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Journey of Vaccine Development against Ebola Virus

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Abstract

The 2014 outbreak of Ebola epidemic in Guinea, Liberia and Sierra Leone affected more than 28000 individuals and killed around 11300 persons. The situation exposed unpreparedness of the world towards this neglected tropical disease confined to the African continent and highlighted the need for a vaccine. This review tries to cover the excursion of EBOV vaccine development from animal models to the clinical trials and finally on-field trials during the hours of emergency.

Introduction

Since its discovery in 1976, Ebola virus (EBOV) has caused sporadic outbreaks in Sub-Saharan Africa. Ebola is the etiologic agent of Ebola Hemorrhagic Fever (EHF) and remains one of the most lethal transmissible infection responsible for high fatality rate of upto 90% and substantial morbidity in humans and non-human primates (NHPs) [1-4]. Ebola viruses belong to the Filoviridae family and are enveloped, negative single-stranded RNA viruses with a genome of ~19 kb in size that encodes seven structural proteins and two non-structural proteins, Ebola glycoprotein (GP), dispersed throughout the viral envelope as trimeric spikes, consists of two fragments; an extracellular protein (GP1) and a membrane-anchored protein (GP2) [5-8]. Due to their possible exploitation as bioterrorism agents, these filoviruses pose a significant health alarm worldwide as the infection lead to uncontrolled viral replication and multi-organ infection and failure [9,10]. This virus infection apparently first disable the immune system followed by vascular system failure that leads to hemorrhage, drop in blood pressure, and finally shock and death within days to weeks of exposure [11]. Treatment for EHF has been purely supportive with no effective interventions and thus development of broadly protective vaccine conferring long lasting immunity is critical and for that there is need to understand the mechanisms by which EBOV suppresses, distracts, or otherwise evades the host immune response [12]. Various studies have indicated the critical role of viral glycoprotein (GP) in the pathogenesis as it facilitates binding of the EBOV to endothelial and monocytic cells [13-16]. A 17-amino acid sequence within GP region resembles to an immunosuppressive motif present in a number of retrovirus envelope proteins [17-19]. This sequence mediates viral binding with target cells critical in the immunopathology and apoptosis during Ebola infection [20]. For this reason, GP is the focus of most EBOV vaccine research, and it is generally accepted that a robust anti-GP antibody response is crucial for protection against lethal EBOV challenge [21].

Generally, vaccines are either live-attenuated, killed or inactivated or subunit vaccines (including recombinant vaccines) that can be used as preventive vaccines to provide 'active immunization' prior to infection. Live attenuated is not suitable for viruses like EBOV for the fear of reversion, while inactivated vaccines induce short term immunity. Another approach is 'passive immunization', where antibodies produced either in animals or individuals who survived from infection are

administered to the patients (10). However, in case of EBOV, survivors do seroconvert but the neutralizing antibody titers in serum remain very low [22-24]. Development of vaccine is a long, time-consuming route, which includes various milestones before successful delivery of an effective product. Establishment of animal models is invaluable and crucial to understand pathophysiology and develop diagnostics, vaccines, and therapeutics [25].

Several animal models have been developed for EHF using non-human primates (NHPs) and rodents with a mouse-adapted Ebola virus [26]. However, in contrast to Ebola virus infection in other animal models, it is relatively easy to protect mice from infection with the mouse-adapted Ebola virus.

Mouse Model

Early in 1998, Vanderzanden, et al. developed two DNA vaccines expressing GP or nucleocapsid protein (NP) of EBOV and evaluated in adult immunocompetent mice [27]. Both the vaccines required multiple boosters (3-4) to provide only partial protection. With advancement in technologies and understanding, Shedlock, et al. developed a synthetic polyvalent plasmid DNA vaccine against the GP region of Marburg marburgvirus (MARV), Zaire ebolavirus (ZEBOV), and Sudan ebolavirus (SUDV) and the preclinical efficacy studies were performed in guinea pigs and mice using rodent-adapted viruses [28]. The vaccine was highly potent and completely protected challenged mice by eliciting robust neutralizing antibodies against MARV and ZEBOV. Similarly, in another study, Adenovirus (Ad) 26 and Ad35 vectors expressing five filoviruses (Ebola Zaire and Ebola Sudan; Marburg Angola and Marburg Ravn; Ebola Ivory Coast) GP were explored to develop a vaccine providing universal filovirus protection. Both adenoviral vectors induced a potent cellular and humoral immune response in mice after single vaccination in dose dependent manner [29]. These rodents based studies yield results but with a drawback that mouse adapted EBOV did not give the real picture of disease. Although in a recent study, Ling et al., evaluated vaccine effectiveness of a novel recombinant adenovirus type 5 vector-based Ebola vaccine (Ad5-EBOV) based on the 2014 Zaire Guinea epidemic strain and tested for humoral and cellular response in mice. The study showed EBOV GP-specific antibodies titers peaking at week 10 and lasted up to 6 months in mice [30]. Thus, to get a better prospective with improved available facilities, researchers advanced to Rhesus and cynomolgus macaques, which were superior representative models of filovirus infection as they exhibit extremely similar symptoms to those observed in humans.

