Ebola Virus Disease: The Biology,Pathology, Treatments and Advancements

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Put Class No. : BIO 4963: IR/ Biology of the Ebola Virus

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Abstract

Ebola virus disease (EVD) is caused by a virulent pathogen, which is a member of the viral family *Filoviridae.* It is a filamentous viral particle containing a single stranded, negative RNA. It causes extreme fatal hemorrhagic fever in both humans and non-humans. It is mainly found in Africa. Transmission of EVD occurs primarily through contact with infected body fluids. It causes immune suppression that eventually leads to multiple organ failure due to the proliferation. The World Health Organization (WHO) classified the 2013-2016 outbreak and after the current Ebola outbreak on August 1, 2018 in Dominican Republic of Congo (DRC), the outbreak has been considered a "Public Health Emergency of International Concern". As of December 16, 2019, the DRC Ministry of Health reported 3,348 cases of Ebola from which 2,210 people died, the fatality ratio for this outbreak being as high as 66%. The objective was to investigate the pathology and mechanisms of the virus and current methods that are used in order to tackle and impede the virus with treatments. Current scientific research explores how the -ssRNA is transcribed by VP35, VP30 and RNA dependent RNA polymerase into +ssRNA, which are then translated into proteins in humans. The research also reviewed current treatments, therapies and the ones that are still under development. This research will provide information about the pathological insights for the ongoing epidemic with further information and understanding about the potential development with creative ideas to make the advancements with Ebola treatments to work. As of the current situation there is no cure for Ebola virus. The goal is to make it more understanding amongst the population worldwide.

Introduction

The viruses are smaller than a bacteria that lives inside of the living organisms. These viruses need a host to survive. They invade the living cells to proliferate and produce more of themselves. This can kill, damage or change the host cells which makes us sick. The Ebola Virus belongs to the family Filoviridae. Filoviridae comes from the Latin word meaning ‘‘filum’’, which means it is as thin and light as a thread. EVD was first found in DRC where it caused large outbreaks by causing hemorrhagic fever in infected people (Center for Disease Control [CDC], 2019). According to the 2013-2016 outbreak in west Africa, more than 28,000 confirmed cases and 11,000 deaths were confirmed (Denis, 2019). The pathogenesis of this virus transmits very fast, which makes the fatality rate high. There are six types of Ebola virus species: Zaire ebola virus; Bundibguyo ebola virus; Reston ebola virus; Sudan ebola virus; Bombali ebola virus and Tai Forest ebola virus (CDC, 2019). The primary reservoir is said to be fruit bats but, due to many factors, the reservoirs might be different (Calisher et al., 2006). The pathogenesis of the ebola virus is a very complex yet quick process. It can go from acute to serious phase due to septic shock if not treated properly. Not all of the ebola virus species infect humans. The most dangerous ones are the Zaire ebola virus and Sudan ebola virus. Both of them have vaccines available, but they are limited in number and were just discovered in 2019. The fatality rate on an average is 42% (CDC, 2019). Early supportive care with rehydration and symptomatic treatment improves the survival of the affected person (WHO, 2018)

Signs and Symptoms of the Ebola Virus

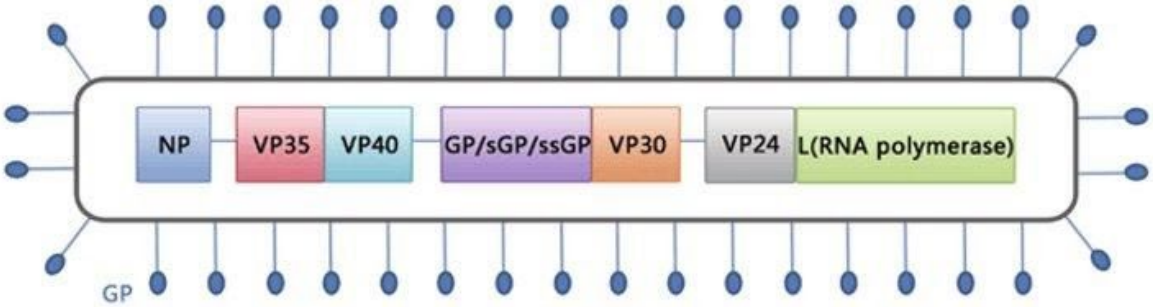
The incubation period of EVD is 2-21 days, which means that the symptoms may appear anywhere from day 2 to day 21 after the person has been in contact with the virus. From day 1-7 after the viral exposure through nose, mouth, eyes, ears or breaks into the skin, the virus invades

the normal cells throughout the body and replicates itself. The initial symptoms in between days 8-12 are fever, chills, headache, joint and muscle ache, weakness, which makes the disease contagious. Thirty percent of the infected population may survive this phase of the disease if receiving proper care (CDC, 2014). As the disease progresses, symptoms start to worsen. After two weeks of exposure to the virus, patients start to develop abdominal pain, diarrhea, vomiting, red eyes, difficulty in breathing, rash and bleeding. In the later stages, which are in between 16-21 days, EVD causes septic shock, coma, organ failure, and eventually leads to death of the person (CDC, 2019).

Causative Agent and the Structure of the Ebola Virus

Filoviridae being the genetic family of the Ebola virus, causes the hemorrhagic fever. It has the genetic material of -ssRNA. The virus is surrounded by the infected cells and the glycoproteins studded on the outside it. The Ebola virus has seven viral genes which are shown in the figure.

