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EBOLA HAEMORRHAGIC FEVER VIRUS: PATHOGENESIS, IMMUNE RESPONSES, POTENTIAL PREVENTION

Abstract: Ebola zoonotic RNA *filovirus* represents human most virulent and lethal pathogens, which induces acute hemorrhagic fever and death within few days in a range of 60–90% of symptomatic individuals. Last outbreak in 2014 in West Africa caused panic that Ebola epidemic can be spread to other continents. Number of deaths in late December reached almost 8,000 individuals out of more than 20,000 symptomatic patients. It seems that only a coordinated international response could counteract the further spread of Ebola. Major innate immunity mechanisms against Ebola are associated with the production of interferons, that are inhibited by viral proteins. Activation of host NK cells was recognized as a leading immune function responsible for recovery of infected people. Uncontrolled cell infection by Ebola leads to an impairment of immunity with cytokine storm, coagulopathy, systemic bleeding, multi-organ failure and death. Tested prevention strategies to induce antiviral immunity include: i. recombinant virus formulations (vaccines); ii. cocktail of monoclonal antibodies (serotherapy); iii. alternative RNA-interference-based antiviral methods. Maintaining the highest standards of aseptic and antiseptic precautions is equally important. Present brief review summarizes a current knowledge concerning pathogenesis of Ebola hemorrhagic disease and the virus interaction with the immune system and discusses recent advances in prevention of Ebola infection by vaccination and serotherapy.

Key words: Ebola virus disease pathogenesis, immunity, vaccination.

INTRODUCTION

Ebola (EBOV) and Marburg (MARV) viruses are the members of the *Filoviridae* zoonotic RNA viruses representing the most virulent pathogens for human and great apes (non-human primates). EBOV is even more contagious and lethal than human immunodeficiency virus (HIV). EBOV and MARV induce acute hemorrhagic fever and death within few days in a range of 60–90% of symptomatic individuals [1].

There have been 15 Ebola outbreaks since the first outbreak of Ebola hemorrhagic fever (EHF) in 1976 in Africa (Sudan, Zaire). For years, in spite of extremely high mortality of EHF, Ebola considered a rare virus with local affair, draws little interest from funders and scientists [1, 2]. It resulted in a slow progress in prevention and treatment of Ebola infections.

However, the last outbreak of EBOV in 2014 in West Africa caused panic and fear that Ebola epidemic can be spread to other continents including Europe and North America. On August 8th 2014, the WHO declared the Ebola epidemic as a Public Health Emergency of International Concern, its highest level of alert. Continuously increasing number of deaths in West African countries, which in December reached more than 8,000 individuals out of approximately 20,000 symptomatic patients and additional few hospitalized in Europe, clearly indicated that only a coordinated international response, including Poland, is able to counteract the international spread of Ebola.

The aim of this brief review is to summarize a current knowledge concerning pathogenesis of Ebola hemorrhagic disease and EBOV interaction with the immune system. Moreover, we will discuss recent advances in prevention of Ebola infection by vaccination and serotherapy.

PATHOGENESIS OF EBOLA VIRUS DISEASE (EVD), FORMERLY KNOWN AS THE EBOLA HEMORRHAGIC FEVER (EHF)

Viral pathogenesis is the process by which virus infection leads to the disease. Pathogenic mechanisms include implantation of the virus at a body site, replication at the portal of entry, spread to and multiplication within target organs/tissues, where disease occurs. Ability of pathogen to damage the host is related either to a direct cytotoxic effect, e.g. by a toxin production, or to an uncontrolled stimulation of the immune system and overproduction of toxic agents (e.g. nitric oxide, TNF-α). Nevertheless, most viral infections are asymptomatic and subclinical, indicating that the immune responses against viruses inhibit infections before clinical symptoms appear. In a striking contrast Ebola virus infection is characterized by an extremely high pathogenicity with a fatal outcome [2, 3]. Only in a minority of cases the infection results in a transient flu-like syndrome and full recovery, whereas in majority of infected population, EBOV evokes severe illness associated with fever, myalgia, general malaise, gastro-intestinal symptoms (vomiting and diarrhea), conjunctival hemorrhage and encephalopathy [3, 4]. Why EBOV shows such extreme virulence and pathogenicity?

