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Interaction of Ebola Virus with the Innate Immune System

Felix B. He, Krister Melén, Laura Kakkola and Ilkka Julkunen

Abstract

Ebola viruses (EBOV) are zoonotic pathogens that cause severe diseases in humans and have been responsible for several disease outbreaks over the past 40 years. Ebola virus disease (EVD) leads to death on an average of 45–50% of cases, but in some outbreaks, the figures have been higher. The largest EVD outbreak in West Africa in 2014–2015 led to more than 28,000 cases and 11,300 fatalities. Host innate immune responses are vital in restricting the spread of viral infections including that of Ebola virus. EBOV and some other filoviruses are known to trigger uncontrolled virus replication by suppressing host innate immune responses, mainly by targeting the antiviral response through virus proteins. At least EBOV VP24 and VP35 proteins have been shown to inhibit the expression of type I and III interferon (IFN) genes as well as to inhibit IFN signaling leading to downregulated IFN-induced antiviral responses. In this review we concentrate on describing the mechanisms by which EBOV contributes to the pathogenesis of severe disease and on how the virus interacts with the host innate immune system.

Keywords: Ebola virus, filovirus, innate immunity, RIG-I pathway, MDA5 pathway, VP24

1. Introduction

Ebola virus (EBOV) belongs to the family of filoviruses which include seven viral species. Currently, eight virus types have been identified within this virus family [1]. The virus particles have a uniform diameter of 80 nm but can extend even up to 10,000 nm [2]. So far the largest outbreak of Ebola virus disease (EVD) has taken place in West Africa, in Guinea, Sierra Leone, and Liberia in 2014–2015 [3, 4]. In humans EVD is characterized by a severe disease with high fever, diarrhea and vomiting, occasionally hemorrhagic manifestations, and suppressed immune and inflammatory responses which often lead to sepsis-like symptoms and hypovolemic shock [5]. Because of its high case-fatality rate and limited treatment and vaccination options, EBOV is classified as a biothreat pathogen of category A [6] and should be handled at biosafety level 4 (BSL-4) laboratories. EBOV is also considered as one of the deadliest human pathogens and a potential bioterrorism agent [7].

EBOV infection targets many tissues and cell types leading to dysregulation of inflammatory mediators, disrupted homeostasis, and impaired host immune responses. Together with abnormalities in the coagulation and vascular system, the infection often leads to a fatal outcome in humans due to a multiorgan failure [8–10].

Invading and replicating viruses are recognized by the host via cellular pattern recognition receptors (PRRs). PRRs recognize pathogens via pathogen-associated molecular patterns (PAMPs), such as viral structural components and nucleic acids, which then activate host innate immune responses. RNA virus infection activates different PRRs like Toll-like receptors (TLRs), retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), and nucleotide-binding oligomerization domain-containing (NOD)-like receptors (NLRPs). Cell membrane-associated TLR3 and intracellular vacuole-located TLR7 and TLR8 are activated by viral dsRNA and ssRNA molecules, respectively, leading to the activation and nuclear translocation of transcription factors NF- κ B, interferon regulatory factor 3 (IRF3) and IRF7 as well as MAP kinases activated transcription factors (MAPK TFs). Cytosolic RLRs, RIG-I, and melanoma differentiation-associated antigen 5 (MDA5) are activated by viral ss/dsRNA molecules leading to activation and nuclear translocation of IRF3 (and IRF7), NF- κ B, and MAPK TFs [11–13]. NLRP activation, especially NLRP3, leads to the activation of the inflammasome and the production of inflammatory cytokines IL-1 β and IL-18 [14].

It has been shown that the RIG-I pathway has a significant role in host innate immune responses when the pathogen is an RNA virus. RIG-I recognizes 5'-triphosphate and short ss/dsRNA structures present in genomic and replicated viral RNAs. RIG-I activates mitochondrial antiviral signaling protein (MAVS) which is located in mitochondrial membranes. MAVS triggers the activation of inhibitor kappaB kinases (IKK $\alpha/\beta/\gamma/\epsilon$) and TANK binding kinase 1 (TBK1) through tumor necrosis factor receptor-associated factor (TRAF) adaptor proteins. Activated TBK1 and IKK ϵ then phosphorylate IRF3 [15], which forms dimers and translocates into the nucleus. At the same time, the canonical IKK $\alpha/\beta/\gamma$ complex activates NF- κ B by phosphorylating the inhibitor of NF- κ B (I κ B) leading to degradation of I κ B and the release and nuclear translocation of active p50-p65 NF- κ B complex. NF- κ B and dimerized IRF3 bind to the promoter elements of type I and type III IFN genes. This then leads to RNA polymerase II complex-initiated expression of IFN genes and secretion of type I IFN- α/β and type III IFN- λ s [16]. The produced interferons are important in activating the second phase of innate immune responses in epithelial cells, fibroblasts, leukocytes, or basically any cell that has functional IFN receptors. IFN α/β and IFN- λ s bind to their specific type I and type III cell surface IFN receptors (IFNAR and IFNLR, respectively) leading to activation of janus kinases (JAK) and phosphorylation and activation of signal transducers and activators of transcriptions 1 and 2 (STAT1 and STAT2). Activated STAT1-STAT2 complexes translocate into nucleus and together with IRF9 induce the expression of hundreds of host genes, which include antiviral genes like Viperin, IFITMs, PKR, OAS, and Mx genes [17].

