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Ebola Virus: A wide perspective on the disease

Carbajal-Navarro VA*, Rivera-Cáceres CA, Carreón-Félix M, García–Muñoz A.

Universidad Autónoma Metropolitana Unidad Xochimilco. División de Ciencias Biológicas y de la Salud, Modulo Procesos Celulares Fundamentales. Departamento Atención a la Salud. Calzada del Hueso 1100, Col. Villa Quietud, Coyoacán, México, D.F. C.P. 04960. Tel: (044) 5535100294.

*Corresponding author: acilegnalegna@gmail.com

ABSTRACT

Ebola is a disease caused by an enveloped RNA virus, which causes severe hemorrhagic fever. Its surface glycoproteins undergo to proteolytic cleavages and rearrangements to allow the fusion of the membrane, so the virus can enter the cell. We give an overview of the history, pathogenesis and the efforts being made in order to find a cure. Because currently, there is no standard treatment to fight the virus, but there are significant efforts being placed to identity the most promising candidates for the treatment and prevention of the disease.

Keywords: Infectious disease, *Filovirus* sp. VP40, epidemy

RESUMEN

El Ébola es una enfermedad causada por un virus envuelto de genoma ARN, que provoca fiebre hemorrágica grave. Sus glicoproteínas de la superficie se someten a escisiones proteolíticas y reordenamientos para permitir la fusión de la membrana y la entrada en la célula. Aquí damos una perspectiva general sobre la historia, patogenia del virus y los esfuerzos que se realizan, con el fin de encontrar una cura ya que actualmente, no existe un tratamiento estándar para combatir el virus del Ébola, pero si un esfuerzo significativo para identificar varios candidatos prometedores para el tratamiento y prevención para esta enfermedad.

Palabras clave: Enfermedad infecciosa, *Filovirus* sp., VP40, epidemia.

INTRODUCTION

Currently, humans are exposed to different types of health risks, an example of this are the types of viral infectious diseases. In 1976, a new *Filovirus* sp. was identified in the country of Zaire (now Democratic Republic of Congo) and was named Ebola. Its name comes from the belief that the cause of the disease was a mosquito that reproduces in the Ebola River, located in Congo. (Feldmann and Geisbert, 2011). The genus is named after the first known outbreak occurred in the village of Yambuku, in Zaire, near Ebola River. (Johnson *et al*. 2012).

Although medical facilities have improved over the years, mortality of this disease in West Africa, by the year of 2014, it remained over 50% (Bishop, 2014). This *Filovirus* sp. is considered as a severe and fatal infection, of which there are five types: Zaire Ebola Virus; Sudan Ebola Virus, Ebola Tai Forest Virus, Bundibugyo Ebola Reston Virus and Ebola Virus. Zaire Ebola Virus is responsible for cases in 2014 in West Africa, and for the epidemic that struck the African Continent in 1976.

Virus transmission occurs through contact with body fluids of infected patients. Incubation period lasts five to nine days after infection. The virus causes a severe hemorrhagic fever. It is believed that dendritic cells and macrophages are key places where Ebola virus attacks in humans and non-human primates (Feldmann and Geisbert 2011).

Despite treatments for Ebola virus infection are being developed, these treatments have not been fully tested to analyze their effectiveness and how safe they are to humans (Bishop, 2014).

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EPIDEMIOLOGY

After the first outbreak, registered in 1976, alarms over virus infection have occurred regularly. Over the past 35 years there have been numerous outbreaks of Ebola. The latest deaths by the virus were recorded in July 2012 in Uganda and in August to October of the same year at the Democratic Republic of Congo (DRC) (Bishop, 2014). A new registered virus began to appear in November 2012 (Bishop, 2014).

Ebola virus was first identified in two, nearly simultaneous, outbreaks in Central Africa in 1976, which presented two different species with fatality rates up to 90%: Zaire Ebola virus (EBOV) and Sudan Ebola virus (SUDV) (Webster and Granoff 1994).

The largest registered outbreak of this disease was in 2013 in Guinea, which was spread to Liberia, Sierra Leone, Nigeria, Senegal, United States, Spain, Mali and the United Kingdom (WHO, 2015).

World Health Organization's (WHO) records mentions that until November 3, 2014, 13,633 infections and 5,000 deaths worldwide were caused by this outbreak, most of which occurred in countries of West Africa (WHO, 2015). In 2015 (February 15) infected people reached 23.253 and 9,380 had died worldwide (WHO, 2015).

