Ebola virus: structure, pathogenesis and treatment

Named after the river valley in Zaire, now known as the Democratic Republic of Congo, where it was first recognized, Ebola began its publicity in the spotlight of an epidemic. It is one of two members of RNA viruses called Filoviridae. Filoviridae were first discovered 9 years before the initial outbreak of Ebola, in 1967, in workers who were exposed to blood from African green monkeys imported from Uganda that had the Marburg virus [6]. The family Filoviridae constitutes, together with the families Paramyxoviridae and Rhabdoviridae, the order Mononegavirales. Within the family there is a single genus, filovirus, and a separation into two sero-/genotypes, Marburg and Ebola [6]. Filoviruses are classified as “ Biological Level 4″agents [5] based on their high mortality rate, person-to-person transmission, potential for aerosol infectivity, and absence of vaccines and chemotherapy [6].

There are five identified subtypes of the Ebola virus. Four of the five have caused disease in humans: Ebola-Zaire, Ebola-Sudan, Ebola-Ivory Coast and Ebola-Bundibugyo. The fifth, Ebola-Reston, has caused disease only in primates [2]. In 1976, the first subtype of Ebola was discovered, Ebola-Zaire. A local was admitted to a hospital in Zaire with a fever. The nurse assumed he had malaria and gave him a quinine shot. When the patient went home he died and a traditional African funeral was organized. In preparation, the woman from his family removed the blood from his body with their bare hands; most of the women died shortly after [4]. Meanwhile, the nurses at the hospital reused the needle for the quinine injection without sterilizing it, spreading the virus to everyone who came in contact with it. A doctor was called in to show how to sterilize their needles, purify their water, and give

tips on how to bury the bodies that were now piling up. Quarantine followed after an autopsy was performed on a corpse and was held until every person who had contracted the virus had died [4]. Ebola-Zaire spread through the hospitals through reused needles and dead bodies, claiming an average 82. 6% fatality rate from 1976 to 2003 [5].

The Zaire strain claims the most outbreaks and highest fatality rate of any strain of Ebola virus, although, it is not the only strain to take lives. As the Ebola-Zaire strain was being discovered the Ebola-Sudan strain also emerged. The first case appeared in a worker exposed at a cotton factory. The second case caused the death of a nightclub owner when he was introduced to an unsterilized needle [4]. Scientists were able to isolate these events, but a reemergence in the same location cased a smaller epidemic to occur just 3 years later in 1979. It rested at an overall 53. 76% fatality rate spanning from 1976 to 2003 [5]. Ebola-Reston caused disease in a group of Macaques; some of the people exposed to the virus developed antibodies and none became ill [1]. The Ebola-Ivory Coast strain has only one known case of infection, that of a scientist dissecting a wild chimpanzee in 1994. The scientist fully recovered from the strain. Given the low infection rate, Ebola virus natural habitats to this day remain unknown [2].

Structure

Seen through an electron micrograph, the Ebola virus appears as long rods, 800-1000 nanometers in length. The filamentous structure is often found in a distinguishing “ U”-shape arrangement, but is pleomorphic; meaning it can take on many shapes. Other shapes include branched, circular, or a “ 6” shape. The outer envelope of the virion is covered in small spikes, made of

virally encoded glycoproteins [12]. These spikes are 7nm long, spaced 10nm apart, and allow the virus to attach itself to host cells.

Ebola virus is an enveloped negative-sense RNA virus which is associated with zoonotic infections in humans [8]. Its genome consists of a single-stranded molecule of non-segmented, negative-sense RNA. The RNA is noninfectious, not polyadenylated, and complementary to polyadenylated viral subgenomic RNA species [6]. Gene signals are distinct by transcriptional start signals at their 3â€² (3â€²-CUNCNUNUAAUU-5â€²) and the termination signals at their 5â€² (3â€²-UAAUUCUUUUU-5â€²) end [6]. The RNA is enclosed by a capsid known as the nucleocapsid. The nucleocapsid is formed by viral proteins, primarily VP24 and VP35. The space between the outer viral envelope and the nucleocapsid is known as the matrix space. Several viral proteins are located in the matrix space. Although little is known about the molecular mechanics of filoviruses, scientists focus on the mechanics of viral proteins as they are thought to function primarily as immune antagonists.

Viral protein 24 (VP24), functions primarily to inhibit a signaling pathway known as JAK-STAT. The JAK-STAT pathway is a secondary method of transmitting information from chemical signals outside the cell, through the cellular membrane and into the cell. By inhibiting this signaling pathway, several cellular activities are disrupted including transcription. Studies have identified several regions within VP24 that are important for nucleocapsid formation [8].

As part of the body’s first line of defense against viral infections, interferons, which are released by lymphocytes during a non-specific immune response, disrupt a virus’s ability to replicate. Viral protein 35 (VP35) is thought to play a central role in the synthesis of viral RNA, serving as an interferon antagonist [12]. The degree of interferon antagonist production is said to determine the pathogenicity of the virus and may account for the varying degrees of virulence among different strains of the Ebola virus [12]. Additionally, VP35 is critical for viral replication, suppression of RNA silencing, and nucleocapsid formation [8]. The viral protein 30 (VP30) is known to act as a transcription activator. Studies have suggested that VP30 halts the host cell transcription complex at its start site allowing the Ebola virus transcription to begin [13].

