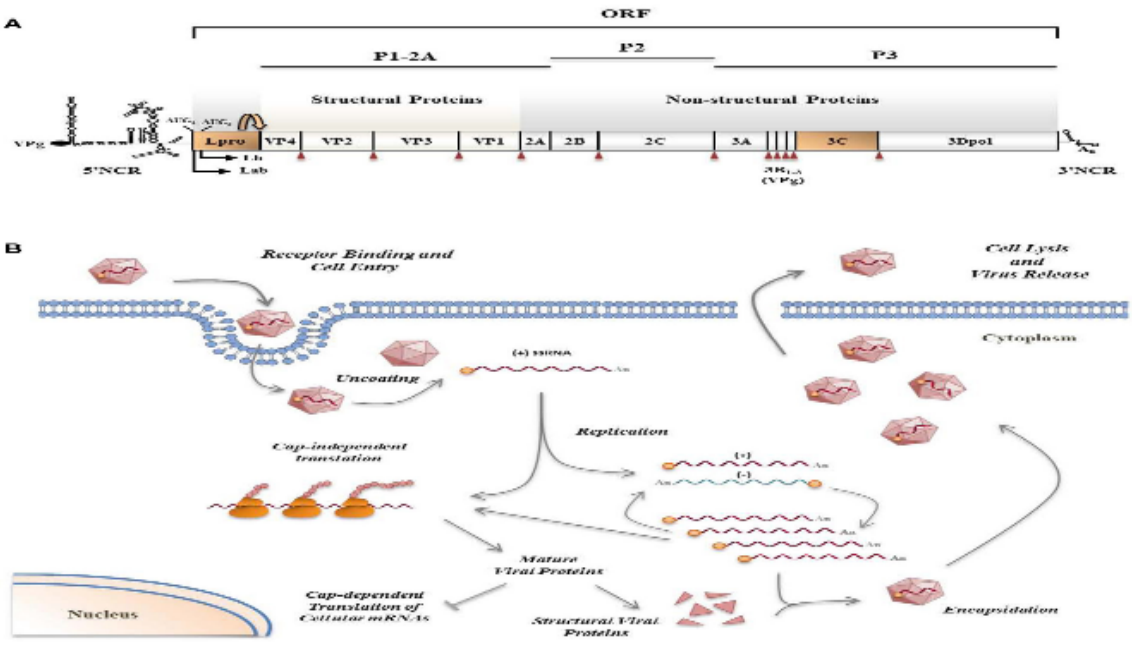

Figure 3: FMDV genome (A) and viral life cycle (B)(40)

All FMDV replication cycle occurs in the cytoplasm. The information required to inhibit the host cellular machinery and induce the shut-off the host macromolecular synthesis in infected cells is carried on viral RNA. The positive-strand RNA transcribed into a complementary, negative-strand RNA molecule by the RNA-dependent RNA polymerase. Then, 3Dpol generates multiple positive-strand RNAs which either enter a new round of translation and RNA replication, or are packaged by the capsid proteins to form new virus particles which are finally released by cell lysis (40).

2.3.1.1 Integrin receptors of host

For its entry to the host cell, The FMDV has the Arg-Gly-Asp (RGD) ligand which makes its complementary with integrin receptors of host cells. Amino acid sequence at residues about 141–160 of VP1 in the O serotype, which corresponds to the G-H loop, contain the most immunogenic site and RGD ligand (11). The interaction of host cell receptor (integrin αvβ6) with the FMDV is determined by cation. Type -I interferon is induced in cultured cells and experiments by the FMDV 28 non-coding RNA fragments (48). Induction of type I interferon (IFN-α/β) mRNA is the first responses of the host to viral infection during host viral interactions. Expression, secretion, and binding of IFN-α/β protein to specific receptors on cells results in initiation of a signal transduction pathway and induction of a virus-resistant state in these cells by activation of a series of genes whose protein products can inhibit various steps in the virus life cycle (18).

2.3.2 FMDV life cycle

After entry through the upper respiratory tract or lung, the virus is rapidly replicated. The virus shed from an infected animal through host secretions and excretions and cause infection across damaged epithelium (7). First replicates of virus occur in the pharynx. In 24–48 h the virus spread across the blood stream and lesions appear in the mouth and feet of susceptible animals. However, the Viremia disappears after 3–4 days, virus replicates to very high titers (>8 log 10 infectious units per ml) at lesions sites and shed in the air and body fluids. The virus establishes persistence in the pharyngeal region of approximately half of the infected animals, even vaccinated animals protected from clinical disease, that become long-term carriers (43). The other viral NS proteins are involved in various aspects of the viral replication cycle. 3D is the viral RNA-dependent RNA polymerase, 3B (also termed VPg), a protein covalently linked to the 50 end of virions RNA, has a role in the initiation of RNA synthesis, and 2B, 2C, and 3A are involved in membrane rearrangements required for viral RNA replication and capsid assembly (19).

