The immunological war: Do or Die mechanism of Marburg virus

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Abstract

Marburg and Ebola viruses are filamentous filoviruses that are distinct from each other but that cause clinically similar diseases characterized by hemorrhagic fevers and capillary leakage. Infections with the Ebola virus are significantly more virulent than infections with the Marburg virus. There are nonspecific initial clinical signs of these diseases and they can resemble other endemic pathogens. This makes it difficult to have a confident diagnosis based on clinical symptoms alone. Present molecular tests are focused on the identification of virus material in the blood to classify infections with high-consequence viruses such as the Ebola virus and the Marburg virus. These viruses do not experience extensive early replication in the blood and replicate in organs such as the liver and spleen instead. Therefore, after significant replication has already occurred in certain tissues, the virus starts to accumulate in the blood, rendering viremia an indication of infection only after initial stages have been identified. The function of the immune cell molecular mechanism against the Marburg virus and Ebola virus remains vice versa. In addition, this would help us figure out the difference between the Marburg virus and the Ebola virus. However, the researchers were also puzzled between the Marburg virus and the Ebola virus with the concept of the molecular mechanism of immune cells. We would like to summarise the exact function of the molecular mechanism of immune cells in the Marburg virus in this review.

keywords: Marburg virus infection, Natural killer cells, Monocyte gate, MHC class II molecules, MHC class I molecules.

Abbreviations

MARV Marburg virus

CFR Case fatality ratio

TLR1 Toll like Receptor 1

TLR2 Toll like receptor 2

IgM Immunoglobulin M

IgG Immunoglobulin G

IFN- γ Interferon- Gamma

NK cells Natural killer cells

Type I IFNs Type I Interferons

1.Introduction

Marburg virus (MARV) is a member of the family ***Filoviridae*** within the species of ***Mononegavirales***. MARV is an undifferentiated negative-strand RNA gene that is approximately 19 kb. The MARV genome contains seven monocistronic genes that encode seven viral proteins **(Figure1)**. MARV chiefly can cause severe hemorrhagic fever in both humans and animals (1). Symptoms of MARV infection, which includes inflammation of the pancreas, jaundice, severe weight loss, delirium, shock, multi-organ dysfunction (2). This virus was first identified in 1967, during epidemics in Marburg and Frankfurt in Germany and Belgrade in the former Yugoslavia from the importation of infected African green monkeys from Uganda (1). The WHO reports the case fatality ratio (CFR) of MARV infection cases in humans ranging between 24% and 88% (3). Epidemiologists tested bats, monkeys, spiders, and ticks for the virus and came up with definitive data (4). The bats **(*Rousettus aegyptiacus*)** is identified as a natural reservoir of MARV but the beauty of the infection is there are no possible symptoms for detecting this type of infection in bats. However, this type of bats overlaps with each other and helps in the geographical distribution of MARV infection. Moreover, this MARV infection started to transmit from bats to monkeys and humans (5). During the 1967 eruption, most of the people get victim by MARV due to direct contact with the organs and blood of infected African green monkeys or was involved in autopsies of infected animals. Moreover, MARV infection has starts transmits from Human-to-human itself. This type of transmission occurs through direct contact with blood or other secretions (e.g., sweat, saliva feces, breast milk or, urine) of an infected person **(Figure 2)**. This virus can continue to seep into a patient's semen for up to 3-4 months after infection. Sexual transmission of the disease occurs in one instance (6). The mechanism of MARV replication was well explained (Review (1)).

