HHS Public Access

Author manuscript

ACS Infect Dis. Author manuscript; available in PMC 2020 August 24.

Published in final edited form as:

ACS Infect Dis. 2015 May 08; 1(5): 186–197. doi:10.1021/id5000426.

Pathophysiology of Ebola virus infection: Current challenges and future hopes

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Abstract

The filoviruses, Ebola virus (EBOV) and Marburg virus (MARV), are amongst the deadliest viruses that cause disease in humans with reported case fatality rates of up to 90% in some outbreaks. The high virulence of EBOV and MARV is largely attributed to the ability of these viruses to interfere with host immune response. Currently, there are no approved vaccines or post-exposure therapeutics and treatment options for patients infected with EBOV are limited to supportive care. In this review, we discuss mechanisms of EBOV pathogenesis and its ability to subvert host immunity as well as several vaccines and therapeutics with respect to their evaluation in small animal models, nonhuman primates, and human clinical trials.

Keywords

Ebola virus; viral hemorrhagic fever; innate immunity; adaptive immunity; immunoevasion; antivirals; Ebola vaccines; Ebola therapeutics

Ebola virus (EBOV) is a filamentous enveloped virus containing a negative strand RNA genome 19 kb in length that encodes for a nucleoprotein (NP), glycoprotein (GP), RNA dependent RNA polymerase (L), and four structural proteins termed VP24, VP30, VP35 and VP40. Viral replication is carried out by NP, VP35 and L; the active polymerase complex is composed of VP35 (a polymerase cofactor) and L (polymerase) while NP drives RNA encapsidation. VP30 is a transcriptional activator and is also involved in nucleocapsid formation and assembly[1]. VP24 is a matrix protein that contributes to nucleocapsid formation while matrix protein VP40 facilitates budding of progeny virion from infected cells [1b, 2]. Glycoprotein (GP) covers the surface of the virion and is the sole host attachment factor for EBOV [3]. Moreover, EBOV expresses a two soluble forms of GP, sGP and ssGP through RNA editing [4].

Infection with EBOV results in severe viral hemorrhagic fever with fatality rates that can reach 90% in humans depending on the species. Infection with *Zaire Ebola virus* (EBOV), *Sudan Ebola virus* (SUDV) and *Bundibugyo Ebola virus* (BDBV) is associated with 70-90%, 50% and 40% mortality rate, respectively [5]. In contrast, infection with either *Tai Forest Ebola virus* (TAFV) or *Reston Ebola virus* (RESTV) have not been associated with human fatalities [5]. EBOV is transmitted by direct contact with infected bodily fluid. The

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incubation period ranges from 2 to 21 days with an average incubation period of 5-7 days. Early symptoms are general and nonspecific including fever, general malaise and myalgia. Following early symptoms, cases can show maculo-papulary rash, petichae, conjunctival hemorrhage, melena, hematemesis, shock and encephalopathy. During the terminal stage of disease, there is an increase in vascular permeability, massive tissue injury, dysregulation of the coagulation cascade and hemorrhage. Multiorgan failure and shock are usually the main causes of death [6].

Previous EBOV outbreaks have occurred mostly in remote regions of central Africa including the Democratic Republic of Congo, Sudan, Gabon and Uganda. However, in March 2014, the World Health Organization (WHO) reported an outbreak of Ebola virus disease originating in the Guinean capital, Conakry, marking the first large urban setting for EBOV transmission. This has led to the first known epidemic in West Africa and is the largest and longest outbreak since the virus was first discovered in 1976 [7]. Genome sequencing of the Guinea strain show 97% identity to EBOV [8]. Sequencing studies of 99 EBOV genomes from 78 patients in Sierra Leone reveal an accumulation of inter- and intra-host genetic variation. Patterns of viral transmission suggest this variant diverged from central African lineages around 2004 [9]. As of March 8, 2015 the CDC reports a total 24,247 confirmed, probable and suspected cases of EBOV disease and 9,961 reported deaths in eight countries (Guinea, Liberia, Sierra Leone, Mali, Nigeria, Senegal, Spain and United States). Currently, there are no FDA-approved treatment strategies. Supportive care, consisting of oral fluid rehydration and nutritional supplementation, is the mainstay in treating Ebola hemorrhagic fever (EHF). The high mortality rate has caused concern to public health officials worldwide, prompting a sense of urgency to accelerate clinical trials to identify effective vaccines and post-exposure therapeutics.

Nonhuman primates, particularly cynomolgus macaques and rhesus macaques, are the gold standard animal models used in filovirus study because they are susceptible to infection by the same strains that cause disease in humans and exhibit strong similarity of viral hemorrhagic fever to humans [10]. Small animal models, such as inbred mice and guinea pigs have also been used, however, these animal models require the use of adapted EBOV strains and do not exhibit the characteristic hemorrhagic manifestations seen with human and nonhuman primate infection [11]. In a recent study using Collaborative Cross mice, animals exhibited a spectrum of disease outcomes following infection with mouse adapted EBOV (MA-EBOV), including hemorrhagic fever [12]. However, MA-EBOV has diminished virulence in nonhuman primates. Of three rhesus macaques injected with a large challenge dose of 5000 pfu of MA-EBOV, two showed mild illness and survived infection [13]. A single amino acid mutation in both NP and VP24 are the determinants of virulence of MA-EBOV in mice [14]. Although MA-EBOV infection in mice correlated with evasion of IFN induced responses [14], the determinants for virulence of EBOV may differ between mouse and primate models. The purpose of this review is to summarize our current understanding of the pathogenesis of EBOV and discuss the various vaccine platforms and therapeutics currently being investigated.

