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Review

Animal models of viral hemorrhagic fever

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ABSTRACT

The term "viral hemorrhagic fever" (VHF) designates a syndrome of acute febrile illness, increased vascular permeability and coagulation defects which often progresses to bleeding and shock and may be fatal in a significant percentage of cases. The causative agents are some 20 different RNA viruses in the families *Arenaviridae*, *Bunyaviridae*, *Filoviridae* and *Flaviviridae*, which are maintained in a variety of animal species and are transferred to humans through direct or indirect contact or by an arthropod vector. Except for dengue, which is transmitted among humans by mosquitoes, the geographic distribution of each type of VHF is determined by the range of its animal reservoir. Treatments are available for Argentine HF and Lassa fever, but no approved countermeasures have been developed against other types of VHF. The development of effective interventions is hindered by the sporadic nature of most infections and their occurrence in geographic regions with limited medical resources. Laboratory animal models that faithfully reproduce human disease are therefore essential for the evaluation of potential vaccines and therapeutics. The goal of this review is to highlight the current status of animal models that can be used to study the pathogenesis of VHF and test new countermeasures.

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1. Introduction

Viral hemorrhagic fever (VHF) is a syndrome of acute febrile illness characterized by increased vascular permeability that may lead to shock and coagulation defects that may result in bleeding. The causative agents are some 20 different RNA viruses in the families *Arenaviridae*, *Bunyaviridae*, *Filoviridae*, and *Flaviviridae*. They range from the well-recognized filoviruses, Ebola (EBOV) and Marburg (MARV) and the flaviviruses yellow fever virus (YFV) and dengue virus (DENV), to more obscure pathogens such as Omsk hemorrhagic fever virus (OHFV) and Sabia virus. Newly emerging HF viruses include Alkhumra virus (AHFV) in Saudi Arabia (Qattan et al., 1996; Zaki, 1997) and severe fever with thrombocytopenia syndrome virus (SFTSV) in China (Yu et al., 2011).

With the exception of DENV, which is transmitted among humans by mosquitoes, the HF viruses are maintained in a variety of animal species. Human infections result from direct or indirect contact with the reservoir host or the bite of an arthropod vector. The geographic distribution of each type of VHF therefore reflects the range of its maintenance host, with most being localized to Africa, Southeast Asia or South America. In Europe, VHF is limited to infections by hantaviruses and Crimean-Congo HF virus (CCHFV), while New World hantaviruses are the only cause of VHF in the United States.

The various types of VHF differ in their average severity and overall case fatality rate, but all of them are characterized by increased permeability of the endothelial lining of blood vessels (“vascular leak”) and by coagulation defects that usually produce only minor hemorrhagic phenomena, but in some cases may lead to fatal bleeding (Schnittler and Feldmann, 2003). Major contributing factors to severe infection include viral subversion of the type I interferon response (Basler, 2005) and an uncontrolled proinflammatory cytokine/chemokine response (Bray, 2005). While all types of VHF share a common syndrome, specific pathogenic mechanisms vary by virus and host response. A recent review summarizes current understanding of the pathogenesis of VHF caused by filoviruses, flaviviruses and arenaviruses (Paessler and Walker, 2013).

Therapies are available for Lassa fever and for Argentine HF, but there are no approved countermeasures against other types of VHF. The relative infrequency and sporadic occurrence of these zoonotic diseases coupled with ethical considerations constitute a major impediment to the conduct of human clinical trials, hindering the development of new intervention strategies. Animal models that faithfully reproduce most aspects of human disease are therefore essential for the evaluation of new candidate vaccines and therapeutics. The US Food and Drug Administration (FDA) has developed an “Animal Rule”, which allows for the demonstration of drug or vaccine efficacy in laboratory animals instead of humans, when limited frequency and predictability or the severity of a disease makes clinical trials impossible. To satisfy FDA requirements, testing of potential vaccines and therapeutics should be performed using a well-characterized model, ideally employing an immunocompetent animal, a wild-type virus and a realistic challenge dose and route of exposure. Most importantly, the model should recapitulate the principal features of the human disease (FDA, 2009; Snoy, 2010). However, the development of animal models to mimic the full spectrum of HF disease presentation is complex and as discussed in the sections on specific virus families, it is not always possible to use immunocompetent animals, a wild-type virus and a realistic challenge dose and route of exposure.

Nonhuman primates (NHPs) are the “gold standard” for evaluating medical countermeasures for several types of VHF, especially for advanced development efforts (Safronetz et al., 2013a). However, because of the cost-prohibitive nature, ethical concerns, and complicated logistical and safety aspects of NHP experiments, rodent models are frequently used for preclinical efficacy studies. The goal of the present article is to review NHP and rodent models currently available to study the pathogenesis of the various types of VHF and test new vaccines and therapies.

2. Animal models of acute arenaviral infection and HF

2.1. Old World arenaviruses

Lassa virus (LASV) causes by far the greatest morbidity and mortality due to infection by arenaviruses that cause hemorrhagic fever (HF). Exposure to LASV and mortality associated with Lassa fever (LF) in hyperendemic areas of West Africa (Fig. 1) are estimated to be as high as 300,000 infections and 10,000 deaths annually, with 15–20% of hospitalized patients succumbing to the disease (McCormick, 1999; McCormick et al., 1987a). LASV is carried by chronically infected rodents (*Mastomys* species) and human exposure most often occurs through inhalation of infectious virus particles aerosolized from rodent excreta or direct contact that may result in virus entry through abrasions in the skin (Yun and Walker, 2012). Nosocomial transmission via contact with contaminated medical devices or body fluids during patient care can occur, but is effectively mitigated by barrier nursing (Helmick et al., 1986).