From Bats to Humans: Transmission and Pathogenesis of Ebola Virus

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Abstract

Ebola virus disease (EVD) is a highly lethal zoonotic disease with a mortality rates of 90% caused by Ebola viruses (EBOV) belonging to *Filoviridae* family and *Ebolavirus* genus. The disease was identified in 1976 in Zaire, close to the Ebola River which is today part of the Democratic Republic of Congo (DRC). Since that time numerous outbreak have been observed in various regions globally, particularly in Africa, resulting in the discovery of 5 distinct viral strains that can infect human and primates. Fruit bats are thought to be the main reservoirs for the Ebola virus. The virus spreads by contact with infected animal's bushmeat and body fluids, as well as direct person-to-person transmission through bodily fluids, contaminated utensils and equipment, damaged skin, and mucous membranes. EVD pathogenesis involves fast viral multiplication and immunological evasion, resulting in extensive infection of immune and endothelial cells. This leads to systemic inflammation, vascular damage, and a reduced immune response, all of which result in severe symptoms such as bleeding, multiple organ malfunction, and, in many cases, death. This chapter discusses Ebola virus virology, reservoirs, transmission, pathogenesis, clinical symptoms, diagnosis, treatment, vaccination, and preventative methods.

Keywords: Ebola virus, Ebola virus disease, Fruit bats, Zoonotic disease

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Introduction

Ebola Virus (EBOV) is an emerging and re-emerging zoonotic disease that leads to severe Ebola hemorrhagic fever (EHF) in humans (Malik et al., 2023) and has a high mortality rate of 57% to 90% (Moghadam et al., 2015; Ghosh et al., 2021). It has a single-stranded RNA genome with a negative sense and belongs to the *Filoviridae* family (Hussein, 2013; Burk et al., 2016). It was called "Ebola" after the River Ebola near Yambuku, which served as the epicenter of the 1976 EBOV outbreak (Barrette et al., 2009). The first outbreak was discovered in Nizara (Sudan), at the end of June 1976, though the mode of transmission was not identified (Ascenzi et al., 2008). Later, in September of the same year, another outbreak took place near the village of Yambuku in the Democratic Republic of Congo (DRC, previously Zaire). The outbreak resulted in over 500 cases with a fatality rate of 53% in Sudan and 88% in Zaire (Ahmad et al., 2015). The latest epidemic in West Africa, occurring from 2013 to 2016, resulted in approximately 28,000 confirmed cases along with deaths of around 11,000 people, highlighting the high fatality rate of this disease (Garske et al., 2017). Ebola virus disease (EVD) affects humans as well as non-human primates (Feldmann & Feldmann, 2013; Weingart et al., 2013). It is classified as a category agent, which requires biosafety level 4 (BSL 4) precautions when working with suspected materials. Disease manifestation begins with fever as well as stomach ache, then vomiting, intravascular coagulation, diarrhea, bleeding and failure of multiple organs. In extreme situation the patient can experience hypovolemic shocks which results in mortality according to Mendoza et al. (2016). EBOV is spread by direct contact with the blood and body fluids of an infected animal or human and contact with their dead body (Passi et al., 2015). EBOV may have emerged from fruit bats. For instance, the 2007 EVD outbreak in Luebo, was connected to the ingestion of newly killed bat (Leroy et al., 2009). Likewise, the 2014 West Africa outbreak emerged with a zoonotic transmission from fruit bats to a 2-year-old Guinean kid (Marí Sa'ez, et al., 2015).