Figure 1



Note. Genes of the Ebola Virus (Bio-Connect, 2007)

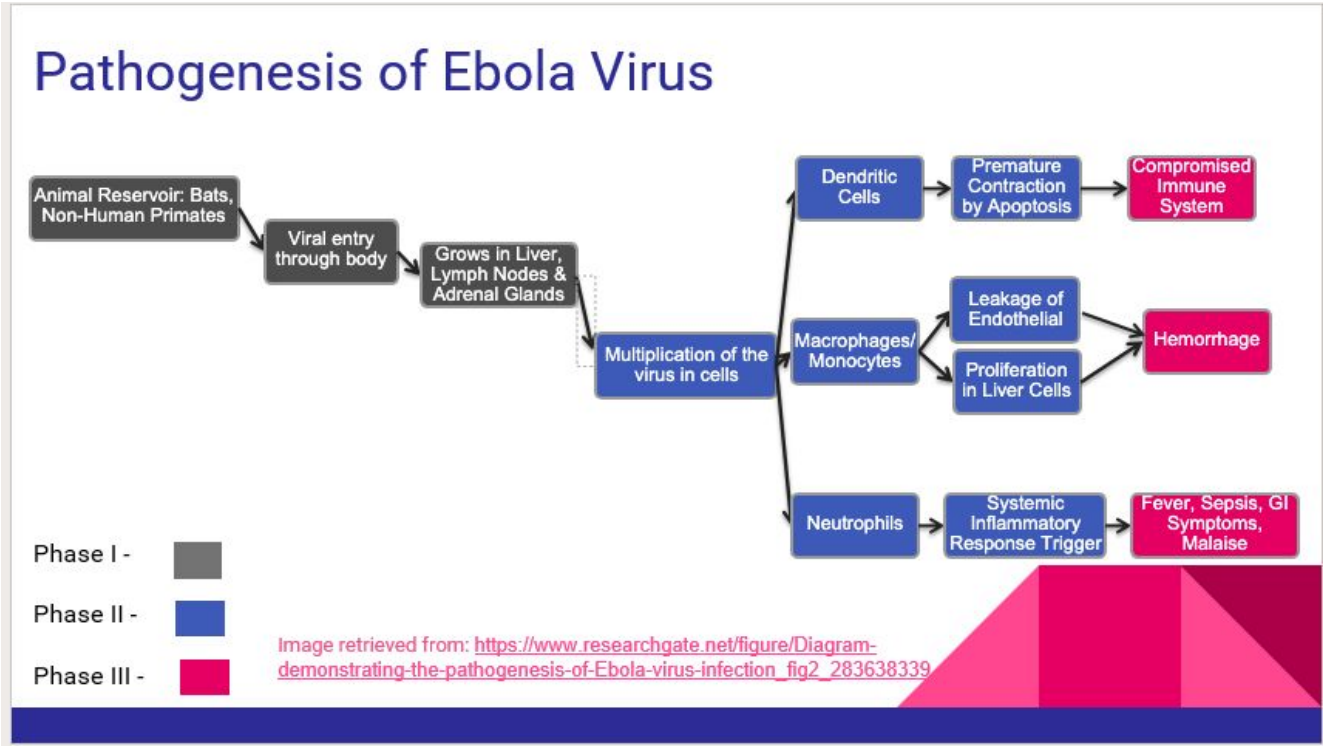
The function of the nucleoprotein is that it plays a central role in viral replication. The glycoproteins are divided into glycoprotein 1 (GP1) and glycoprotein 2 (GP2) (Lee and others, 2008) . GP1 is responsible for attachment and GP 2 is responsible for bringing fusion of the envelope of the virus with the host endosomal membranes. It is the only protein on the surface of

the virus and looks like a pointed spike. With the help of the spike-like structure, GP2 sticks to the target cells, subsequently brings about membrane fusion and releases the virus into the host cell (Lee and others, 2009). There are four types of viral proteins (VP) in the genes of the ebola virus. VP24 and VP35 inhibit the interferon. Interferons are the natural proteins that are produced by the immune system of many animals as a defense mechanism to afford protection from the foreign agent that enters in the body. The immune cells such as the T-helper cells and B-cells produce these interferons and are important components of antiviral response (Goodsell, 2014). They stimulate both macrophages and NK cells and make it easy for evasion of host immune response (Snelgrove and others, 2004). VP30 is responsible for viral genome transcription, which is making copies of the m-RNA and replicating the -ssRNA. VP40 drives the viral assembly and budding, coordinating the viral cycle regulation of mature virions. L is the RNA dependent RNA polymerase, which is the catalytic subunit. It works with VP35 and is the key for replication and transcription (Goodsell, 2014). The journey of the virus from the reservoir to the host is extremely complex (Schmidt et al., 2017).

Pathogenesis of the Ebola Virus

The symptoms of Ebola virus particles show in secreted GP with different biological properties of each (Snelgrove et al., 2004). The animals that have transmitted EVD to non-human primates and humans are still unknown, but according to the CDC, the vectors can be fruit bats or any other mammal (CDC, 2019). Figure 2 shows the pathogenesis of how the virus enters the human body through transmission of the virus by animal reservoirs to the damage of the immune system, leading to death.

Figure 2.



Note. Chart showing Pathogenesis of the Ebola Virus (Gebretadik et al., 2015).

