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Development of vaccines for prevention of Ebola virus infection

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Abstract

Ebola virus infection causes severe hemorrhagic fevers with high fatality rates up to 90% in humans, for which no effective treatment is currently available. The ongoing Ebola outbreak in West Africa that has caused over 14,000 human infections and over 5000 deaths underscores its serious threat to the public health. While licensed vaccines against Ebola virus infection are still not available, a number of vaccine approaches have been developed and shown to protect against lethal Ebola virus infection in animal models. This review aims to summarize the advancement of different strategies for Ebola vaccine development with a focus on the discussion of their protective efficacies and possible limitations. In addition, the development of animal models for efficacy evaluation of Ebola vaccines and the mechanism of immune protection against Ebola virus infection are also discussed.

Keywords: Ebola; Vaccine; Immune response; Animal model

1. Introduction

Since their first identification during the Ebola virus outbreak in 1976 in Zaire, five different Ebola virus species including Zaire (EBOV), Sudan (SUDV), Bundibugyo (BDBV), Tai Forest (TAFY), and Reston (RESTV), have been isolated from outbreaks in humans as well as non-human primates (NHPs), and they differ by as much as 40% in amino acid sequence [1]. Among them, EBOV, SUDV, and BDBV have caused large human outbreaks with high fatality rates ranging from 20 to 90% [1–5]. On the other hand, while there has been no fatal human infection reported for TAFV or RESTV, they are nonetheless highly pathogenic in non-human primates. In addition, with the exception of RESTV, which seems to have originated in the Philippines, all other filovirus species are endemic in tropical Africa along the equator, and the African green bat has recently been identified as their natural reservoir [6,7]. In addition to causing lethal infections in humans and non-human primates, EBOV has also been found to infect dogs during human outbreaks in Africa [8] whereas RESTV has been indicated to cause widespread non-pathogenic infection in pigs in Asia [9,10]. More gravely, EBOV has been shown to infect pigs and transmit from infected pigs to cause lethal infection of NHPs with no direct contact, indicating possible aerosol transmissibility of this highly lethal virus [11,12]. The ability of Ebola virus to infect domestic animals without causing severe disease underscores the danger for these viruses to become endemic and cause zoonotic transmission to humans. Of particular concern, human outbreaks of Ebola virus infection have become increasingly frequent in recent years [7,11], and the current EBOV outbreak which has been estimated to have caused over 14,000 human infections with over 5000 deaths as of November 14, 2014, once again demonstrates that its serious threat to public health is real and imminent.

The high fatality rate associated with Ebola virus infection and lack of effective approach for prevention or treatment signify the importance and urgency of developing an

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efficacious vaccine strategy to protect against human outbreaks. A number of vaccine strategies including inactivated virus, purified viral proteins, DNA vaccines, recombinant viral vector-based vaccines, as well as virus-like particles (VLPs) are under development and have been shown to protect small laboratory animals with various efficacies [11,13,14]. Further, evaluation of several vaccine strategies for protection against Ebola virus infection of non-human primates has yielded highly promising results. To date, at least five vaccine approaches including viral-vector based vaccines such as recombinant adenovirus replicons [15], recombinant VSV [16], recombinant Rabies virus [17], recombinant parainfluenza virus [18], recombinant VRP [19], and protein-based vaccines such as virus-like particles (VLPs) [20,21], have been demonstrated to protect against filovirus infection in both small animal models such as mice and guinea pigs as well as in non-human primates (NHPs). This review summarizes current state of Ebola vaccine development with a focus on approaches that have demonstrated protective efficacy in non-human primates. In addition, correlation of vaccine-induced immune response for protection against Ebola virus infection as well as the implication of Ebola virus immune subversion on vaccine development is also discussed.