2. Ebola Virology

Ebola virus's family *Filoviridae*, which belongs to the *Mononegavirales* order, has three genera: *Cuevavirus*, *Ebolavirus*, and *Marburgvirus*. Within the *Ebolavirus* genus, five species have been discovered, each with its own virus: The species include *Ebola virus* (EBOV previously classified as *Zaire ebolavirus*), *Bundibugyo ebolavirus* (BDBV), *Sudan ebolavirus* (SUDV), *Reston ebolavirus* (RESTV), and *Tai ebolaforestvirus* (TAFV) (Feldmann & Geisbert, 2011). EBOVs are 50 - 80 nm in diameter and 10 000 - 14 000 nm in length.The Virions differ in structure; they are of cylindrical structure, branched and looped structure. However, all, members of the family *filoviridae* retain a unique thread like filamentous morphology (Majid et al., 2016). Ebola virus (EBOV) possess a large, un-fragmented, negative-sense single strand RNA genome of around 19kb, comprising seven genes arranged sequentially. They include 3' leader, nucleoprotein (NP), virion protein (VP35), matrix protein VP40, glycoprotein (GP), VP30, VP24 genes and the RNA dependent RNA polymerase (L), and at the last part the 5' trailer (Figure 1). Each gene

gives only one protein product excluding the GP gene which coded for three different glycoproteins (Mbala-Kingebeni et al., 2021). Sequence differences exist between all five EBOV species including positioning and number of gene overlaps, SUDV, EBOV, RESTV TAFV and BDBV all contain different sequences (Zheng et al., 2015; Goldstein et al., 2019).

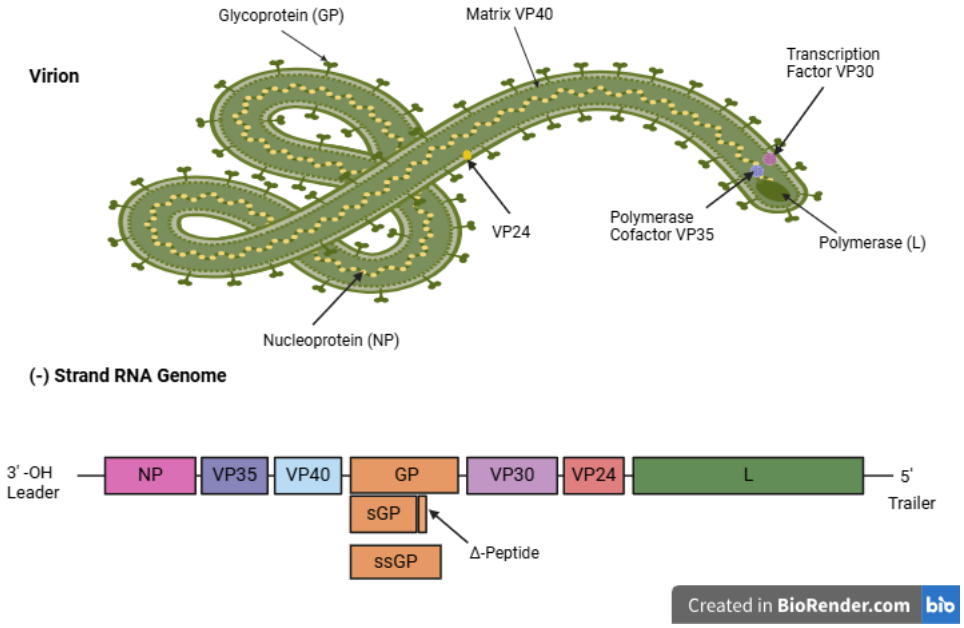

Fig. 1: Virology of Ebola virus.

3. Viral Reservoir

Fruit bats (*Myonycteristorquata*, *Epomopsfranqueti*, and *Hypsignathusmonstrosus*) from the family *Pteropodidae* are thought to be natural reservoirs for the EBOV. Bats have been confirmed to be natural reservoirs of Ebola virus (EBOV) with historical connections to outbreaks since 1976 and 1979, and Marburg virus diseases since 1975 and 1980. Experimental studies showed that out of 19 vertebrate and 24 plant species treated with Ebola virus, only bats exhibited no clinical indications of disease, supporting their role as reservoirs. A survey conducted between 2002 and 2003 involving 1,030 animals, which includes 679 bats from Congo and Gabon, detected EBOV RNA in 13 fruit bats (Gebretadik et al., 2015). Potential or accidental intermediate hosts comprise nonhuman primates, rodents, porcupines, antelopes, pigs, foxes, cats and duikers. Unlike bats, these animals normally get deadly and acute diseases once infected. They may carry the Ebola virus asymptotically and spread the virus through their body fluids, and in turn infect humans who come across them while hunting or butchering bushmeat (Osterholm et al., 2015; Singh et al.,2017; Laing et al., 2018).