There are three phases. In the first phase, the animal reservoirs such as the bat or other non-human primates transmit the ebola virus through busch meat, feces of the infected animals, a dead animal that was a carrier of the EVD, or their migration to the host. The virus enters inside the host via mucous membranes such as broken skin, close contact with infected patients, direct parental dissemination or corpses (CDC, 2019). Upon entering the body, the virus attacks specific cell types in the body such as the liver cells (hepatocytes), immune cells (T-helper cells, B-cells), lymph nodes and endothelial cells that line the inside of the blood vessels (RJ et al., 2015). It attacks the liver cells because the liver purifies the blood. If the virus attacks the liver, it would be difficult to purify the blood and pass the detoxified blood to the rest of the body. The endothelial cells are attacked, which causes internal bleeding of the blood vessels (RJ et al.,

2015) . This may lead to the blood vessels to burst. Attacking the blood means reaching the immune system.

In the second phase, the virus starts to multiply in those organs, damaging the healthy cells by macrophages and converting them into itself, which is a virus. The macrophages destroy the monocytes, which are the white blood cells that have the ability to fight off infections against foreign particles in the body. All the powers of the dendritic cells and the neutrophils get taken up by proliferation of the virus as the virus disguises itself as a good antigen to these antigen presenting cells and smoothly moves up to the next step (Doucleff, 2014). Destruction of dendritic cells leads to premature cell death, which is called apoptosis. The neutrophils lose their ability to fight off the viral infection, which triggers the systemic inflammatory response (Doucleff, 2014). The macrophages and monocytes take place by leakage of the blood vessels and lymphatic vessels of the endothelial cells. The virus also proliferates in the liver cells causing liver failure.

In the third stage, the immune system is compromised due to premature cell apoptosis. Due to leakage of endothelial cells and the virus being proliferated in the liver cells, the blood vessels leak by causing the inner lining of the organs to bleed, which leads to hemorrhage. The systemic inflammatory response triggers the immune system making it highly active and unable to fight against infections, which causes gastrointestinal symptoms, septic shock, malaise, and high fever. According to Johnson (2019),“Over time, infection of cells throughout the body can cause organ failure, while fever, internal bleeding, diarrhea and vomiting can cause severe loss of electrolytes, blood plasma, and fluid. Ultimately, organ failure and shock caused by the internal bleeding lead to death”.

Pathogenesis Continuation

Attack on the Innate Immune System

The mechanisms for distinguishing the virulence between the different ebola species are still not well defined, but their viral entry methods and replication processes have shown to be very similar to one another. The primary focus of this research was on the Zaire Ebov (Ebola Virus) strand.

Ebola's Host Target Cells

Zaire Ebola Virus targets cells of its host's innate immune system when it enters a new host's bloodstream or tissue. It also infects endothelial cells of the liver called hepatocytes as the spread of the viral infection progresses. "The leukocytes that the virus prefers to infect upon entering the blood are monocytes and dendritic cells that are in an immature state." (Rhein & Maury, 2015). "As the virus spreads it infects macrophages found in tissue that have differentiated from monocytes" (Italiani & Boraschi, 2014). These cells are considered non specific in nature and engage with particles they deem are foreign and potentially a threat. Monocytes/macrophages and dendritic cells are phagocytic and professional antigen presenting cells. This means they uptake the contents of a pathogen by engulfing them and present them to lymphocytes that aid in stopping the spread of the infection. All nucleated cells express major histocompatibility complex 1, but these professional antigen presenting cells also produce major histocompatibility complex 2. "In other types of viral infections the MHC-1 complex presents the pathogen to cytotoxic t-cells and MHC-2 presents part of the virus to t-helper cells" (Wieczorek et al., 2017). However, Ebov inhibits the expression of these complexes, which will be discussed later on. Ebov contains cohesive properties on its viral envelope that are involved

in binding to particular receptors of these cells. The virus is also able to utilize certain properties within these leukocytes that enable its replication process, and also disable important functions that relate to fighting infection.

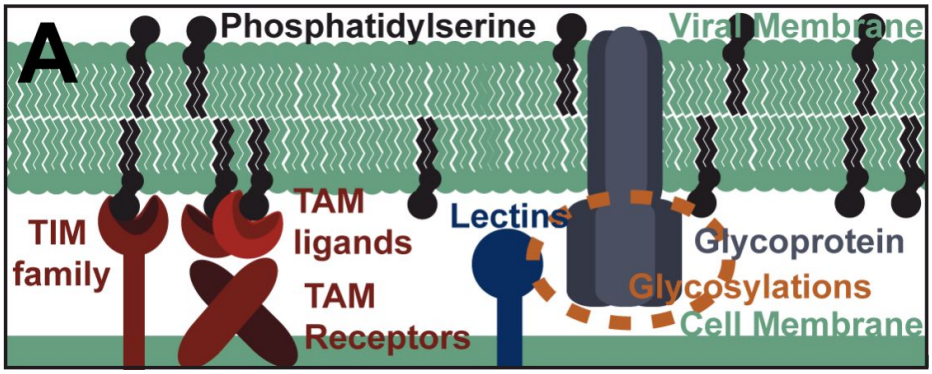
Attachment to Target Cells

The Virus must adhere to non specific receptors of its targeted cells before viral entry can take place. There are two different types of receptors responsible for inducing the endocytic reaction of viral internalization. These are C-type Lectins and Phosphatidylserine receptors. (Takada et al., 2004). Glycoproteins located along the viral envelope are glycosylated with glycans, containing polysaccharide chains that bind to C-type Lectin receptors on target cells. (Moller-Tank & Maury, 2015). C-type Lectins that are found on the surface of dendritic cells and monocytes/macrophages are known as DC-SIGN (dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin) and hMGL (human macrophage galactose- and N-acetylgalactosamine-specific C-type lectin), respectively. (Moller-Tank & Maury, 2015). These receptors are also found on endothelial cells in blood vessels within the liver and are called L-SIGN (liver/lymph node-specific ICAM-3 grabbing non-integrin). (Moller-Tank & Maury, 2015).

