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Marburg Virus: Emerging Zoonotic Infectious Agents

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Abstract

Marburg Virus is a highly pathogenic virus that belongs to the Filoviridae family, which also includes Ebola virus. Marburg Virus (MARV) is responsible for causing severe outbreaks of Marburg Virus disease (MVD) in Africa, with a high case-fatality rate of up to 90%. MVD is characterized by a range of symptoms, including fever, hemorrhagic manifestations, and multi-organ dysfunction, and there are currently no approved treatments or vaccines for the disease. This review provides an overview of the current knowledge on MARV and MVD, including the virus's epidemiology, pathogenesis, clinical features, and diagnosis. It also discusses the various strategies that are being explored for the prevention and control of MVD, including the development of vaccines, antiviral drugs, and other therapeutics.

Keyword: Marburg Virus, zoonotic infection, pathogenesis, MVD, hemorraghic fever

Background

Emerging virus infections, including Marburg Virus (MARV), have become a growing public health concern in recent years (Bente et al., 2009). The emergence of new viral pathogens is often due to a combination of factors, including changes in land use and agriculture, urbanization, international travel and trade, and climate change. MARV, like other emerging viruses, is a zoonotic pathogen, meaning that it is transmitted from animals to humans. The natural reservoir for MARV is thought to be fruit bats of the Pteropodidae family, although other animals, such as monkeys and rodents, may also play a role in transmission (Messaoudi et al., 2015).

The virus is transmitted to humans through contact with the bodily fluids of infected animals, particularly fruit bats, which are thought to be the natural host. Human-to-human transmission can also occur through contact with blood, secretions, or other bodily fluids of infected individuals (Brauburger et al., 2012). The virus can cause severe and often fatal disease, with symptoms including fever, chills, headache, muscle aches, and bleeding from various parts of the body. The infection previously refered to as Marburg Hemorrhagic fever is now known as Marburg Virus Disease (MVD).

Outbreaks of MARV have typically occurred in areas where the virus is endemic, such as in parts of Africa (Kuhn et al., 2008). However, due to global travel and trade, there is a risk that the virus could be introduced into new areas and cause outbreaks. In addition, there is always the possibility of the virus mutating and becoming more transmissible or virulent. The global response to emerging virus infections, including MARV, has included increased surveillance, research, and collaboration between public health agencies and the scientific community. There have also been efforts to develop new vaccines and treatments for these diseases.

The MARV was first identified in 1967 when a deadly outbreak occurred among laboratory workers in Marburg and Frankfurt, Germany, as well as in Belgrade, Yugoslavia (now Serbia) (Brauburger et al., 2012). The outbreak was linked to the use of African green monkeys, which were imported from Uganda for research purposes (Kuhn et al., 2008); WHO, 2018). The initial cases involved laboratory workers who became infected after handling tissues and blood samples from the infected monkeys. The disease rapidly spread among the laboratory workers, leading to severe symptoms such as fever, headache, muscle pain, and hemorrhagic fever. The outbreak ultimately resulted in 31 cases and seven deaths. Following the initial outbreak, additional cases of MARV were reported in the Democratic Republic of Congo (formerly Zaire) in 1998-2000, Angola in 2004-2005, and Uganda in 2007-2008 (Gear et al, 1975; Smith et al., 1982). The outbreaks in these countries were also linked to the handling of infected animals or their bodily fluids (Brauburger et al., 2012).

Virus Morphology and Replication

MARV belongs to the Marburgvirus genus, which contains only one species, the Marburg Marburgvirus (Messaoudi et al., 2015). The virus is a single-stranded RNA virus, and its genetic

material is surrounded by a lipid envelope. The MARV has a characteristic filamentous shape and measures between 800-1000 nanometers in length and 80 nanometers in diameter. The virus contains several structural proteins, including the glycoprotein (GP), which is responsible for attachment and entry into host cells, and the nucleoprotein (NP), which is responsible for encapsulating the viral RNA genome (Figure 1) .

MARV is classified as a Biosafety Level 4 (BSL-4) pathogen, which is the highest level of biological safety classification (WHO, 2018). This is due to the high risk of infection and the lack of specific treatments or vaccines. BSL-4 pathogens require the highest level of containment facilities and personal protective equipment to prevent the accidental release of the virus. Despite research efforts, there is currently no licensed vaccine or specific treatment for the MARV.