The Ebola virus causes in humans the Ebola virus disease (EVD), which mortality rate can reach to 90%. Several organizations, including Centers for Disease Control and Prevention, the European Commission and the Economic Community of West African States, have donated funds to help

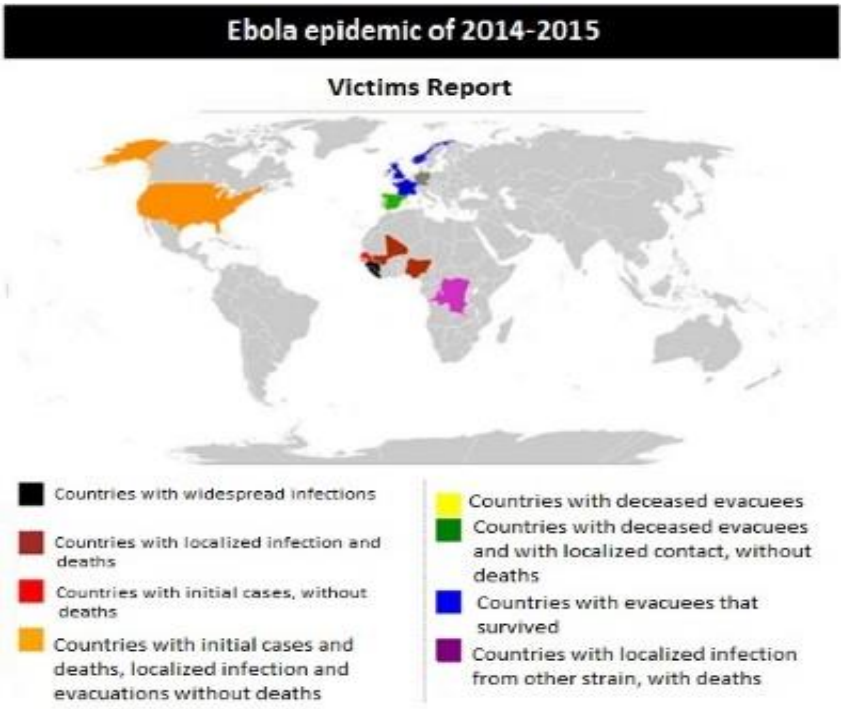

Fig. 1. World Map of the epidemic of Ebola Virus 2014 – 2015)
(Source: Modified from http: who.int/ebola-situation-reports)

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deceased patients, with a mortality rate of almost 70%. According to the Emergency Committee convened by WHO, there are the conditions for declaring a public health emergency of international concern (WHO, 2014). (Fig. 1)

PATHOGENY

Ebola is a RNA genome virus. When it is studied under an electron microscope, morphologically is approximately 19 kilobases, viral particles resemble long stretched filaments with some particles that tend to curl in a way that look like number six (Fig.2). So far, Ebola virus is composed of five species (Feldmann and Geisbert 2011).

Ebola virus is composed by particles with a molecular weight of 3-6 × 10^8 and a sedimentation coefficient of 13,000 to 14,000 Da Ineffectiveness is stable at room temperature.

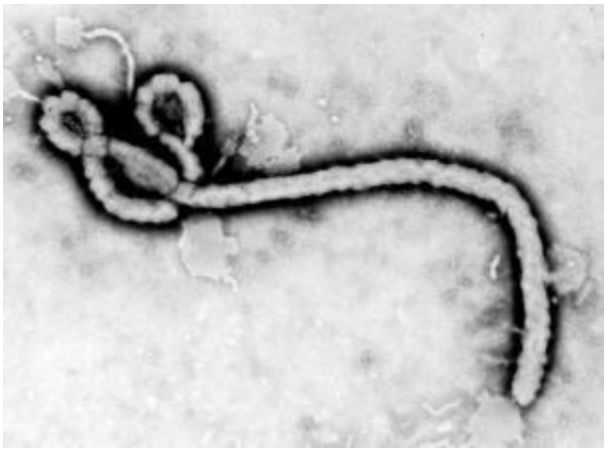

Fig. 2. Ebola virus
(Source: zoonosesdiseases.com)

Ebola virus can be inactivated by: 1) ultraviolet rays (UV), 2) Gamma irradiation, 3) Formaldehyde 1%, 4) beta propyl ketone and 5) brief exposure to phenolic disinfectants and solvents (Webster and Granoff 1994).

Filovirus sp. genome is 1.1% of the total weight of the virion, with a length of 19 Rb3. The linear arrangement of the gene from 3 'region to 5' end, includes 7 bases between them. These genes are separated by intergenic sequences either or overlays of genes (Webster and Granoff 1994).

The virus has shown a high level of genetic stability in nature. Over the course of 19 years, between Yambuku and Kikwit, the virus has shown a difference of only 1.6% in their nucleotide sequences. But between subtype Congo, Gabon and Ivory Coast it has been observed a difference up to 40% in the nucleotide sequence (Webster and Granoff 1994; Sanchez *et al*., 1996). These subtypes are distinguished by four arrays in the RNA genetic sequence, and clinical severity of the disease depends on these sequence arrangements. In each RNA structure, seven structural genes of the Ebola virus are arranged linearly, the fourth gene encodes two glycoproteins, a virion surface glycoprotein (GP) that help the virus by compromising the cell attachment and a secretory glycoprotein (PEC) (Sanchez *et al.* 1996).