A nonstructural glycoprotein has only been discovered with viruses of the Ebola type. This protein, designated sGP, shares ~ 300 N-terminal amino acids with glycoprotein, but has a different C terminus (~70 amino acids) containing many charged residues as well as conserved cysteines [6]. Ebola virus glycoproteins, specifically the envelope-glycoprotein and the secretory-glycoprotein, play critical roles in the pathogenesis of the virus. The envelope-glycoprotein is responsible for receptor binding and fusion of the virus with host cells. Because Ebola is an enveloped virus, cleavage activation of membrane glycoproteins is essential for fusion between the viral envelope and the host cell membrane. This fusion allows the virus entry into host cells. The secretory-glycoprotein is secreted from infected cells [12]. Glycoproteins can also produce cytotoxicity by inducing cell rounding and detachment of cell surface integrins [9].

Specific cells targeted by Ebola virus differ depending on the strain of virus. Studies have shown glycoproteins of Zaire Ebola virus induced pathogenic changes in endothelial cells in both human and primate cells, where Reston Ebola virus glycoproteins induced similar effects in the primate cells but not in the human cells [12]. Endothelial cell dysfunction is thought to explain hemorrhagic characteristic of filovirus infections [12]. Often the proteins target the endothelial cells lining the blood vessel wall, which eventually leads to internal bleeding.

Replication

Replication of RNA viruses differ from that of DNA viruses in several ways. One important difference is that replication occurs in the cytoplasm of the host cell, and not in the nucleus. The virion then releases an enzyme into the cytoplasm, known as RNA-dependent RNA transcriptase, to begin transcription of positive-RNA. This positive strand of RNA then acts as the template for viral protein translation [7]. The virus proceeds to integrate itself into the DNA of the host cell allowing the viral RNA to become part of the host cell’s genetic material. The virus (at this point called a prophage) now can replicate every time the host cell replicates.

Ebola virus replicates via both lysogenic and lytic phases. The lysogenic cycle is a process in which the virus enters the host cell but doesn’t immediately destroy it. The virus enters through endocytosis in which the entire encapsidated virion is engulfed and released into the cytoplasm of the cell. After some time, the prophage is excised from the chromosome and the cell reenters the lytic phase, where the host cell lyses and newly assembled

virions are released. At this point, symptoms of viral infection become evident [13].

Pathogenesis and Manifestation

The Ebola causes the disease Ebola hemorrhagic fever. Within the first week of contracting the virus, mild headaches occur. The headaches intensify and flu-like symptoms, backache and chills are present. Fever, diarrhea, fatigue, and nausea then set in. Vomiting may occur within the first two weeks. By the end of two weeks, coughing and vomiting of blood occurs. Late symptoms arise. Blood purges from the mouth and rectum; eyes, ears, and nose follow. The eyes begin to inflame and the genitals swell. Rash overtakes the body, often containing blood. Seizures, coma, and delirium ensue. Death commonly comes from shock rather than blood loss [10]. Hemorrhaging is generally found macroscopically in most organ systems in human death scenarios. Focal necrosis in the liver, lymphatic organs, kidneys, testes, and ovaries are observed under a microscope. Incubation of the virus ranges from 2 to 21 days depending on the strain; the subtype Zaire is 4 to 16 days [6].

Treatment

There is no known cure or standard treatment for Ebola hemorrhagic fever. Antivirals generally given to fight similar viral infections do not work well against the Ebola virus. Those who are infected can only receive supportive treatment for their symptoms until their body is able to fight off the virus. Most importantly, the patient’s blood volume and electrolytes are maintained to prevent the patient from going into shock. Fever, blood pressure, and oxygen levels are also monitored. The best option is to prevent infection

through early diagnosis and isolation when outbreaks occur. Although cases are rare, vaccines can be a vital tool. Filoviruses can be harvested from wild monkeys in possibly infected areas to process for future vaccines.

Epidemiology and Avoidance

Since the natural reservoirs are unknown, prevention is merely suggestion. Wearing protective equipment such as gloves, masks, goggles, gowns, and practicing sterilization is recommended when in contact with the virus. When traveling to epidemic areas, it’s important to wear such equipment, and learn of possible symptoms as a preventive measure. The goal is to avoid contact with blood or secretions of any patient, as person-to-person contact is the main route of infection in human outbreaks. Premise concludes an infected animal is the primary determinant for contracting Ebola virus. Transmission can occur from direct contact with blood and/or secretions prevalent when caring for the infected [3].

History of the virus shows that nosocomial transmission provides high outbreak potential when sterilization is not practiced consistently. In lab setting, research suggests Ebola has the ability of spreading through airborne particles, but this type has not been documented among humans in a real-world setting [2]. In the case of a diagnosis, several infectious diseases need to be considered before making a proper diagnosis of filovirus. Detection can be done in the lab by measuring the host-specific immunological response to the infection, or by detecting viral antigens and genomic RNA in the infected host [6].

Conclusion

The Ebola virus poses significant threat to humans and animals. Although the incidence of outbreak is low, the infection is very serious and often fatal. So far, Ebola has been confined and isolated but there is always a risk of it spreading rapidly to the rest of the world. Without effective treatment and prevention the threat is enhanced. More extensive knowledge is needed to understand how the virus spreads and its development, specifically Ebola’s natural reservoir. Therefore, while traveling the world, people should be aware of the threats from the Ebola virus in order to avoid infection, and hopefully scientists will do their best to develop a treatment and vaccination.