2. Ebola virus, virus proteins, and virus replication

Single-stranded viruses with negative-sense RNA genomes can be assigned to three different subgroups whether they are multisegmented, circular, or unsegmented [18]. Unsegmented viruses belong to the order of *Mononegavirales*, and the filovirus group is one of the eight mononegaviral families [19]. Filoviruses are enveloped, non-segmented, negative-stranded RNA viruses of varying morphology. They are called filoviruses because of their filamentous particle structure [20]. Filoviruses are assigned to seven species in three genera *Cuevavirus*, *Ebolavirus* (EBOV), and *Marburgvirus* (MARV) [21]. Most of the filoviruses are human pathogens, and the diseases caused by two of these viruses, EBOV and MARV, are well-known because of their high case-fatality rate [3].

Ebola virus group includes five virus species, *Zaire ebolavirus* (ZEBOV), *Bundibugyo ebolavirus* (BEBOV), *Ivory Coast ebolavirus* (ICEBOV), *Sudan ebolavirus* (SEBOV), and *Reston ebolavirus* (REBOV). Filoviruses consist of ssRNA genomes of 19 kilobases. EBOV genome encodes eight different proteins that all have specific functions [22]. **Table 1** summarizes the major characteristics of EBOV proteins. The gene order of EBOV genome is NP, VP35, VP40, GP/sGP, VP30, VP24, and L (**Figure 1**). Nucleocapsid-associated proteins include the major nucleoprotein NP and the minor nucleoprotein VP30. Both of these proteins interact with the RNA genome and protect the viral RNA. Nucleocapsid structures also include VP35 and RNA-dependent RNA polymerase (RDRP) protein L [23]. Ribonucleoprotein complex regulates viral replication and transcription of the viral genome. The RDRP complex consists of L polymerase and VP35, the latter of which acts as a polymerase cofactor [24–26]. NP with RDRP complex catalyzes the viral genome with VP30 to initiate transcription and replication. VP40 is required for viral particle formation, and it is the major matrix protein [27]. Viral envelope glycoprotein (GP) is the only viral envelope protein, and its function is to attach the host cell surface and mediate the entry of viral nucleocapsids [28]. EBOV GP is heavily N- and O-glycosylated. On the surface of virus particles, GP is cleaved into two subunits (GP1 and GP2), and it exists as a trimeric protein complex (peplomers). In addition to full-length GP, there are several other forms of proteins encoded by the GP gene: nonstructural soluble glycoprotein (sGP) and a small soluble GP (ssGP) [29]. The functions of sGP and ssGP are presently not known, but they have been suggested to neutralize EBOV GP-specific antibodies. The viral genome encodes also VP24 which is a minor matrix protein, and its functions are dealing with virion assembly and downregulation of host innate immune responses (see below).

VP24	• Minor matrix protein, virion assembly • Inhibits type I and type III interferon (IFN) gene expression • Inhibits type I and III IFN signaling reducing the expression of IFN-induced genes (blocks STAT1/2 nuclear import)
VP30	• Minor nucleoprotein • Transcription activator
VP35	• Polymerase cofactor • Binds dsRNA and inhibits type I IFN production • Inhibits dendritic cell maturation • Blocks IKKε/TBK1 activation and IRF3 phosphorylation
VP40	• Viral matrix protein • Required in virion assembly and budding
NP	• Structural protein of nucleocapsid complex • Catalyzes viral replication and transcription of the RNA genome
GP	• Viral envelope glycoprotein • Attachment to host cell surface • Mediates virus entry • Target of anti-GP neutralizing antibodies
sGP (ssGP)	• Soluble glycoprotein (small soluble GP) • Possible decoy of anti-GP antibodies
L polymerase	• Viral RNA-dependent RNA polymerase

Table 1.
Ebola virus proteins and their functions in virus replication cycle and in host cell functions.

