Recombinant Adeno-vaccine Expressing Enterovirus 71-like Particles against Hand, Foot, and Mouth Disease

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Background/Objective
Enterovirus 71 (EV71) and coxsackieviruses (CV) are the major causative agents of hand, foot and mouth disease (HFMD). There is not currently a vaccine available against HFMD, only a newly developed formalin-inactivated EV71 (FI-EV71) vaccine has been tested in clinical trial and has shown efficacy against EV71.

Method
We have designed and genetically engineered a recombinant adenovirus Ad-EVVLP with the EV71 P1 and 3CD genes inserted into the E1/E3-deleted adenoviral genome. Ad-EVVLP were produced in HEK-293A cells. In addition to Ad-EVVLP particles, virus-like particles (VLPs) formed from the physical association of EV71 capsid proteins, VP0, VP1, and VP3 expressed from P1 gene products. They were digested by 3CD protease and confirmed to be produced by Ad-EVVLP-producing cells, as determined using transmission electron microscopy and western blotting.

Result
Mouse immunogenicity studies showed that Ad-EVVLP-immunized antisera neutralized the EV71 B4 and C2 genotypes. Activation of VLP-specific CD4+ and CD8+/IFN-γ T cells associated with Th1/Th2-balanced IFN-ɣ, IL-17, IL-4, and IL-13 was induced; in contrast, FI-EV71 induced only Th2-mediated neutralizing antibody against EV71 and low VLP-specific CD4+ and CD8+ T cell responses. The antiviral immunity against EV71 was clearly demonstrated in mice vaccinated with Ad-EVVLP in a hSCARB2 transgenic (hSCARB2-Tg) mouse challenge model. Ad-EVVLP-vaccinated mice were 100% protected and demonstrated reduced viral load in both the CNS and muscle tissues. Ad-EVVLP successfully induced anti-CVA16 immunities. Although antisera had no neutralizing activity against CVA16, the 3C-specific CD4+ and CD8+/IFN-γ T cells were identified, which could mediate protection against CVA16 challenge. FI-EV71 did not induce 3C-mediated immunity and had no efficacy against the CVA16 challenge.

Conclusion
These results suggest that Ad-EVVLP plays as a multivalent vaccine to enhance neutralizing antibody and protective cellular immune responses to against EV71 infection and cellular immune responses against CV infection.