The EBOV genome is covered by a lipid envelope that facilitates virus entry into host cells. Most viruses have an affinity for specific tissues. Importantly, in contrast to tissue specificity/tropism of human viruses, EBOV, the zoonotic virus, is able to replicate in a wide range of the human cells including: immune cells, endothelial cells, fibroblast, hepatocytes, and adrenal cells [5]. It is clear that viral envelope glycoprotein (GP) is responsible for both receptor binding and fusion of the viral envelope with the host membrane [5]. Moreover, it has been estimated that Ebola virus primarily targets macrophages and dendritic cells and, subsequently, endothelial cells through a mucin-like domain of GP [6, 7]. Therefore,

EVD first disables the immune system and then, in turn, affects the vascular system. It results in disseminated intravascular coagulation, hemorrhage, shock, circulation failure and death. The virus also affects other organs/tissues, leading to a failure of liver (multi-focal necrosis, decreased production of clotting factors), adrenal glands (that stop the production of steroids and corrupt the regulation of blood pressure) and gastro-intestinal tract (diarrhea) [3]. All these clinical symptoms of EVD are associated with uncontrolled dissemination and replication of the virus in infected host but precise mechanisms are still not fully defined. Current state of knowledge points to the following scenario of the events:

- At a gate of infection — sentinel immune cells, macrophages and dendritic cells are early targets of EBOV. Extensive infection of these cells leads to overproduction of inflammatory mediators and chemokines such as IL-1, IL-6, IL-8, TNF-α, monocyte chemotactic protein-1 and eotaxins (eosinophil chemoattractants). This "cytokine storm" is responsible for attracting inflammatory cells (neutrophils, eosinophils) to the infected tissues, inducing coagulopathy and increasing endothelial permeability [8].
- Then the virus spreads to secondary lymphoid organs and liver where massive replication takes place and other cells are infected. At this stage EBOV infection is associated with disseminated intravascular coagulation which leads to a consumption of coagulation factors, fibrin deposition, microtrombin production and, ultimately, to systemic bleeding [3].
- Finally, multi-focal necrosis of hepatocytes and other tissue damage resulting from direct cytopathic effects and from the host response leads to multi-organ failure, terminal shock and death (Fig. 1).

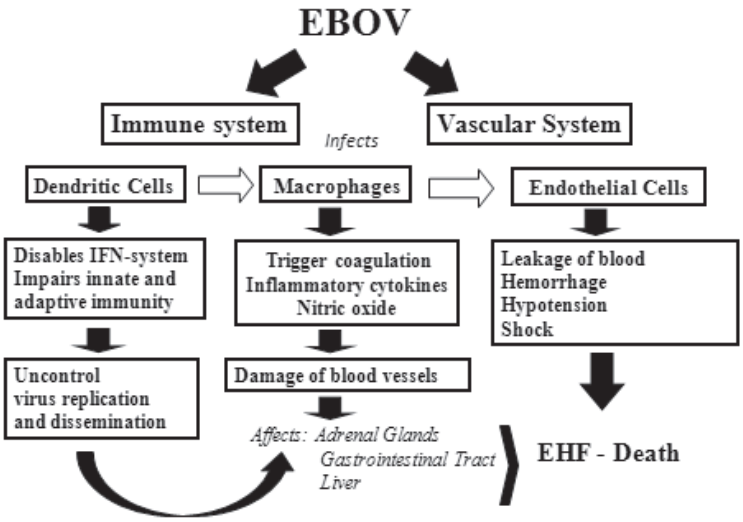

Fig. 1. Cascade of pathological events associated with EBOV infection and the development of severe Ebola hemorrhagic fever (EHF).

EBOV INFECTION AND THE IMMUNE RESPONSE

The outcome of each step of viral infection, starting from the implantation of virus at the gate of entry, through local replication, dissemination (viraemia), multiplication in targeted organs, onset of disease and finally the recovery (shedding of virus) or death, depends on the balance between two factors, virus and host defenses. At each step of virus progression through the body, the local (innate immunity) and systemic recovery mechanisms (specific humoral and cellular immunity) are activated. However, majority of EBOV infections leads to a fatal outcome that is in striking contrast with the effective control of other viral infections associated with the balanced immune response [8].

As stated above, inflammatory immune cells (macrophages) and antigen presenting cells (dendritic cells) are the first targets of EBOV, and it results in an impaired innate and adaptive immune response that facilitates uncontrolled viral replication and dissemination.

