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Development of therapeutics for treatment of Ebola virus infection

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Abstract

Ebola virus infection can cause Ebola virus disease (EVD). Patients usually show severe symptoms, and the fatality rate can reach up to 90%. No licensed medicine is available. In this review, development of therapeutics for treatment of Ebola virus infection and EVD will be discussed.
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1. Introduction

Ebola virus disease (EVD), which is caused by infection with Ebola viruses (EBOVs), has existed as an endemic infectious disease sporadically occurring in Central Africa since it first appeared in 1976 [1,2]. At present, people along the West African coast, especially in Guinea, Liberia, and Sierra Leone, are going through the largest, most severe, and most complex Ebola outbreak [3–6]. Indeed, the United States and European countries have reported domestic infection cases, and the epidemic situation may last into next year and spread to other countries, according to estimates of WHO [7] and a computational epidemic prediction from Northeastern University in the USA [8]. As of November 2, 2014, more than 13,000 people have been confirmed with, or suspected of, contracting the disease in the present epidemic, out of which about 4818 have died [9]. Ebola viruses transmit through direct contact with infectious bodily fluids, such as blood, sweat, saliva, and tears, from EVD patients or wild animal carriers, such as nonhuman primates (NHPs) [10,11], and the incubation period is 2–21 days [10,12]. In the early stages, EVD patients usually show symptoms like fever, intense weakness, muscle pain, and headache, while both internal and external bleeding, as well as kidney and liver dysfunction, will arise as the course of EVD progresses [10,12]. The fatality rate of EVD is 40–90%, according to the historical analyses of Ebola outbreaks [10]. Although EVD is considered a potential public health threat, no licensed drug or vaccine is currently available [13–15]. The most efficient measure for controlling disease propagation is insolation of patients and strict barrier nursing procedures to protect healthcare workers. Meanwhile, symptomatic and supportive treatment is the sole choice for patients suffering from EVD [10,16]. However, based on the fundamental research of EBOVs and EVD, several promising drugs and vaccine candidates [6,17] are under development. These therapeutic treatments will be compared and discussed in this review article.

Ebola viruses, which belong to the family *Filoviridae*, are classified into five species: *Zaire ebolavirus* (ZEBOV), *Sudan ebolavirus* (SEBOV), *Bundibugyo ebolavirus* (BEBOV), *Tai Forest ebolavirus* (also known as *Cote d'Ivoire ebolavirus*, CIEBOV), and *Reston ebolavirus* (REBOV) [2,18]. ZEBOV and SEBOV are predominant and more pathogenic than the others, as they have been historically associated with about 90% of EVD outbreaks and higher mortality [2,10]. The

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causative agent of the current outbreak is also a variant strain of ZEBOV [19,20].

EBOVs form a threadlike shape, with a uniform diameter of 80 nm [21], and the typical length of a virion with peak infectivity is about 1200 nm [22]. One Ebola virion consists of a nonsegmented, single-stranded negative-sense RNA genome, and seven kinds of viral proteins serve as structural or multifunctional proteins [2]. Major nucleoprotein (NP) and virion protein 30 (VP30, minor nucleoprotein) are associated with the RNA genome and are required for RNA encapsidation [23,24], while VP30 is also a viral transcription activator [25]. Like phosphoproteins of other minus-stranded RNA viruses, virion protein 35 (VP35) links NPs with the viral RNA-dependent RNA polymerase (RdRP, polymerase L) to construct the viral RNA synthesis complex for transcription and genome replication [26,27]. The matrix proteins, virion protein 40 (VP40) and virion protein 24 (VP24), which have specific affinity for membranes, play essential roles in the process of virus assembly and budding [28]. Glycoprotein (GP) spikes, which embed on the virion surface, mediate virus entry [29] (Fig. 1). The GP gene also encodes soluble GP (sGP) and small soluble GP (ssGP), which are secreted from the host cell [2]. After being synthesized, the glycoprotein precursor (GP0) is cleaved by furin enzyme into GP1 and GP2 (GP2 has a transmembrane domain), which are further modified to form a heterodimer in the Golgi apparatus, and three of these dimers constitute a functional GP tripolymer spike. GP1 contains an excessively O-linked glycosylated mucin-like domain and a heavily N-linked glycosylated glycan cap domain, and these exterior domains are responsible for binding with a variety of host cell surface factors, as well as covering the receptor binding domain (RBD) under them [30]. The specific or nonspecific interactions between GP1 and cell surface host factors, such as T-cell immunoglobulin mucin domain-1 (TIM-1), facilitate virus attachment and endocytosis without changing the conformation of GP trimers [31]. While the whole virion is endocytosed and transported into mature endosome, GP1 is cleaved by endosomal proteases Cathepsin L and B (CatL/CatB) to remove the hyperglycosylated region

