ECRONICON OPEN ACCESS

MICROBIOLOGY
Mini Review

Ebola Virus Disease: Pathophysiology and Clinical Aspects

Attapon Cheepsattayakorn[1,2] and Ruangrong Cheepsattayakorn[3]

[1]10th Zonal Tuberculosis and Chest Disease Center, Department of Disease Control, Ministry of Public Health, Thailand

[2]10th Office of Disease Prevention and Control, Department of Disease Control, Ministry of Public Health, Thailand

[3]Department of Pathology, Faculty of Medicine, Chiang Mai University, Thailand

***Corresponding Author:** Attapon Cheepsattayakorn, 10th Zonal Tuberculosis and Chest Disease center, 143 Sridornchai Road Changklan Muang, Chiang Mai, 50100, Thailand.

Received: February 13, 2015; **Published:** March 30, 2015

Abstract

Ebola virus, a RNA virus, was discovered in 1976 as "*Zaire ebolavirus*" and currently is responsible for outbreak in the West Africa. The mucin-liked region of the *Ebola virus* envelope plays a significant role in viral infection in non-human primates and humans through attachment of the membrane anchored C-type lectins rather than specific receptors. Both humoral and cellular immunities are responsible for the survival. Several novel chemotherapeutics are developed and progressive, such as ZMapp, PMOs, BCX-4430, AVI-602, T-705, TMK-Ebola, CMX-001, etc. Nevertheless, strategic prevention of this virus is the most significant control measures.

Keywords: *Ebola; pathophysiology; clinical*

Abbreviations: IFN: Interferon; IL: Interleukin, IP: Inducible Protein; kDA: kiloDalton; KO: Knocked Out; M-CSF: Macrophage-Colony Stimulating Factor; MIF: Migration Inhibitory Factor; MIP: Macrophage Inhibitory Protein; NK: Natural Killer; PPE: Personal Protective Equipment; RNA: Ribonucleic Acid; RT-PCR: Reverse Transcriptase-Polymerase Chain Reaction; TNF: Tumor Necrosis Factor; US CDC: United States Centers for Disease Control and Prevention; VP: Viral Protein

Introduction

The virus is classified into the family "*Filoviridae*" and genus "*Ebolavirus*" [1]. There are five species of Ebola virus: Reston ebolavirus, *Taï Forest ebolavirus, Sudan ebolavirus, Bundibugyo ebolavirus,* and Zaire ebolavirus [2-4]. *Zaire ebolavirus* was discovered in 1976 and is responsible for the current outbreak in the west Africa [2,4,5]. The filamentous and pleomorphic Ebolavirus is enveloped non-segmented negative strand RNA virus of 19 kb in length with a mean unit length of 1,200 nm [3,5]. Each of its five species is pathogenic for humans except *Reston ebolavirus* that only has been demonstrated to be pathogenic for nonhuman-primates [3,4]. This enveloped virus consists of a lipid bilayer coat that protects the virus genome and facilitates its host-cell entry [3]. The viral genome encodes for RNA dependent RNA polymerase, four structural proteins namely VP24, VP30, VP35, and VP40, a glycoprotein (a soluble 60- to 70-kDa protein and a full-length 150- to 170-kDa protein [5]), and a nucleoprotein [3,5]. The viral heavy glycosylation and the lipid content of the viral envelope allow the immune evasion [3]. The natural reservoir of virus remains unknown [3-5], nevertheless, the little collared bat (*Myonycteris torquata*) is believed to be the most likely reservoir [3,4].