Major mechanisms of the innate immunity against viral implantation and local replication are associated with the production of type 1 interferons (IFNα/β) [9]. Unfortunately, EBOV, as well as other filoviruses, encodes two different proteins (VP24, VP35), components of the viral nucleocapsid, that block host interferons production and signaling. VP24 directly inhibits IFNα/β and IFNγ signaling through an interaction with STAT1 and blocking its nuclear import. On the other hand, Ebola VP35 inhibits the production of IFNα/β by several mechanisms, as described elsewhere [7, 9]. This total inhibition of interferon-dependent innate immunity by Ebola VP35 and VP24 proteins is strongly correlated with an increased virulence of *filoviruses* and has also an impact on other immune responses in the severe EVD.

Evasion of the immune response by Ebola virus, except for disabling of the IFN-system, is also associated with an impaired humoral and cellular adaptive immunity [7, 10]. It has been documented that infection of macrophages and dendritic cells, primarily antigen presenting cells (APC), contributes to the inflammation, coagulopathy and ineffective immune response characteristic for a fatal outcome of Ebola hemorrhagic fever. One of the detrimental consequences of APCs infection for host immunity is a massive apoptosis of T cells (T helper and T cytotoxic cells) and NK cells [1]. In addition, the production of specific anti-virus antibodies is inhibited [10]. Fatal EHF is characterized by the absence of specific IgG and by barely detectable IgM. On the contrary, an early and strong humoral response is correlated with survival in symptomatic patients [1, 3].

Taken together, these reports suggest that deregulated and impaired adaptive immunity accompanied with the “cytokine storm” is characteristic for the severe Ebola infection and indicates that vaccination is the best strategy to prevent the disease.

ADVANCES IN EVD IMMUNE PREVENTION

Owing to a very high mortality of infected patients, difficulty in elaboration of treatment ensuring full recovery and necessity for the professional health care for symptomatic individuals, fast elaboration of efficient and commonly available prevention method(s) should be the center of urgent attention. Furthermore, lack of awareness leading to risky behavior of unqualified people and professionals as well as ignorance of standard assessment procedures and failure of public health system (including crowded emergency rooms, delay in isolation and long-lasting diagnostic procedures, and, finally, low number of health staff), all results in unexpectedly fast spreading of EBOV epidemic [11–13]. Activation of host immune defense mechanisms, specific antiviral immunity by vaccination especially, seems to be the best way to assure resistance of population to EBOV infection. However, the main problem is the virus capability to avoid immune response. As mentioned previously, EBOV infected host cells produce protein inhibitors of interferons (VP24 and VP35) encoded by viral genetic material. Both inhibitors block production of endogenous interferons as well as intracellular signalization pathways activated by interferons even if delivered in therapy [4, 9].

At the beginning, the alarming problem was also a very weak effort of the World Health Organization (WHO) to prevent the spread of current Ebola outbreak. As an example, it could be pointed out that when the GlaxoSmith-Kline (GKS) contacted the WHO to show their vaccine in March at the start of this outbreak, no one expressed much interest. The response was "thanks, we will get back to you" [14]. Fortunately, now the situation has changed. On 3rd of October the WHO reported 7470 cases of infection and 3431 deaths [15]. However, in the main three affected countries (Guinea, Sierra Leone and Liberia) the number of cases is still growing [16]. Further, on December 31th the number of deaths reached 7905 people among 20.206 infected individuals. In this Ebola outbreak all that can be offered is the isolation and quarantine instead of effective vaccines and treatment. During current outbreak approximately 150 medical doctors and nurses died and 240 members of medical staff were infected as estimated on September 12th [11], and the still growing numbers in December reached 382 and 672, respectively, which significantly influenced the health care system and public attitudes to EBOV progressive epidemic [17]. Because of such unexpected situation the WHO announced that compassionate use of experimental therapies is ethically justified, even if they had not yet been tested in humans, arguing that an exceptional crisis requires an exceptional response [11]. At the time of growing Ebola epidemic problem in the middle of July 2014 scientists from research laboratories working with EBOV were strongly against the use of laboratory methods to control Ebola invasion. They were still waiting for an official permission rather than forgiveness in case of failed results of treatment. But now they are frustrated. The worst Ebola outbreak since the current one killed 600

people. At present a representative for the WHO claimed that using the vaccines now would not be ethical, feasible nor wise [18]. Such feelings of helplessness and unresponsiveness during a new huge outbreak of Ebola epidemic infection was typical before the August 8th since when the WHO declared the crisis and threatening situation with the highest level of alert.