According to (Moller-Tank & Maury, 2015), phosphatidylserine is a phospholipid that is present in abundance along the viral envelope of Ebov. These phospholipids bind to Ptdser receptors located on the target phagocytes. One of the phosphatidylserine receptors responsible for viral entry is the TAM receptor ligand complex composed of receptor tyrosine kinases TYRO3, AXL, and MERTK along with their ligands PROS1 and GAS6. Another is the T-cell immunoglobulin and mucin domain, including members of the TIM family TIM-1 and TIM-4

(Moller-Tank & Maury, 2015). Mechanisms for how binding to C-type lectins and Ptdser receptors initiate virion internalization is still misunderstood, but researchers continue to look for answers as to how this process works.

Figure 3.



Note. Glycans on the glycoprotein bind to c-type lectins and Phosphatidylserine on viral membrane binding to Phosphatidylserine receptors. TIM receptors and TAM receptor ligand complexes. (Moller-Tank & Maury, 2015)

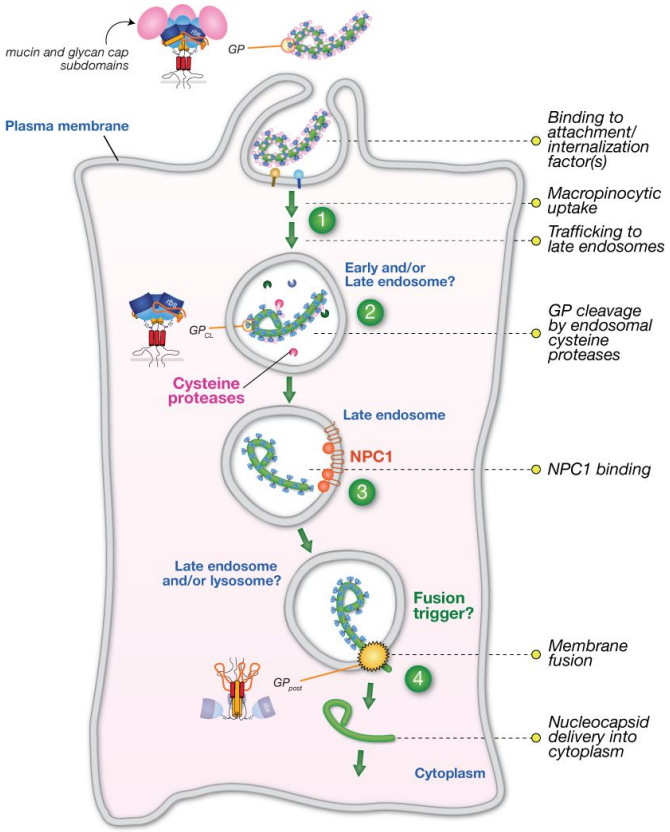
Viral Internalization

Ebov enters host cells by the process of macropinocytosis, after the viral envelope reacts with receptors on the membrane of targeted cells. “Macropinocytosis refers to a process by which a cell can “gulp” extracellular fluid by ruffling its plasma membrane and forming a vesicle around a relatively large volume of fluid” (Mak & Saunders, 2006). The virus becomes encapsulated by this vesicle which is known as a macropinosome as the membrane ruffles inward. During this process a cholesterol transporter located on the membranes of the target leukocytes called NPC1 (Niemann Pick Disease type C1) also becomes enclosed within the macropinosome. It is embedded within the vesicles involved in endocytosis and remains inactive until the end of the endocytic pathway. “The various membranous compartments of the

endocytic system constantly fuse with and fission from each other, mixing portions of their contents in a process that progressively lowers the internal pH of successive endocytic compartments" (Mak & Saunders, 2006). An endosome is the next vesicle formed in the endocytic process. The endsome's environment is mildly acidic, which causes the degradation of the glycoprotein on the virus's envelope. Cysteine proteases known as cathepsins (CatB and CatL) cleave the glycan cap and mucin domain of the glycoprotein. This enzymatic reaction exposes the binding site on the GP for reactivity with NPC1.

Next, the endosome containing the virus with degraded glycoproteins fuses and forms a late endosomal compartment. Within this vesicle of the endocytic pathway the exposed binding site of the GP binds to the now active NPC1. As the virus moves into the final vesicle of endocytosis, a late endosome or lysosome, fusion of the membrane with the cytoplasm is induced by the reaction of the GP with NPC1. This causes Ebov's nucleocapsid to be expelled, promoting the viral replication process.

Figure 4.



