A NEW PROTECTIVE MRNA FLAVIVIRUS VACCINE FORMULATION

Background

Infections caused by the tick-borne flavivirus Powassan virus (POWV) are increasing in North America and Russia. In North America, lineage 1 and lineage 2 (also called deer-tick virus) are circulating and are clinically indistinguishable. The amino acid sequence of their envelope glycoprotein E shows 96% identity. While no POWV vaccine has been developed so far, only a very limited cross-neutralizing activity has been shown by antibodies induced by current TBE vaccines. The authors have developed a new vaccine platform, in which mRNA coding for the proteins prM and E is formulated in a lipid nanoparticle (LNP) resulting in co-expression of the two proteins and secretion of subviral particles (SVPs).

Results

The new platform was used to develop a lineage 1 strain (LB) and a lineage 2 strain (Spooner) vaccine which were tested in C57BL/6 mice 7 to 14 weeks of age. When mice were subcutaneously infected with 10^2 focus-forming units with strain LB, lethal infection was induced in 93% in about 9 days post infection, while infection with strain Spooner resulted in mortality rate of about 60% within 13 days. In mice, in which interferon signaling was blocked, Spooner lethality reached 100% within 10 days.

After one intramuscular injection with the Spooner vaccine, high neutralizing antibodies were induced measured in a reporter virus particle (RVP) assay, and after a second injection, the neutralizing titers were boosted 15-fold. These results were confirmed in a focus-reduction neutralization (FRNT) assay using Vero cells and with an experimental LB strain vaccine. Challenge experiments revealed 100% protection after two immunizations and the animals maintained body weight, whereas placebo-vaccinated mice lost about 40% of their weight. Viremia was undetectable in vaccinated mice upon infection. Serum from vaccinated mice was able to protect mice from a viral challenge showing that humoral immune response is enough to protect mice from a lethal POWV challenge. In a further experiment, it was shown that one dose of mRNA vaccine was sufficient to induce protection. The POWV mRNA vaccine induced antibodies with cross-neutralizing activity against other flaviviruses with 20 to 30% difference in protein sequence - TBE virus, Langat virus and Gadgets Gully virus. After two immunizations with the POWV mRNA vaccine mice could be fully protected against a heterologous challenge with Langat virus. Challenge with TBE virus and Gadgets Gully virus could not be carried out due to the requirement of a BSL4 facility lab.

Discussion

In summary, the LNP-mRNA vaccine platform may be adaptable for development of vaccine against other flaviviruses and it has the potential for the development of flavivirus vaccines with broad protection against multiple viruses. These results contrast with prior observations that there is little cross-reactivity of sera from TBE virus-infected and TBE virus–vaccinated humans against POWV. It remains possible that there is a directionality to the cross-reactive response, such that POWV induces more cross-reactive antibodies than the TBE virus due to differential display of conserved epitopes. Alternatively, the SVPs induced by the mRNA vaccine may induce more cross-reactive epitopes than inactivated or fully infectious TBE virus due to differences in the arrangement of E proteins. Finally, the antibody repertoire produced in mice vs. humans in response to TBE virus may be more cross-reactive.

Literature

VanBlargan et. al.
An mRNA vaccine protects mice against multiple tick-transmitted flavivirus infections
Cell Reports 2018; 25:3382-3392

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