Pathophysiologic Mechanisms

Tissue invasion by the Ebola virus occurs via the infected fluid that contacts with the mucosal or skin breaks [3], and preferably replicate in the monocytes, macrophages, and dendritic cells [2]. *In vitro* studies, the viral envelope glycoprotein is responsible for both receptor binding and fusion of the viral envelope with the host cell membrane [3]. The viral envelope is heavily glycosylated that includes both N- and O-linked glycan, which protects the host-immune attack [3]. Recent studies indicated that cysteine protease, likes cathepsins B and

L promote the viral glycoprotein-host cell membrane fusion [3]. Due to a wide range of cell- lineages targeting, it is difficult to define the specific mechanisms (receptors) of viral entry into such cell types [3]. When the virus triggers expression of a host of pro-inflammatory cytokines, including interleukin (IL)-2, IL-6, IL-8, IL-10, tumor necrosis factor α, interferons (IFNs), and interferon inducible protein, the severe disease-progression occurs [2]. The mucin-like region which is rich in glycosylated residues of the Ebola virus envelope play an important role in viral infection of the monocytoid lineages, hepatocytes, and endothelial cells and is believed to involve membrane anchored C-type lectins that can be attachment factors rather than specific receptors [3]. The soluble glycoprotein of the Ebola virus may contribute to the immune evasion by inhibiting the early steps of the neutrophil activation that would assist in virus clearance [5].

Immunogenic Mechanisms

IFN system, one of the major innate immune responses that is counteracted by the Ebola virus, has been demonstrated to inhibit the synthesis of host cell IFN-inducible transmembrane proteins 1-3, tetherin and other virus restricting molecules that could serve as barriers against the virus [3]. Monocyte and macrophage infection with virus contributes to increased synthesis of tumor necrosis factor (TNF)-α, release of IL-1, IL-6, IL-8, IL-15, IL-16, eotaxin, IP-10, M-CFS, MIF, MIP-1 α and β, and contributes to lymphoid cell apoptosis, the characteristic of Ebola virus infection [3].The depletion of NK cells abolishes the Ebola virus protection [3]. A murine model study revealed that mice with KO strains deficient in CD8+ T cells did not survive infection, while those deficient in CD4+ T cells survived indicating the role of cytotoxic T cells in protection against Ebola virus [3]. The same results were demonstrated in nonhuman primate studies [3].

Patient's History

Two main factors of initial evaluation of a patient with suspected Ebola infection are arrival from, living or working in endemic area in the past 21 days and history or presence of a fever in the past 24 hours [2]. Persons who work with high risk clinical samples or with bats or primates are also at high risk [2]. In symptomatic patients, use of personal protective equipment (PPE) and precautionary isolation procedures are mandated [2].

Clinical Manifestations

In the 2014 outbreak, the most common symptoms reported between symptom onset and case detection were fever (87.1%), fatigue (76.4%), vomiting (67.6%), diarrhea (65.6%), loss of appetite (64.5%), headache (53.4%), abdominal pain (44.3%), and unexplained bleeding (18%) [2]. Maculopapular rash can develop in early stage, approximately 25-52% [6]. Lymphadenopathy has been rarely reported [2]. In advanced stage of Ebola virus disease, multiple organ dysfunctions are common that includes liver damage, pancreatitis, acute renal injury, and adrenal failure [2]. Serum level of aspartate aminotransferase is higher than the serum level of alanine aminotransferase indicating hepatitis [2]. In late stage of renal involvement, the Ebola virus can directly damage to the kidneys or may be disseminated intravascular coagulation [2]. In advanced Ebola virus-infected cases, they usually reveal hypotension, tachycardia, hiccup, hepatosplenomegaly, confusion, and seizures [2]. In fatal cases, massive gastrointestinal bleeding is frequently found [2].

Investigations

Reverse transcriptase polymerase chain reaction (RT-PCR) is the main confirmatory test [2]. Ebola viral RNA can be detected in the blood by the RT-PCR from day 3 to day's 6-17 of the symptoms [2]. If the RT-PCR test reveals negative, the test should be repeated within 48 hours [2]. Other useful investigations include Ebola virus specific IgM and IgG antibodies, serum amylase, coagulation studies, renal function tests, liver function tests, blood cultures, chest radiography, arterial blood gases, antigen capture-enzyme-linked-immunosorbent assay tests, and complete blood count [2].

Infection Control

Isolation of patients identified as being at risk of infection must be immediately performed in a room with private bathroom facilities, while all attending healthcare personnel must wear PPE [2]. All specimens for laboratory investigations must be collected and sent off [2]. To reduce the risk of transmission and needlestick injuries, judicious selection of investigations and early placement of a central line are needed [2].