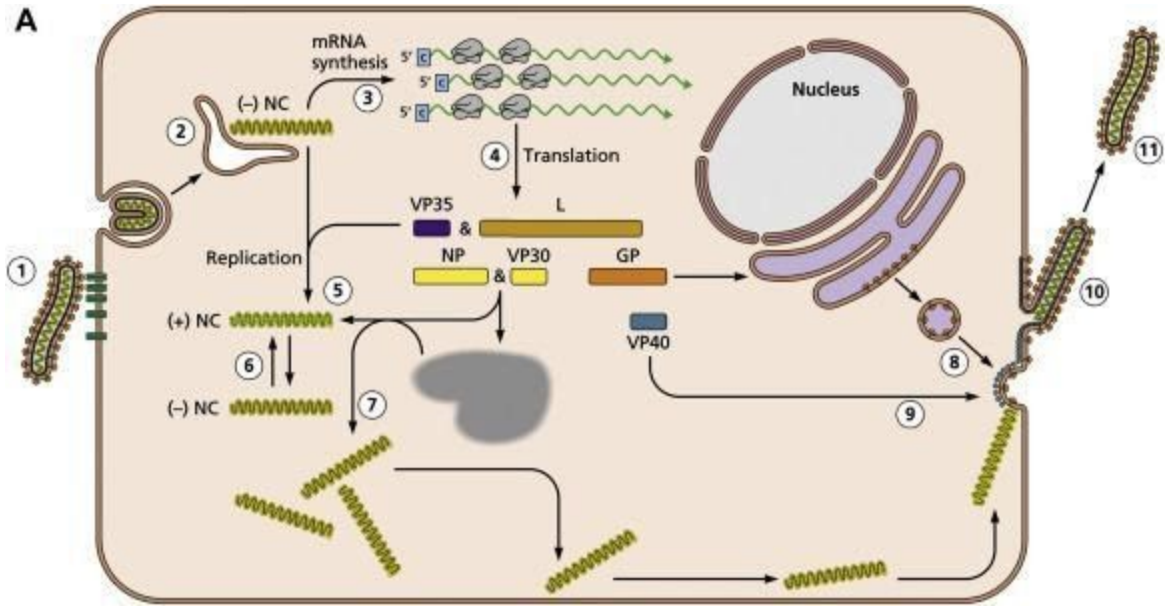
Note. Viral Entry and Ebov GP binding to NPC1. (Miller & Chandran, 2012)

Viral Replication and Assembly

Ebov's -ssRNA genome, which is encapsulated by the nucleocapsid, can not directly initiate the translation of viral proteins. Instead, it must be used as a template strand that is read from 3' to 5'. (Hammou et al., 2016). The template strand is used in the production of new viral proteins as well as to synthesize new progeny -ssRNA genomes for new virions. The -ssRNA is transcribed to seven different complementary monocistronic positive strand mRNAs that read 5'to 3'. These mRNAs are no longer encapsulated and translate into proteins NP, L, GP/sGP, VP24, VP30, VP35, VP40. The newly produced L and VP35 initiate the transcription of the -ssRNA (3' to 5') to full length complementary +ssRNAs, however the mechanisms for inducing transcription for promoting the replication viral RNA is not fully understood (Burrell et al.,

2017). These complementary strands are encapsulated and form ribonucleoprotein (RNP) complexes with VP30, VP35, L (polymerase), and NP (Mühlberger, 2007) . The full length +ssRNAs are used as templates in the replication process and are transcribed into new full length -ssRNAs for the formation of new Ebov virions. VP40 mediates microtubule activity by inducing the relocation of the RNP complexes towards the cell surface. The replicated Ebov particles fuse with the infected cell's plasma membrane and are now able to infect a new host cell.

Figure 5.



Note. Translation of viral proteins and Ebov replication. (Burrell, Howard, & Murphy, 2017) .

Evading the Immune Response

Ebola behaves as a very sneaky pathogen. It can avoid detection from other immune cells and inhibit functions that are significant for viral defense of the cells it infects. One of the ways it evades the immune response to viral infection begins during the translation of viral proteins in infected cells. The GP protein is responsible for producing the glycoproteins that reside along the

viral membrane of ebola, but according to (Vega et al., 2015) it also forms small soluble glycoproteins that bud from its host cell and migrate around the extracellular environment. These sGPs neutralize antibodies that may be specific for GP. This ruse by the virus to employ a decoy of secreted sGP allows newly budded viral particles to go undetected by antibodies, and are able to adhere to new host cells.

Double stranded RNA is created as a by-product during the transcription of -ssRNAs to monocistronic positive strand mRNAs and synthesis of the full length +ssRNAs used for viral replication. In monocytes/macrophages and dendritic cells that are functioning normally, dsRNA is recognized by what are known as pattern recognition receptors, which alerts these proteins that a pathogen is present. These pattern recognition receptors induce a signaling cascade toward the production of interferons. Interferons are proteins that act as the body's alarm bells that a virus has infected a new host, and are classified as a type of cytokine. According to (Kühl & Pöhlmann, 2012), two of these PRRs that recognize the dsRNA in the cytoplasm are retinoic acid inducible gene-1 (RIG-1) and melanoma differentiation associated protein-5 (MDA5). These proteins activate the mitochondrial antiviral signaling protein (MAVS). MAVS induces the activation of protein kinases known as tank binding kinase 1 and IKKA. Another pattern recognition receptor that recognizes the viral RNA, exists in the extracytoplasmic space, and is known as toll like receptor 3 (TLR3). TLR3 also stimulates protein kinase activity when it senses the presence of dsRNA. These enzymes are of extreme importance, because they activate and phosphorylate transcription factors called interferon regulatory factor 3 (IFR3) and interferon regulatory factor 7 (IFR7). Tank binding kinase 1 and IKKR phosphorylate these transcription factors, which allows them to be transported to the nucleus. Once these proteins reach the

nucleus, they regulate the rate of Type 1 Interferon (IFN-α and IFN-β) production. IFN-α and IFN-β then bind to other cells that express the Type 1 IFN receptors IFNAR1 and IFNAR2. Binding to these receptors stimulates the migration of transcription factors towards the nucleus. These proteins are known as signal transducers and activators of transcription 1 and 2, or (STAT1 and STAT2). A transporter protein called importin α binds to STAT1 and STAT2 and shuttles the transcription factors to the nucleus. After they arrive there, they regulate the production of more cytokines and also produce genes necessary for translating the MHC 1 complex. (Kühl & Pöhlmann, 2012)