4. Transmission

4.1. Transmission from Animals

EBOV outbreaks are usually initiated by direct contact with infected animals and their bodily fluids (for instance, when in hunting, butchering, or consuming infected animals) (Weingart et al., 2013). Members of the fruit bat family *Pteropodidae* are believed to be natural hosts of EBOV. People become infected with the virus either through contact with bats or other animals who are already infected (Figure 2) (Asare et al., 2023). Marí Sa'ez et al. (2015) have pointed out that the first contact of EVD in West Africa from 2014 to 2016 was linked to contacts with bats. Fruits and vegetables may become contaminated with the blood of infected animals, which people consume raw: eating infected bat meat is a major route of oral transmission of the EBOV, especially in African countries (Pandey et al., 2015; Caron et al., 2018; Munster et al., 2018). Apart from bats, cases of EVD have been observed in individuals who have interacted with intermediate hosts of EBOV such as infected chimpanzees, forest antelopes, gorillas, monkeys, and porcupines, both alive and dead, in Congo, Cote d'Ivoire, and Gabon (Jain et al., 2023). For instance, in 1996, in Mayebout, Gabon, a deceased chimpanzee discovered in the forest was slaughtered and consumed by 19 individuals and all of those individuals fell seriously sick within a short period. Since then, multiple similar incidents have occurred due to human interaction with infected chimpanzees or gorillas through hunting activities (Nkoghe et al., 2005). Pigs infected with EVD have significantly higher levels of virus in their lungs, than in their bloodstream. As a result, they can spread the disease by releasing infectious particles in the air or on to surfaces when they cough or sneeze (Funk & Kumar, 2015; Meyer et al., 2018).

4.2. Human to Human Transmission

Transmission among humans primarily occurs via physical contact with the bodily fluids of people who have fallen sick with EVD or who have passed away from it, especially when proper personal protective equipment (PPE) is not used (Figure 2) (Asare et al., 2023). Those at high risk include caregivers providing hands-on medical care and individuals preparing bodies for burial (Reichler et al., 2018). For instance, a meta-analysis containing nine researches of household transmission of EBOV, found that the secondary attack rates was 47.9% for individuals offering patient care, while it was 2.1% for those family members who had close physical interactions without offering patient care (Dean et al., 2016). Cleansing ritual of EBOV victims during funerals has significantly contributed to the spread of the virus in previous outbreaks,

including the West Africa epidemic. For Instance, a funeral ceremony in Guinea in late 2014 was associated with 85 consequent cases of EBOV disease (Victory et al., 2015). In the initial stages of the West African outbreak, hundreds of African doctors along with nurses contracted EVD while providing patient care without proper personal protective equipment. A historical investigation of within-household transmission during the West African outbreak discovered that virus propagated more frequently in bigger families. Additionally, transmissions were more common in elderly patients along with those individuals with severe illness, with an approximately 18% of secondary attack rate (Glynn et al., 2018). Lab workers in any biosafety level 4 facilities studying EBOV may face the risk of accidental infection. It can also be transmitted by the potential use of Ebola Viruses as biological weapons (Borio et al., 2002; Green, 2014).

