BROAD CROSS-PROTECTION BY DIFFERENT TBE VACCINES AGAINST VARIOUS TBE VIRUS SUBTYPES

Background

TBE is a disease caused by the TBE virus of which at least three subtypes have been described, the European (EU), the Siberian (Sib) and the Far-Eastern (FE) subtype, and newly phylogenetic virus groups have been described like the Transbaikal and the Himalayan strains (see e.g. Snapshot 25). TBE vaccines have been developed either based on EU strains Neudörfl (marketed by Pfizer; Vac3) and strain K23 (marketed by GSK; Vac4) or on FE strain Sofjin (marketed by Chumakov FSC R&D IBP RAS, Russia; Vac1), strain 205 (marketed by Virion Company, Microgen, Russia; Vac 2) and Senzhang (produced by a Chinese company). All these TBE vaccines are inactivated whole virus vaccines, and they differ not only regarding the antigen subtype but also in antigen amount, inactivation process and excipients. However, all these TBE vaccines have shown immunogenicity in clinical trials and induce neutralizing antibodies not only to the homologous strain but also to other strains of the same subtype and to strains from other subtypes. The informative value about cross-protection is nevertheless still limited because in most studies only a few heterologous strains have been tested, sometimes only one representative of a certain subtype.

Results

In this study, the in vivo protective efficacy in mice of four TBE vaccines (Vac1 to Vac4) has been analyzed. Mice received two intramuscularly injected 1/10 human doses 2 to 4 weeks apart, and 2 to 4 weeks later were subcutaneously infected with a wide range of TBE virus strains. Among the strains tested were three strains of the FE subtype, two of the EU subtype, six of the Sib subtype , one Transbaikal and one Buryat-Mongolian strain.

The mice were monitored for 21 days. In addition to the challenge experiments, plaque reduction neutralization test (PRNT50) was carried out of sera of immunized mice.

The European vaccines provided a high level of protection (80-100%) against strains belonging to the EU subtype, and after immunizing with Vac3, animals were also protected against a lethal challenge with the Sib strains but showed disease signs. When infected with the FE strain Sofjin, 73% of the mice died. Vac3 provided much better protection against the EU strain Absetterov than against LK-138, while Vac1 protected against both Eu strains. Vac1 and Vac2 provided a high-level protection from Sofjin strain, while Vac4 did not protect mice from this strain. Vaccines based on FE or EU strains induced a pronounced immune response against TBE virus strains of the Sib subtype. Vac4 induced the highest titer against the Sib strain EK-328. However, Vac1 showed the lowest variance against different strains and Vac3 showed the highest variance. The variance of neutralizing antibodies (nAB) induced by a particular vaccine against a set of TBE virus strains was used to estimate the breadth of the nAB spectrum in the sera. The authors also analyzed the association between the PRNT50 results with the differences in the primary sequence of the glycoprotein E. The results showed that even a single amino acid substitution in protein E of a vaccine strain can affect the spectrum of induced nAB. On the other hand, single amino acid substitution in protein E of the TBE virus strain

used in the PRNT50 can also be of great importance, e.g. nAB induced by Vac4 effectively neutralized strain 178-79 and poorly neutralized strain 205KGG that both carry individual substitutions at position 306 of protein E.

Discussion

The results suggest that almost all TBE vaccines protected the mice from all known lineages. However, the protective efficacy of vaccines against some TBE virus strains can significantly differ. The authors concluded that when a low protective efficacy was observed in the experiments against various strains this could not only be associated with match/mismatch between the spectrum of vaccine-induced antibodies and the antigenic structure of the virus used for the challenge, but also with other characteristics of the viruses not related to antigenic structure, e.g. rate and level of viral replication at the early stage of infection, the rate of penetration into the cell and the ability of the virus to modulate the immune response. Thus, the phylogenetic relations between a vaccine and a challenge virus are important but are not the only characteristics determining the vaccine protective efficacy against a particular virus. The neutralizing efficacy of nAB induced appears to be dependent not only on the presence of the nABs to the particular epitope of the protein E of the challenge virus but also, less directly, on the intrinsic properties of the protein E structure. Unique point substitutions appear in different regions of the protein E which can alter the exposed sidechains and may easily influence the recognition of certain epitopes. The protective efficacy of the vaccines depended on the individual properties of the vaccine strain and the challenge virus, rather than on the subtype.

Literature

Chernokhaeva et al.

Experimental evaluation of the protective efficacy of tick-borne encephalitis (TBE) vaccines based on European and Far Eastern TBEV strains in mice and in vitro.

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