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Genetically engineered live-attenuated cytomegalovirus (CMV) vaccines improve pregnancy outcome in the guinea-pig model of congenital CMV infection

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Background

Congenital CMV infection is a major cause of disability in newborns. An effective preconception vaccine is a major public health priority. The guinea-pig cytomegalovirus (GPCMV) model was utilized to evaluate the efficacy of live, attenuated CMV vaccines generated using a bacterial artificial chromosome (BAC) approach.

Methods

The GPCMV genome was cloned as a BACmid in *E. coli* and used to regenerate a wild-type viral vaccine (wt), and a highly attenuated recombinant vaccine deleted of the gene encoding the dominant T-cell target, *UL83* (pp65). Seronegative animals were immunized with a two-dose series of each vaccine (0- and 3- week schedule), or placebo. Following establishment of pregnancy, dams were challenged with salivary gland-passaged (SG) GPCMV (5×10^5 pfu) in the second trimester, and pregnancy outcomes were compared.

Results

Vaccinated dams seroconverted to GPCMV antigen. ELISA titers were significantly higher in the wt (2.8+/−0.3 $\log_{10}$) compared to the 409 group (2.5+/−0.2 $\log_{10}$; $p<0.05$). Vaccination resulted in highly significant reductions in the magnitude and duration of DNAemia post-SG challenge, and was associated with improved pregnancy outcomes. Among 13 litters in the control group, there were 29 live and 22 dead pups (43% mortality, mean pup weight of 89 g), compared to 45 live and 14 dead pups born to 15 litters in the vaccine group (26% mortality, mean pup weight 106 g; $p<0.05$ vs. control). The two vaccines were comparable in reducing GPCMV transmission at the placental and fetal levels.

Conclusions

Live, attenuated CMV vaccines are effective at preventing congenital infection and disease in the guinea pig model. Of interest, although *UL83* is an effective subunit vaccine in guinea-pigs, immune responses to *UL83* are not essential for fetal protection in the context of a live-virus vaccine. Recombinant CMV vaccines with targeted mutations of pathogenesis or immune evasion genes warrant further consideration in clinical trials.