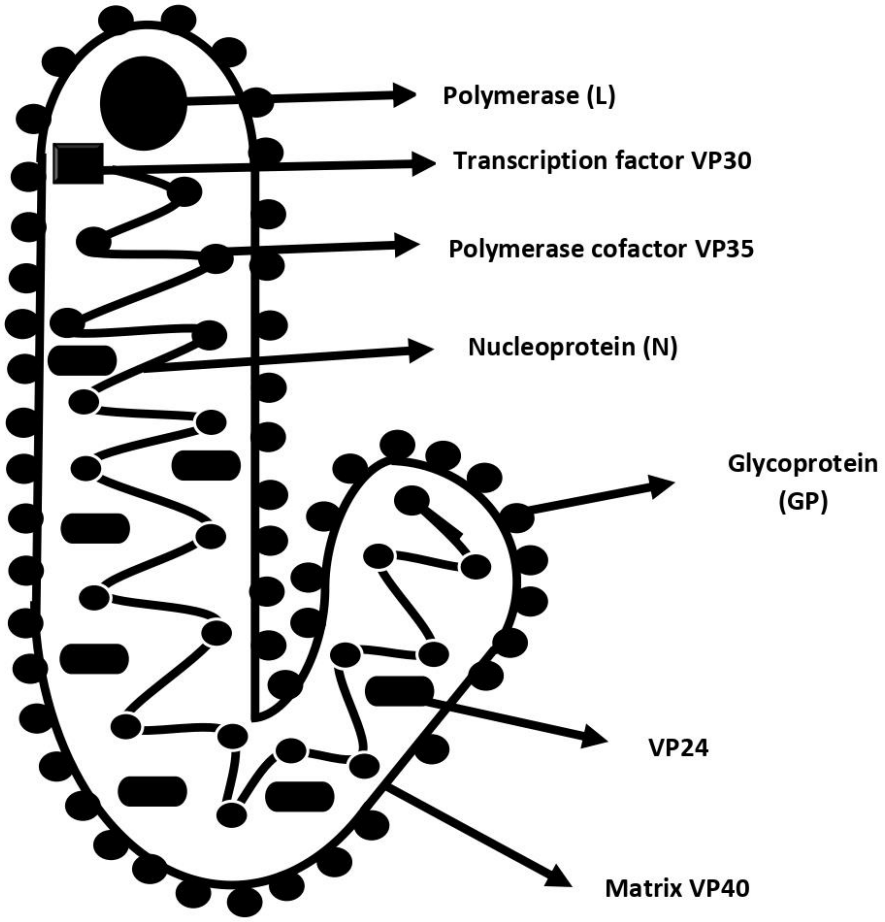

Figure 1: Structure of MARV proteins

The diagram illustration represents the MARV proteins, such us, glycoprotein (GP), Matrix VP40, Nucleoprotein(N), Polymerase (L), Polymerase cofactor VP35, Transcription protein VP30, VP24.

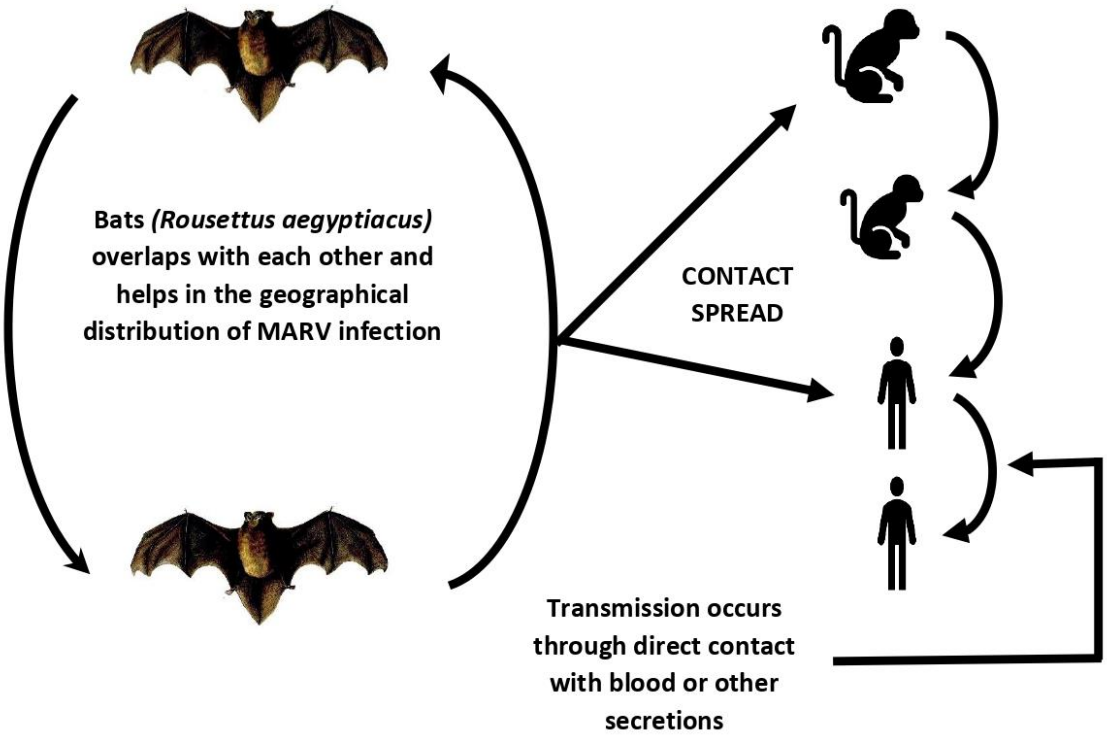

Figure 2: Transmission of MARV Infection

The typical transmission occurs in the MARV virus from Bat to Bat, Monkey, and Human, Monkey to Monkey and Human, Human to Human.