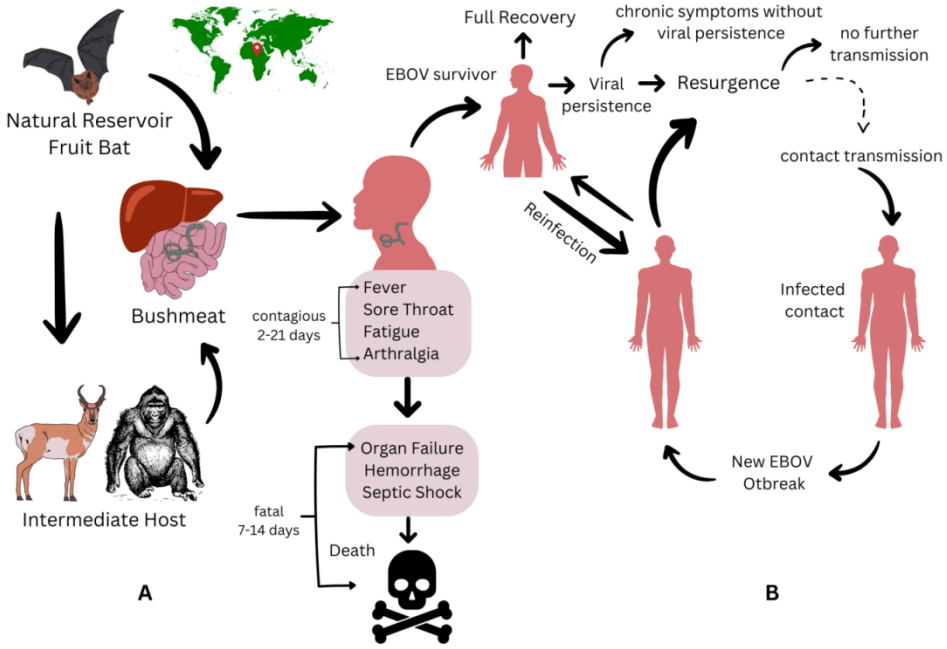

Fig. 2: Transmission of Ebola virus disease.

4.3. Transmission through Different Body Fluids

The type of bodily fluid an individual encounters along with the viral load it carries impacts their risk of disease. The most common mode of Transmission is physical contact with unprotected mucous membranes or damaged skin exposed to virus-carrying bodily fluids from someone exhibiting disease symptoms (Figure 2) (Asare et al., 2023). Ebola virus transmission within hospital wards during the newly documented EBOV disease epidemic in 1976 in the DRC was associated with the usage of un-sterilized needles (Judson et al., 2015). The World Health Organization identifies blood, vomitus, and feces as highly infectious bodily fluids. Also, the Ebola virus has been found in saliva, semen, aqueous humor, urine, breast milk, and vaginal fluid (Kreuels et al., 2014; Nordenstedt et al., 2016). Reverse-transcription Polymerase chain reaction tests revealed viral RNA in sweat as well as in tears, indicating that these fluids may contain the pathogenic EBOV. It also transmits by close interaction with the patient's skin, although the danger of EVD from this kind of exposure is considered lesser compared to contact with bodily fluids or blood. The virus present over the skin may originate from viral replication inside the epidermal as well as dermal layers, contamination by blood as well as other bodily fluids, or a combination of both. The amount of virus present in the fluid also determines the risk of EBOV transmission. In the initial stages of disease, the viral load inside the blood might be relatively low, however it can quickly increase, potentially exceeding 10^8 RNA copies/mL of serum in critically sick also dying patients (Towner et al., 2004). Epidemiological researches indicated that household members were at the highest likelihood of disease when they came into direct exposure with ill relatives especially their bodily fluids in the final stages of disease or when assisting in the preparation of a dead body for burial (Glynn et al., 2018).