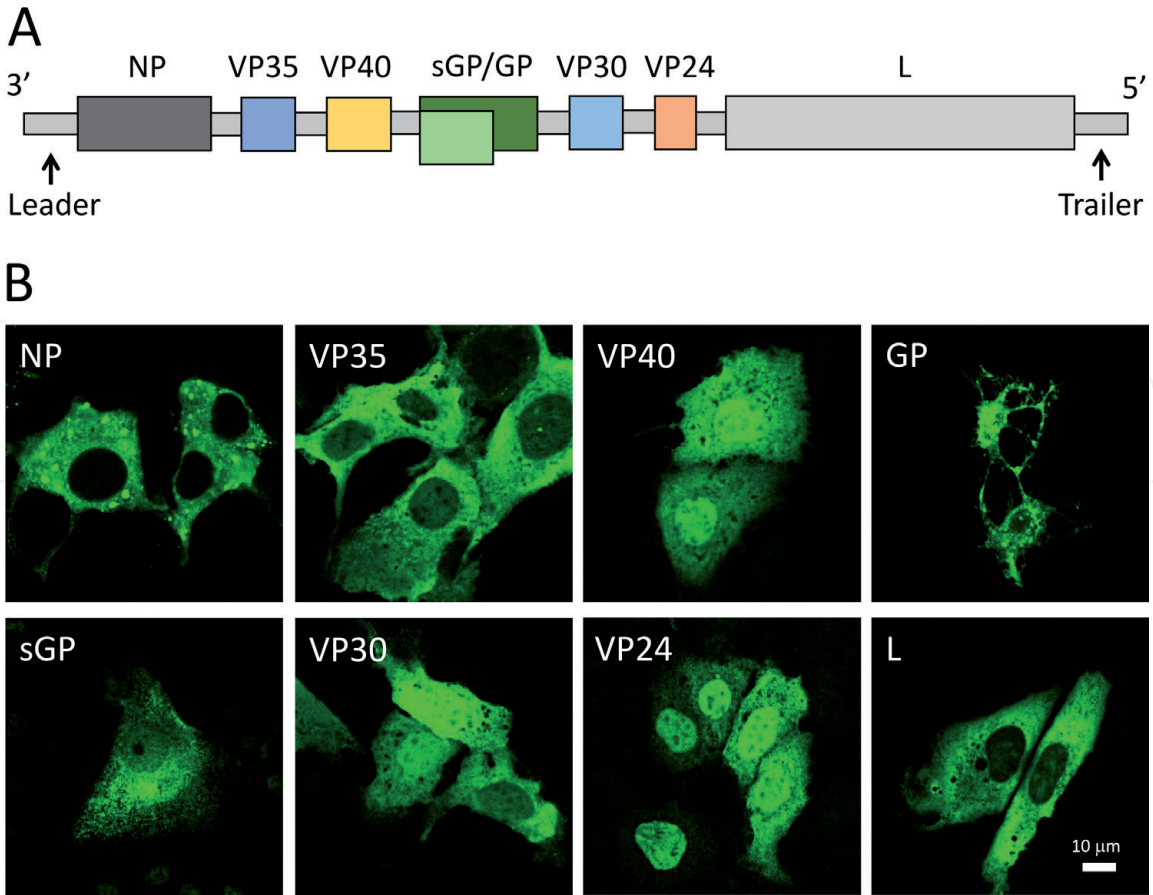


Figure 1. Ebola virus genome structure and the expression of individual EBOV proteins in transfected cells. Panel A. EBOV genome encodes for eight different proteins, nucleoprotein (NP), viral protein 35 (VP35), VP40, secreted glycoprotein (sGP), GP, VP30, VP24, and RNA polymerase L are schematically shown. Panel B. Human hepatoma HuH7 cells were transfected with pcDNA3-His or HA-EBB expression constructs for different EBOV genes, and 24 h after transfections, the cells were stained with monoclonal anti-His (NP, VP35, VP40, GP, sGP, and VP30) or anti-HA (VP24 and L) antibodies and secondary rabbit anti-mouse immunoglobulin. Note that VP40 and especially VP24 are localized into the cell nucleus, and GP-expressing cells show significant cytotoxicity.

EBOV can infect a wide variety of cells, which may explain the ability of the virus to spread to many tissues and different types of cells. At present there is no direct evidence of one specific EBOV receptor; rather many types of molecules such as integrins, C-type lectins, and TIM-1 have been suggested to function as a cellular receptor. After attachment EBOV is endocytosed followed by a fusion of viral and endosomal membranes and release of viral nucleocapsid into the cell cytoplasm. In the cytoplasm virus-specific mRNAs are synthesized from the genomic RNA template. Viral RNA polymerase complex is responsible for the synthesis of individual mRNA molecules for each EBOV proteins. Both the transcription and translation of EBOV proteins takes place in the cell cytoplasm. Virus replication is regulated by the L polymerase, VP30, VP35, and NP followed by the assembly of viral nucleocapsid (NC) structures. GP synthesis and glycosylation occurs in the Golgi complex, and the assembly of newly produced virus particles takes place at the plasma membrane where NCs, VP40, VP24, and GP are assembled followed by virus budding from the plasma membrane [22–27].