General and Symptomatic Management

In patients with mild dehydration, oral rehydration can be used [2]. In cases with signs of shock and fluid losses, the volume of intravenous fluid needed should be assessed on the basis of clinical examination [2]. Daily monitoring of the serum electrolyte levels should be performed [2]. In cases with hypo perfusion, high serum lactate levels are the reliable measure for fluid resuscitation need [2]. Renal replacement therapy has been administered in anuria cases without response to fluid resuscitation need [2]. Platelet and plasma transfusion should be administered in advanced cases with major bleeding [2]. Broad spectrum antibiotics (such as meropenem, piperacillin-tazobactam, or ceftriaxone) should be included in cases with septic shock or sepsis in the first hour after sending the blood cultures, appropriate airway management and oxygen administration, urine output monitoring, and rapid intravenous fluid resuscitation [2]. Inotropic support with a central venous catheter in an intensive care unit where invasive monitoring enables more aggressive corrections of fluids, acid-base balance, and electrolytes, should be considered in cases without response to the initial management [2].

Emerging Treatments

AVI-7537 consists of antisense phosphorodiamidate morpholino oligomers (PMOs) that target the Ebola virus VP24 gene, whereas AVI-602 consists of two PMOs (AV-7537 and AV-7539), which targets the VP35 gene [2]. BCX-4430 is an adenosine analogue that is active against Ebola virus in rodents by inhibition of viral RNA dependent RNA polymerase of paramyxoviruses, arena viruses, bunya viruses, and flaviviruses [2]. FAvipiravir or T-705 selectively viral RNA dependent RNA polymerase of the foot and mouth disease virus, alpha viruses, bunya viruses, arena viruses, flaviviruses, yellow fever virus, West Nile virus, and influenza viruses [2]. TKM-Ebola consists of a combination of small interfering RNAs that target Ebola virus RNA polymerase L, formulated with lipid nanoparticles technology [2]. Brincidofovir or CMX-001 demonstrated activity against Ebola virus *in vitro* [2]. These mentioned compounds will be undergone clinical trials for Ebola virus treatment soon [2]. Amiodarone, interferons, chloroquine, and clomiphene inhibit Ebola virus interactions with human cells in models will be in clinical trial soon [2].

Vaccines against Ebola virus

Important preventive vaccines include human parainfluenza virus 3 that revealed 100% protection following a single vaccination in guinea pigs, but it required 2 vaccinations to induce protective immunity in non-human primates [7] and rabies virus-recombinant Ebola virus vaccine that demonstrated 100% of protection in mice model following challenge with Zaire Ebola virus [8]. The most effective strategies for therapeutic vaccines are the use of selectively monoclonal antibodies with high neutralizing potential [3]. ZMapp, the best known therapeutic vaccine, is a combination of three humanized monoclonal antibodies targeted at three Ebola virus glycoprotein epitopes [2]. ZMapp had been proved protective to rescue 100% when administered to non-human primates, particularly rhesus macaques, 24-72 hours after infection for initiation up to 5 days post-challenge [2,3,9]. Despite its potential, numbers are too small to conclude about its safety and efficacy [2]. More doses are needed to conduct larger clinical trials [2].

Convalescent plasma or whole blood

The evidence from past Ebola outbreaks that transfusion of blood from convalescent cases might be beneficial in the acute phase of infection and may decrease the mortality [10].

Other Measures of Control

Ebola virus spreads through human-to-human transmission via direct contact with the secretions, blood, other bodily fluids or organs of infected persons, and with materials contaminated with these fluids [11-13]. Thus, hand hygiene is a component of infection prevention and control recommendations for persons and hospitalized patients under investigations for Ebola virus disease, recommended by the United States Centers for Disease Control and Prevention (US CDC) in addition to patient placement, patient care equipment, PPE, safe injection practices, monitoring, duration of infection control precautions, and management of potentially exposed personnel, and environmental infection control [14]. Outbreak containment measures include identifying persons who may have been in contact with persons infected with Ebola virus, monitoring the health of contacts for 21 days, the importance of separating the healthy from the sick to prevent further Ebola virus spread and safe and prompt burial of the death [11]. The rapid case identification and promptly forceful intervention can stop the virus transmission [15]. In current Ebola virus disease outbreaks, under-resourced African regions not only

suffer from a critically low ratio of health-care workers to total population, but also lack essential PPE to practice standard infection control measures, and also lack the infrastructure and local capacity essential to effectively trace the contacts and isolate infectious persons [16]. Socio-cultural factors in these regions, particularly, touching the body of the decease greatly allow the dissemination of the Ebola virus [16].