2.The primary role of the immune system

MARV firstly targets the mononuclear phagocytic system (7), such as Monocytes, macrophages, dendric cells, etc (8). Monocyte gate (The term monocyte gate refers to both monocyte and dendritic cells (9)), has specific kind of pattern recognizing receptor, which is known as a toll-like receptor. When the MARV gets infected, these toll-like receptors TLR1 and TLR2 help to recognize the genetic pattern of MARV. These TLR1 and TLR2 start producing a cytokine such as type I Interferons (type I IFNs). Moreover, the MARV Protein VP35 & VP24 helps to inhibit the synthesis of type I IFNs (10).Due to this type I IFNs inhibition, the uninfected cells unable to protect themselves from the MARV [8]. However, TLR 1 & TLR 2 gives a strong signal to the $CD4^{+}$T-cells (11). These $CD4^{+}$T-cells further gives the signal to the B-cells by b-cell growth factor or interleukin-4 (IL-4). These signals

cause the activation of b-cells and the differentiation of b-cells and also convert b-cells into plasma cells. These plasma cells secrete a large amount of IgM antibody (12,13). These IgM antibodies bind with the MARV antigen (13). However, these antigen-coated antibodies have an Fc portion (14). The monocyte gate contains Fc receptor, which helps the antigen-coated antibodies bind on the surface and it triggers the activity of the monocyte gate(15). The cellular mechanism of monocyte gate are well explained against the viral infections (reviewed in (16)). Since the primary target of MARV infection was the monocyte gate and the lymphocyte. However, MARV-infected Cynomolgus Macaques study, reported that 84% of the macrophages are got infected with MARV. Moreover, MARV also infects the dendritic cells. The percentage of MARV infected dendritic cells compared to the MARV infected cells double the amount (9).

3.The brilliant move of MARV

During the double-positive stage, the immature T- cell express both $CD4^+$& $CD8^+$ co-receptors (17). Due to the infected monocyte gate (9), unable to present the MHC class II molecules to $CD4^+$ T-cells. Anyway, $CD4^+$ T-cells recognize the peptide with MHC class II molecule. So, during maturation, the immature T-cells downregulate the $CD4^+$ coreceptor and it upregulates the $CD8^+$coreceptor (17). MHC class I molecules are expressed on the cell surface of all normal and viral cells except the erythrocytes and contain peptide fragments obtained from proteins inside the cell. In normal cells, these peptides are obtained from the cell 'own housekeeping' proteins. In the viral cells, these peptides are obtained from the viral protein (18). However, in MARV these MHC class I molecules are made up of protein GP (it is also called MARV-GP). These MARV proteins have the ability to remove or hide their own MHC class I molecules from the cell surface in order to protect themselves from the activation of $CD8^+$ cells **(Figure 3)**. However, the independent overexpression of GP, which causes the morphological changes of other viral proteins and it leads to the detachment of other GP proteins from the cell surface especially the MHC class I molecules. In plasma membranes, the glycan forms a shield **(Figure 3)**. This shield protects the MHC class I molecules present on the surface MARV cell, which helps prevents the activation of the immune system and it also disturbs the function of host proteins, which is nearby the MARV-GP (19). These are the sequences of methods used by MARV to block the MHC Class I pathway to escape cytotoxic T-lymphocytes lysis (18).