Unfortunately, in cells infected by Ebov these pathways are inhibited by viral proteins. VP35 directly binds to the backbone of dsRNA in the cytoplasm, after it is formed in the transcription process. "It caps the ends of the dsRNA and prevents detection from pattern recognition receptors RIG-1 and MDA5" (Bale et al., 2013). VP35 also directly interferes with the mechanisms involved with protein kinase phosphorylation. The viral protein inhibits the addition of phosphates to transcription factors IFN 3 and IFN 7, and prevents them from translocating to the nucleus for IFN-α and IFN-β production. (Kühl & Pöhlmann, 2012). "VP24 inhibits the karyopherin importin α from reacting with STAT1 and STAT2" (Reid et al., 2006). In fact, the viral protein binds to the transcription factors, and blocks the transporter protein from interacting with them. (Reid et al., 2006). Studies over the years have also shown that VP35 is not only responsible for inhibiting MHC-1 activity but also MHC-2 as well. VP35 inhibits the expression of costimulatory molecules CD80 and CD86 of Dendritic cells. These costimulatory molecules are vital for inducing MHC 2 activity (Jin et al., 2009).

These inhibited pathways caused by viral proteins prevent the immune system from being able to fight the pathogen in the early stages of infection . Infected cells eventually leave the blood and reach the lymphatic system where they pass through lymph nodes. However, they can not interact with cells of the adaptive immune system properly, because their antigen presenting abilities are disabled. This prohibits CD8+ cells ability to directly destroy the infected cells and also prevents CD4+ cells from recruiting more cells of the adaptive immune system for viral defense. Infected cells that contain the virus will then leave the lymph nodes unaffected and travel to other parts of the body including the liver and lungs.

Cytokine Storm

Dendritic cells never fully mature in the lymphatic system and they lose their ability to release interferons and other cytokines. However, even though monocytes and macrophages can also no longer express interferons, they are able to produce other types of cytokines, while circulating throughout the body. According to (Bixler & Goff , 2015), Some of these cytokines have proinflammatory properties and can recruit other cells nearby to help battle the spread of the virus. Chemokines, interleukins and tumor necrosis factor are different types of cytokines expressed by Monocytes and Macrophages. Many chemokines and interleukins have proinflammatory abilities and can cause inflammation. Chemokines can also attract other nearby leukocytes to the site of infection. (Bixler & Goff , 2015). Tumor necrosis factor is a driving force in the coagulation system and can also cause inflammation.

According to (de Louw, 2017), these cytokines are involved in a feed forward loop that creates an onslaught attack on the body. Leukocytes become infected with Ebov, their ability to alert other cells of the innate immune system becomes disabled, and communication with the

adaptive immune system is also inhibited. The virus spreads rapidly and is virtually unaffected by the host's immune system. Monocytes in the blood and Macrophages in tissue release cytokines. Infected leukocytes continue to release cytokines for prolonged periods, because they are immune to the body defense's. They recruit other leukocytes that can be infected, which then also migrate through the body and release cytokines. The over expression of these proteins from infected cells and cells that are recruited by cytokines that will inevitably become infected induce what is known as a cytokine storm. This promotes inflammation, which can lead to the endothelial cells that line blood vessels to become more permeable. This leads to bleeding and hemorrhaging. (de Louw, 2017). Constant release of tumor necrosis factor can stimulate the activation of tissue factor, which produces clotting. Excessive coagulation and build up of platelets within the blood vessels can cause them to burst which leads to additional bleeding. (Geisbert et al., 2003)

When the virus reaches the liver it can infect hepatocytes and kupffer cells. Kupffer cells are also macrophages that can join in the feed forward loop of participating in a cytokine storm within that organ. The constant inflammatory assault of tumor necrosis factor along with other cytokines in the liver leads to fibrosis. "The damaged tissue exhibits cell death and hemorrhaging from the influx of immune mediators" (Shuh et al., 2013). Necrosis of the liver will eventually lead to organ failure and cause the organ to lose its ability to detoxify the blood. (Yang & Seki, 2015).

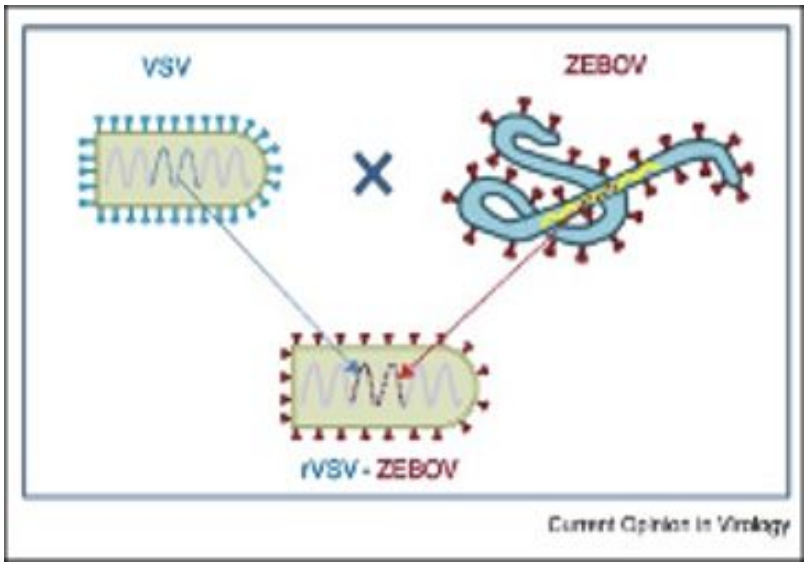
Treatment of different species of the Ebola Virus