Dysregulation of innate immunity by EBOV infection

Although EBOV targets a wide range of cell lineages, *in vivo* studies in nonhuman primates using immunohistochemistry and in-situ hybridization suggest that EBOV replicates preferentially in monocytes, macrophages, and dendritic cells [10b, 15]. Infection of monocytes and macrophages triggers the robust expression of inflammatory mediators [16] (Figure 1). Indeed, several studies have shown that fatal infections were associated with uncontrolled secretion of proinflammatory cytokines, chemokines and growth factors such as IL-1β, IL-6, IL-8, IL-10, MCP-1, MIP-1α, MIP-1β and TNFα as well as nitric oxide and reactive oxygen species, which, at the time of death, can reach 5 to 1000 times the levels detected in survivors and healthy individuals [17]. In contrast, survivors show a transient and moderate upregulation in levels of IL-1β, IL-6, TNFα, MIP1α and MIP1β early in the disease [17a]. These studies suggest that protection from fatal EBOV infection may depend on an early yet regulated inflammatory response.

Ebola virus infection is also characterized by a suppressed type I interferon (IFN) response, which is an integral part of the innate immune response against viral infections. This suppression is mediated by VP24, which prevents the nuclear transport of tyrosine phosphorylated STAT1 (pSTAT1), a key downstream outcome of IFN signaling, thereby preventing IFN-induced gene expression [18]. VP24 binds the C-terminus of karyopherin α proteins (karyopherin α1, α5, α6), which normally transport pSTAT1 through the nuclear pore, therefore competing with pSTAT1 for binding the nuclear transporter [19]. In addition to VP24, VP35 was also found to block activation of the transcription factor IFN regulatory factor 3 (IRF-3), thus decreasing IFN production [20]. VP35 interacts with the SUMO E2 enzyme Ubc9 and the E3 ligase PIAS1, which in turn leads to increased SUMOylation and degradation of the transcription factor IRF-7 [21]. VP35 can also inhibit retinoic-acid inducible gene-I (RIG-I) helicase signaling by binding to dsRNA [22] or binding to PKR activating protein (PACT), which activates RIG-I [23]. Moreover, VP35 can decrease IFN production by impairing IKKε and TBK-1 kinase function [24]. Interference with RIG-I signaling can also inhibit the upregulation of a number of co-stimulatory molecules on dendritic cells (CD40, CD80, CD86, and MHC class II) needed to activate T cells [25]. Additional, *in vitro* studies have shown that EBOV infection inhibits dendritic cells maturation into mobile, antigen presenting cells and impairs their ability to stimulate antigen specific T cell responses [26] (Figure 1).

Dysregulation of lymphocyte function by EBOV infection

One major consequence of EBOV infection is severe lymphopenia [10a]. EBOV infection leads to loss of both human $CD4^+$ and $CD8^+$ T cells after 4 days of *in vitro* culture [27]. Similarly, EBOV infection resulted in loss of peripheral $CD4^+$ and $CD8^+$ T cells in both mouse models at 2-3 dpi [28] and in nonhuman primates at 4 dpi [29]. Significant loss of circulating natural killer (NK) cells was also described in mice [28] and in cynomolgus macaques [10b, 29]. B cell loss is more controversial with some studies reporting the loss of B lymphocytes in mice [28] and macaques [15] and other studies reporting no changes in B cell counts in nonhuman primates [29–30]. Flow cytometric analysis of peripheral blood mononuclear cells (PBMCs) from humans and cynomolgus macaques infected with EBOV

revealed an increase in the percentage of $CD4^+$ and $CD8^+$ T cells expressing the cell death receptor Fas (CD95) suggesting that apoptosis is the primary mechanism of lymphocyte death [17f, 29]. Transmission electron microscopy and TUNEL staining confirmed lymphopenia *in vivo* and *in vitro* occurred by apoptosis [15]. Increased plasma levels of apoptosis mediators such as soluble Fas (sFas) and 41/7 nuclear matrix protein, upregulation of Fas and FasL mRNA in PBMCs, and dramatic DNA fragmentation in leukocytes were detected during the terminal stage of human EBOV infection [31]. Furthermore, PBMCs from survivors showed an upregulation of anti-apoptotic Bcl-2 mRNA whereas fatalities showed a significant decrease in Bcl-2 mRNA as well as a decrease in CD3, CD8, and TCR-Vβ mRNA [15, 31b].