Discussion

Because of the wide range of cell-lineages targeting of the Ebola virus, the identification of specific mechanisms of viral entry into human cells is difficult [3]. The mucin-like region of the Ebola virus envelope play an important role in viral infection by human-cell attachment via membrane anchored C-type lectin involvement [3] and finally inhibits the neutrophil activation [5]. Several previous studies revealed that both humoral and cellular immunities involved in survival. Several agents have been the emerging treatments for the Ebola virus disease, whereas ZMapp is currently the best known one, but larger clinical trials are needed [2]. There were some evidences that the convalescent plasma or whole blood could be beneficial in the acute Ebola-virus infection, nevertheless, further studies should be conducted [10].

Conclusion

During the acute period of illness, Ebola virus is shed in a wide variety of bodily fluids, but the risk of transmission from fomites in an isolation ward and from convalescent patients is low when presently recommended infection control guidelines for the Ebola virus are followed. Strategic measures of disease prevention are still the key success for Ebola-virus-disease control, while individual treatments with the novel agents, particularly ZMappare necessary for whom developed severely clinical manifestations.

Bibliography

1. Bausch DG., *et al*. "Assessment of the risk of Ebola virus transmission from bodily fluid and fomites". *The Journal of Infectious Diseases* 196.Suppl 2 (2007): S142-S147.
2. Beeching NJ., *et al*. "Ebola virus disease". *British Medical Journal* 349.7348 (2014).
3. Ansari AA. "Clinical features and pathobiology of Ebolavirus infection". *Journal of Autoimmunity* 55 (2014): 1-9.
4. Centers for Disease Control and Prevention. "About Ebola virus disease". (2015).
5. Sullivan N., *et al*. "Ebola virus pathogenesis: implications for vaccines and therapies". *Journal of Virology* 77.18 (2003): 9733-9737.
6. WHO Ebola Response Team. "Ebola virus disease in West Africa-the first 9 months of the epidemic and forward projections". *The New England Journal of Medicine* 371.16 (2014): 1481-1495.
7. Bukreyev A., *et al.* "Successful topical respiratory tract immunization of primates against Ebola virus". *Journal of Virology* 81.12 (2007): 6379-6388.
8. Blaney JE., *et al*. "Inactivated or live-attenuated bivalent vaccine that confer protection against Rabies and Ebola virus". *Journal of Virology* 85.20 (2011): 10605-10616.
9. Qiu X., *et al*. "Reversion of advanced Ebola virus disease in non-human primates with ZMapp". *Nature* 514.7520 (2014): 47-53.
10. Roddy P., *et al*. "Clinical manifestations and case management of Ebola hemorrhagic fever caused by newly identified virus strain, Bundibugyo, Uganda, 2007-2008". *PLoS One* 7.12 (2012): e52986.
11. World Health Organization. "Ebola virus disease". (2015).
12. United States Centers for Disease Control and Prevention."Transmission: Why Ebola is not likely to become airborne". (2015).
13. Public health Agency of Canada. "Statement on infection prevention and control measures for Ebola virus disease". (2015).
14. United States Centers for Disease Control and Prevention. "Infection prevention and control recommendations for hospitalized patients under investigations for Ebola virus disease in U.S. hospitals". (2015).
15. Fasina FO., et al. "Transmission dynamics and control of Ebola virus disease outbreak in Nigeria, July to September 2014". *Eurosurveillance* 19.40 (2014).

16. Chowell G and Nishiura H. "Transmission dynamics and control of Ebola virus disease (EVD): a review". *BMC Medicine* 12.1 (2014): 196.

Volume 1 Issue 2 March 2015