Before considering the different treatments of the Ebola virus, one must consider that there are six different species of the virus according to the CDC. The six species are *Zaire Ebola*

virus, *Sudan Ebola virus*, *Bundibugyo Ebola,Reston Ebola virus*, *Taï Forest Ebola virus,* and *Bombali Ebola virus*. Some of those species may be considered more dangerous and widely spread than others.

Starting with *Zaire Ebola virus*, on Dec 19, 2019, the FDA approved the first vaccination for the *Zaire Ebola virus*. Merck has introduced a pre-exposure vaccination during the 2014 and 2016 Ebola outbreak in individuals 18 years of age and older who had not been exposed to the virus yet. The patients who were given the vaccine during testing were people who were in close contact within the same household or social network with a patient with *Zaire Ebola virus*. Ervebo is a live vaccine to fight the *Zaire Ebola virus*. (CDC, 2019) The vaccine contains a weakened version of the virus in order to inject it to the patient without any dramatic symptoms. The engineered virus is then attacked by B-cells and T-cells until the virus is completely destroyed. The goal for the pre-exposure to the engineered virus is to create memory B-cells and T-cells, which then helps the body to quickly attack and understand how to destroy that specific virus. In the case of the *Zaire Ebola virus*, a VSV which is a Vesicular Stomatitis Virus, contains a protein from the *Zaire Ebola virus,*is injected into the patient for a pre-exposure to the virus.

Figure 6.



Note. The rVSV-ZEBOV (Ervebo) Vaccine is a recombinant virus in which the VSV glycoprotein is replaced with the Zaire Strain glycoprotein to produce rVSV-ZEBOV. (Medaglini & Siegrist 2017)

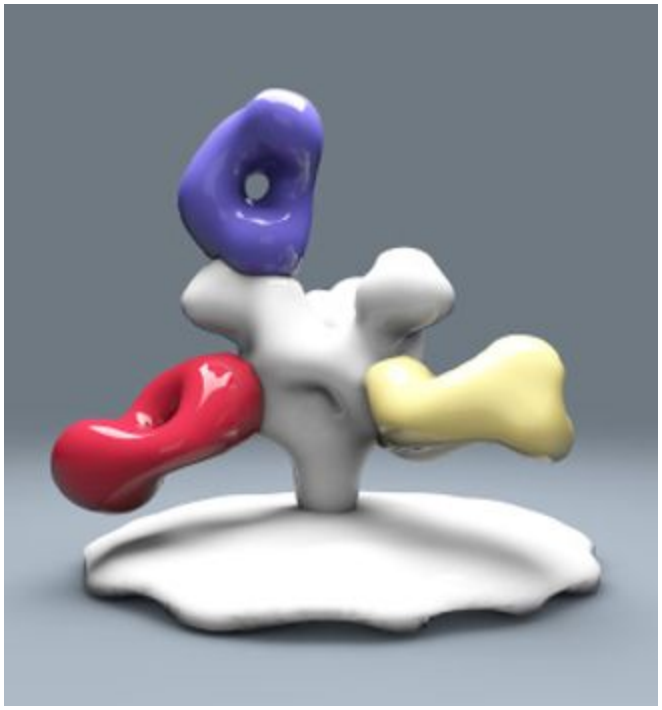
Ervebo vaccine is administered within the intramuscular route. There are two sites that the vaccine can be administered, which are the deltoid area of the non-dominant arm or in other cases the anterior or lateral area of the thigh. The vaccine should not be injected intravascularly. It is given in a single 1 mL colorless to a brownish-yellow dose containing "Ebola Zaire Vaccine (rVSVΔG-ZEBOV-GP1,2 live, attenuated) ≥72 million pfu3" (Merch Sharp & Dohme B.V., 2019)

Immunocompromised patients will not respond to the Ervebo vaccine as well as immunocompetence individuals because the immune system plays a big role when treating this virus through this vaccine. Pregnant and breast-feeding women are to be supervised after the

vaccination. The vaccinated virus RNA was detected anywhere from Day 1 to Day 299 by PCR in the blood of most subjects, which includes breast milk, urine, saliva, semen, and sweat. Vaccination should also be postponed to subjects who are experiencing any febrile illness. Such illness will compromise the immune system leading it not to fight the vaccine.

