V 10 Molecular basis of several tick-borne encephalitis virus virion properties

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Tick-borne encephalitis virus (TBEV) is a flavivirus with an enveloped virion. The outer surface of the viral particle is formed by the E glycoprotein that determines all first stages of the viral cycle, including virion-receptor interactions and entry. Arboviruses, like TBEV, are host switch viruses, and receptors play an important role in their life cycles. Glycosaminoglycans (GAGs) are widespread molecules and one of the low-affinity receptors for TBEV.

In the present work, we used variants of one TBEV strain that were obtained during adaptation to the ticks (variant M) and readaptation to the mammalian cells (revertants). The tick-adapted variant contained a charge-increasing mutation in the E protein, several mutations in non-structural proteins, and NTR in comparison with the parental strain and performed GAG-binding phenotype with low neuroinvasiveness for laboratory mice. One of the revertants contained a reverse mutation in the E protein, the others – 3 different compensative amino acid substitutions – a decreasing charge of the E glycoprotein molecule.

Revertants showed different sorption levels on GAG analogue – Heparin-Sepharose that correlated with neuroinvasiveness. Analysis of data received after molecular dynamics simulation of E protein ectodomains of all investigated variants allowed us to find an appropriate explanation for differences in Heparin-Sepharose sorption of the TBEV variants and hypothesize the virion stability properties of observed viruses. Experimental analysis of thermoinactivation at 37°C and hemagglutination stability to detergents confirmed our hypothesis. Thus, conformative stability of the E protein ectodomain is one of the factors determining virion stability (stability to thermoexposure and hemagglutination stability to detergents).

This novel approach based on molecular dynamics could allow us to find an explanation or even predict the biological properties of flavivirus virions.