4.4. Persistent Risks of Transmission after Recovery

Even when EBOV or its viral RNA is no longer detectable in the bloodstream of an EVD recovered patient it can still be present in certain bodily fluids (Figure 2) (Asare et al., 2023). Men who have recovered from EVD can spread the virus via their semen. For instance: In follow-up tests with arround 40 survivors from the 1995 epidemic in Kikwit, Congo, RT-PCR identified viral RNA sequences in the male patient's semen for a period of three months. Additionally, an infectious virus was isolated from one individual's semen 82 days following the commencement of the disease (Bray et al., 2015). A Research conducted on patient samples gathered at the time of Sudan ebolavirus disease outbreak in 2000 in Gulu, Uganda, identified the presence of virus in a patient's breast milk long after the virus had become undetectable in the blood (Bausch et al., 2007). Two infants who were breastfed by infected moms succumbed to EVD. In a similar case, during the West Africa outbreak, a 9-month old baby succumbed to EVD, despite his mother's good health. Viral RNA was later discovered in her breast milk, however the blood as well as urine tests returned negative results (Sissoko et al., 2017).

4.5. Transmission through Contaminated Surfaces

Ebola virus (EBOV) can spread though exposure to contaminated surfaces or objects. Using infected needles as well as medical equipment

without sanitizing them first increases the risk of EBOV transmission. The virus can remain pathogenic for several hours to days on surfaces like clothing, utensils, doorknobs, electrical switches, furniture, bedding, and other objects that may become infected through bodily fluids (Osterholm et al., 2015). While there is no definitive evidence confirming transmission through contact with contaminated surfaces, proper environmental cleaning can significantly reduce or mitigate this potential risk (Chertow et al., 2022).

4.6. Airborne Transmission

Airborne or aerosol transmission of a virus happens as tiny, virus-containing droplets vaporize before landing on surfaces, leaving infectious droplet nuclei capable of traveling over long distances. These tiny droplets that can produce such droplet nuclei are commonly referred to as aerosols. More broadly, aerosols are defined as any solid particles or small liquid that are suspended in air (Tellier, 2009). Currently, there is no evidence of reported cases of EBOV transmission from individual to individual via the respiratory route. Nonetheless, laboratory investigation demonstrated that EBOV, when released as a tiny-particle aerosol can infect nonhuman primates and rodents (Zumbrun et al., 2012). A research using the Makona virus strain from the 2013-2016 West African outbreak showed that even minimal quantities of aerosolized virus proved fatal to cynomolgus macaques with the time until mortality depending on the dosage. As a result, health-care professionals may face a danger of EVD when subjected to aerosols produced throughout surgical treatments (Prasad et al., 2023).

5. Pathogenesis

Laboratory studies using non-human primates have yielded information on the pathogenesis of the Ebola virus disease (Kreuels et al., 2014). Ebola virus enters the body through mucous membranes, skin breaks or mother to child transmission (parenteral infection). It infects various cell types, particularly dendritic cells and macrophages, where it replicates, resulting in cell necrosis (Bray & Geisbert, 2005). The virus disseminates throughout the body by inhibiting type I interferon responses and replicating in the lymph nodes. It enters the bloodstream and infects macrophages and dendritic cells in various organs including the spleen, liver, and thymus along with other lymphoid tissues (Figure 3). It can also infect endothelial cells, epithelial cells, adrenal cortical cells, hepatocytes, and fibroblasts. Fatal infections result from multiple necrotic lesions in tissues like the liver and spleen (Basler, 2005).

Patients then experience diarrhoea and vomiting, leading to severe volume depletion, hypotension and shock. It remains unclear whether the gastrointestinal dysfunction directly induced by viral infection of the gastrointestinal tract (GIT) or as a result of circulating cytokines (Kortepeter et al., 2011). The viral infection triggers a systemic inflammatory syndrome through promoting the secretion of cytokines, chemokines, along with other pro-inflammatory substances by various cells like macrophages (Mahanty & Bray, 2004).