Non-Human Primates Model

There is vast amount of research done in NHPs to understand EBOV infection. Almost all the studies related to development of vaccine against EBOV exploited the GP region of the virus while some also included nucleoprotein region. Warfield et al., demonstrated protective efficacy of virus-like particle (VLP)- based vaccines containing GP, NP and VP40 matrix protein in both rodents and Cynomolgus macaques as promising vaccine candidates [31,32]. Blaney, et al. generated Rabies virus (RABV) based bivalent vaccines expressing EBOV GP and used it in both mice and NHPs [33,34]. Their vaccines induced potent immune responses against both RABV and EBOV demonstrating safety, immunogenicity, and protective efficacy of these live or inactivated RABV/EBOV vaccines. Some other studies used different vaccine platforms such as recombinant vesicular stomatitis virus (rVSV) expressing the filovirus GP providing protection in Cynomolgus macaques [35]; or Venezuelan equine encephalitis virus (VEEV) replicon particle (VRP) vaccine expressing GP providing complete protective efficacy against Sudan virus (SUDV) and EBOV in NHPs after two vaccinations and many similar studies. After the 2014-2016 outbreak, the vaccine development approach was modified for immediate and robust protection against EBOV [36]. Marzi, et al. developed recombinant vesicular stomatitis virus (rVSV)–EBOV vaccine which generated a robust immune response in macaques within days (3-7 days) of single dose immunization [37]. While Meyer et al., used aerosolized human parainfluenza virus type 3–vectored vaccine expressing EBOV GP (HPIV3/EboGP) delivered to the respiratory tract of Rhesus macaques [38]. HPIV3/EboGP induced high EBOV-specific IgG, IgA, and neutralizing antibody titers as well as cellular response in the macaques, hence a potentially useful and feasible vaccine candidate. Thus these findings helped to develop better vaccine for human use. Taking lead from here, researchers developed vaccines which were finally suitable for clinical trials.

Human Trials

Some of the candidate vaccines that were suitable for human trials included Adenovirus and VSV based platforms. Zhu, et al. developed a recombinant Ad5 vector based vaccine expressing EBOV GP region, which showed good safety and immunogenicity in Phase 1 trial of healthy Chinese adults [39]. They conducted a

randomized Phase 2 clinical trial in Sierra Leone in a dose dependent manner and even the lower dose was safe and highly immunogenic as assessed by EBOV-specific antibody responses against the vaccine-matched glycoprotein with ELISA. Another group used recombinant VSV based vaccine to conduct Phase 1 trial in a dose dependent manner and required booster dose that elicited good antibody response [40]. Ledgerwood, et al. rapidly advanced a Ad3 vectored EBOV GP into phase 1 clinical trial where the vaccine provided specific antibody response up to 48 weeks [41]. Finally, Henao-Restrepo et al., developed a recombinant, replication competent vesicular stomatitis virus based candidate vaccine expressing EBOV GP (rVSVZEBOV) and tested its efficacy in 'contacts' of confirmed Ebola infection cases in Guinea [42]. This vaccine was manufactured by Merck, Sharpe & Dohme and recommended by WHO for field use [43]. Apart from the vaccines that have potential candidature, there are some promising vaccine candidates lined up against Ebola but a continuous research in this direction is required to successfully combat this deadly disease and be able to eradicate it in the future.

References

1. Feldmann H, Geisbert TW (2011) Ebola haemorrhagic fever. Lancet 377(9768): 849-862.

2. Marzi A, Engelmann F, Feldmann F, Haberthur K, Shupert WL, et al. (2013) Antibodies are necessary for rVSV/ZEBOV-GP-mediated protection against lethal Ebola virus challenge in nonhuman primates. Proc Natl Acad Sci USA 110(5): 1893-1898.

3. Hill-Batorski L, Halfmann P, Neumann G, Kawaoka Y (2013) The cytoprotective enzyme heme oxygenase-1 suppresses Ebola virus replication. J Virol 87(24): 13795-13802.

