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PATHOPHYSIOLOGY OF EBOLA VIRUS INFECTION: A REVIEW OF CURRENT LITERATURE

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ABSTRACT:
By September 2014 the Ebola outbreak in West Africa had claimed more than 2600 lives. The disease has no approved drug or vaccines and cases have been treated with experimental drugs. Supportive care is the main stay of treatment of cases. Although research into understanding the pathophysiology of the Ebola virus has been going on for years, difficulty in conducting clinical studies because of outbreaks occurring in isolated remote villages have meant that most of the current literature on the pathophysiology of Ebola virus is from animal models. The 2014 outbreak in West Africa has put a spot light on this infection. Ebola virus infection results in cell necrosis and the ensuing systemic inflammatory responses that occurs causes the clinical symptoms and death in severe cases with a case fatality rate of 50%. Ebola virus targets mainly endothelial cells and macrophages but cells from other tissues can also be infected. Immunity to Ebola virus is not well defined and poorly understood, making development of therapeutic drugs and vaccines challenging. This is a brief review of some current literature on the pathogenesis of Ebola virus.

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INTRODUCTION:

The *Ebola virus* (EBOV) and *Marburg virus* are the two genera of the family *Filoviridae* and are among the most virulent pathogens to humans [1]. The Ebola virus disease (EVD) cause by the EBOV was first recognized in an outbreak in the village of Yambuku along the Ebola river in Zaire (now Democratic Republic of Congo (DRC)) in 1976 [2, 3]. Other EVD outbreaks have occurred in different countries in Sub-Saharan Africa after the DRC report [2, 3]. The latest outbreak occurred in early 2014 in the West African

country of Guinea, and then spread across the border to Liberia and Sierra Leone [1]. The outbreaks were confirmed by the WHO in March 2014 [1]. The mortality rate of the current 2014 outbreak has reached 70% although in previous outbreaks the mortality rates were as high as 90% [2]. The current outbreak is larger than all previous outbreaks combined [1]. Other West African countries affected in the current EVD outbreak include Nigeria, Mali, Senegal, and Cote d'ivoir. The World health authorities and governments responded to the outbreaks with assistance to the various countries affected. The WHO declared the EVD outbreak over in Senegal and Nigeria in August 29 and September 5 2014 respectively [1]. Efforts to contain the 2014 EVD outbreak in other affected countries are continuing [4, 5].

Classification and Structure of the Ebola Virus (EBOV):

The Ebola virus (EBOV) and the related Marburg virus belong to the family *Filovirus*. This family belongs to the order *Mononegavirales*, which are pleomorhic, negative sense RNA viruses whose genome organization is similar to *Paramyxsoviridae, Bornaviridae*, and *rhaboviridae* [2, 3]. The Ebola virus genus is divided into five species: EBOV (Zaire), Sudan ebolavirus (SUDV), Tai forest (Ivory Coast) ebolavirus (TAFV), Bundibugyo ebolavirus (BDBV) and Reston ebolavirus (RESTV) [1, 2]. The current outbreak in West Africa is caused by the EBOV species [1].

The EBOV genome is 19kb long with seven open reading frames coding for its structural proteins including the virion envelope glycoprotein (GP), nucleoprotein (NP) and matrix proteins VP24 and VP40 [3]. Nonstructural proteins are VP30 and VP35 and the viral polymerase [3]. Unlike the Marburg virus, the GP open reading frame of EBOV gives rise to two gene products, a soluble 60 to 70 kDa protein (sGP) and a full length 150 to 170 kDa protein that through transcriptional editing inserts into the viral membrane [3]. The GP plays a significant role in the pathogenesis of Ebola virus infection.

Pathogenesis:

Transmission of the EBOV is by contact with an infected person's skin, blood and body fluids or contact with the meat or body fluids of an infected animal [1]. There is no evidence that the virus can be transmitted via the respiratory route but animal studies show that the virus can infect rodents and non-human primates when the virus is released as small particle aerosol [1]. The EBOV has an incubation period of 14 to 21 days and infected individuals initially present with flu like symptoms of fever, myalgia and malaise [3]. As the infection progresses patients develop bleeding and coagulation abnormalities [3]. Full blood examination at this stage may show lymphopenia and neutrophilia [3]. A

comprehensive review of clinical symptoms and treatment is given by Goeijenbier et al [2].

