COMBATTING FUTURE BIOLOGICAL THREATS – HOST-DIRECTED INTERVENTIONS TO EMERGING THREATS FOR RAPID RESPONSE

A Lipid Nanoparticle Mrna Vaccine Expressing Ebola Virus Glycoprotein Elicits Strong Immunological Response And Protection Against Challenge With A VSV-ZEBOVgp Model Of ZEBOV Infection

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Zaire Ebola virus (ZEBOV) is the causative agent behind ebola virus disease (EVD), a disease characterized by hemorrhagic fever and a high case fatality rate. Current treatments for EVD are limited to monoclonal antibody therapies, and a vesicular stomatitis virus (VSV)-vectored vaccine. Although the available therapies and vaccine have shown promise during recent ZEBOV outbreaks, long term protection and cross-protection against other viral species associated with EVD remain unknown. The rVSV-ZEBOV glycoprotein (gp) vaccine is currently considered the gold-standard and is recommended for pre-exposure prophylactic use in the US among high-risk populations, including military and health-care workers deployed in EVD response areas. Here, we developed a lipid nanoparticle (LNP) mRNA vaccine against ZEBOVgp, and compared immunological responses from a prime-boost regimen of the LNP mRNA vaccine formulation versus a rVSV-ZEBOVgp platform vaccine in an immunocompetent mouse model. C57BL/6 mice were vaccinated with 2.5 mg of mRNA per leg by intramuscular (IM) injection in each hind leg, for a total of 5 mg/animal, or sham vaccinated with PBS, with an n=7 per group. Animals were boosted at day 28 and sacrificed for analysis at day 35. The mRNA vaccine elicited antibody and neutralizing antibody responses comparable with the highest prime-boost dose of the rVSV-ZEBOVgp platform vaccine, which was administered with glycoconjugate at 2x106PFU/animal. Specific epitopes were identified for anti-EBOVgp responses. Following confirmation of immunogenicity of the LNP mRNA ZEBOVgp vaccine, we performed a lethal challenge experiment in immunocompromised mice, using a VSV-ZEBOVgp model of ZEBOV infection. IFNAR-/- mice were vaccinated with a prime-boost regimen (days 0 and 28), followed by challenge with a VSV-ZEBOVgp model of ZEBOV infection at day 35 post-vaccination, with an n=7/group. All vaccinated mice survived to the sacrifice date at 14 days post-infection, while all sham vaccinated animals experienced substantial weight loss and were euthanized within 4 days post-challenge. Future studies will test efficacy against authentic Ebola virus. Overall, this work seeks to enhance our ability to protect both the nation and warfighters operating in environments with ZEBOV.

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