Infected macrophages release tumor necrosis factor (TNF)-alpha, interleukin (IL)-1beta, IL-6, and macrophage chemotactic protein (MCP)-1, nitric oxide (NO), which contribute to coagulation disorders in EVD via the host inflammatory reaction (Figure 3). Viral-infected macrophages produce tissue factor (TF), activating the extrinsic coagulation pathway, while pro-inflammatory cytokines further stimulate macrophages for the production of TF51. This dual mechanism leads to rapid and severe coagulopathy in EVD, with EBOV infected monkeys exhibiting elevated D-dimers within 24 hours. Furthermore, decreased dendritic cell activities and T lymphocyte apoptosis in infected persons hinder the adaptive immune responses, leading to severe illness (Bray, 2005).

EBOV infection disrupts antigen-specific immune reactions primarily by replicating within dendritic cells, crucial for commencing adaptive immunity (Figure 3). In vitro researches indicate that infected dentritic cells do not mature properly and cannot provide antigens to naive lymphocytes, which may explain the absence of antibody formation in patients who die from Ebola virus disease (Sanchez et al., 2004). The viral infection impairs Adaptive immune responses through apoptosis stimulated by inflammatory substances as well as a lack of support signals from dendritic cells, a process also seen in septic shock (Geisbert et al., 2003).

6. Clinical Manifestations and Diagnoses

The duration from Ebola virus infection along with the appearance of symptoms is 2-21 days, on an average of 8 to10 days. Humans become infectious only after they begin to show symptoms. Initial symptoms include fever, sore throat, fatigue, severe headache, muscle pain, as well as weakness. This is accompanied by diarrhoea, vomiting, stomach discomfort, and rash, signs of damaged liver and kidney function, as well as bleeding. Laboratory tests reveal low counts of white blood cells as well as platelets, along with increased levels of liver enzyme (Xu et al., 2016).

Differentiating Ebola from other pathogenic diseases like fever, meningitis, typhoid, and malaria is challenging. As stated by World Health Organization, confirming EVD involves several methods, such as electron microscopy, reverse transcriptase polymerase chain reaction (RT-PCR) test, serum neutralization test, antigen capture detection tests, virus isolation by cell culture, and antibody-capture enzyme-linked immunosorbent assay (ELISA) (Wambani et al., 2016).

7. Treatment

Today, US FDA has approved only two drugs for the management of the Ebola virus disease. The first one is Inmazeb—a pharmaceutical preparation containing three monoclonal antibodies such as odesivimab, maftivimab, as well as atoltivimab; it acts on virus glycoproteins and thereby interferes with their direct connection with cells of a host organism. The second is ansuvimab (mAb114) which is a kind of monoclonal antibody that prevents the virus from adapting to the receptors of the cells in order to easily enter into the cell (Sivanandy et al., 2022). These medicines have been critically shown to raise the survival rates to the higher degree. Furthermore, individualized supportive care is recognised to be significant in sustaining organ functions in the patients. This includes maintainance of adequate water and electrolyte balance by the use of oral or intravenous fluids, treatment of symptoms of the underlying cause and the use of analgesics for pain relief. Facilitating the fluid balance and providing intensive care to such patients can significantly improve the survival chances (Dhama et al., 2015).

8. Prevention

To prevent Ebola virus disease and its spread, people traveling to EVD-endemic areas should avoid contact with or consumption of wild animals. Those returning from such areas should monitor their body temperature for 21 days. Healthcare workers should use personal protective equipment (PPE) correctly when caring for suspected or confirmed Ebola patients. Blood examination should be done using safety needles. If exposed to blood or body fluids, the exposure site must be thoroughly cleaned with soap and water, and body temperature of the individual should be monitored for a duration of 21 days. Patients should be kept in a negative pressure chamber or a solitary room with its own facilities. Isolation can be removed after two negative test results within a 48-hour period. In the case of death from Ebola virus disease, bodies should be burned within 24 hours (Tseng & Chan, 2015). Strict implementation of disease control measures is crucial to prevent the transmission of the virus when infected.