Secondly is the *Sudan ebolavirus*; FDA granted the vaccine to a fast track status in September of 2015. The fast track can be made any time during the development of the drug or vaccine and allows for certain benefits including the opportunity for frequent interaction with the FDA which can allow the vaccine to reach the market and the people at a faster rate (Mapp Biopharmaceutical, 2015). Mapp Biopharmaceutical has created a vaccine named ZMapp, which is an antibody vaccine. A monoclonal antibody vaccine can specifically bind to the substance and be used to detect and destroy the virus in various ways. These antibodies are attached to the *Sudan Ebola virus* glycoprotein and suggest how they inhibit the infection. The ZMapp contains three monoclonal antibodies c13C6, c2G4, and c4G7. In order to determine how each of those antibodies work, they were color coated c13C6 with purple, c2G4 with Red, and c4G7 with yellow. Each antibody is individually mixed with the *Sudan Ebola virus* glycoprotein and were monitored by an electron microscopy and image reconstruction (Erin E H, and others, 2016). This procedure gives the opportunity to see where each of the antibodies were binding to the *Sudan Ebola virus* glycoprotein.

Figure 7.



Note. The three monoclonal antibodies (c13C6, c2G4, and c4G7) attached to the Ebola virus glycoprotein. (Acaniello, 2014)

The monoclonal antibodies attach at different parts of the Ebola virus glycoprotein. After close monitoring it was revealed that c2G4, and c4G7 that were color coated in red and yellow bind to the base of the *Sudan ebolavirus* glycoprotein. Their task is to neutralize the virus and inhibit it from creating further damage, it is unknown on how this is possible. On the other hand c13C6 which was color coated in purple binds to the top of the viral glycoprotein but does not neutralize it nevertheless it can still protect animals from the Ebola virus infection. The c13C6 antibody works in concert with the complement system, collection of serum proteins, in order to block the Ebola Virus infection (Tran et al., 2016).

To determine the validity and activation of the vaccine a trial was constructed. The trial included 72 participants of the average age of 24 years old. The participants were 53 patients from Sierra Leone, 12 were from Guinea, 5 from Liberia, and 1 from the United States which was a health care worker who was evacuated from Leone. The Investigation had to stop in January 2016 because it was not able to recruit patients to the 200 patient mark due to the decline in the new Ebola virus cases because the outbreak was diminished. Everyone in the group was given the ZMapp vaccination but half of the group was randomly selected to receive 3 intravenous ZMapp three days apart. After twenty eight days of monitoring, thirteen deaths out of the thirty five patients who received the optimal treatment died which equates to a 37% death rate for those who received the optimal treatment. Eight out of the thirty six that were given the three doses died which equates to a 22% death rate for those who received the three doses treatment (NIH, 2016). Leaving off with one patient who left treatment early and was not included in the statistics.

Not all species of the Ebola Virus are severely harmful. *Reston Ebola virus* does infect humans, but there is no illness to the patients or death that has been reported to this date (Cantoni et al., 2016). *Taï Forest Ebola virus* only infected one person by contact from a chimpanzee and through medical attention the patient survived (Vincent, 2017). *Bombali Ebola virus* has no current evidence that it infects people (Forbes, 2019).

Last but not least, is the *Bundibugyo ebolavirus*. While it is considered as deadly as the *Zaire ebolavirus* and *Sudan ebolavirus*, it has not received enough attention. There is no pre-treatment for this virus, but as any Ebola virus, it is treated once it occurs into the patient's body. Health care providers administer fluids and electrolytes intravenously, offer oxygen therapy to maintain oxygen status, using medication to treat other infections if they occur such as any other species of the Ebola virus. The question here is even though *Bundibugyo Ebola virus* is a very serious causing agent of many deaths, why has it not gotten as much attention as the other species of the Ebola virus?

Conclusion

The Ebola Virus has been a big threat to humans because of its highly dangerous and aggressive nature since the first case in 1976 in Africa (CDC, 2018).In summary, after the literature was reviewed, it was discovered by us that the sneaky virus has multiple ways to invade a human body. The spread of the ebola virus was able to be followed with the help of the information that we used. It also showed that cytokine storms are very important to notice because it can provoke other cells in the body to form a military and invade the human immune system. The epidemic that occurred in the years 2014-2016 in West Africa caused a huge delay in treatments (WHO, 2018). This might be because of less medical equipment, unhygienic environments and less funding in the local surroundings. However, during the EVD outbreaks in DRC in 2018, WHO released rapid responses because the delays in the West Africa epidemic caused an increase in awareness. Due to WHO responding quickly, improvements were seen on the spread of the infection during burying or cremating an EVD infected body, solving cases with better understanding and respecting the needs of the patients (Malvy et al., 2019). The community, medical professionals and many others need to be educated about sanitary methods like frequent handwashing, eating healthy, avoiding meats that are not sold at a clean place, exercise regularly and much more. Standard precautions for all the patients in a healthcare setting should be practised with new and clean injections. More isolation facilities and laboratories need to be established so that more vaccines can be found (WHO, 2015). A deadly and sneaky virus like Ebola should have all possible treatments for the affected people. We have to work together as a community and educate others in need. With this we can help as many people as we can. Advancements that have been made in recent years are being used as an

effective Ebola virus vaccine and also for anti-Ebola virus drugs, but there remain challenges like the lack of knowledge about the vaccine, the surroundings of the infected person, and few diagnostic tests that are specific for EVD (Johnson, 2019). The European Commission has approved the vaccines from Merck and Johnson and Johnson which was a big achievement after many laboratories and medical testing centers were burned in the fear of the spread of ebola virus. The cases in DRC has been observed to be decreased. Even though it is decreased, this sneaky virus can spread its outbreak anytime if proper cleanliness measures are not taken by the community. EVD has been a threat to humans since 1976, so with the advancements in treatments, awareness to people and efforts to gain more knowledge about potential drugs and involving more laboratories, the world can get through this menace with careful actions (Rajak et al., 2015).

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