The fact that EBOV does not replicate within lymphocytes during infection suggests that lymphocyte apoptosis is an indirect result of viral replication [15, 31a]. Some of the proinflammatory mediators released by EBOV-infected monocytes such as TNFα, reactive oxygen species and nitric oxide have been shown to induce apoptosis [32] (Figure 1). Furthermore, immunohistochemistry, flow cytometry, and RNA analysis showed high expression of TNF related apoptosis inducing ligand (TRAIL) in 90% of EBOV infected adherent human monocytes/macrophages [17c]. In addition to lymphopenia, EBOV infection interferes with T cell activation as evident by decreased expression of the activation marker CD44 [26, 29]. The absence of EBOV-specific T cell responses is consistent with the lack of T cell cytokines (IL-2, IL-4, IL-5, IL-12 and IFNγ) in the plasma of EBOV infected patients [17f, 33].

EBOV also subverts the host humoral immune response, as fatalities are associated with a lack of EBOV specific IgG antibodies [31b]. The loss of CD4+ T cells, which are required for isotype class switching, may explain the lack of Ebola specific IgM and IgG antibodies observed in patients who succumb to infection. In contrast, asymptomatic EBOV infected patients developed IgM responses between 10-18 days and IgG responses between 17 −25 days specific to GP, NP and VP40 [34]. EBOV also subverts humoral responses through the production of sGP [30], which sequesters GP-specific antibodies needed to control viral replication [35] (Figure 1). The importance of antibodies in protection against EBOV infection is highlighted by passive immunization studies. During one of the EBOV outbreaks in the Democratic Republic of Congo, 7/8 patients treated with blood transfusions from 5 convalescent patients who generated EBOV-specific IgG antibodies, survived [36]. Similarly, 100% of naïve mice were protected against infection when treated with serum from vaccinated mice that survived challenge with mouse-adapted EBOV [37].

Vaccines Against Ebola

Several vaccine platforms against EBOV have been developed. Replication deficient vaccines include DNA based vaccines, virus like particles (VLPs) and recombinant adenovirus vectors (rAd). Replication competent constructs include recombinant human parainfluenza virus 3 (rHPIV3), recombinant vesicular stomatitis virus (rVSV) and more recently recombinant rabies virus (RABV) and recombinant cytomegalovirus (CMV) [38]. Two promising vaccine candidates, rAd and rVSV vectors expressing GP (Table 1), have entered clinical trials.

Vaccination of cynomolgus macaques with the replication deficient rAd serotype 5 vector expressing EBOV-GP (rAd5-EBOVGP) resulted in the generation of EBOV-GP specific antibodies and GP-specific $CD8^+$ T cell responses within 3 weeks of immunization and protected 100% of the animals against challenge [39]. Passive transfer of EBOV-specific IgG purified from nonhuman primates vaccinated with DNA and rAd5 vectors expressing EBOV GP to naïve animals only protected 25% of naïve animals 6 or 16 hours before EBOV challenge, whereas, depletion of CD8+ T cells in vaccinated animals 4 days before challenge resulted in 4/5 nonhuman primates succumbing to infection, suggesting that CD8+ T cells play a more important role in protection compared to antibodies in this vaccine platform [40]. Despite these promising results, humans have preexisting immunity against Ad5, which may interfere with the efficacy of the rAd5-EBOVGP vaccine [38]. On the other hand, adenoviruses isolated from chimpanzees (ChAds) provide better vaccine vectors because of their low seroprevalence in humans. Immunization of cynomolgus macaques with a single inoculation of recombinant ChAd3 expressing EBOV GP (rChAd3-EBOVGP) resulted in complete protection when challenged with EBOV 5 weeks after vaccination but only conferred 50% protection when the animals were challenged 10 months after immunization. To improve long-term efficacy of this vaccine platform, a booster vaccination using recombinant modified vaccinia Ankara expressing EBOV-GP was added 8 weeks after the rChAd3-EBOVGP vaccination, which resulted in complete protection at 10 months [41]. Phase I clinical trials of rChAd3 began in September 2014 by the National Institute of Allergy and Infectious Diseases (NIAID) to evaluate the vaccine's safety and immunogenicity. Twenty adults were vaccinated with either 2×10^{10} or 2×10^{11} particles. Reactivity to rChAd3 was dose dependent as two participants developed fever 1 day after vaccination with the 2×10^{11} dose. Similarly, immunogenicity was also dose dependent with higher GP-specific antibodies and T-cell responses detected in the group that received the $2x10^{11}$ dose four weeks after vaccination [42]. In parallel, the NIH partnered with the United Kingdom-based international consortium to test the safety and efficacy of rChAd3, at a dose of either 2×10^{10} or 2×10^{11}, among 60 volunteers at the University of Oxford in England and 40 volunteers in Mali and have observed similar results in regards to safety and immune response [43]. The vaccine will enter a Phase II/III trial called Partnership for Research on Ebola Vaccines in Liberia (PREVAIL). This study will enroll 27,000 healthy men and women to investigate rChAd3 and rVSV/ΔG/GP and is estimated to be completed in June 2016 [43].