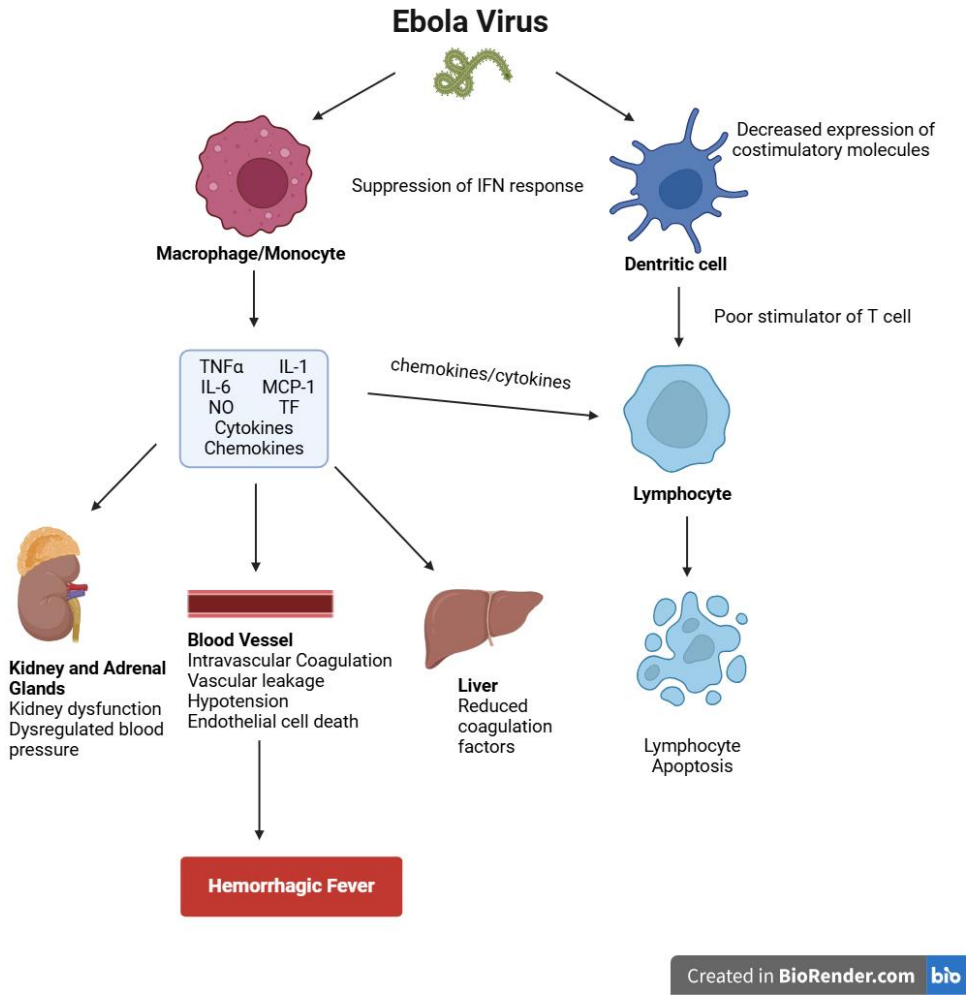

Fig. 3: The pathogenesis of Ebola virus disease.

Conclusion

Ebola virus disease is a deadly zoonotic disease with a high mortality rate. The transmission and pathogenesis of the Ebola virus from bats to humans emphasize the complex interplay between wildlife and human health. Understanding the ecological dynamics that facilitate spillover events is crucial for predicting and preventing future outbreaks. The evidence linking bats as potential reservoirs highlights the need for targeted surveillance and research to identify and mitigate risks associated with zoonotic transmission. Continued investigation into the virus's behavior, host interactions, and immune evasion mechanisms will enhance our understanding of its pathogenesis and inform the development of effective therapeutic and preventive strategies. Awareness of these issues is crucial for managing future epidemics in underprivileged and remote areas where deadly infectious diseases such as Ebola could re-emerge. A multidisciplinary approach, integrating veterinary and public health efforts, is essential for safeguarding both human and animal population from threat posed by Ebola Virus.

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