MARV replication involves several steps, beginning with attachment and entry into host cells (Brauburger et al., 2012). The virus primarily targets macrophages and dendritic cells of the immune system, as well as liver cells and endothelial cells lining blood vessels (Martines et al., 2015). The attachment and entry of MARV into host cells is mediated by the viral glycoprotein (GP), which binds to specific receptors on the surface of host cells. The virus then enters the cell by endocytosis, a process where the virus is engulfed by the host cell membrane and brought into the cell. Once inside the cell, the viral RNA genome is released from its lipid envelope and transported to the cytoplasm, where it serves as a template for viral replication. The viral RNA polymerase, which is packaged within the virus, begins synthesizing new viral RNA strands, which are then used to make viral proteins. The viral proteins are translated from the viral RNA and assembled into new virus particles within the cytoplasm. These virus particles are then transported to the cell surface, where they are released by budding from the host cell membrane. This process of budding allows the virus to avoid detection by the host immune system and facilitates its spread to other cells in the body (Kuhn et al., 2008).

During the course of infection, MARV can cause significant damage to host tissues, particularly the liver and endothelial cells lining blood vessels. This damage can lead to severe symptoms such as hemorrhagic fever and shock, which can be fatal in some cases (Massaoudi et al., 2015).

Viral Pathogenesis

Marburg Virus Disease (MVD), previously known as Marburg hemorrhagic fever (MHF) is a severe and often fatal viral disease that is caused by the MARV (Martines et al., 2015). The viral transmission can occur from one human to another due to direct contact with body fluids such as blood, feces, saliva, urine, teardrops, mucous, and breast milk (Kahn et al., 2008). The MARV pathogenesis may vary depending upon various factors, including strain virulence, physical status, host susceptibility, and medical maintenance. The incubation period ranges between 2–21 days, with an average of about 5-9 days in humans (Messaoudi et al., 2015)

MHF disease progression can be divided into 3 distinct phases; Phase I- generalization phase; followed by Phase II- early organ phase, and then Phase III-late organ phase or convalescence phase (Martines et al., 2015). MARV mainly infects macrophages, monocytes, Kupffer cells, and DCs, triggering the cellular activation and permitting damage to secondary targets, such as endothelial cells and parenchymal cell (Stroher et al., 2001). Macrophages, monocytes and dendritic cell activation leads to the release of cytokines and pro-inflammatory mediators such as Interleukin 6 and Tumor Necrosis Factor (TNF α). Increased levels of nitrix oxide and pro-inflammatory cytokines cause induce intravascular apoptosis (Geisbert et al, 2000). The infected mononuclear cells cause viral dissemination as well as bystander activation of lymphocytes leading to immunosuppression. Tissue factors production by infected immune cells causes disseminated intravascular coagulation and vascular permeabilization leading to hemorrhages. MAR infection of adrenal cortical cells causes metabolic dysfunctions, blood pressure dysregulation and eventually multiple organ failure and fatal shock (van Paassen et al., 2012).

MAR viral capsid protein vp 40 is implicated in immune evasion strategies inducing interferon-stimulated gene (ISG) production in liver cells, by preventing type 1 and type 2 IFN signaling, induce inflammatory cytokine response for rapid viral replication (Ramanan et al., 2011).

MARV replication and the inflammatory cytokine storm manifests as the MVD characterized by a sudden onset of fever, chills, headache, muscle pain, and weakness, followed by vomiting, diarrhea, and bleeding from multiple organs. The disease has a high mortality rate, ranging from 24% to 88% depending on the outbreak (Kuhn et al., 2008; Massaoudi et al., 2015).

Management of MVD

Prevention measures for MHF include avoiding contact with infected animals or their bodily fluids, practicing good hygiene, and using personal protective equipment, such as gloves and masks, when caring for infected individuals (Brauburger et al., 2012).

