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A review on the antagonist Ebola: A prophylactic approach

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ABSTRACT

Ebola virus (EBOV), a member of *Filoviridae* virus family under the genus *Ebolavirus,* has emerged as a dangerous and potential threat to human health globally. It causes a severe and deadly hemorrhagic fever in humans and other mammals, called Ebola Virus Disease (EVD). In recent outbreaks of EVD, there has been loss of large numbers of individual's life. Therefore, EBOV has attracted researchers and increased interests in developing new models for virus evolution, and therapies. The EBOV interacts with the immune system of the host which led to understand how the virus functions and effects immune system behaviour. This article presents an exhaustive review on Ebola research which includes EVD illness, symptoms, transmission patterns, patho-physiology conditions, development of antiviral agents and vaccines, resilient health system, dynamics and mathematical model of EBOV, challenges and prospects for future studies.

1. Introduction

Ebola virus (EBOV) has emerged as a potential threat to human health worldwide, which cause a critical and serious ailment, often deadly if not cured properly. It is a member of "Filoviridae" virus family, under the genus "Ebolavirus", having five species: *Zaire Ebola*, *Tai Forest Ebola*, *Sudan Ebola*, *Bundibugyo Ebola*, and *Reston Ebola Virus* [1]. Out of these species, former four cause illness in humans, whereas the Reston Ebola Virus causes illness in primates. Ebola virus causes an illness called as hemorrhagic fever [2], especially in humans and other mammals, named as "Ebola Virus Disease" (EVD), and therefore EVD is also known as "Ebola Hemorrhagic Fever" (EHF). Ebola viruses are native to a number of African countries. The disease was firstly recognized in 1976 in two concurrent outbreaks: one of them in Nzara, an state in South Sudan, and another one in village Yambuku, previously known as Democratic Republic of Congo, adjacent to 'Ebola River', and hence the name Ebola Virus Disease [3].

1.1. EBOV and the immune system

EBOV is an enveloped virus having a 19 kb single-stranded, negative-sense RNA genome which encodes 7 proteins [4]. The core of the virus is composed of the RNA genome, called nucleoprotein (NP), that covers the genomic RNA and nucleocapsid viral protein 30 (VP30) which is covered by a lipid envelope having projected surface composed of a glycoprotein (GP). The surface glycoprotein is a multimer having roles in cell attachment, fusion and cell entry, helps in immune evasion and pathogenesis of disease [5]. The diagrammatic representation of Ebola genome is shown in Fig. 1.

Zaire Ebola Virus triggers the immune response and then punctures the vascular system. When the virus enters the body, it infects various types of immune cells by initially targeting monocytes and macrophages, and cause the release of proinflammatory cytokines and chemokines [98]. In the previous studies it was shown that host Toll-like receptor 4 (TLR4) is a sensor for EBOV glycoprotein (GP) on virus-like particles (VLPs) and that resultant TLR4 signaling pathways lead to the production of proinflammatory cytokines and suppressor of cytokine signaling 1 (SOCS1) in a human monocytic cell line and in HEK293-TLR4/MD2 cells stably expressing the TLR4/MD2 complex. EBOV GP interacts with TLR4, and on VLPs it was able to stimulate expression of NF-κB in a TLR4-dependent manner. It was also found that budding of EBOV VLPs was more pronounced in TLR4-stimulated cells than in unstimulated control cells. These findings identify the host innate immune protein TLR4 as a sensor for Ebola virus GP and play an important role in the immune-pathogenesis.

The immune system forms a complex network of cells communicating to each other with the help of soluble mediators such as cytokines. Immune system has both innate and adaptive immunities to protect the body against pathogens. Nucleotides from RNA viruses are recognized by retinoic acid inducible gene I (RIG-I)-like helicases (RLHs) and Toll-like receptors (TLRs). It triggers signaling cascades that induce anti-viral mediators such as type I interferons (IFNs) and proinflammatory cytokines.

In many viral infections, the early action of cytokines produced by

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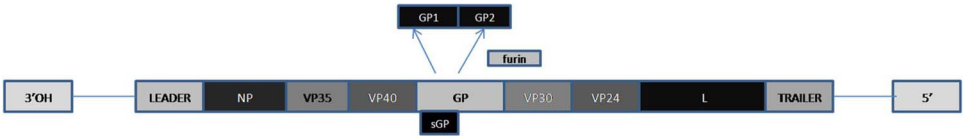

Fig. 1. Diagrammatic representation of Ebola genome (7 identified genes).

infected cells and dendritic cells is sufficient to eliminate the pathogen [6]. In some cases, innate defenses are not able to handle viral infection, and second-line of defenses is mobilized to ensure host survival. The adaptive defense consists of antibodies and lymphocytes, often called the humoral response and the cell mediated responses which are essential for destruction of viruses [6]. Innate and adaptive responses usually work together to eliminate the viruses, but in some cases both these immune responses are not able to eradicate the viruses which led to diseases. Filoviridae family of viruses is one of the examples which are not destroyed by the immune system.

