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Overcoming maternal antibody interference by vaccination with human adenovirus 5 recombinant viruses expressing the hemagglutinin and the nucleoprotein of swine influenza virus

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Abstract

Sows and gilts lack immunity to human adenovirus 5 (Ad-5) vectored vaccines so immunogens of swine pathogens can be expressed with these vaccines in order to immunize suckling piglets that have interfering, maternally derived antibodies. In this study 7-day-old piglets, that had suckled H3N2 infected gilts, were sham-inoculated with a non-expressing Ad-5 vector or given a primary vaccination with replication-defective Ad-5 viruses expressed the H3 hemagglutinin and the nucleoprotein of swine influenza virus (SIV) subtype H3N2. The hemagglutination inhibition (HI) titer of the sham-inoculated group ($n = 12$) showed continued antibody decay whereas piglets vaccinated with Ad-5 SIV ($n = 23$) developed an active immune response by the second week post-vaccination. At 4 weeks-of-age when the HI titer of the sham-inoculated group had decayed to 45, the sham-inoculated group and half of the Ad-5 SIV vaccinated pigs were boosted with a commercial inactivated SIV vaccine. The boosted pigs that had been primed in the presence of maternal interfering antibodies had a strong anamnestic response while sham-inoculated pigs did not respond to the commercial vaccine. Two weeks after the booster vaccination the pigs were challenged with a non-homologous H3N2 virulent SIV. The efficacy of the vaccination protocol was demonstrated by abrogation of clinical signs, by clearance of challenge virus from pulmonary lavage fluids, by markedly reduced virus shedding in nasal secretions, and by the absence of moderate or severe SIV-induced lung lesions. These recombinant Ad-5 SIV vaccines are useful for priming the immune system to override the effects of maternally derived antibodies which interfere with conventional SIV vaccines.

Keywords: Maternal antibody interference; Swine influenza virus; Ad-5 vaccines

1. Introduction

Swine influenza virus (SIV) causes a severe respiratory disease, particularly in finishing pigs and

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pregnant sows (Janke, 2000; Olsen, 2002). Clinical signs include pigs with high fever, coughing, labored breathing, abortions and a low percentage of deaths in sows (Easterday and Van Reeth, 1999). The genome of SIV consists of 8 segments of single-stranded, negative-sense RNA encoding 10 viral proteins (Lamb and Krug, 2001). RNA segment 4 contains the gene encoding the large hemagglutinin (HA) glycoprotein that projects from the surface envelope of the virion. Segment 5 encodes the nucleoprotein (NP) gene. The HA immunogen induces predominately subtype-specific humoral immunity (Andrew et al., 1987; Macklin et al., 1998). The conserved NP is group-specific stimulating cytotoxic T lymphocytes for cross-protection (Yewdell et al., 1985; Wraith et al., 1987; Ulmer et al., 1993).

Human adenovirus type 5 (Ad-5) vectors have been used to express foreign genes for use in gene therapy and for vaccine development (Berkner, 1988; Prevec et al., 1989; Graham and Prevec, 1992; Grunhaus and Horwitz, 1992; Eloit, 1995; Hitt and Graham, 2000). The Ad-5 recombinant viruses are rendered replication-defective by introducing a large deletion in the early transcription region 1 (E1) of the genome. These replication-defective Ad-5 viruses grow to very high titers in 293 cells that complement the E1 region of the adenovirus genome (Graham et al., 1977). Similarly, many of these vectors contain an E3 region deletion which results in an enhanced immune response to the expressed foreign genes (Chengalvala et al., 1994). Moreover, high levels of expression are achieved in the Ad-5 vector system when foreign genes are under the control of a constitutive promoter (Ambriovic et al., 1997). Other advantages of the human Ad-5 vectors include their broad host range and the lack of preexisting, maternally derived antibodies which can interfere with vaccine efficacy in young and growing pigs. Sows and gilts generally have some immunity to ubiquitous porcine adenoviruses but they lack immunity to human adenoviruses.

Vaccination strategies using non-replicating virus vectors (Eloit et al., 1990; Konishi et al., 1992; Brockmeier et al., 1993; Le Potier et al., 1997; Mayr et al., 1999, 2001; Monteil et al., 2000; Moraes et al., 2002) or DNA-based vaccines (Macklin et al., 1998; Larsen et al., 2001) have been used experimentally to prime or to immunize pigs. Direct comparisons for efficacy between naked DNA and Ad-5 vectored vaccines using the pseudorabies virus gD glycoprotein have been carried out in pigs with maternal antibodies (Le Potier et al., 1997; Monteil et al., 1997). Theoretically, critical immunogenic proteins of numerous swine pathogens can be expressed with Ad-5 vectored vaccines in order to immunize suckling piglets that have acquired interfering, maternally derived antibodies. These passively acquired antibodies are important for the early protection of piglets but are a common cause of vaccine failure if vaccines are administered to young suckling or nursery-age pigs. Thus, inactivated influenza vaccines for swine are not administered until maternally derived antibodies have decayed to background or to a sufficiently low level. Since this time interval is dependent on the initial amount of passive antibody ingested by each piglet, the actual timing for a successful vaccination is only estimated. Generally, killed influenza vaccines are given twice to weaned pigs as late as 12 weeks and again at 16 weeks-of-age. Consequently, a vaccine that can stimulate immunity in the neonatal pig even in the presence of maternally derived antibodies would offer additional protection and safety.

In this study we used replication-defective, recombinant Ad-5 viruses to prime immunity in 1-week-old piglets that had natural field exposure levels of maternally derived SIV antibodies. Three weeks later, the primed piglets were vaccinated with a commercial SI vaccine yielding an anamnestic humoral immune response and strong protective immunity.

2. Materials and methods

2.1. Experimental design

Six gilts were purchased from a high-health swine herd free of porcine reproductive and respiratory syndrome virus (PRRSV) and delivered to the National Animal Disease Center (NADC) at 70 days of gestation. The gilts were tested and found to be seronegative for PRRSV but had hemagglutination inhibition (HI) titers to SIV (range: 80–320) indicating that the gilts had been naturally infected with SIV subtype H3N2 at some previous time on the farm. The gilts were seronegative for SIV subtype H1N1. All experimental procedures carried out with the gilts and