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Development of BSL-2 neutralization assays for Ebola virus and Marburg virus based on replication-competent recombinant VSV pseudotypes

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Background: Ebola virus (EBOV) and Marburg virus (MARV), two members of the Filoviridae, cause severe hemorrhagic fever in humans and nonhuman primates with high morbidity and mortality rates up to 90%. Due to the required BSL-4 containment, it is difficult to use infectious Filoviruses to evaluate preclinical and clinical vaccine studies. We hypothesized that replication-competent VSV-G-deleted recombinant VSV containing the Filovirus glycoprotein (rVSV-FiloGP) could be used to develop a BSL-2 neutralization assay that mimics Filovirus neutralization.

Methods: We constructed an rVSV-FiloGP containing the EBOV glycoprotein (rVSV-ZEBOVgp) or MARV glycoprotein (rVSV-MARVgp). These recombinant viruses grew in VeroE6 cells and produced plaques that were smaller than wt VSV.

Results: Using a plaque reduction test (PRNT) in VeroE6 cells, we analyzed specificity, sensitivity, and reproducibility of neutralization of rVSV-FiloGP. We also developed a semi-automated endpoint reduction neutralization test (ERNT) that is less time consuming and laborious than the PRNT. Normal mouse and human sera did not neutralize rVSV-FiloGP or wt VSV. Sera from C57BL/6 or Balb/c mice vaccinated with an Fc fusion protein of the EBOV glycoprotein (EBOVgp-Fc) but not control FLAG-Fc specifically neutralized rVSV-ZEBOVgp but not rVSV-MARVgp. Human normal sera spiked with different concentrations of human anti-ZEBOV mAb KZ52 neutralized rVSV-ZEBOVgp but did not affect wt VSV and rVSV-MARVgp titers. The neutralization assay was highly reproducible during 1-year of evaluation in our lab. We have used the PRNT and ERNT to analyze correlates of protection in small animal challenge models.

Conclusions: Our data showed that rVSV-FiloGP is a practical tool to evaluate neutralizing antibodies against EBOV and MARV under BSL-2 conditions. These PRNT and ERNT could be used for research purposes and to assess consistency of production, potency of vaccines and immunoglobulin preparations, and efficacy of vaccines in clinical trials.

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