3. Ebola virus disease (EVD)

Ebola virus disease was first recognized in 1976 simultaneously in two different geographic locations, in Sudan and in the Democratic Republic of Congo [9, 30]. The newly identified viral agent was named Ebola virus, and the symptoms resembled

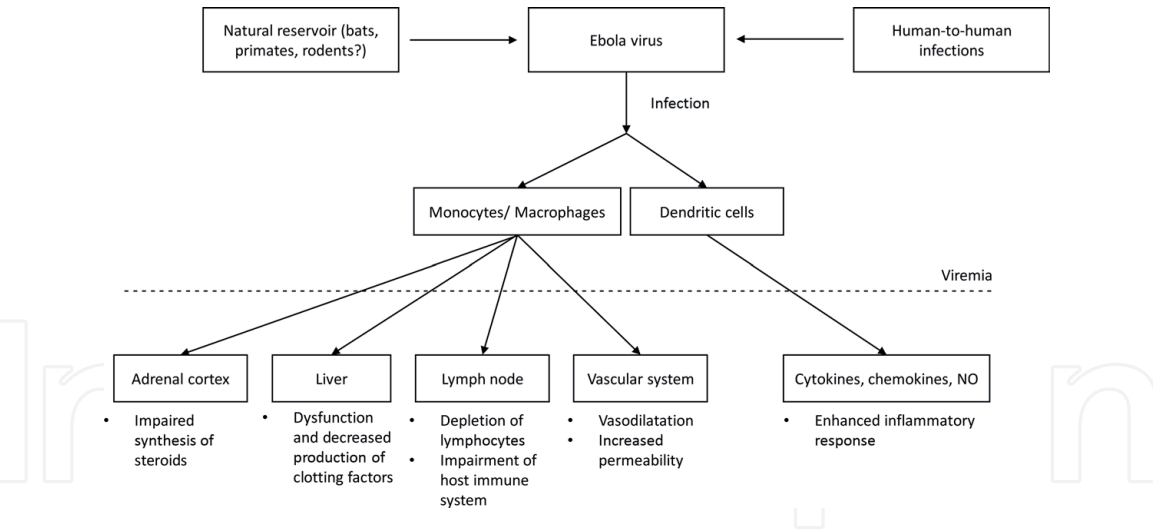


Figure 2.
Target cells and tissues infected by EBOV. Zoonotic and human-to-human transmission of EBOV through initial infection sites lead to viremia which targets the lymph nodes, liver, spleen, adrenal cortex, and vascular system. The widespread viral dissemination leads to tissue and vascular damage in these organs possibly resulting in sepsis-like state and multiorgan failure.

those of Marburg virus disease (MVD). Most human cases have been caused by the ZEBOV species, and most of the outbreaks have occurred in Central and West Africa [5]. Like in many other zoonotic diseases, EBOV is considered to have a natural reservoir in animals, but humans may also transmit the disease via blood, serum, and bodily secretions (**Figure 2**). Patients that recovered from the primary infection were found to excrete the virus for several weeks or months also via the genital tract, especially in semen [31]. Humans and possibly some other mammalian species like primates are considered as the dead-end hosts [32]. Even though there are no firm links to natural reservoirs of EBOV, many studies suggest that rodents and bats likely play a role in virus transmission [33–36]. There is strong evidence that fruit bats, in case they are in close contact with humans or when they are used as food, transmit the disease to humans. EBOV may exist silently in reservoir species and be activated through certain stimuli such as stress, coinfection, pregnancy of the carrier animals, ecological changes, and change in food habits [37, 38].

Nevertheless, the route of primary transmission from possible reservoirs to humans needs to be studied in more detail in order to prevent direct infection routes from animals to humans. During outbreaks the dominant mode of transmission is human-to-human either through mucosa or lacerations [39]. An average incubation time in EBOV epidemics with human-to-human spread has been around 9–10 days [40]. Analysis of EBOV transmission between the patient and the secondary case(s) indicates an association with an exposure to infectious bodily fluids [41]. A large meta-analysis conducted on the secondary transmissions in the same household showed that the risk of transmission was less than 1% when the person was not in direct contact with an EVD patient [42].