Based on the study provided by Gire *at al.* it is suggested that the lineage of the three most recent outbreaks of Ebola infections and EVD (Democratic Republic of Congo 2007–2008, and Guinea and Sierra Leone both 2014) all derived from a common ancestor at roughly the same time around 2004, which supports the hypothesis that each outbreak represents an independent zoonotic event from the same genetically diverse viral population in its natural reservoir [19]. Although according to the WHO description from September 2014, the last outbreak of EVD is evidenced as Zaire species (and not two others Sudan and Bundibungyo Ebola viruses that were formerly associated with large outbreaks in Africa) [20].

Several tested preventing strategies (in nonhuman primate models) have been introduced into clinical investigation. These include methods based on the use of: i. recombinant formulations (based on adenovirus, vesicular stomatitis virus (VSV), rabies virus); ii. cocktail of monoclonal antibodies (such as ZMapp); iii. alternative RNAi-based approaches (such as TKM-Ebola and antisense-based e.g. AVI-7537) [3]. Presently, it is also known that seven independent proteins are encoded by EBOV genome. Starting from 5' end they include nucleocapsid protein (NP), VP35 (interferon antagonist) VP40, glycoprotein (GP), VP30, VP24 (interferon antagonist) and the last one, RNA-dependent RNA Polymerase L protein, which is localized at the 3' end of the codon. The antiviral vaccine approach is dedicated mainly against GP, mediating internal fusion of the virus with targeted host cells (mainly monocytes/macrophages and dendritic cells, but also cells of interstitial organs that could be used in post-mortal infection confirmatory testing) [21] suspected to be dependent on TIM-1 (T-cell immunoglobulin mucin-1) domain expressed on mucosal membranes [9]. The Zaire EBOV glycoprotein (ZGP) structure expresses 164 amino acids long peptide (MFL) that contains furin site and internal fusion loop recognized as a main contributor of immunogenicity of glycoprotein determinant domain of Zaire EBOV. The MFL structure of both Zaire (ZGP) and Sudan (SGP) Ebola virus Glycoprotein Structures is introduced as a leading structure in the single recombinant VSV (rVSV) vector of bivalent vaccines against EVD [21]. The first activity of rVSV vaccine is the activation of neutralizing function of antibodies involved in clearing of Ebola viraemia and blockade of introducing the EBOVs into host cells. The data obtained from experiments on the efficiency of GP-expressing recombinant adenovirus vaccine in animal models of Ebola viral infections suggest that T CD8+ dependent cytotoxic cellular immune response plays the key protective role. In humans that survived EVD, the activation of host NK cells immune response against viral invaders was recognized as leading immune function responsible for recovery. Thus, the vaccine should be

able to induce cellular immune response, and this promotes methods based on modified viral vectors resembling infectious and replicating living viruses. On the other hand, due to the extraordinary fast multiplication of EBOV after host cell invasion there is the need to block the TIM-1 dependent interaction of virus with cell membrane by actively (vaccines) or passively (monoclonal antibodies) delivered neutralizing antibodies against GP. The first two clinical trials of filovirus vaccines showed the possibility of successful induction of filovirus-specific humoral and cellular responses directed against EBOV. The latter, T dependent response, was estimated in flow cytometry and ELISPOT assays [10]. The aforementioned methods are now considered the standards for evaluation of vaccination efficiency. It should also be noted that vaccination initially is dedicated for health care workers (12.000 people according to the WHO) as they are at a high risk of exposure and provide a critical service in fighting the EBOV outbreak [22, 23].

At the moment, the strongest activities of pharmaceutical companies are focused on the production of Ebola vaccines. Aforementioned Ebola vaccine made by GlaxoSmith-Kline (GSK) in Rixensart, Belgium, is the furthest along, and has entered phase I human trials on September 2nd. By the end of 2014, GSK committed to manufacture up to 10,000 doses of the vaccine, containing Ebola surface protein stitched into attenuated chimpanzee adenovirus [24]. The vaccine could be given to health workers as soon as in November 2014 [14]. Initially it was even estimated that GSK vaccine production level would achieve even up to 100,000 doses per month [14]. Now the chance to multiply the production is estimated up to 230,000 doses by April 2015 and even 1 million by December 2015 [25].