2.3.3 Clinical signs of FMDV

There is some variability in the clinical signs among species. Foot-and-mouth disease is typically an acute febrile illness with vesicles on the feet in and around the mouth and the mammary gland. Vesicles occur occasionally at other locations, including the vulva, prepuce, or pressure points on the legs and other sites. The vesicles usually rupture rapidly, becoming erosions. Pain and discomfort from the lesions lead to clinical signs such as depression, anorexia, excessive salivation, lameness and reluctance to move or rise. In serious cases, the hooves or footpads may be sloughed. Reproductive losses are possible, particularly in sheep and goats. Deaths are uncommon except in young animals (36).

2.3.4 Routes of Transmission of FMDV

Spread of FMD virus is most commonly associated with the movement of infected animals and their contact with susceptible animals. During the early stages of disease, infected animals shed virus in all their excretions and secretions, including their breath. In cattle and pig's peak production of virus coincides with the onset of clinical signs, whereas in sheep it occurs before the appearance of lesions, and then in all species it declines rapidly as antibody production and other immune responses bring the infection under control. FMD virus can also be carried mechanically by people, vehicles, brushes, surgical equipment and other fomites from infected to

susceptible animals (Kitching .2005). 44% of FMDV transmission is airborne or environmental transmission. Its travel over water is estimated at maximum distance of 250kms. The intensity of the disease is determined by the. Dose of virus, Species of the sick animal and the susceptible host (46).

2.3.5 Incubation period of FMDV and Excretion of Virus by Infected Animals

The incubation period of FMDV from farm to farm is in 4 to 14 days' range of spread, while it's in range of 2 to 14 days within the farms even if it may be as short as 24 h in pigs and in highly dense population. The incubation period for FMD is highly variable depends on: the strain and dose of virus, route of infection, species of host and the husbandry conditions of animals (5). The virus may secreted and excreted from an infected animal occur through: urine, milk nasal droplet, damaged epithelium and orally (7)**.** The animal body secretion and excretion may contain a significant titer of virus before the development of clinical signs, particularly in saliva, nasal and lachrymal fluid, milk, but Urine and feces contain virus in the lesser extent. Since preputial lesions are sometimes present it is possible that these are the origin of infectivity in urine (5). FMD viruses persisted in naso-pharynx of chronically infected animals (Thomson *et al*.,2011). During the first three months after infection of FMD small amounts of FMDV may persist in the throat, which may reach 50% in recovered cattle. However, the number virus in infected anima is decreases with time, the small percentage of virus remaining at two years post infection. In Vaccinated animal which may exposed to FMD virus, the virus can persist for longtime without showing clinical signs. FMD virus is found only in small quantities in the pharyngeal area of carriers (IAEA, 2007). Most of the time the sheep shows mild or no clear clinical signs of FMD, however they can secrete and excrete certain amounts of FMDV as a its carrier (1).

2.3.6 Immune response of foot-and-mouth disease virus infection

The protective immune response against foot-and-mouth disease (FMD) virus is demonstrated as depend on the interaction between virus specific antibody and the phagocytic cells of the reticuloendothelial system (35). VP1 carries important immunogenic sites recognized by host immune cells, including amino acids (aa) 141–160, a major B cell site, and aa21–40, a T-cell site (29). FMDV-specific antibody secreting cells (early B-cell response to aerosol infection) are established in the lymphoid tissue of the respiratory tract and spleen after four days of infection. The same group has extended this work to show that systemic vaccination is able to induce a B-

cell response which extends to the lymph nodes draining the respiratory system, and can result in a rapid recall response in the respiratory mucosa upon aerosol exposure to live virus (42).

FMDV disease rapidly induce strong and long-lasting antibody against the FMDV antigen in susceptible hosts. Following the first detection of antibody in host, the virus can be cleared from blood and lymphatic circulation and the virus shedding from host secretion can be reduced gradually. Although the circulated antibodies are expected prevent viremia and generalized FMDV disease, it does not prevent localized virus in organ such as pharynx (14). Recognition receptors in the host cell can recognize the virus-associated molecular patterns upon the infection of the host. The recognition of virus-associated molecular receptors causes interferon type 1 (type 1 IFN) and interferon-stimulated genes (ISGs) to be transcribed. The down regulation of interferons is a stimulatory factor for enhanced expression of natural killer cells; thus, an antiviral state is established in the host (37).