Once the transmission has occurred, symptoms normally arise after 4–10 days of exposure, though there is a wide variation in the incubation time ranging from 2 to 21 days [43, 44]. The typical symptoms of EVD are flu-like symptoms with fever, myalgia, and chills. Also, gastrointestinal symptoms occur as vomiting and diarrhea. After these common symptoms, the disease may rapidly evolve as hemorrhagic complications, anuria, dysthesia, and sepsis-like symptoms resulting in multiorgan failure [44, 45]. Other reported symptoms include headache, profound weakness, coughing, and rhinorrhea. Also, when systemic symptoms related to cardiovascular system occur, they often result in septic shock and edema [5, 44, 45]. Hematological changes in laboratory parameters include leukopenia, decreased neutrophil counts,

and increase in liver enzymes. When the infection proceeds, patients develop thrombocytopenia, prolonged prothrombin time, and activated partial thromboplastin time. This may result in disseminated intravascular coagulation, which finally leads to a multiorgan failure and death [5]. Patients who have survived EVD were found to develop long-term symptoms and disorders such as recurrent hepatitis, myalgia, arthralgia, prolonged hair loss, psychosis, and uveitis [5, 43, 45], which in rural areas often do not receive adequate therapy.

Rapid EVD diagnosis is done by antigen detection methods (e.g., ELISA) or by the detection of viral RNA using RT-PCR techniques. High levels of viruses/viral RNA are generally seen after 48 h of clinical infection. ELISA-based EBOV-specific IgG and IgM antibody detection methods have also been developed [2]. Due to rural conditions and the fatal nature of the disease, EVD is often diagnosed based on anamnestic information and patient's symptoms [46].

Fortunately, there are promising novel therapeutic alternatives of antiviral compounds identified in *in vitro* and in animal studies [46]. Humanized monoclonal neutralizing antibody cocktails have also been used to treat EVD patients [47]. Due to the very high case-fatality rate of EVD, WHO has declared that it is ethical to use experimental drugs to treat and prevent EVD. However, to date, there are no EBOV-specific therapies that have proven their efficiency in controlled studies in humans, and thus, supportive care remains the main treatment modality for EVD patients [5, 48]. Possible future therapies would include slowing down virus replication and disease progression allowing host innate and adaptive immune responses to overcome the infection [49, 50].

Another way to approach EBOV epidemics is to use vaccines in high-risk areas. Vaccine candidates must show good efficacy in experimental EVD models [51]. Recent reviews summarize the progress made in the field of EBOV vaccines [52, 53]. Currently there are two promising vaccine candidates that have entered clinical studies: monovalent and bivalent recombinant adenovirus and VSV-based vaccines [52], the latter of which has been used in the most recent epidemic in the Democratic Republic of Congo.

4. The effect of Ebola virus infection and EBOV proteins on cytokine gene expression

Filoviruses can infect many different cell types, for example, macrophages, monocytes, dendritic cells, Kupffer cells in the liver, fibroblasts, hepatocytes, cells of adrenal gland tissue, endothelial cells, and epithelial cells (**Figure 2**) [54, 55]. In nonhuman primates it has been shown that the virus first replicates in macrophages and dendritic cells. These cells are considered to be responsible for an unbalanced immune response [55]. Studies have shown that EBOV efficiently infect these cells after they differentiate from monocytes [56–58]. Histopathological studies in human tissues have proven that macrophages are readily infected [59]. The data on cytokines and inflammatory responses show that there is a correlation between poor prognosis and intense inflammatory response characterized by excessive cytokine and chemokine production [60]. After the initial infection phase in monocyte/macrophages and dendritic cells, the virus is spreading to lymph nodes and other organs such as the liver and the spleen which takes place via the lymphatic system [54, 55]. EBOV infection in these target organs leads to strong inflammatory responses and the release of pro-inflammatory cytokines and chemokines, such as interleukin-1 β (IL-1 β), IL-6, IL-8, IL-10, monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein 1 α (MIP1 α), MIP1 β , and tumor necrosis factor (TNF) as well as to reactive oxygen species and nitric oxide [8, 61, 62].

MIP1 α and MCP1 create a positive feedback loop where secreted cytokines recruit more monocyte/macrophages to the site of infection enabling EBOV to infect more target cells [55]. The infection caused by EBOV inhibits the maturation of dendritic cells and prevents antigen presentation to T cells. This event is due to EBOV infection to inhibit upregulation of CD40, CD80, CD86, and major histocompatibility complex (MHC) class II molecules [63, 64]. A commonly seen characteristic of EBOV infection is lymphopenia which occurs among CD4⁺ and CD8⁺ T cells and natural killer (NK) cells [65, 66]. The same effect was detected in vitro with EBOV-infected human CD4⁺ and CD8⁺ T cells [67]. The differences in lymphopenia profiles between the survivors and deceased patients have been linked to uncommon innate immune response and suppression of adaptive immunity [68, 69]. However, the connection between pathogenesis and the consequences of lymphopenia is presently not known. Loss of CD4⁺ T cells may also lead to reduced production of EBOV-specific immunoglobulin M (IgM) and IgG antibodies stating that early events that occur in the immune system in EBOV infection determine the outcome of EVD [70].