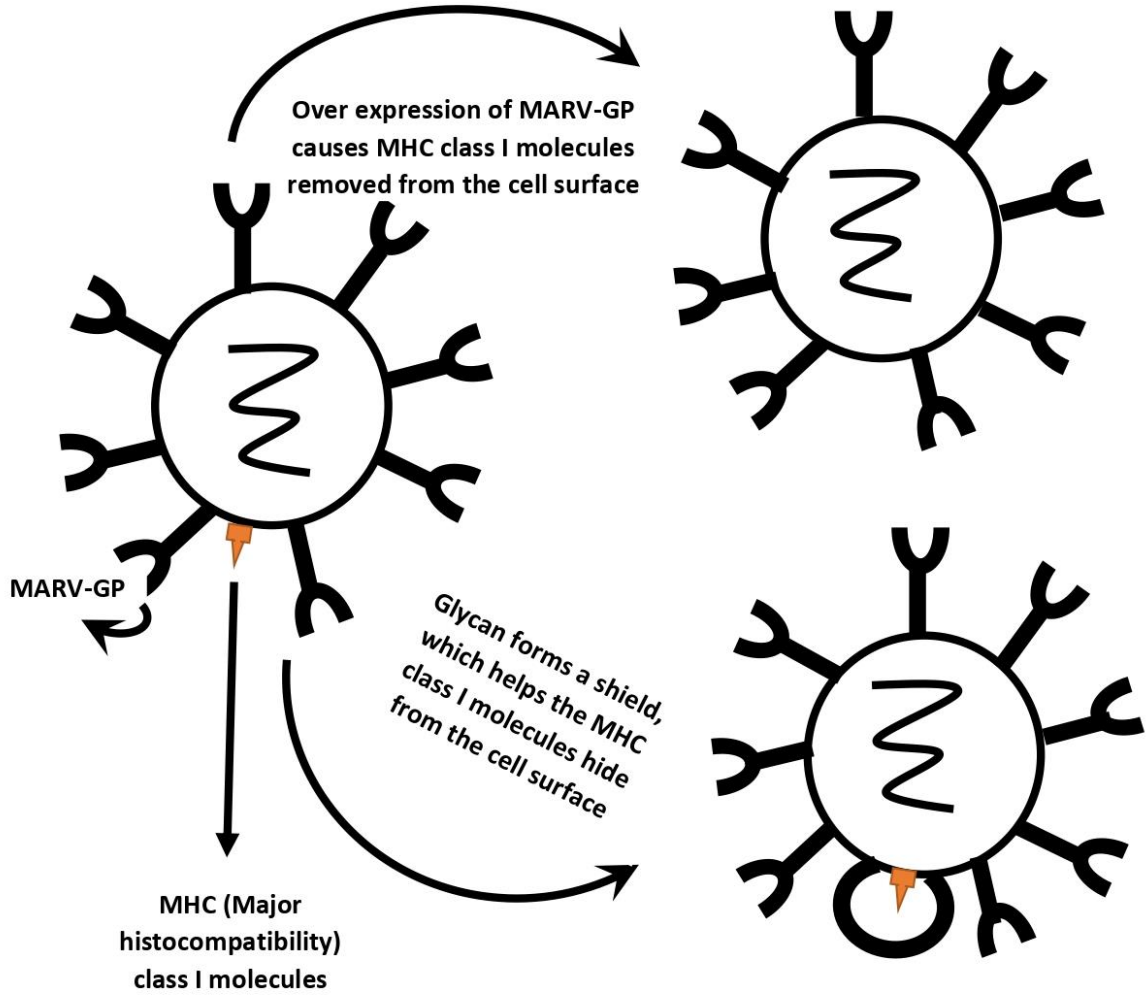

Figure 3: Role of MARV-GP

The Role of MARV-GP to remove or hide their own MHC class I molecules from the MARV cell surface

4.Role of NK cells

During the MARV infection causes $CD16^+$ decreases in the blood but in $CD16^+$ cells are increased in the spleen (9,20). So, MARV infection doesn't cause a decrease in the amount of Natural killer (NK) cells (9). NK cells are unique white blood cell and it also has the ability to act as both Innate and adaptive immunity [19]. The mechanism of NK cell using inhibitory receptors & ligand molecules was well explained in (review (21)).NK cell has an ability to secrete a T-cell type of cytokines which is helping to protect against the viral infections e.g. (Tumor necrosis factor-α (TNFα), and Interferon- γ (IFN- γ)) (22). However, plasma cells also secretes a large amount of IgG antibody (12,13). These IgG antibodies bind with the MARV antigen (13). However, these antigen-coated antibodies have an Fc portion. The $CD16^+$ cells on the surface of NK cells act as an Fc receptor. This Fc receptor

has a capability bind with the Fc portion of the antigen-coated antibodies(14). These lead to NK cell activation and is also responsible for the elimination of MARV. (23,24).

5.Conclusion

In conclusion, the do or die competition between the MARV and the immune system remains a mystery. The MARV plays a magnificent role in escape from the Immunity like TLR, monocyte gate, $CD8^+$ T-cells. However, there is no proper evidence that NK cells can completely eliminate or destroy the MARV infection. Likewise, there is no evidence that suggests MARV infection can cause a decrease in the amount of NK cells. The role of MARV and NK cells remains unknown. However, ln Murine cytomegalovirus (MCMV) in order to escape from the activated NK cell, MCMV upregulates the proteins m152/gp37/40. These proteins peptides look like MHC Class I molecules. So, the NK cell considered the presence of MHC Class I molecules, NK cells don't against the action against the MCMV. So, the evolution or mutation mechanism of MCMV leads to escapes from the NK cells. Similarly, MARV might also undergo evolution or mutation. However, the researchers who are working in MARV infection must want to determine the role of NK cells in MARV. This type of study will help, in case the MARV emerged again and also helps to eradicate of MARV.

Consent for publication

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Conflict of interest

The authors declare no conflict of interest, financial or otherwise.

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Ethical approval

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