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Review

Single-cycle replicable Rift Valley fever virus mutants as safe vaccine candidates

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ABSTRACT

Rift Valley fever virus (RVFV) is an arbovirus circulating between ruminants and mosquitoes to maintain its enzootic cycle. Humans are infected with RVFV through mosquito bites or direct contact with materials of infected animals. The virus causes Rift Valley fever (RVF), which was first recognized in the Great Rift Valley of Kenya in 1931. RVF is characterized by a febrile illness resulting in a high rate of abortions in ruminants and an acute febrile illness, followed by fatal hemorrhagic fever and encephalitis in humans. Initially, the virus was restricted to the eastern region of Africa, but the disease has now spread to southern and western Africa, as well as outside of the African continent, e.g., Madagascar, Saudi Arabia and Yemen. There is a serious concern that the virus may spread to other areas, such as North America and Europe. As vaccination is an effective tool to control RVFV epidemics, formalin-inactivated vaccines and live-attenuated RVFV vaccines have been used in endemic areas. The formalin-inactivated vaccines require boosters for effective protection, whereas the live-attenuated vaccines enable the induction of protective immunity by a single vaccination. However, the use of live-attenuated RVFV vaccines for large human populations having a varied health status is of concern, because of these vaccines' residual neuro-invasiveness and neurovirulence. Recently, novel vaccine candidates have been developed using replication-defective RVFV that can undergo only a single round of replication in infected cells. The single-cycle replicable RVFV does not cause systemic infection in immunized hosts, but enables the conferring of protective immunity. This review summarizes the properties of various RVFV vaccines and recent progress on the development of the single-cycle replicable RVFV vaccines.

Contents

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1. Introduction

Rift Valley fever virus (RVFV), an arbovirus, is the causative agent of Rift Valley fever (RVF), characterized by a febrile illness, resulting in a high rate of abortions in ruminants. In humans, RVFV causes an acute febrile illness followed by fatal hemorrhagic fever, encephalitis, or ocular diseases (Ikegami and Makino, 2011). RVF was first recognized in the Great Rift Valley of Kenya in 1931 (Daubney et al., 1931) after the deaths of lambs and ewes. Initially, the virus was restricted to the eastern region of Africa, but today it has spread to southern and western Africa and also outside of Africa, including Madagascar, Saudi Arabia and Yemen (Bird et al., 2009). The virus periodically causes major epidemics in these countries. Young animals are generally susceptible to the virus infection and show high mortality rates (Bird et al., 2009). Virus infection causes a very high rate of abortions called "abortion storms" in pregnant ruminants, as well as the death of newborns. In the 2007 RVF outbreak in Kenya and Tanzania, approximately 49,000 cattle, goats, and sheep died (Himeidan et al., 2014). RVFV outbreaks have had a significant economic impact due to loss of livestock and the need to curtail livestock trade following outbreaks (Himeidan et al., 2014). Human RVFV infections generally manifest as self-limiting and non-fatal illnesses (Ikegami and Makino, 2011). However, a small number of cases progress to more severe diseases, such as acute hepatitis and delayed-onset encephalitis. In the case of human infection, case fatality rates have varied from 12% to 31% in recent outbreaks (Himeidan et al., 2014). The virus is transmitted by mosquito bites and direct contact with materials from infected animals. Farmers, farm workers, veterinarians, and other health care workers are at high risk for infection, as they handle RVFV-infected animals, e.g., aborted fetal material and body fluids from infected humans. Warm weather, heavy rainfall, and flooding promote breeding of mosquitoes and are often connected to outbreaks (Himeidan et al., 2014). Introduction of RVFV into non-endemic countries, including the U.S., potentially occurs by the movement of infected travelers, animals and, most likely, insect vectors, including mosquitoes (Rolin et al., 2013). RVFV has wide range of vector species, over 30, including mosquito species existing in the U.S. (Turell et al., 2008, 2010). Hence, there is a serious concern that RVFV may be introduced into non-endemic areas and establish infection cycles with resident mosquitoes and domestic animals. The intentional spread of RVFV is also of serious national biosecurity concern. Currently, RVFV is classified as a select agent and belongs to the NIAID Category A list pathogens and the CDC list of potential bioterrorism agents. RVF outbreaks in the non-endemic areas, including the U.S., would cause serious public health, agricultural, and economic problems.