There is no specific treatment for MVD, and supportive care is the mainstay of treatment. This includes managing symptoms, such as fever and dehydration, and providing intravenous fluids and electrolyte replacement. Some of the anti viral drugs include ribavirin, a broad-spectrum antiviral drug that has shown some effectiveness against MARV in laboratory studies and animal models (Brauburger et al., 2012). However, its clinical effectiveness in humans with MVD is uncertain. Remdesivir is a broad-spectrum antiviral drug that has been approved for the treatment of COVID-19, but has also shown some promise in preclinical studies against MARV. Clinical trials are ongoing to evaluate its safety and effectiveness for treating MVD (Porter et al., 2017). Favipiravir is another broad-spectrum antiviral drug that has been approved for the treatment of influenza in some countries. It has also shown some effectiveness against MARV in laboratory studies and animal models, but its clinical effectiveness in humans with MVD is uncertain. Galidesivir is a broad-spectrum antiviral drug that has shown promise in preclinical studies against MARV. BX4430 is another drug that also works by inhibiting viral RNA polymerase, which is required for viral replication (Brauburger et al., 2012).

Experimental treatments, such as monoclonal antibodies and RNA-based therapeutics, are currently being developed and tested (Edwards and Basler, 2019). Small interfering RNAs (siRNAs) are short RNA molecules that can target specific viral genes and inhibit their expression. Several siRNAs targeting MARV have been developed and tested in animal models, and have shown some effectiveness in reducing viral replication and improving survival. Several mRNA vaccines for MARV are currently in development, and have shown promise in preclinical studies (Ursic-Bedoya et al., 2014). Researchers are exploring the use of CRISPR/Cas systems to target MARV genes and improve the immune response to infection (Chen et al., 2018).

A vaccine for MHF is currently in development, but is not yet available for widespread use. Several vaccine candidates are currently in development, including inactivated virus vaccines, recombinant protein vaccines, and viral vector vaccines (Dulin et al,. 2018; Reynolds et al., 2017). These vaccines aim to stimulate an immune response against the virus, which can help prevent or limit infection (Suschak et al., 2019).

Zoonotic viruses like MARV have the potential to cause outbreaks in new areas and may mutate to become more transmissible or virulent (Torvato et al., 2017, WHO, 2018). The global response to these infections has included increased surveillance, research, and collaboration to develop new vaccines and treatments.

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Conflict of Interest

None

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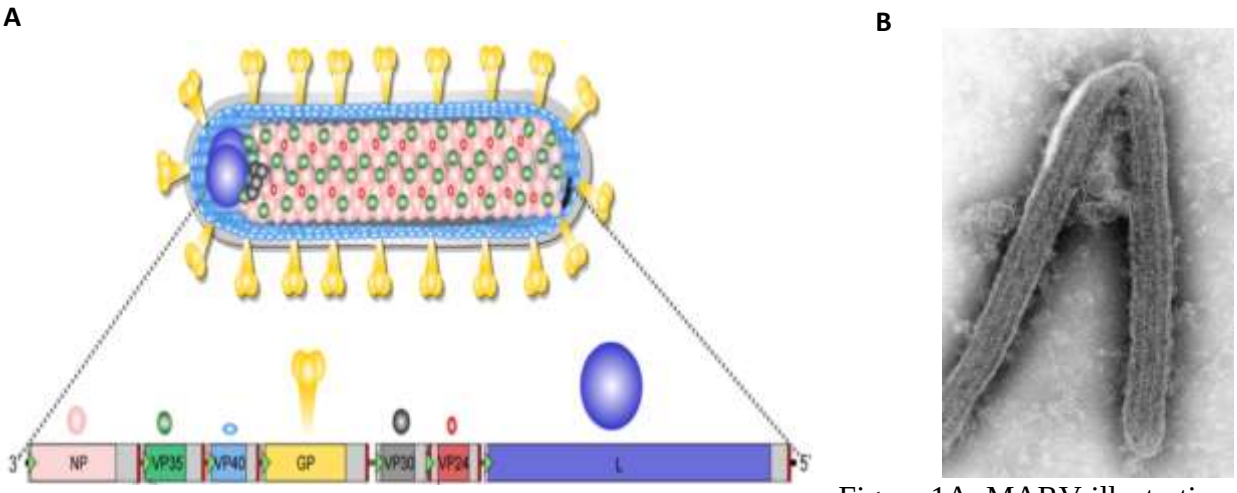

Figure 1A. MARV illustration of virus and seven proteins of the viral RNA genome. NP: Nucleoprotein, VP: Viral Protein (CC-BY-03 Image credit: https://www.mdpi.com/1999-4915/4/10/1878/htm)
B. Electron Micrograph of MARV (Image credit: F. A. Murphy, USCDCP on Pixnio)