DEVELOPMENT OF RECOMBINANT VACCINES AGAINST MACHUPO VIRUS

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Machupo virus (MACV) is the causative agent of Bolivian hemorrhagic fever. Our previous study demonstrated that a single amino acid substitution F438I in the transmembrane domain of MACV glycoprotein (GPC) critically attenuated the pathogenicity of the virus in murine model. However, the reversion to wild-type MACV (wtMACV) was observed in 29% of mice and resulted in death, and we concluded the mutation was not stable in the animals. To prepare a stable, safe and highly immunogenic live-attenuated vaccine, four different chimeric MACVs with partial or entire GPC of attenuated Junin virus Candid#1 strain were created as follows: MCg1 (ectodomain of Candid#1-GPC), MCg2 (ectodomain of Candid#1-GPC plus F427I mutation), MCg3 (ectodomain and transmembrane domain of Candid#1-GPC), MCg4 (entire Candid#1-GPC). All of the wtMACV-infected animals were dead before the end of the study (42 dpi). MCg1-infected animals developed the disease with a delay of several days and 43% of animals were dead before 42 dpi. Viruses were detected in all samples tested from wtMACV-infected animals. 2 of 8 MCg1-infected animals were virus positive in the brain, but the titers were 1000-times lower than that of wtMACV-infected animals. On the other hand, no symptoms and no measurable viral load were detected in the animals infected with MCg2, MCg3, MCg4 or Candid#1. Therefore, the replacement to the ectodomain of Candid#1 GPC contributed to the delay of onset of disease and the reduction of viral dissemination. In addition to the replacement of the ectodomain, the single amino acid substitution in the transmembrane domain critically attenuated the virus and was stable in mice. No neutralizing antibody titer against wtMACV was detected in MCg2- and MCg3-infected animals, while the titer was high in MCg1- and MCg4-infected mice. Taken together, chimeric MACV with entire Candid#1-GPC would be a stable, safe and high immunogenic vaccine candidate. Supported by R01AI093445.