Enhanced Immune Response To Vaccination With Woodchuck Hepatitis Virus (WHV) Surface Antigen (WHsAg) Using Cationic Liposome-DNA Complexes (CLDC) As Adjuvant

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Background

Immunity to hepatitis B virus (HBV) involves efficient antiviral B and T cell responses during the acute phase of HBV infection leading to resolution of viral infection. Humoral and cellular immunity to HBV is also achieved following prophylactic vaccination of healthy individuals with conventional vaccines that are based on the HBV envelope protein and alum-adjunct. Contrary to patients with chronic HBV infection, persistent viral replication is associated with deficient B and T cell responses to HBV proteins. Recovery of both cell activities in chronic HBV carriers by therapeutic vaccination appears a promising approach for viral eradication.

Complexes of cationic lipid carrier and non-coding plasmid DNA (CLDC) are a potent stimulant of innate immunity. Stimulation by CLDC is mainly due to a liposome-mediated potentiation of the inherent responsiveness of the mammalian immune system to non-methylated CpG motifs within the bacterial plasmid DNA. CpG motifs function via interaction with the toll-like receptor 9, an interaction that requires internalization facilitated by the lipid component. CLDC can be combined with specific bacterial or viral antigens to produce pathogen-specific vaccines. These lipid-DNA-antigens complexes result in a potent adjuvant effect with elicitation of robust antibody and cell-mediated immune responses to the target antigen.

Objective

Using the woodchuck animal model of HBV infection the immunogenic effects induced by CLDC were investigated during prophylactic vaccination of woodchuck hepatitis virus- (WHV) negative woodchucks with three doses of WHV surface antigen (WHsAg) adjuvanted with either CLDC or alum and administered intramuscularly (IM) or subcutaneously (SC) (Figure 1).

Results

Antibody response: IM vaccination with CLDC/WHsAg elicited anti-WHs earlier and in more woodchucks than did Alum/WHsAg, with significant different titers at wk 2 (Figure 2). Overall, titers were greater and antibody responses more sustained with CLDC/WHsAg than with Alum/WHsAg (Figure 2, Table 1). Because antibody responses at wk 8 were 2.7 to 5.9 fold higher in the IM than in the SC groups, woodchucks given SC vaccine at wks 0 and 4 received the wk 8 vaccine IM. Antibody responses increased subsequently to titers similar or higher than those in woodchucks given CLDC/WHsAg by the IM route (Figure 2, Table 1).

T cell responses: Differences in T cell responses to WHsAg and selected WHsAg peptides between groups were detected at wk 5 (Figure 3A). Three of 5 woodchucks from the CLDC/WHsAg-IM group had T cell responses to WHsAg and most peptides were recognized in contrast, only 1 of 5 woodchucks from the Alum/WHsAg-IM and Alum/WHsAg-SCM groups (none in the CLDC/WHsAg-SCM group) had T cell responses to WHsAg that were weaker and recognized fewer peptides. After the third immunization, T cell responses were similar in all vaccinated groups but were more sustained in the CLDC/WHsAg group (Figure 4).

Conclusions

- CLDC-adjuvanted WHsAg administered IM results in a more rapid enhancement of humoral and cellular immune responses compared to a conventional alum-adjuvanted vaccine.
- While less rapid, the responses following SC administration of vaccine can prime the IM responses.
- The enhanced adjuvant activity of CLDC over alum could be beneficial for therapeutic vaccination in chronic HBV infection which is currently studied in woodchucks with chronic WHV infection.