The morbidity and mortality of EVD are considered to be due to a burst of immunological mediators better known as a “cytokine storm” [60, 68]. The cytokine storm is a response caused by a wide variety of infectious and noninfectious agents where they induce the production of pro- and anti-inflammatory factors usually consisting of IFNs, TNFs, interleukins, and chemokines [60, 71]. Unfortunately, the precise mechanisms triggering the cytokine storm is not known. Yet there are some studies showing that certain viruses and bacteria trigger cytokine storm through T-cell receptors and CD28 and/or by activating PAMP recognition

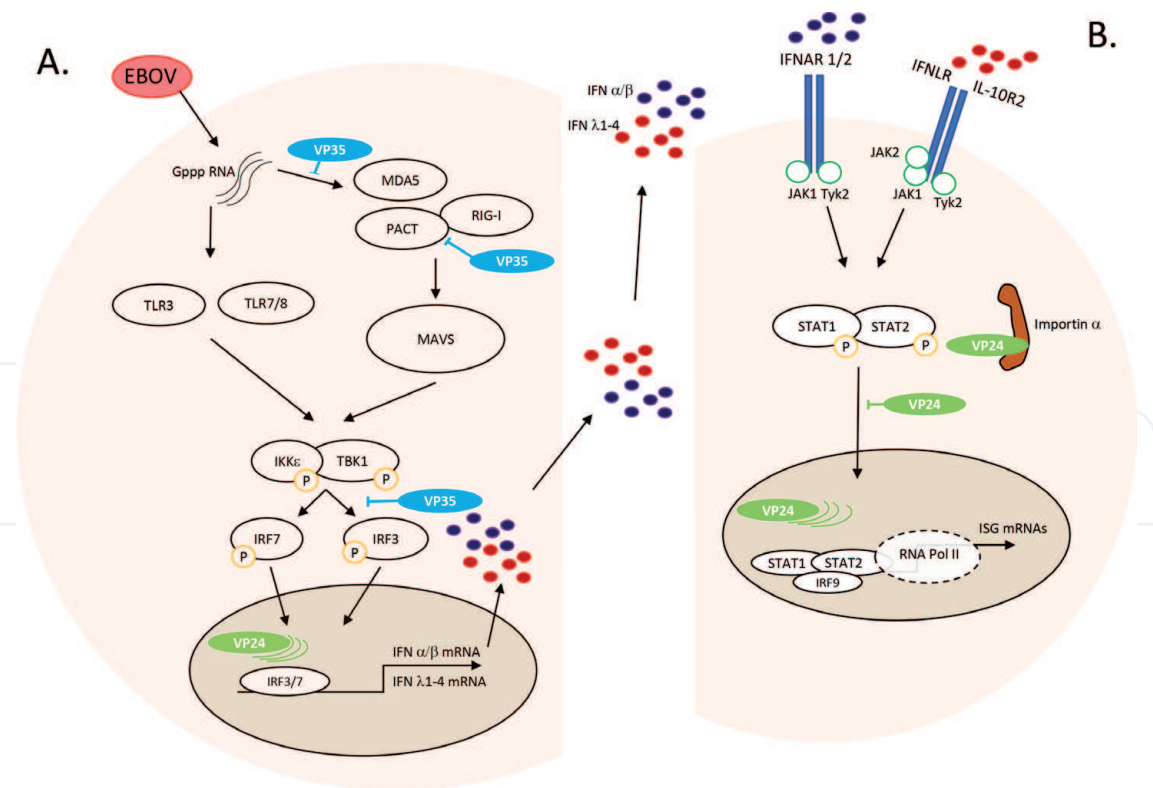


Figure 3. Panel A. EBOV prevents type I and III IFN production and expression. Two of the eight proteins encoded by EBOV have shown inhibitory effect in previous in vitro studies: VP35 and VP24. VP35 blocks RIG-I-like signaling by binding to dsRNA or PACT and prevents IFN α/β production. It also promotes degradation of IRF3 and IRF7 by interacting with host SUMOylation process. VP35 also prevents phosphorylation of IKK ϵ . VP24 instead inhibits IFN- λ 1 gene expression downstream of IRF3. The exact mechanism is still unknown. Panel B. VP24 blocks the nuclear import of phosphorylated STAT1-STAT2 dimers by binding to importin α isoforms which limits the nuclear accumulation of activated STATs and reduces IFN-induced gene expression.

pathways [72, 73]. Since EBOV infection in macrophages and dendritic cells suppresses their cytokine and chemokine production, including that of antiviral IFNs, it is likely that the excessive production of pro- and anti-inflammatory mediators occurs in other cell types apart from macrophages and DCs [74].