Because of the difficulty in conducting clinical studies in outbreak conditions, much of what is known about the pathogenesis of Ebola is from animal studies. After entering the body via mucous membranes, breaks in the skin or parenterally the virus initially infects macrophages and dendritic cells [1]. The exact mechanisms of viral particle binding and entry into various cells type including endothelial cells is still being investigated, but current research suggest viral GP may play a significant role [3, 6]. After entering macrophages and dendritic cells, the virus readily replicates and releases new viral particles causing cell death and extensive tissue necrosis [1]. Rapid systemic spread then ensures by suppression of adaptive immunity [1]. Another round of replication occurs after spread of the virus to regional lymph nodes and eventually to fixed and mobile macrophages in the liver, thymus, spleen, adrenal medulla, endothelial cells and epithelial cells [1]. Extensive necrosis of the involved cells and tissues results in an inflammatory response that produces the clinical manifestations and is the cause of mortality in severe cases [1, 3]. Molecular mechanisms of the viral entry into endothelial cells are poorly understood and are also an active area of research [3].

Late state infection with EBOV results in gastrointestinal dysfunction, coagulation defects and severe systemic inflammatory response [1]. The gastrointestinal dysfunction includes vomiting and diarrhea resulting in acute volume depletion and shock [1]. It is not clear whether this is due to the infection of the gastrointestinal tract by the virus or cytokine response or both [1]. The systemic inflammatory response is caused by release of cytokines, chemokines, and other pro-inflammatory mediators from macrophages and other cells [1]. Some of the mediators identified include tumor necrosis factor (TNF)-alpha, interleukin-1beta (IL-1β), interleukin-6 (IL-6), macrophage chemotactic protein (MCP)-1 and nitric oxide (NO) [1]. This systemic response is thought to play a major role in vascular leakage and multi-organ failure [1]. The coagulation defects observed are thought to be caused indirectly by the host inflammatory response [1]. The extrinsic coagulation pathway is activated by the production of cell-surface tissue factor (TF) by virus infected macrophages and other macrophages activated by pro-inflammatory cytokines [1]. These two mechanisms activating the extrinsic coagulation pathway promote the rapid development of the coagulopathy. Other mechanisms promoting coagulopathy in EVD have also been suggested including decreased activated protein C and decreased level of plasma coagulation factors due to live injury [1].

Immunity:

Immunity to EBOV is not clearly defined. Identification of EBOV in endothelial cells, monocytes and hepatocytes using immune-histochemical techniques showed that these cells were the targets for disease progression [3]. The virus also replicates at a high rate that it overwhelms the protein synthesis machinery of infected cells and host immune responses [3]. Failure of the adaptive immune system due to impaired dendritic cell function and lymphocyte apoptosis is thought to be the mechanism how filoviruses are able to cause severe and fatal diseases [1]. Although antibodies against EBOV are readily detectable from patients who recover from the infection, serum from recovered patients did not consistently inhibit viral replication in cell cultures [3]. Survivors of EVD have been shown to have significantly higher levels of IgM responses, clearance of viral antigen and sustained T-cell cytokine responses [3]. Animal models also suggest antibodies play a role in viral clearance but the role of cellular immunity may be more significant and is yet to be elucidated [3]. Fatal cases of EVD do not have detectable levels of virus specific antibodies [3].

The role of other cytokines such as gamma interferon, alpha interferon, IL-2, IL-10 and TNF-α in immunity and pathogenesis are still being investigated [3]. Current data suggest that the damaging and protective effects of these cytokines may depend on the cytokine profile, a delicate balance between these effects and individual host specific immune response factors [3]. Mechanisms employed by EBOV to evade the host immune system include epitope masking, production of soluble glycoproteins (sGP) that act as antibody sinks and active suppression of host immune system by production of various cytokines [6, 7].

Filovirus-specific cytotoxic T-lymphocyte response can clear the virus in animal models [8]. Research to better understand the immune responses to develop a vaccine against EBOV is ongoing [3, 6, 9].

Summary:

Understanding the pathophysiology and immune response in EVD will lead to the identification of possible targets for vaccine development and clinical intervention. Current evidence shows that the virus has a cytopathic effect causing direct cell injury and death [3].

These effects are thought to be mediated by EBOV GP targeting macrophages and endothelial cell functions [3]. The ensuing systemic inflammatory response produces the clinical effects observed. Immunity to EBOV is not well defined and poorly understood making the development of a vaccine challenging [3, 6]. Currently the major treatment of a patient with EVD is supportive [2]. Although there are currently no approved therapeutic drugs or

vaccines, there are promising signs and it is an active area of research [8, 10, 11].

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