4. Sanchez A, Geisbert TW, Felsmann H (2007) Marburg and Ebola Viruses. Philadelphia PA: Lippincott Williams and Wilkins.

5. Sanchez A, Trappier SG, Mahy BW, Peters CJ, Nichol ST (1996) The virion glycoproteins of Ebola viruses are encoded in two reading frames and are expressed through transcriptional editing. Proc Natl Acad Sci USA 93(8): 3602-3607.

6. Volchkov VE, Feldmann H, Volchkova VA, Klenk HD (1998) Processing of the Ebola virus glycoprotein by the proprotein convertase furin. Proc Natl Acad Sci USA 95(10): 5762-5767.

7. Volchkov VE, Volchkova VA, Muhlberger E, Kolesnikova LV, Weik M, et al. (2001) Recovery of infectious Ebola virus from complementary DNA: RNA editing of the GP gene and viral cytotoxicity. Science 291(5510): 1965-1969.

8. Volchkov VE, Volchkova VA, Slenczka W, Klenk HD, Feldmann H (1998) Release of viral glycoproteins during Ebola virus infection. Virology 245(1): 110-119.

9. Zahn R, Gillisen G, Roos A, Koning M, van der Helm E, et al. (2012) Ad35 and ad26 vaccine vectors induce potent and crossreactive antibody and T-cell responses to multiple filovirus species. PLoS One 7(12): e44115.

10. Herbert AS, Kuehne AI, Barth JF, Ortiz RA, Nichols DK, et al. (2013) Venezuelan equine encephalitis virus replicon particle vaccine protects nonhuman primates from intramuscular and aerosol challenge with ebolavirus. J Virol 87(9): 4952-4964.

11. Ansari AA (2014) Clinical features and pathobiology of Ebolavirus infection. J Autoimm 55: 1-9.

12. Mohamadzadeh M, Chen L, Schmaljohn AL (2007) How Ebola and Marburg viruses battle the immune system. Nat Rev Immunol 7(7): 556-567.

13. Chan SY, Empig CJ, Welte FJ, Speck RF, Schmaljohn A, et al. (2001) Folate receptor-alpha is a cofactor for cellular entry by Marburg and Ebola viruses. Cell 106(1): 117-126.

14. Chan SY, Speck RF, Ma MC, Goldsmith MA (2000) Distinct mechanisms of entry by envelope glycoproteins of Marburg and Ebola (Zaire) viruses. J Virol 74(10): 4933-4937.

15. Chepurnov AA, Tuzova MN, Ternovoy VA, Chernukhin IV (1999) Suppressive effect of Ebola virus on T cell proliferation in vitro is provided by a 125-kDa GP viral protein. Immunol Lett 68(2-3): 257-261.

16. Volchkov VE, Blinov VM, Netesov SV (1992) The envelope glycoprotein of Ebola virus contains an immunosuppressive-like domain similar to oncogenic retroviruses. FEBS Lett 305(3): 181-184.

17. Wool-Lewis RJ, Bates P (1998) Characterization of Ebola virus entry by using pseudotyped viruses: identification of receptor-deficient cell lines. J Virol 72(4): 3155-3160.

18. Yang Z, Delgado R, Xu L, Todd RF, Nabel EG, et al. (1998) Distinct cellular interactions of secreted and transmembrane Ebola virus glycoproteins. Science 279(5353): 1034-1037.

19. Yang ZY, Duckers HJ, Sullivan NJ, Sanchez A, Nabel EG, et al. (2000) Identification of the Ebola virus glycoprotein as the main viral determinant of vascular cell cytotoxicity and injury. Nat Med 6(8): 886-889.

20. Yaddanapudi K, Palacios G, Towner JS, Chen I, Sariol CA, et al. (2006) Implication of a retrovirus-like glycoprotein peptide in the immunopathogenesis of Ebola and Marburg viruses. FASEB J 20(14): 2519-2530.

21. Falzarano D, Geisbert TW, Feldmann H (2011) Progress in filovirus vaccinedevelopment: evaluating the potential for clinical use. Expert Rev Vaccines 10(1): 63-77.

22. Jahrling PB, Geisbert TW, Geisbert JB, Swearengen JR, Bray M, et al. (1999) Evaluation of immune globulin and recombinant interferon-alpha2b for treatment of experimental Ebola virus infections. J Infect Dis 179(1): S224-S234.

23. Ksiazek TG (1991) Laboratory diagnosis of filovirus infections in nonhuman primates. Lab Anim 20: 34-46.

24. McCormick JB, Bauer SP, Elliott LH, Webb PA, Johnson KM (1983) Biologic differences between strains of Ebola virus from Zaire and Sudan. J Infect Dis 147(2): 264-267.

