Vaccination with a Live Attenuated Cytomegalovirus Devoid of a Protein Kinase R Inhibitory Gene Results in Reduced Maternal Viremia and Improved Pregnancy Outcome in a Guinea Pig Congenital Infection Model

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ABSTRACT

Background. Development of a vaccine to prevent congenital cytomegalovirus infection is a major public health priority. Live vaccines attenuated through mutations targeting viral mechanisms responsible for evasion of host defense may be both safe and efficacious.

Methods. Safety and vaccine efficacy was evaluated using a guinea pig cytomegalovirus (GPCMV) model. Recombinant GPCMV Δ145 was generated with a targeted deletion of gp145, a viral protein kinase R (PKR) inhibitor. Attenuation was evaluated following inoculation of 10^7 pfu of Δ145 or parental virus into guinea pigs immunosuppressed with cyclophosphamide. Efficacy was evaluated by immunizing GPCMV-naive guinea pigs twice with either 10^5 or 10^6 pfu of Δ145, establishing pregnancy, and challenging with salivary gland-adapted GPCMV. Immune response, maternal viral load, pup mortality, and congenital infection rates were compared in vaccine and control groups.

Results. Δ145 was substantially attenuated for replication in immunocompromised guinea pigs. Vaccination with Δ145 induced ELISA and neutralizing antibody levels comparable to natural infection. In the higher- and lower-dose vaccine groups, pup mortality was reduced to 1/24 (4%) and 4/29 (14%), respectively, compared to 26/31 (81%) in unvaccinated controls (both groups p<0.0001 vs. control). Congenital infection occurred in 20/31 (65%) of control pups compared to 8/24 (33%) pups in the 10^6 vaccination group (p<0.05). Significant reductions in the magnitude of maternal DNAemia and pup viral load were noted in the vaccine groups, compared to controls.

Conclusion. Deletion of a GPCMV-encoded PKR inhibitor results in a highly attenuated virus that is immunogenic and protective as a vaccine against transplacental infection.

IMPORTANCE Previous attempts to develop a successful immunization against cytomegalovirus have largely centered on subunit vaccination against virion proteins, but have yielded disappointing results. The advent of BAC technologies has enabled engineering of recombinant CMVs, deleted of virally encoded immune modulation genes, toward the goal of developing a safe and potentially more efficacious live attenuated vaccine. Here we report studies of such a vaccine against congenital CMV infection, based on a virus with a targeted deletion in gp145, a virally-encoded inhibitor of protein kinase R, using the guinea pig model of vertical CMV transmission. The deletion virus was attenuated for dissemination in immunocompromised guinea pigs, but elicited ELISA and neutralizing responses. The vaccine conferred protection against maternal DNAemia and congenital transmission, and resulted in reduced viral load in newborn guinea pigs. These results provide support for future studies of...
attenuated CMV vaccines.

FOOTNOTES

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