TBE VACCINATION: CORRELATES OF PROTECTION

Background

Active immunization is the most important protective measure against TBE virus infections. Immune responses which protect an individual against disease are a complex interplay between distinct cell types of the immune system.

Innate immunity represents the (quick) first line defenses. The adaptive immune responses comprise both, the humoral and cell-mediated responses, and needs more time to be established, but provides more specific protection It can maintain for a long time and may be re-activated after re-exposure to the same pathogen even after decades (immunological memory). These memory immune responses form the basis for the correlates of protection after vaccination.

Results and discussion

After infection by TBE virus, specialized immune cells may detect so-called pattern recognition receptors (PRRs) - conserved moieties expressed by potential pathogens. Local skin inflammatory responses already begin one to three hours later. Important PPRs to detect RNA viruses like TBE virus include Toll-Like Receptors (TLRs), Retinoic Acid-Inducible Gene 1 (RIG-1)-Like Receptors (RLRs). PRR activation leads to signaling cascades which result in the activation of Interferon (IFN), dominated by IFN-α and IFN-β, which seem to be key mediators of protection during the initial phase of infection.

After TBE virus infection, skin-localized dendritic cells (DCs) are activated and play a key role between innate and adaptive immune response. Cellular immunity primarily relies on T-cell mediated immune responses. CD4+ T-cells produce cytokines (mainly IL-2, TNF-α and IFN-γ, which help to drive antiviral immune response and help the B cells to produce antibodies, mainly against structural proteins of TBE virus. Cytotoxic CD8+ T-cells play crucial roles by identifying and destroying infected host cells, and here, viral non-structural proteins are important targets.

During secondary disease and CNS disease, strong cytokine expression in the brain, coupled with low neutralizing antibody responses, has been linked to enhanced susceptibility to severe disease and death.

Polymorphisms in the cytokine CCR5 play an important role in leukocyte migration, indicating that high cytokine expression contributes to immunopathology and poor disease outcomes. The role of CD8+ cells in immunopathology versus protection during TBE disease is yet not clear, and it remains open if vaccines which promote strong CD8+ T-cell responses would be desirable.

Humoral immune response, mediated by neutralizing antibodies, plays a vital role in protection by binding of the virus and coating of the viral particles which induces the destruction by phagocytic immune cells. The long-term maintenance of memory B cells (mostly directed against the glycoprotein E (gE) and to some extent to the non-structural protein 1) further enables the immune system to mount faster and more effective response (perhaps also after decades). After re-infection, these cells quickly differentiate into antibody-producing plasma cells helping to eliminate the virus before it can cause widespread infection and disease.

The dominance of antibodies to different gE domains is strongly affected by both host-specific and virus-specific factors, and human immune responses are dominant to the gE regions ED1

and ED2. It is generally believed that TBE vaccines can protect from disease by both homologous and heterologous subtypes, although vaccines based on the European subtype may result in a reduced protection against some Far Eastern and Siberian TBE virus subtypes. Seropersistence studies indicate that TBE virus neutralizing antibody titers induced by primary vaccination decline over time but persist at least between 5 to 10 years. After booster vaccination, decline of antibody titers is slower, and protective titers can subsequently maintain up to 10 years or more.

Monitoring the duration of immunity is key for ensuring long–term protection as well as for developing effective immunization strategies.

Whether infection mediates life-long immunity and by which immune subsets warrants additional investigations. Vaccine effectiveness data indicate that neutralizing antibody titers do not alone track with protection.

Literature

Ackermann-Gäumann et al.

Defining the “correlate(s) of protection“ to tick-borne encephalitis vaccination and infection – key points and outstanding questions.

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Author: Dr. Michael Bröker

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