Vesicular stomatitis virus (VSV) is a nonsegmented, negative-stranded RNA virus and a member of the Rhabdoviridae family. Recombinant VSV, in which the VSV glycoprotein is replaced with EBOV GP (rVSV/ΔG/GP EBOV), confers 100% protection in nonhuman primates and mice challenged 28 days after immunization with EBOV and mouse-adapted EBOV respectively [45]. Antibodies play a critical role in rVSV/ΔG/GP -mediated protection against EBOV. In a nonhuman primate study, only the animals depleted of CD4+ T cells during vaccination, which lacked GP-specific antibodies, succumbed to infection, suggesting that antibodies were required for protection [46]. Because rVSV/ΔG/GP is a live-attenuated virus, several studies have investigated its safety. No toxicity was observed in over 80 nonhuman primates given rVSV/ΔG/GP MARV or rVSV/ΔG/GP EBOV vaccines [45a, 47]. Moreover, this vaccine was safe in a mouse model of severe combined immunodeficiency

(NOD-SCID) and in simian human immunodeficiency (SHIV) infected rhesus macaques [45b, 47b]. Administration of a single dose of rVSV/ΔG/GP confers 100% protection against EBOV challenge for up to 6 months in macaques and 18 months in mice and guinea pigs and this protection correlates with GP-specific IgG titers [48,49]. This vaccine platform has also provided protection in macaques against MARV for up to 14 months after vaccination, further demonstrating the durability of VSV based vaccines against filoviruses [50]. Administration of a mixture vaccine containing rVSV/ΔG/GP from MARV, EBOV and SUDV to cynomolgus macaques resulted in their survival following challenge with MARV, EBOV, SUDV and TAFV, demonstrating that a single-injection of a multivalent vaccine is as efficacious as the administration of a single specificity vaccine [51]. Finally, rVSV/ΔG/GP has also been shown to be effective post-exposure. Administration of rVSV/ΔG expressing EBOV or SUDV GP to rhesus macaques 20-30 minutes after challenge resulted in 50% and 100% protection, respectively [52]. In March 2009 in Germany, a virologist working in a biosafety level 4 sustained a needle stick injury with a syringe that contained EBOV mixed with Freund's adjuvant. A single dose of 5 x 10^7 pfu rVSV/ΔG/GP EBOV was administered to her 48 hours after the injury. Following post-exposure vaccination, the virologist developed a fever 12 hours later in addition to rVSV viremia detected via PCR for 2 days, but remained healthy during the 3-week observation period [53]. During the 2014 outbreak, rVSV/ΔG/GP EBOV was used as an emergency post-exposure vaccination and administered 43 hours after a physician experienced a needle stick injury while working in an Ebola treatment unit in Sierra Leone [54]. Although it is unknown if rVSV/ΔG/GP EBOV was effective as a post-exposure vaccination, the patient had a self-limited febrile syndrome and cytokine and Ebola glycoprotein specific adaptive immune response after vaccination[54]. The NIH and WHO have carried out Phase I clinical trials to test the safety and efficacy of rVSV/ΔG/GP EBOV, with a dose ranging from 3 x 10^6 pfu to 1 x 10^8 pfu, in various locations in the US, Europe and Africa. Although safety data from Phase I studies have not yet been published, there is sufficient safety and efficacy information to push the vaccine forward into the PREVAIL Phase II/III trial[43]. The CDC in collaboration with Sierra Leone has launched another Phase II/III trial called Sierra Leone Trial to Introduce a Vaccine Against Ebola (STRIVE). The study will test a dose of 2 x $10^{7\ pfu}$ of rVSV/ΔG/GP on 6,000 participants[55].

Therapeutics Against Ebola

Various therapeutic candidates that either directly inhibit viral replication, modulate clinical symptoms, or prolong survival time have been evaluated either as sole or adjunctive post-exposure therapies in rodent and nonhuman primates. A complete list of Ebola therapeutics is summarized in Table 2. Two anticoagulant recombinant proteins, recombinant nematode anticoagulant protein c2 (rNAPc2) and recombinant human activated protein C (rhAPC) have been evaluated in preventing increased coagulation during filovirus infection [59]. However, both anticoagulants provided only partial protection in nonhuman primates challenged with EBOV [59]. Administration of rNAPc2 to 6 rhesus macaques 10 minutes after EBOV challenge prolonged survival time from mean time-to-death of 8.3 days to 11.7 days with a 33% survival rate [59a]. Treatment with rhAPC in 11 rhesus macaques starting 30-60 minutes after EBOV challenge and daily for 7 days increased mean time-to-death from 8.3

to 12.6 days with 2 of 11 rhesus macaques surviving [59b]. Although rNAPc2 has gone through Phase II trials for use in prevention of venous thromboembolism after orthopedic surgery [60] and coronary revascularization [61], it has not been assessed in clinical trials for treatment of EBOV exposure. Additionally, rhAPC has not been evaluated in clinical trials for use against EBOV infection. Treatment with interferon beta (IFNβ) to 5 of EBOV infected rhesus macaques 18 hours and 1, 3, 5, 7 and 9 days post infection did not alter mortality but significantly increased mean time-to-death from 8.3 days to 13.8 days [62] and may be used as an adjunctive therapeutic.