The immune evasion mediated by individual EBOV proteins has also been studied. So far two of the eight or nine EBOV proteins, namely, VP24 and VP35, have been shown to interfere with the activation of innate immune responses (**Figure 3**). VP35 has been shown to inhibit the maturation of dendritic cells. It interferes with the RIG-I signaling pathway to prevent enhanced expression of MHC class I and class II and the costimulatory molecules CD40, CD80, and CD86. This leads to impaired antigen presentation to CD8+ and CD4+ T cells and to impaired T-cell activation which disrupts the linkage between innate and adaptive immune responses [75, 76]. VP35 also inhibits RIG-I signaling by preventing IFN- α/β gene expression. VP35 binds to dsRNA which inhibits the interaction of RIG-I with viral RNAs. Also, the interaction between PKR activator PACT and RIG-I is disrupted which does not allow the normal RIG-I ATPase activation to take place [77].

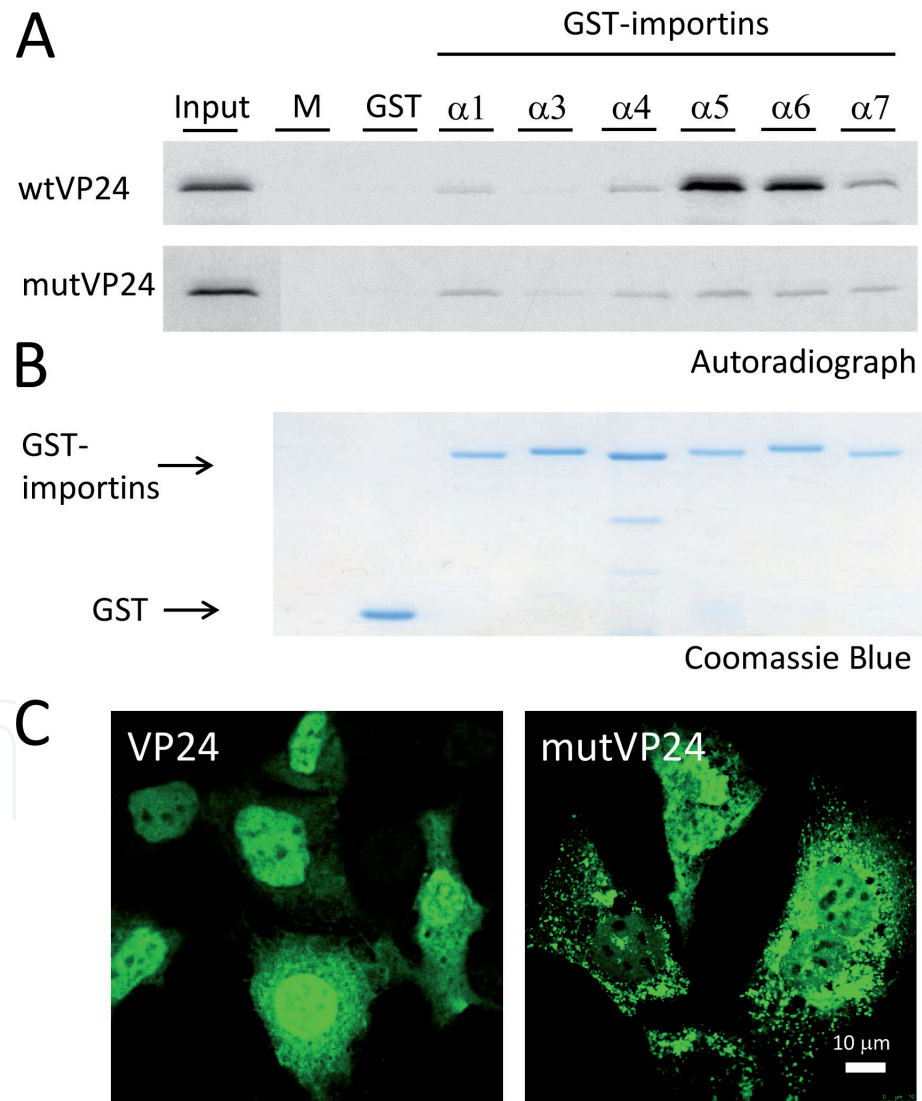


Figure 4. Panel A. Interaction of EBOV VP24 with human importin α isoforms and intracellular location of wild-type (wt) VP24 and NLS mutant (mut) VP24. Baculovirus or *E. coli*-expressed GST-importin α isoforms were allowed to bind to glutathione Sepharose. In vitro-translated 35 S-methionine-labeled wt and mut VP24 proteins were allowed to bind to immobilized GST-importin α isoforms. NLS mutant VP24 shows clearly reduced binding to importin α molecules. Panel B shows the amount of Sepharose-bound GST-importin α molecules. Panel C shows the intracellular location of wt VP24 and reduced nuclear translocation of NLS mutant of VP24.