RVFV is a member of the genus Phlebovirus, family Bunyaviridae, and carries negative-stranded, tripartite RNA genomes, comprised of L, M, and S RNA segments (Walter and Barr, 2011). The anti-genomic sense of L RNA encodes RNA-dependent RNA polymerase (L protein). The anti-genomic sense of M RNA carries 5 in-frame start codons, each of which is used for the expression of 78-kDa protein, the non-structural proteins NSm and NSm′ (Kreher, 2014), and the major glycoproteins Gn and Gc. S RNA uses an ambisense strategy to express nucleocapsid (N) protein and non-structural protein NSs (Fig. 1A). The RVFV particle consists of the segmented viral RNA genomes, L, N and envelope glycoproteins, and several host proteins (Nuss et al., 2014). The glycoproteins, Gn and Gc, are co-translationally cleaved from a precursor polypeptide and form heterodimers which are arranged into an icosahedral lattice with $T = 12$ symmetry (Freiberg et al., 2008). The virus utilizes DC-SIGN or/and heparin sulfate as one of its entry receptors and gets into the cells via caveola-mediated endocytosis (de Boer et al., 2012a; Harmon et al., 2012; Lozach et al., 2011). RVFV L and N proteins are essential for the viral RNA replication and transcription (Accardi et al., 2001; Ikegami et al., 2005; Lopez et al., 1995). NSs, NSm and 78-kDa proteins are not required for RVFV replication in cultured cells (Gerrard et al., 2007; Ikegami et al., 2006; Won et al., 2006), but play important roles in controlling virus virulence and dissemination in infected hosts (Bird et al., 2007; Kreher, 2014; Muller et al., 1995).

Although, the spread of RVFV can be prevented by effective vaccination of animals and humans, there are no licensed RVFV vaccines to immunize general citizens in the U.S. and many other countries. There is a substantial body of literature demonstrating that humoral immunity is necessary and sufficient for protection

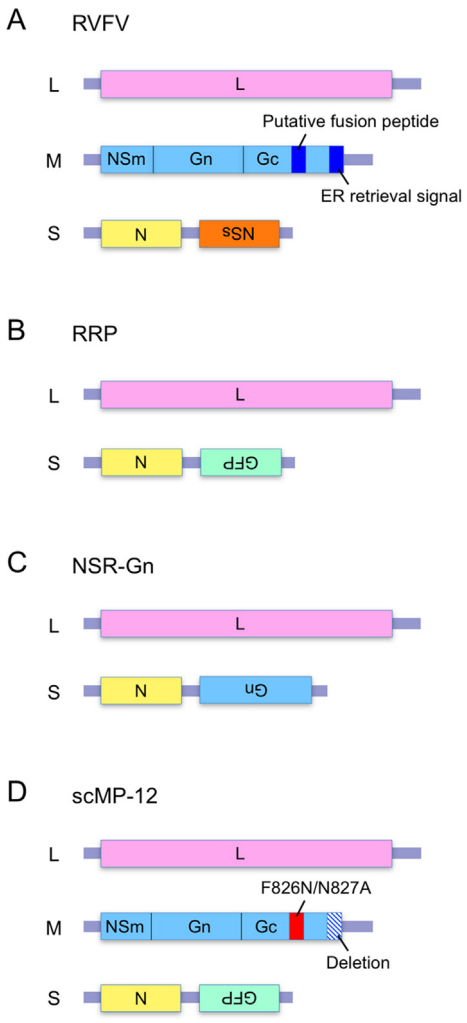

Fig. 1. Schematic diagrams of the anti-genomic sense genomic RNAs of RVFV (A), RRP (B), NSR-Gn (C) and scMP-12 (D). (A) The putative fusion peptide and the ER retrieval signal in M segment are marked in dark blue. (D) The M RNA segment of scMP-12 has F826N and N827A mutations (red box) and a deletion of the C-terminal ER retrieval signal (a box with diagonal lines).