2. Animal models for vaccine evaluation

Despite increasing frequencies of occurrence over that past decade, Ebola outbreaks are unpredictable and mostly sporadic, with the exception of the current outbreak that has spread into several countries in West Africa. This makes it very difficult if not impossible to carry out Phase III efficacy testing of candidate Ebola vaccines due to logistic issues as well as ethical concerns. In response to this difficulty, the US Food and Drug Administration (FDA) in 2002 introduced an "animal rule" that aims to facilitate licensing of vaccines or drug treatment against infection by Ebola virus as well as other highly lethal human pathogens for which efficacy evaluation in humans is not feasible. The application of FDA "animal rule" will allow approval of a candidate Ebola vaccine based on efficacy testing in animal models with clearly defined immune correlates for protection as well as Phase I and II clinical trials for safety and immunogenicity testing in humans. Therefore, the development of animal models is critical for the evaluation and eventual approval of candidate Ebola vaccines. Over the years, a number of animal models for Ebola virus infection have been developed and has been reviewed extensively elsewhere [22]. Here in this review, we present a brief discussion of their application for Ebola vaccine development.

2.1. Non-human primates

Similar to humans, non-human primates (NHPs) are also highly susceptible to Ebola virus infection with a high mortality rate. Ebola infections have also been detected in wild NHP species including, macaques, green monkeys, chimpanzees, etc. and evidence suggests that Ebola outbreaks may also be responsible for massive NHP death in Africa in the region of human outbreaks. Evidence also indicates that many of the past Ebola outbreaks can be attributed to contact with infected NHPs through animal poaching and eating bush meat [6]. Experimental infection of several NHP species including macaques, African green monkeys, and baboons showed that Ebola virus is highly lethal for these NHP species [23]. Among these, rhesus and cynomolgus macaques are most widely used for evaluation of Ebola vaccines as experimental infection of these animals by Ebola virus causes similar disease symptoms as observed in humans. Macaques infected by Ebola virus usually exhibit high fever at 3 days post infection and die within 5–8 days. Symptoms observed in macaques after Ebola virus infection include fever, rash, anorexia, diarrhea, and rectal bleeding that are similar to human infection [23]. Viremia can be detected on day 3 post infection, which rises quickly to 10^7 pfu/ml by day 4 or 5. Virus can also be detected in different organs including liver, spleen, lung, kidney, adrenal, testis, lymph nodes, as well as pancreas by day 4 post infection and then continue to increase in titers by day 6 prior to death. Geisbert et al. systematically investigated pathogenesis of Ebola virus infection in cynomolgus macaques [24]. The results showed that the course of Ebola virus infection starts with monocytes/macrophages and DC in the lymphoid tissues and Kupffer cells in liver, progressing to infection of parenchymal cells in liver and adrenal gland, endothelial cells lining sinusoids in liver and adrenal gland, as well as HEV in lymphoid tissues, fibrocytes, and endothelial cells of connective tissue, and finally to infection of the epithelium. Ebola virus infection also caused massive lymphocyte apoptosis that leads to lymphopenia and lymphoid depletion, which are also characteristics of human Ebola hemorrhagic fever. Similar findings were also made with Ebola virus infection of rhesus macaques [25]. Due to the close resemblance of disease symptoms as well as host responses in cynomolgus and rhesus macaques to human Ebola hemorrhagic fever, these animals are considered the ultimate animal model for efficacy evaluation of Ebola vaccines.

2.2. Small laboratory animals

While NHPs serve as gold standard for Ebola vaccine evaluation, their cost and space-requirement for handling in a BSL-4 facility make it difficult to conduct large scale testing. Therefore, the development of small laboratory animal models for Ebola virus infection offers valuable alternative tools for Ebola vaccine evaluation. Guinea pig is the first small laboratory animal model for Ebola virus infection and vaccine efficacy evaluation [26]. In early studies, it was found that guinea pigs were susceptible to infection by wild type EBOV (Ebola virus Zaire specie) that caused fever in all infected animals with death of only 1 in 12 experimentally infected guinea pigs [26]. Later studies showed that sequential passage in guinea pigs led to adaptation of EBOV in guinea pigs with increased viremia titer and lethality, resulting in killing of 100% infected guinea pigs at 7–9 days post infection by 4th passage [27]. Virus replication can be detected in various