FMDV have the FLAG epitopes polypeptide with Arg-Gly- Asp (RGD) tripeptide sequence motifs. The animal did not produce antibodies against FLAG as it remained cryptic site and not detected by the immune system (36). However, adjuvant boosted inactivated virus (FMDV) vaccine induce effective protective immunity related antibody (Ab) responses (25), vaccination with one serotype does not provoke immune protection to the other serotypes (49). Also, low cross-reactivity are due to high sequence variability in Beta-cell epitopes (37). In vaccinated animals' induction of cell-mediated immune responses low as comparing with naturally infected animal as a result of the NSP removed from viral genome of inactivated vaccine viruses. In both the capsid proteins and NSP of viruses, helper T-cells (Th) recognize epitopes which are presented by Dendritic cells as it responds to B-cells, However, NSP removed from in inactivated vaccine, the T-cell responses is induced by CD4+ cells which contribute in the production of FMDV antibodies. (39). The potential importance of non-neutralizing opsonic antibodies that facilitate uptake of bound FMDV by dendritic cells (DC), which are potent immune modulators. Opsonizing antibodies increased plasmacytoid DC-mediated release of antiviral Type I IFNs in response to both homologous and heterologous serotypes (42).

The viral leader proteinase, Lpro, limits the host innate response by inhibiting the induction of interferon beta (IFNb) mRNA and blocking host cell translation. A second viral proteinase, 3Cpro, may affect host cell transcription because it cleaves histone H3. Viral protein 2B in conjunction with 2C or their precursor 2BC inhibits protein trafficking through the endoplasmic reticulum and Golgi apparatus. A decrease in surface expression of major histocompatibility

class I molecules during FMDV infection suggests that 2B, 2C and/or 2BC may be involved in delaying the initiation of the host adaptive immune response and also adversely affect the secretion of induced signaling molecules (19). High IFN activity is detectable in tissues of FMDV-infected animals, but it is restricted to sites of virus replication (14).

2.3.6.1 Neutralizing antibody of FMDV

Innate immunity plays an important role in defending a host from invading pathogens. Type-I IFNs, such as IFN-a and -b, are key players in the innate antiviral response (28). B-cell induce the response by T-cell help or in the absence of T-cell help by type II T-cell independent (TI-2) antigens, such as viral capsids, that have regular repeating epitopes within their structure (16). The specific site for binding to neutralizing antibody of FMD capsid is the G-H loop in the VP 1 peptide. B lymphocytes recognizing epitopes on the virus particles to produce specific antibody following antigen processing and presentation by the major histocompatibility complex type II, the growth and differentiation factors necessary for developing the immune response.is resulted from stimulation of the T-helper (Th) lymphocytes (Motamedi-Sedeh *et al.*, 2015). Production of virus-antibody complexes early in the infection stimulating the production of interferon and consequently stopping the production of virus within the cells. Increasing this parameter therefore produces virus-antibody complexes sooner and stops the production of virus in the cells sooner (22).

3. CONCLUSION

Foot-and-mouth disease virus (FMDV) has significant socio-economic consequences due to losses in production and constraints on export of live animals and associated products to disease-free countries. Many works have been carried out to develop and validate diagnostic tests and vaccine regard to the prevention and controlling the FMDV. Antigenic and genotypic characterization of FMDV and the ability of antibody produced by host bound it is required for formulation of appropriate diagnosis tests and vaccine for effective control and eradication of the disease. In this review, antigenic and genetic variation of virus and neutralizing ability of antibody produced by the host after its exposed to field virus or inactivated vaccine is stated.

LIST OF ABBREVIATIONS

cre: cis-acting replication element

DC: dendritic cells

ER: endoplasmic reticulum

FMDV: Foot-and-mouth disease Virus

IFN: interferon

IRES: internal ribosome entry site

ISGs: interferon-stimulated genes

OFR: Open frame region

Th: T-helper

UPR: unfolded protein response

UTR: Untranslated region

Ethical Approval

No ethical clearance is needed for review

Conflict of interest

The review was prepared by authors by revising of different papers by self; so there no one can cause issues of interest with this review.

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The author was contributing in selection of the topics, reviewing different research papers and organizing in scientific ways for publications

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