DEVELOPMENT OF REPLICATION-DEFECTIVE VIRUSES AS VACCINES FOR FLAVIVIRUS DISEASES

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Viruses in the flavivirus family cause some of the most important arthropod-borne diseases. Current vaccines for these diseases include live-attenuated virus vaccines (LAV) and inactivated virus vaccines (INV). The methods used to produce these vaccines have NOT yielded approved vaccines to prevent the most important arthropod-borne viral disease in the world (dengue fever/hemorrhagic fever). We hypothesized that safe vaccines for flavivirus diseases could be made by engineering replication-restricted flaviviruses that synthesize the essential viral immunogens, producing a new type of vaccine to protect against flavivirus diseases: a gene-deleted flavivirus that cannot complete its replication cycle in the vaccinated host. This product (RepliVAX) consists of a virus with a large deletion in the essential capsid (C) protein gene, and thus cannot cause disease or produce progeny virus in vaccinated hosts or in cultured cells. However, RepliVAX can be efficiently propagated in cultured cells that express C. When inoculated into animals RepliVAX produces all viral proteins (except C), including a sub-viral particle (SVP) with demonstrated capacity to induce antiviral immunity in man. We have produced RepliVAX vaccine candidates for West Nile encephalitis (WNE) that reach titers of over 10^7 infectious units (U)/ml in cultures of C-expressing cells. RepliVAX is over $1x10^6$-fold less virulent than WNV in baby mice, but is potent and protective in adult mice. WN RepliVAX has been engineered to produce the critical immunogens of JE virus (JEV) and dengue virus (DV), indicating that RepliVAX can serve as a platform for producing vaccine candidates for other flavivirus diseases.

KEY WORDS: vaccine, flavivirus, replication-defective