Antivirals that have been evaluated as therapeutics against EBOV include nucleotide analogs (Favipiravir and BCX4430), Brincidofovir and antisense therapeutics (phosphorodiamidate morpholino oligomers (PMOs) and siRNAs) and are summarized in Table 2. Favipiravir (T-705) is an oral nucleotide analog that, when converted into its active metabolite ribofuranosyl triphosphate, inhibits the viral RNA-dependent RNA polymerase by directly competing with GTP. Currently licensed for influenza outbreaks, Favipiravir (T-705) was shown to suppress EBOV replication by 4 $\log_{10}$ units in Vero E6 cells 1 hour after infection [63]. In a mouse model in which mice lack type I IFNα/β receptor and are susceptible to wild type EBOV, treatment with Favipiravir 6 hours after EBOV challenge resulted in complete survival of all five mice [63]. To date, Favipiravir has been used to treat 1 French nurse infected with Ebola who recovered [64]. Favipiravir entered Phase II evaluations in December 2014 in Guinea and is sponsored by Institut National de la Sante Et de la Recherche Medicale, France. Nucleoside analogue inhibitor BCX4430 is an adenosine analog with a C-nucleoside instead of the N-glycoside and a 1,4 imino group instead of the 1,4 oxygen. Once metabolized to the active triphosphate nucleotide form and after pyrophosphate cleavage, it is incorporated into the nascent viral RNA chain and terminates transcription. It is not incorporated into mammalian RNA or DNA. Administration of BCX4430 in cynomolgus macaque as late as 48 hours following infection with Marburg virus resulted in 100% protection [66]. BioCryst Pharmaceuticals and NIAID have initiated a Phase I clinical trial of BCX4430 in the United Kingdom [67].

PMOs are synthetic antisense molecules that are able to target mRNA in a sequence-specific fashion and suppress translation through steric hindrance. AVI-6002 consists of PMO AVI-7537, which targets VP24, and AVI-7539, which targets VP35. AVI-6003 consists of PMO AVI-7287, which targets MARV VP24 and AVI-7288, which targets MARV NP. AVI-6002 protected 62.5% of rhesus monkeys against EBOV infection when given 30-60 minutes post infection and daily for 14 days. AVI-6003 protected 100% of cynomolgus macaques from MARV infection when given 30-60 minutes post infection and daily for 14 days [70]. A follow up study discovered AVI-7537 alone protected 75% (6 out of 8) cynomolgus macaques against EBOV when administered 1 hour ± 30 minutes after challenge and daily for 14 days while treatment solely with AVI-7539 did not result in any survival past 10 days post infection [71] Results from a Phase I clinical trial evaluating the safety and pharmacokinetic profiles of AVI-6002 and AVI-6003 in two groups of 30 individuals revealed both AVI-6002 and AVI-6003 were safe and well tolerated with doses ranging from 0.005 to 4.5mg/kg per component[72]. Small-interfering RNA (siRNA) can inhibit translation of mRNA and has been shown to specifically downregulate MARV transcription of nucleocapsid protein in Vero E6 cells, significantly decreasing viral protein

production and viral release [73]. The design of stable nucleic acid-lipid particles (SNALP) to efficiently deliver siRNAs *in vivo* to target cells facilitated therapeutic evaluation. SNALP-encapsulated siRNAs targeting the EBOV polymerase L gene completely protected 5 guinea pigs from viremia and death when administered at a dose of 0.75mg/kg 1 hour after challenge and daily on days 1-6 post infection [74]. Treatment with a SNALP carrying siRNAs targeting EBOV L polymerase, VP24, and VP35, called TKM-Ebola, resulted in the survival of 2/3 macaques that were given a 2mg/kg dose after 30 minutes and on days 1, 3, and 5 after EBOV challenge and 4/4 macaques that were a 2mg/kg dose after 30 minutes and on days 1, 2, 3, 4, 5, and 6 post challenge [75]. However, Phase I trials of TKM-Ebola in early 2014 were halted after elevated cytokine levels were detected in healthy participants. In October 2014, the FDA expanded access to TKM-Ebola on an emergency basis [76]. Brincidofovir (CMX001) is a lipid conjugate of cidofovir that can be converted intracellularly into cidofovir diphosphate, which has been shown to inhibit DNA polymerase. Although Brincidofovir is in clinical trials for diseases caused by DNA viruses, *in vitro* studies carried out at the CDC and NIH revealed Brincidofovir is active against Ebola virus [68]. While the mechanism by which Brincidofovir acts against Ebola is unknown, Brincidofovir has been used to treat two patients infected with Ebola in the United States (one survived and one died). Although Chimerix initiated a Phase II clinical trial in October 2014 [69], they withdrew the study in January 2015.

Given the large body of both experimental and clinical data supporting the role of antibodies in protection against EBOV infections, several monoclonal treatment modalities were tested. Human monoclonal antibody (mAb) KZ52, which targeted one epitope in EBOV-GP was able to protect guinea pigs [77], but failed to protect rhesus macaques against lethal challenge with EBOV strain Kikwit when administered 1 day before challenge and 4 days after challenge [78]. On the other hand, the administration of a combination of two human-mouse chimeric neutralizing mAbs to three nonhuman primates 1 day prior to as well as 1 and 3 days after lethal EBOV challenge, resulted in protection of 1/3 nonhuman primates and prolonged time-to-death in a second animal [79]. Passive transfer of polyclonal IgG purified from vaccinated NHPs that survived challenge with either EBOV or MARV as late as 48h after virus challenge protected naïve NHPs against both MARV and EBOV lethal challenge [80]. Together with the previously failed trials of monoclonal antibodies, these observations strongly suggested the need to target multiple epitopes on GP in order to achieve protection against EBOV.