Another company which already prepared 1,500 doses of the Ebola vaccine is NewLink Genetics of Ames from Iowa collaborating with Canadian National Institute of Public Health. The vaccine is based on a crippled vesicular stomatitis virus (VSV), which infects livestock, with the introduced gene encoding EBOV surface protein. Profectus BioScience from Maryland prepares a similar vaccine that should be ready for human testing next June. However, each company needs a commitment from a fund-raiser before it can scale production from the planned 5,000 to 20,000 doses. Noteworthy is the fact that VSV vaccine possibly could also be used in post-exposure condition as it happened in case of accidental contact of a German researcher with EBOV in 2009 [18], although there is no evidence yet for the effectiveness and pertinence of such procedure.

Monoclonal antibodies against EBOV GP were the first experimental therapeutics used for symptomatic medical professionals during current outbreak. Attempts to use serotherapy as a first step prevention method after contact with EBOV were also made. Combination of monoclonal antibodies called ZMapp was shown to be able to rescue 100% of rhesus macaques, when treatment was initiated up to 5 days post contact with EBOV. The high fever, viraemia and advanced EVD indicated by elevated liver enzymes, mucosal haemorrhages and generalized petechiae could be reversed leading to a full recovery. ELISA and neutralizing

antibody assays demonstrated that ZMapp is cross-reactive with Guinea variant of Ebola [26]. ZMapp, made by Mapp Biopharmaceutical of San Diego, California, contains three monoclonal antibodies produced in tobacco plants. The processing from plants to biologically active product takes a few months and only ten doses were yet prepared, out of which seven were used to treat seven Ebola infected human individuals [14].

The U.S. Congress supported the institution named HHS's Biomedical Advanced Research and Development Authority (BARDA) and established to speed up the development of treatment methods and vaccines for emergencies with 58 million USD dedicated for defense against EBOV. BARDA contacted two other outfits that can possibly produce the antibodies against Ebola in tobacco plants or in Chinese hamster ovary cells — the standard system for monoclonal antibodies processing. However, according to manufacturer reports the efficiency of production will never be as high as that of vaccines [14] despite the fact that at present over 25 laboratories from 7 countries are involved in the production of monoclonal antibodies against EBOV. This project has already consumed 28 million USD founded by the National Institute for Allergy and Infectious Diseases (NIAID) [18].

Most studies have been funded by the U.S. Government in response to worries about biowarfare and bioterrorism. The compound identified by U.S. Army researchers and based on RNA interference is in the course of development of Tekmira Pharmaceutical Corporation. But at the beginning of July 2014 the Food and Drug Administration held it on the first trial phase because of the need to clarify the protocol to protect safety of participants. The U.S. Army Medical Research Institute of Infectious Diseases developed a project on a powerful nucleoside analog, which is now stopped. Similarly, the promising project concerning anti-sense-based compound tested by Sarepta Therapeutics in Cambridge, Massachusetts, has unsuccessfully ended after Pentagon stopped funding in 2012 [18]. Nevertheless, RNAi-based methods are now abandoned and the financial support is dedicated to work on vaccines and monoclonal antibodies. There is the information that new studies on EBOV vaccines start soon in Switzerland and Germany. According to Norwegian Institute of Public Health the total cost of vaccine development will reach 73 million USD and next 78 million USD will be consumed by vaccination of population at risk [23].

CONCLUSIONS

All the above data clearly indicate that the evasion of the immune response by EBOV is responsible for a fatal outcome of Ebola virus disease. Better understanding of mechanisms of the virus interaction with the immune system and a proper prevention (vaccines, at present undergoing final phase of clinical trial) is a great hope for the future combat against Ebola.

However, it should be highlighted that in the overall Ebola outbreak perspective prevention plays the most important role, not only in the form of vaccination and serotherapy, but also as maintaining the highest standards of aseptic and antiseptic precautions.

Finally, we would like to conclude to follow the Science (12.08.2014) [11]: "Let us hope that this is the last Ebola outbreak where all we have to offer is isolation and quarantine, instead of a vaccine and treatment."

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ABBREVIATIONS

EBOV — Ebola Virus
EHF — Ebola Hemorrhagic Fever
EVD — Ebola Virus Disease
GP — glycoprotein
HIV — Human Immunodeficiency Virus
MARV — Marburg Virus
SGP — Sudan Ebola virus glycoprotein
VSV — Vesicular Stomatitis Virus
WHO — World Health Organization
ZGP — Zaire Ebola virus glycoprotein

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