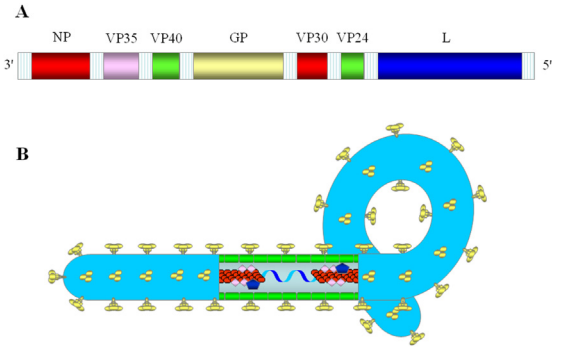

Fig. 1. The organization of genome of Ebola virus (A) and schematic representation of Ebola virion (B). Different building blocks are represented with different colors: nucleoproteins (red), phosphoprotein (pink), polymerase (dark blue), matrix proteins (green), glycoprotein (yellow), genome RNA (blue helix).

[32,33]. Then the exposed RBD interacts with endosomal lumen receptor Niemann-Pick C1 (NPC1) to transform the conformation of GP1 and GP2 at low pH [29]. Meanwhile, three fusion peptides on the N terminal of GP2 trimer insert into endosomal membrane, launching the six-helix bundle (6-HB) formation between the N- and C-terminal heptad repeats (NHR and CHR, respectively) and viral-host cell membrane fusion, in a manner similar to that mediated by other type I viral membrane proteins [34,35] (Fig. 2). Sequentially, the genome and RNA synthesis machinery is released into cytoplasm for another cycle of transcription, protein translation, genome replication, and virion assembly [2] (Fig. 3).

Notwithstanding that Ebola viruses have the replication tropism of a large range of cell types like hepatocytes, kidney cells and other epithelial cells, it is believed that EBOVs prefer to use mononuclear cells in the early stage of infection, such as tissue macrophages, monocytes and dendritic cells, for rapid virus replication [2,36]. This kind of massively unchecked replication is mainly because of the viral proteins that antagonize the host interferon response. VP24 interferes with the expression of IFN-stimulated genes by preventing dimerization of STAT, while VP35 keeps the viral dsRNA away from RIG-I and Dicer and inhibits the activation of other antiviral responsors in host cell, such as IRF-3, IRF-7 and dsRNA-dependent PKR [37]. At the same time, cytokines released from infected cells recruit more mononuclear cells to the initial infection site, in turn amplifying infection and apoptosis of mononuclear cells. At the same time, virions are systemically spread through blood circulation. The quantitative and functional loss of dendritic cells and macrophages causes acute lymphocytic apoptosis, although Ebola viruses cannot infect lymphocytes productively. During the middle or advanced stage of EVD, inflammatory molecule-caused vasodilatation results in both internal and external bleeding. Worse still, since hepatocyte infection leads to liver damage, the coagulation system becomes disordered [2,38,39]. Body injury and viral spread in blood circulation and organs lead to a vicious downward spiral. If viral spread cannot be controlled, patients can succumb to organ failure or secondary bacterial infection [2,10].

However, before the advanced stage of EVD, the use of efficacious treatments might limit virus replication to the extent necessary to allow successful mounting of adaptive immune response. The glycoprotein and RNA synthesis machinery, which play important roles in viral entry and RNA replication, respectively, are promising drug targets for Ebola therapies. Ebola investigators have developed several research models at both cell culture [40–43] and animal model levels [44–47]. EBOVs can be cultured with the Vero E6 cell line, and this model provides the entire virus replication cycle for drug research [42,48]. However, since EBOVs are biosafety level 4 pathogens, the facility limitation restricts the development of antivirals. To screen for antivirals that inhibit viral entry, Ebola pseudotyped systems based on either lentivirus backbone [40] or vesicular stomatitis virus (VSV) backbone [41], which is conjugated with luciferase reporter gene, can be performed in BSL-2 laboratories. Mini-genome replicon and

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