In order to develop a multi-specificity antibody cocktail, several EBOV GP-specific mAbs generated using the rVSV/ΔG/GP EBOV vaccine were evaluated in immunocompetent mice and guinea pigs individually or as pools of 3–4 mAbs. In contrast to individually administered mAbs, which were ineffective, pools of 3 mAbs were found to give complete protection in guinea pigs when administered 2 days post infection [81]. These studies paved the way for the development of two cocktails of monoclonal antibodies (either chimeric (c) or human (h)) termed MB-003 (clones c13C6, h13F6 and c6D8) and ZMab (clones m1H3, m2G4 and m4G7) that mediated complete protection of nonhuman primates when administered 1–3 days post-EBOV challenge [82]. Further refinement of these cocktails led to the generation of ZMapp™ containing the monoclonal antibodies with the highest efficacy (c13C6, c2G4 and c4G7). This combination is a highly effective post-exposure therapeutic

that can protect nonhuman primates even when administered 5 days post-exposure to Ebola to symptomatic animals [83] (Table 2). ZMapp has been used to treat 7 patients infected with EBOV, resulting in 5 patients surviving [84]. In February 2015, the NIAID initiated Phase I clinical trial evaluations of ZMapp in Liberia and the United States. The study will be conducted on 200 patients positive for Ebola virus infection who will be randomly assigned to one of two groups: the control group will receive the current standard of care while the second group will receive three infusions of ZMapp administered three days apart[85].

Conclusion and Future Outlook

EBOV is one of the most feared pathogens due to its high lethality rates. Subversion of innate immune response by Ebola virus occurs at various levels from suppression of IFN response, generation of robust cytokine storm, and inhibition of dendritic cell maturation. Dysregulation of innate immune pathways together with the characteristic lymphopenia of Ebola prevent the development of cellular and humoral responses as evident by lack of EBOV-specific T and B cell responses, and sequestration of neutralizing antibodies. The current Ebola outbreak in West Africa has spurred a public health emergency and highlighted the need for licensed vaccines and post-exposure therapeutics. With the substantial amount of data pointing to the critical role for antibody-mediated protection against Ebola, it is imperative that research efforts focus on evaluating the safety and efficacy of monoclonal antibody cocktails. The highly promising antibody cocktail ZMapp is grown in tobacco plants, which is thought to take less time and money to produce than in rodents. However, clinical evaluations of ZMapp were delayed until early of 2015 due to the slow production of ZMapp. The production of one course treatment (14g) requires 78 tobacco plants to produce [86]. Consequently, efforts must be allocated to developing novel methods to increase yields of the monoclonal antibody cocktail. Although using more traditional methods of generating monoclonal antibodies in rodents may be a slower route than tobacco plant production, this established technique might enable increased production in order to ensure enough of the treatment is available for further clinical evaluations and future outbreaks.

In addition to monoclonal cocktails, efforts to evaluate and license the rVSV/ΔG/GP EBOV vaccine should be increased. Compared to the rAd vaccine platform, advantages of the rVSV/ΔG/GP EBOV platform include limited pre-existing immunity, the ability to administer it mucosally, long duration of immunity after one dose, and its potential use as a post-exposure vaccination. With the Ebola outbreak slowing down, the opportunity to obtain efficacy data through human trials may decrease. In this case, the FDA animal rule should be used, in which laboratory animal data is used to show efficacy, in order to move vaccine candidates through the approval process and start stockpiling the most promising candidate. This will ensure that we have immediate immunization available to protect frontline healthcare workers and contain the spread of a future outbreak.

The 2014 outbreak highlights that Ebola virus disease in not limited to central Africa and is a global problem that requires global cooperation. The World Health Organization’s role in the event of an outbreak should be to effectively coordinate regional collaboration where data and expertise relevant to the outbreak in addition to critical information about disease

surveillance is shared. Efforts to improve the infrastructure of healthcare in African nations should be undertaken, such as developing inexpensive systems to equip hospitals to be able to manage routine healthcare needs as well as outbreaks. Educating the public is also equally important, as many individuals in Ebola outbreak countries are fearful of modern health care, preventing those who have come into contact with the disease to seek health care and contributing the spread of the virus. Therefore, increased training of local health care force to build trust and effectively communicate with the public in times of crisis is urgently required. Community engagement is absolutely required especially when preventive measures are at odds with cultural beliefs and religious practices. Public health education regarding the dynamics of Ebola transmission is also urgently needed, especially with traditional burial practices, which involves washing and touching of the deceased. It is clear that our approaches in combatting Ebola virus disease will engage many areas ranging from vaccine and therapeutic discovery to improving healthcare infrastructure, training and community participation.