25. Nakayama E, Saijo M (2013) Animal models for Ebola and Marburg virus infections. Frontiers in Microbiology 4: 267.

26. Bray M, Davis K, Geisbert T, Schmaljohn C, Huggins J (1999) A mouse model for evaluation of prophylaxis and therapy of Ebola hemorrhagic fever. J Infect Dis 179(1): S248-S258.

27. Vanderzanden L, Bray M, Fuller D, Roberts T, Custer D, et al. (1998) DNA Vaccines Expressing either the GP or NP Genes of Ebola Virus Protect Mice from Lethal Challenge. Virology 246(1): 134-144.

28. Shedlock DJ, Aviles J, Talbott KT, Wong G, Wu SJ, et al. (2013) Induction of broad cytotoxic T cells by protective DNA vaccination against Marburg and Ebola. Mol Ther 21(7): 1432-1444.

29. Zahn R, Gillisen G, Roos A, Koning M, van der Helm E, et al. (2012) Ad35 and Ad26 Vaccine Vectors Induce Potent and Cross-Reactive Antibody and T- Cell Responses to Multiple Filovirus Species. PLoS ONE 7(12): e44115.

30. Wang L, Liu J, Kong Y, Hou L, Li Y (2018) Immunogenicity of Recombinant Adenovirus Type 5 Vector-Based Ebola Vaccine Expressing Glycoprotein from the 2014 Epidemic Strain in Mice. Human Gene Therapy 29(1): 87-95.

31. Warfield KL, Swenson DL, Olinger GG, Kalina WV, Aman MJ, et al. (2007) Ebola Virus-Like Particle–Based Vaccine Protects Nonhuman Primates against Lethal Ebola Virus Challenge. J Infect Dis 196(2): S430- S437.

32. Warfield KL, Swenson DL, Demmin G, Bavari S (2005) Filovirus-like particles as vaccines and discovery tools. Expert Rev Vaccines 4(3): 429-440.

33. Blaney JE, Marzi A, Willet M, Papaneri AB, Wirblich C, et al. (2013) Antibody Quality and Protection from Lethal Ebola Virus Challenge in Nonhuman Primates Immunized with Rabies Virus Based Bivalent Vaccine. PLoS Pathog 9(5): e1003389.

34. Blaney JE, Wirblich C, Papaneri AB, Johnson RF, Myers CJ, et al. (2011) Inactivated or live-attenuated bivalent vaccines that confer protection against rabies and Ebola viruses. Journal of virology 85: 10605-10616.

35. Marzi A, Engelmann F, Feldmann F, Haberthur K, Shupert WL, et al. (2013) Antibodies are necessary for rVSV/ZEBOV-GP-mediated protection against lethal Ebola virus challenge in nonhuman primates. PNAS 110(5): 1893-1898.

36. Herbert AS, Kuehne AI, Barth JF, Ortiz RA, Nichols DK, et al. (2013) Venezuelan equine encephalitis virus replicon particle vaccine protects nonhuman primates from intramuscular and aerosol challenge with ebolavirus. J Virol 87(9): 4952-4964.

37. Marzi A, Robertson SJ, Haddock E, Feldmann F, Hanley PW, et al. (2015) VSV-EBOV rapidly protects macaques against infection with the 2014/15 Ebola virus outbreak strain. Science 349(6249): 739-742.

38. Meyer M, Garron T, Lubaki NM, Mire CE, Fenton KA, et al. (2015) Aerosolized Ebola vaccine protects primates and elicits lung-resident T cell responses. J Clin Invest 125(8): 3241-3255.

39. Zhu F, Wurie AH, Hou LH, Liang Q, Li Y, et al. (2017) Safety and immunogenicity of a recombinant adenovirus type-5 vector-based Ebola vaccine in healthy adults in Sierra Leone: a single-centre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet 389(10069): 621-628.

40. Regules JA, Beigel JH, Paolino KM, Voell J, Castellano AR, et al. (2017) A Recombinant Vesicular Stomatitis Virus Ebola Vaccine. N Engl J Med 376: 330-341.

41. Ledgerwood JE, DeZure AD, Stanley DA, Coates EE, Novik L, et al. (2017) Chimpanzee Adenovirus Vector Ebola Vaccine. N Engl J Med 376(10): 928-938.

42. Henao-Restrepo AM, Camacho A, Longini IM, Watson CH, Edmunds WJ, et al. (2017) Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!). Lancet 389(10068): 505-518.

43. WHO (2016) Final trial results confirm ebola vaccine provides high protection against disease.