The nucleocapsid made by nucleoprotein, VP24, VP30, VP35, and L protein, is crucial for viral transcription and replication (Boehmann 2005; Weik *et al*., 2002). Glycoprotein is exposed on the surface of the viral envelope and is responsible for the entry of virions through the interaction with small molecule inhibitors Niemann Pick C1 in the host cell (Coté, 2011). Matrix proteins VP40 and VP24, which are associated with the viral lipid coat, are important for virus consistency, structure and stability. (Licata *et al*. 2003; 2011 Reynard *et al.*).

VP40 is the most abundant protein expressed by the virus and has been demonstrated that it has the ability to form virus-like particles (VPLs) when it is expressed in human cells (Hoenen *et al.* 2005; Liu *et al*. 2010) (Fig. 3).

Usually, there is an incubation period of 2-21 days before EVD symptoms begin to be felt. At first, it manifest as nonspecific flu symptoms (general malaise, chills and fever) and quickly progress to nausea, diarrhea, breathing difficulty,

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hypotension, hemorrhage and finally coma (Kopeter *et al*. 2001).

Vascular injury due to endothelial cell damage, hepatocyte necrosis caused by virus replication, coagulation disorders and uncontrolled secretion of cytokines / chemokines by infected monocytes and macrophages contribute to an hemorrhagic shock and eventual death of the patient (Martinez *et al*. 2012; Paessler and Walker 2013; Sullivan *et al.* 2000).

VACCINATION

Although many cutting-edge and interdisciplinary research programs, coordinated worldwide, are focused on the Ebola virus, currently there are no available effective vaccines or medicinal products for human use that help to fight against this deadly pathogen.

However, these efforts have accelerate the identification of many new molecular targets and promising therapeutic candidates in preclinical test. The first vaccine that was made against Ebola virus consisted of whole inactivated virions by heat, formalin and gamma irradiation (Sullivan *et al*. 2000) and it was largely ineffective in rodents and nonhuman primates. Since then, overexpression of genes encoding proteins of Ebola virus have been the main focus for vaccine development. The basis of this strategy was to induce target cells to produce enough virus protein and provoke potent immune responses mediated by T cells and B cells that confers protection against Ebola virus.