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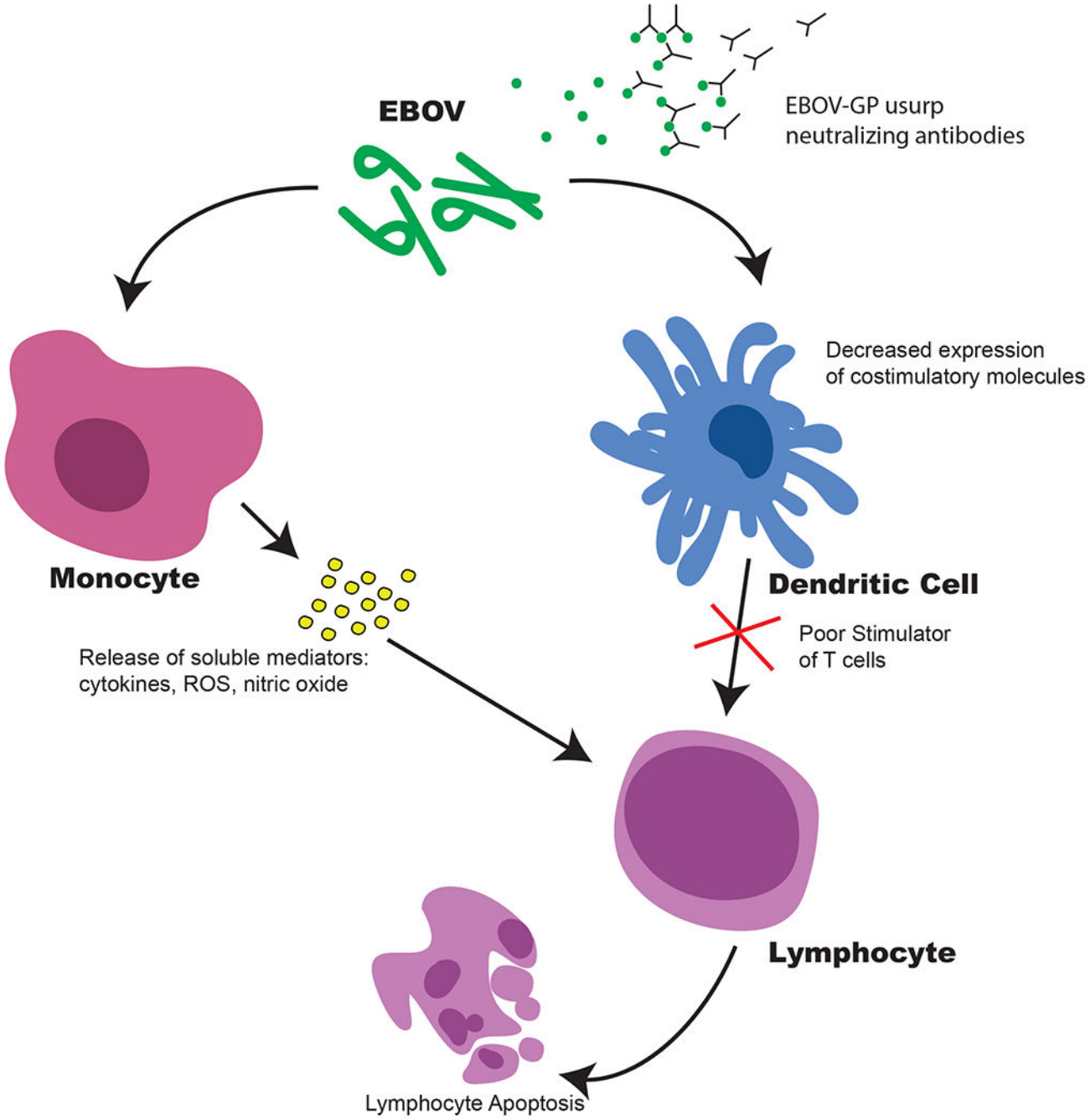

Figure 1. Dysregulation of Immune System by Ebola virus.

Monocytes, macrophages, and dendritic cells are preferred sites of filovirus replication. Infection of monocytes and macrophages triggers robust expression of inflammatory mediators. Inflammatory mediators, reactive oxygen species and nitric oxide can induce apoptosis leading to lymphocyte death. Infection of dendritic cells impairs their maturation and suppresses type I (IFN) responses thereby preventing T cell activation. Production of EBOV soluble glycoprotein (sGP) usurps GP-specific antibodies.

Table 1.

Vaccines against Ebola Virus

Vaccine	**rAd5/ChAd3**	**rVSV/ΔG/GP EBOV**
Replication potential	Replication deficient	Replication competent
Mechanism of protection	$CD8^+$ T cell mediated	Antibody mediated
Booster requirement	Modified vaccinia Ankara	
Durability	10 months with booster vaccination in nonhuman primates	12-18 months in rodents 14 months in nonhuman primates (MARV)
Clinical trial	Phase II/III	Phase II/III

Table 2.