VP35 has also been reported to increase the SUMOylation of IRF7 by SUMO-conjugating enzyme UBC9 and SUMO E3 protein ligase PIAS1 leading to reduced transcriptional activity of IRF7 [78]. IRF7 is one of the key transcription factors regulating IFN- α/β and IFN- λ gene expression [79]. EBOV VP35 also inhibits IKK ϵ /TBK1 kinase complex functions [80]. In addition to all the abovementioned functions, VP35 has an inhibitory effect on PKR activation that contributes to inhibition of dendritic cell maturation [61, 81].

EBOV VP24, in addition of having a role in virion assembly, is downregulating the activation of innate immune responses. In virus-infected and in VP24 gene-transfected cells, VP24 protein is expressed in the cell cytoplasm and especially in the nucleus (**Figure 1**) [82]. The expression of VP24 genes from different EBOV viruses has shown that they all inhibit RIG-I-induced IFN gene expression [83]. The analyses have been done by cotransfecting cultured cells, often human embryonal kidney cells (HEK293 cells), with the expression constructs for VP24 and activators of the RIG-I pathway (deltaRIG-I, MAVS, IKK ϵ , or TBK1) together with IFN promoter-reporter constructs (e.g., luciferase). These analyses have revealed that VP24 is efficiently inhibiting IFN gene expression on all components of the RIG-I pathway. Interestingly, the IFN expression-inducing capacity of constitutively active form of IRF3, dimerized IRF35D construct was also inhibited by VP24. However, a mutant VP24 protein, which lacked a nuclear localization signal and was thus mostly cytoplasmic, could not interfere with RIG-I-induced IFN gene expression (**Figure 4**) [82]. This indicates that VP24 likely interferes IFN gene expression by presently unidentified mechanism in the cell nucleus.

5. Downregulation of IFN-induced antiviral activities by EBOV proteins

One of the factors dictating EBOV lethality is its ability to replicate in many cell types and evade host immune responses. There are multiple mechanisms that allow filoviruses to surpass the host innate antiviral responses, for instance, interferon-induced antiviral responses [84]. Type I and III IFNs (IFN $\alpha/\beta/\lambda$) have a major role in antiviral response in viral infections [82, 85]. The activation of RLRs and TLRs and their downstream signaling cascades lead to the expression of type I and type III IFNs [11]. Type I IFNs (mainly IFN- α/β) bind to their specific cell surface receptors IFNAR1 and IFNAR2, while type III IFNs (IFN- λ 1-4) have their own cell-specific receptor composed of IFNLR and IL-10R2 receptor chains (**Figure 3**). Activation of type I or type III IFN receptors leads to activation of JAK-STAT signaling pathway which ultimately leads to phosphorylation and dimerization of STAT1 and STAT2 and the expression of IFN-stimulated genes [86]. Several studies have shown that especially EBOV VP24 protein interacts with this antiviral defense system by interfering with nuclear translocation of activated STAT1-STAT2 dimers (**Figure 3B**). VP24 has a nuclear localization signal (NLS), which mediates a tight interaction with importin α molecules that mediate the nuclear translocation of nuclear-targeted proteins together with importin β . Humans have six different importin α isoforms, and VP24 is capable of binding to all importin α molecules, especially to importin α 5, α 6, and α 7 [82]. Importin α -bound VP24 is able to prevent the interaction of STAT1-STAT2 complexes with the NLS-binding armadillo domains of importin α isoforms and thus prevent the nuclear import and subsequent STAT-induced activation of IFN-stimulated genes (ISGs). However, if the NLS of VP24 is mutated, VP24 is incapable of inhibiting importin α -STAT interaction, and IFN-induced genes are expressed normally [82].

As mentioned above, EBOV VP35 is able to inhibit dsRNA-induced PKR activation. PKR is one of the ISGs that has antiviral activity against many different viruses. EBOV GP is also able to induce cytotoxic activities in cells (**Figure 1**) even though the precise mechanisms behind this activity are present unknown.

6. Concluding remarks

Filoviruses target many cell types and tissues that regulate the activation of host immune responses and blood coagulation and hemostatic systems. Even if many of the processes in EBOV-host cell interactions have recently been revealed, there are still many open questions, e.g., by which molecular mechanisms are involved in EVD. In addition, more detailed information is needed to determine the activity of individual EBOV proteins, in addition to VP24 and VP35, on host innate and adaptive responses. Collectively, with this information it would be possible to design novel drugs or new modalities of treatment of Ebola and other filovirus infections.

7. Conclusions

Ebola virus infection is characterized by a severe infection with distorted regulation of blood coagulation and hemodynamic system and enhanced expression of inflammatory cytokines. In human infections Ebola virus targets macrophages and dendritic cells followed by systemic spread to the liver, spleen, and adrenal tissues. Individual EBOV proteins, such as VP24 and VP35, can interfere with the activation of host interferon gene expression and downregulate host antiviral responses.

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Conflict of interest

The authors declare no conflict of interest.

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