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Review

Steps of the tick-borne encephalitis virus replication cycle that affect neuropathogenesis

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Abstract

Tick-borne encephalitis virus (TBEV) is an important human pathogen that causes severe neurological illness in large areas of Europe and Asia. The neuropathogenesis of this disease agent is determined by its capacity to enter the central nervous system (CNS) after peripheral inoculation ("neuroinvasiveness") and its ability to replicate and cause damage within the CNS ("neurovirulence"). TBEV is a small, enveloped flavivirus with an unsegmented, positive-stranded RNA genome. Mutations affecting various steps of its natural replication cycle were shown to influence its neuropathogenic properties. This review describes experimental approaches and summarizes results on molecular determinants of neurovirulence and neuroinvasiveness that have been identified for this virus. It focuses on molecular mechanisms of three particular steps of the viral life cycle that have been studied in some detail for TBEV and two closely related tick-borne flaviviruses (Louping ill virus (LIV) and Langat virus (LGTV)), namely (i) the envelope protein E and its role in viral attachment to the cell surface, (ii) the 3′-noncoding region of the genome and its importance for viral RNA replication, and (iii) the capsid protein C and its role in the assembly process of infectious virus particles. Mutations affecting each of these three molecular targets significantly influence neuropathogenesis of TBEV, particularly its neuroinvasiveness. The understanding of molecular determinants of TBEV neuropathogenesis is relevant for vaccine development, also against other flaviviruses.
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Keywords: Tick-borne encephalitis virus; Neuropathogenesis; Central nervous system; Flavivirus

Contents

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1. The disease, its epidemiology, and prevention

Tick-borne encephalitis virus (TBEV) is the causative agent of one of the most dangerous neuroinfections of humans in Europe and Asia. More than 10,000 hospitalized cases of TBEV disease are reported annually within its endemic area with numbers varying considerably from year to year (Burke and Monath, 2001; Gritsun et al., 2003a, 2003b). The actual incidence of the disease, however, is estimated to be significantly higher as mild cases of TBEV infections frequently remain undiagnosed. In the natural environment, the virus circulates between ticks (mainly of the species *Ixodes ricinus* and *Ixodes persulcatus*) and various wild vertebrate hosts (Burke and Monath, 2001). Rodents of several different species are known to be amplifying hosts, whereas insectivores, such as shrews, moles and hedgehogs act as important reservoirs. Although the virus can inefficiently be transmitted transovarially to the progeny of an infected female tick and is then maintained throughout the developmental stages (from larvae to nymphs to adults), horizontal transmission between ticks and vertebrates is necessary for endemnicity (Nuttall and Labuda, 2003). Uninfected larvae and nymphs can get infected by feeding on a viremic animal or by co-feeding next to an infected tick. The latter mechanism enables transmission in the absence of significant viremia, even on immune hosts, and is probably the most relevant pathway for viral spread among ticks in nature (Labuda et al., 1997). The strict ecological requirements of the natural transmission cycle explain why the disease occurs mainly in foci, generally within the 7 °C isotherm, with very little geographic variation from year to year (Suss, 2003). Endemic areas are found in most European countries (except Great Britain, the Benelux countries, Portugal, and Spain) and in large parts of Asia, including the countries of the former Soviet Union, Northern China, and Northern Japan.

Humans usually acquire the disease by the bite of an infected adult tick or, in rare cases, by the consumption of unpasteurized milk or cheese from goats or sheep, which can also get infected by tick bites and secrete the virus into the milk during the viremic phase (Burke and Monath, 2001). Humans are a dead-end infection host for the virus and do not play a role in the maintenance of the virus in nature.

Severe cases of TBEV infections with neurological manifestations typically take a biphasic course (Haglund and Gunther, 2003). After an incubation period of 3–7 days, the first phase is usually an influenza-like illness with uncharacteristic symptoms, such as fever, headache, muscle pain, and malaise. After these symptoms are resolved, 20–30% of the patients develop the second phase of the disease involving neurological symptoms of variable severity. Meningeal, meningoencephalitic, poliomyelitic, and polyradiculoneuritic forms of the disease can be distinguished (Gritsun et al., 2003a, 2003b). A chronic form of the disease has only been described in patients from Siberia and Far East Russia. The case:fatality rate is 1–2% in Europe, but reported to be considerably higher in Siberia (6–8%) and in the Far East (20–40%). It is not clear, however, whether these higher fatality rates are caused by the circulation of more virulent strains in these areas or biased by differences in the diagnosis and hospitalization rates. In general, the disease takes a more severe course in adults than in children, and severe forms often cause long-lasting or permanent neuropsychiatric sequelae.

Formalin-inactivated whole virus vaccines are available and provide a very high degree of protection against the disease. In Austria, where almost 90% of the population has been vaccinated, the number of hospitalized cases has dramatically decreased from as many as 700 per year at the time before the onset of the mass vaccination campaign to about 60 per year in recent years (Kunz, 2003).

2. The infectious agent and its classification

Tick-borne encephalitis virus is a member of the genus *Flavivirus*, family *Flaviviridae* (Heinz et al., 2000). All members of the genus *Flavivirus* share a very similar architecture of their virions, genomic organization and life cycle (Lindenbach and Rice, 2001). Flavivirus virions are small, round enveloped particles (Fig. 1A). The lipid envelope

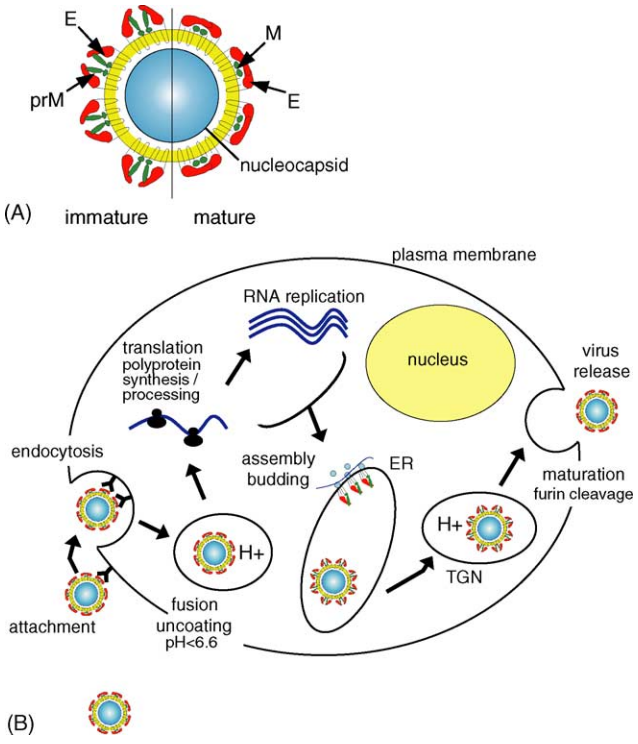

Fig. 1. Schematic diagrams of the structural organization (A) and the replication cycle (B) of TBEV. The viral nucleocapsid, formed by the positive-stranded RNA genome and protein C, is surrounded by a lipid envelope in which two surface proteins are carboxy-terminally anchored. In immature virions, proteins prM and E form heterodimers, whereas infectious, mature virus particles carry the small protein M and homodimers of protein E. ER, endoplasmic reticulum; TGN, trans-Golgi network. For a description of the individual steps of the replication cycle, refer to the main text.