Therapeutics for EBOV infection

Molecule	Mechanism of Action	Development Phase	Reference
Favipiravir	A nucleotide analog that inhibits RNA polymerase.	Has been shown to protect mice against EBOV. Administered to one EBOV infected patient who survived. Currently in Phase II trial.	63
PMOs AVI-6002 (AVI-7537 and AVI-7539) AVI-6003 (AVI-7287 and AVI-7288)	AVI 7537 targets EBOV VP24; AVI-7539 targets EBOV VP35 AVI-7287 targets MARV VP24; AVI-7288 targets MARV NP	AVI-6002 has been shown to provide partial protection of rhesus macaques against EBOV. AVI-7537 confers sole protection observed. AVI-6003 has been shown to completely protect cynomolgus macaques from MARV infection. Completed Phase I clinical trial.	71
ZMapp	Monoclonal cocktail of antibodies against different epitopes of EBOV-GP.	Has been shown to completely protect cynomologus macaques. Protected 5/7 patients infected with EBOV. Currently in Phase I clinical trial.	8385
BCX4430	An adenosine analog that inhibits RNA transcription.	Shown to protect cynomolgus macaques against Marburg virus. In Phase I clinical trial.	66
Brincidofovir	Inhibits DNA synthesis. Mechanism against RNA viruses is unknown.	Shows efficacy against EBOV *in vitro*. Protected 1 of 2 US patients infected with EBOV. Withdrawn from Phase II clinical trial	6968
TKM-Ebola	Treatment with SNALP carrying siRNAs against EBOV L polymerase, VP24, and VP35.	Protected macaques following EBOV challenge. Phase I trial were halted. FDA expanded access to TKM-Ebola on an emergency basis.	74–75
rhAPC	Anticoagulant	Recombinant human activated protein C is an anticoagulant that prolongs survival time and provides partial protection in nonhuman primates.	59b
rNAPc2	Anticoagulant	Recombinant nematode anticoagulant protein c2 prolongs survival time and provides partial protection in nonhuman primates.	59a
IFNβ	Interferon	Prolongs mean time-to-death in rhesus macaques infected with EBOV. May be possible adjunctive post-exposure therapy	62
Chloroquine	The antiviral mechanism is unknown.	FDA approved as an antimalarial agent. Through a screening study evaluating 1012 FDA-approved drugs, chloroquine was found to possess *in vitro* activity against EBOV. Found to protect mice against EBOV infection *in vivo*.	87
Selective estrogen receptor modulators: clomiphene and toremifene	Inhibits EBOV entry.	Clomiphene and toremifene inhibit EBOV infection *in vitro* and show partial protection in mice challenged with mouse adapted EBOV.	88
FGI compounds: FGI-103, FGI-104, FGI-106	FGI compounds are broad-spectrum viral inhibitors. Antiviral mechanism against EBOV is unknown.	Exhibited efficacy against EBOV *in vitro* and in mouse models.	899091
SAH hydrolase inhibitor Deazaneplanocin A	Targets SAH hydrolase, indirectly resulting in reduced methylation of 5' cap of viral messenger RNA. May also increase IFNα production	Early dose protected mice against EBOV challenge.	92
Glucosidase inhibitors: CM-10-18, IHVR11029, IHVR17028 and IHVR19029	Glucosidase inhibitors inhibit Endoplasmic reticulum α-glucosidases I and II and prevent maturation of viral glycosylated envelope and, inhibiting viral entry.	CM-10-18, IHVR11029, IHVR17028 and IHVR19029 has been shown to suppress mortality of MARV and EBOV infection in mice.	93
Antioxidant NSC62914	Acts as a scavenger of reactive oxygen species and upregulates oxidative stress-induced genes.	Exhibits anti-filovirus activity *in vitro and in vivo* in mice infected with EBOV or Marburg virus.	94

Molecule	Mechanism of Action	Development Phase	Reference
HSPA5 inhibitors	Targets HSPA5 chaperone (EBOV-associated host factor).	PMOs targeting HSPA5 reduced viral replication and protected mice against lethal EBOV infection.	95
SAH hydrolase inhibitor Neplanocin A, 3-	Targets SAH hydrolase, indirectly resulting in reduced methylation of 5' cap of viral messenger RNA	Efficacy of Neplanocin A against EBOV has been shown *in vitro.*	9697
Benzylpiperazine adamantine diamides	Inhibits EBOV entry via cholesterol transporter Niemann-Pick C1 *in vitro*	Shown to inhibit EBOV entry *in vitro.*	9899
LJ-001	A rhodamine derivative, which prevents fusion of viral and cellular membranes and prevents viral entry.	Shown to inhibit EBOV entry *in vitro.*	100
CMLDBU3402	Broad-spectrum antiviral Inhibits EBOV RNA transcription	Shown to inhibit EBOV entry *in vitro*	101
Ion channel blockers: amiodarone, dronedarone, verapamil	Inhibit EBOV entry	Shown to inhibit EBOV entry *in vitro.*	102
Heme oxygenase-1 (HO-1)	Inhibit EBOV replication. Mechanism unknown	HO-1 induction significantly suppressed EBOV replication *in vitro.*	103
Lamivudine	Cytosine analog approved for treatment of HIV and hepatitis B virus. Unknown mechanism against EBOV	Not yet evaluated in context of EBOV. Studies against EBOV *in vitro* are currently being conducted	104
duY11	A rigid amphipathic fusion inhibitor (RAFI) targets entry of enveloped viruses and may potentially inhibit entry of EBOV	Not yet assessed in *in vitro* or *in vivo* studies against EBOV	105
Inhibitors of cathepsin L cleavage	Prevention of cathepsin L cleavage of viral glycoproteins may inhibit EBOV entry.	Not yet assessed in *in vitro* or *in vivo* studies	106
Statins	Anti-inflammatory	No *in vitro* or *in vivo* studies in efficacy against Ebola. However, may be used to treat viral sepsis during EBOV infection. FDA approved	107