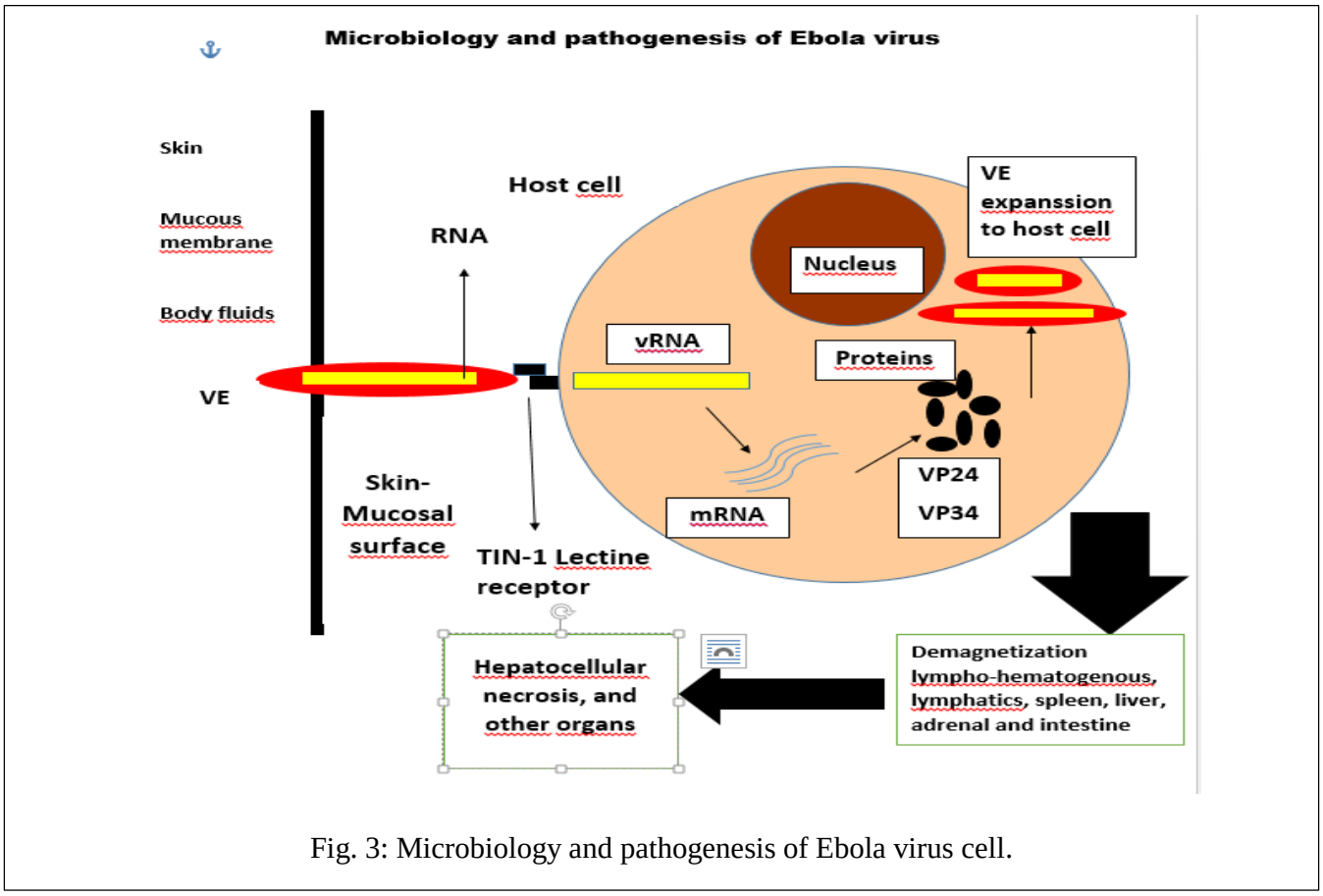

Fig. 3: Microbiology and pathogenesis of Ebola virus cell.

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The first vaccine platform that successfully protects NHP from the infection of Ebola virus was a recombinant adenovirus serotype 5 (rAd5), vector that expresses EBOV GP (Sullivan *et al.* 2003). One intramuscular (IM) dose of adenovirus after three consecutive priming doses of plasmid DNA that encodes EBOV GP and NP, SUDV GP and GP TAFV fully protecting primates against the lethal challenge. This combinatorial approach, the primary DNA / reinforcement rAd5, largely improved the circulating levels of anti-Gp antibodies and generated antigen specific CD4 + and proliferative responses of CD8 + T cells in cynomolgus monkeys.

Other improvements of the rAd5 based vaccine platform by Richardson *et al.* in 2009, are involved in optimizing expression cassette of GP so that more antigens are produced (Jin and Maria, 2013). As a result, this vaccine dose could be reduced to 100 times without compromising the antigen specific immune responses. This approach was so successful that a single intramuscular injection of the vaccine protected mice when they were injected 30 minutes after exposure to a lethal dose of EBOV, suggesting that this platform may be useful for prophylaxis and for post-exposure applications.

Despite of these promising results, the concern remains that rAd5 based vaccines may have limited clinical utility due to the fact that a significant part of the world population has significant amounts of anti-Ad5 neutralizing antibodies (NABS) in their blood.

Increasing doses of vaccine can override pre-existing immunity (PEI) and achieve a remarkable expression of the antigen (Jin and Maria 2013; Sullivan *et al*. 2003). This approach, however, is undesirable, since higher doses of adenovirus particles may precipitate a severe inflammatory and toxic response in humans (Aldhamen, 2011).

CONCLUSIONS

The arrival of the disease for the first time in densely populated urban areas has been the main concern since the outbreak. High population density favors the transmission of the virus and limit the options for disease containment.

In previous outbreaks, occurred in rural areas with low population density, an aggressive containment response was sufficient to prevent the spread of the disease, but in the last review by WHO, presented on September 23, 2014, give unflattering points: if it is unable to contain the disease, there is a risk that the disease becomes epidemic, with a spread similar to malaria or influenza (Anaya and Duran, 2014).

Therefore it is important to strengthen efforts to identify an effective vaccine against EBOV, because until now, it has not been sufficient since it has not been found an effective vaccine.

Clinicians should consider the possibility of virus infection in people who travel frequently, because, it could strike anywhere in the world, although it seems that for the moment, that the virus is limited to one part of the earth.

Providers should also have be very aware of preventive measures that must be taken. So it is important to raise awareness and increase knowledge of the disease, train health workers and strengthen the implementation of prevention measures and infection control in all levels of health care services.

That is why, each country should have a protocol of action against an emergency of this level. The probability of this disease being present in Mexico is not canceled, today it is considered as an extremely low risk of its presence in our country, even so there is the Manual of the Disease by Ebola Virus made by the Health Department (Subsecretaría de Prevención y Promoción de la Salud, Dirección General de Epidemiología) for any case that might occur in our Country.

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