Many studies shown that the induction of an innate immune response lead to infection or stimulation of macrophages/monocytes and DCs with Ebola virus or VLPs, respectively. For example, incubation of Ebola virus VP40 + GP VLPs with DCs led to the induction of interleukin-6 (IL-6), IL-8, NF-κB and ERK1/2. Ebola virus VP40 + GP VLPs, but not VP40 VLPs, induced cytokine and SOCS1 expression in a TLR4/MD2 dependent manner both in a human monocytic cell line (THP-1 cells) and in 293T cells expressing a functional TLR4/MD2 receptor. Stimulation of TLR4 by Ebola virus envelope GP results in an innate host response, induction of SOCS1 protein, and potential enhancement of virus egress. The detailed coverage of various genes involved in immune response can be found in [5,6,7,46].

There were several EVD outbreaks in the past years, but the most severe and the largest was the recent widespread outbreak in West Africa (2013–2016), having 28,616 cases and 11,310 deaths, and estimated case fatality rate of 71% [8,9]. Fig. 2 presents country and year-wise outbreaks, number of cases registered, and number of deaths..

1.2. Clinical features and complications

Signs and symptoms of EVD start between 2–21 days after contacting the virus, and the most common symptoms are fever, sore throat, muscular pain and headache [10] (Fig. 3). With high concentration of virus, vomiting, diarrhoea, and rashes are usually occurred which decrease the function of liver and kidneys. It also causes bleeding both internally and externally which lead to high risk of death and killing 90% of infected people due to low blood pressure from body fluids [11]. The severity of symptoms of EVD compared with ZikV [12], Dengue, Chikungunya and West Nile are presented in Table 1.

Ebola virus is responsible for haemorrhagic fever leading to various complications such as malaise, fever, vascular permeability, decreased plasma volume, coagulation abnormalities, and varying degrees of hemorrhage [13]. It is also notified that the incubation period of filoviruses is 2–21days after infection, with identifying symptoms such as chills, fever, myalgia and malaise, which is followed by lethargy, nausea, vomiting, abdominal pain, anorexia, diarrhea, coughing, headache, hypotension, maculopapular rash and mucosal bleeding, in the gastrointestinal and genitourinary tracts. With the pertaining of these diseases, specially as a result of hypotensive shock and multi-organ failure (including hepatic damage and renal failure), death usually occurs in 6–16 days after the onset of symptoms [14].

In a statistical study of EVD cases [15], the amount of survived and died individuals are determined by various parameters such as age, sex and symptoms as shown as charts in Fig. 4. It can be inferred from Fig. 4 that mortality rate of EVD patients are higher in males than females. Similarly, the bleeding events from faeces show a high mortality rate during admission as well as hospitalization.

Cote d'Ivoire (1994) 1/0, **Gabon** (1994) 52/13 (1996) 31/21 (1996) 60/45 (2001-02) 65/53, **Guinea** (2014-2016) 3811/2543, **Italy** (2015) 1/0, **Liberia** (2014-2016) 10675/4809, **Mali** (2014) 8/6, **Nigeria** (2014) 20/8, **Republic of the Congo** (1976) 318/280 (1977) 1/1 (1995) 315/254 (2001-2002) 59/44 (2003) 143/128 (2003) 35/29 (2005) 12/10 (2007) 264/187 (2008) 32/14 (2012) 57/29 (2014) 66/49 (2017) 8/3, **Russia** (2004) 1/1, **Senegal** (2014) 1/0, **Sierra Leone** (2014-2016) 14124/3956, **South Africa** (1996) 1/1, **Spain** (2014) 1/0, **Sudan** (1976) 284/151 (1979) 34/22 (2004) 17/7, **Uganda** (2000) 425/224 (2007) 149/37 (2011) 1/1 (2012) 31/21, **UK** (2014) 1/0, **USA** (2014) 4/1

Fig. 2. Country and year-wise EVD outbreaks statistics (1976 – 2017) showing year of outbreaks, number of cases registered (numerator) and number of deaths (denominator). Data sources: http://www.who.int/mediacentre/factsheets/fs103/en/, https://www.cdc.gov/vhf/ebola/outbreaks/history/summaries.html.