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Transmission and evolution of tick-borne viruses

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Ticks transmit a diverse array of viruses such as tick-borne encephalitis virus, Powassan virus, and Crimean-Congo hemorrhagic fever virus that are reemerging in many parts of the world. Most tick-borne viruses (TBVs) are RNA viruses that replicate using error-prone polymerases and produce genetically diverse viral populations that facilitate their rapid evolution and adaptation to novel environments. This article reviews the mechanisms of virus transmission by tick vectors, the molecular evolution of TBVs circulating in nature, and the processes shaping viral diversity within hosts to better understand how these viruses may become public health threats. In addition, remaining questions and future directions for research are discussed.

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Introduction

Tick-borne viruses (TBVs) are highly focal infections that persist in nature by continuous transmission among vector ticks and wild animal hosts [1]. Although the natural history varies considerably for each virus, at their core, they all require a permissive environment that supports the spatial and temporal overlap of the virus, vector, and vertebrate host. These viruses often remain undetected until humans encroach upon the natural transmission cycle, become infected, and develop clinical illness leading to their identification. In recent decades, a number of established TBVs have emerged as public health concerns including tick-borne encephalitis virus (TBEV) in Europe and Asia [2], Crimean-Congo hemorrhagic fever virus (CCHFV) in Asia and Africa [3], and Powassan virus (POWV) in North America (Table 1) [4•]. Meanwhile, new TBVs are continually being discovered including severe fever with thrombocytopenia syndrome virus or Huaiyangshan virus in East Asia [5], and Heartland and Bourbon viruses in the U.S. [6,7]. These trends are driven by the proliferation of ticks in many regions of the world and by human encroachment into tick-infested habitats. In addition, most TBVs are RNA viruses that mutate faster than DNA-based organisms and replicate to high population sizes within individual hosts to form a heterogeneous population of closely related viral variants termed a mutant swarm or quasispecies [8]. This population structure allows RNA viruses to rapidly evolve and adapt into new ecological niches, and to develop new biological properties that can lead to changes in disease patterns and virulence [9]. The purpose of this paper is to review the mechanisms of virus transmission among vector ticks and vertebrate hosts and to examine the diversity and molecular evolution of TBVs circulating in nature. This article also describes recent research on viral genetic changes occurring during tick-borne transmission to better understand how these viruses interact with their hosts and emerge as health problems.

Taxonomy of tick-borne viruses

TBVs comprise a diverse array of viral entities that are classified into to six virus families: *Flaviviridae*, *Bunyaviridae*, *Orthomyxoviridae*, *Rhabdoviridae*, *Reoviridae*, and *Asfarviridae* (Table 1). The most important TBVs belong to the family *Flaviridae* and *Bunyaviridae* and include numerous viral agents that cause encephalitis or hemorrhagic fever in humans. Virus families differ in many fundamental characteristics including nucleic acid type, morphology, and replication strategy that are the basis for their classification into distinct viral families. Details of their genome organization and replication process are beyond the scope of this article.

The inclusion of TBVs into multiple virus families suggests that this mode of transmission arose independently in several different viral lineages as a successful evolutionary strategy for infecting new hosts. All of the viruses listed in Table 1 are considered true arthropod-borne viruses (arboviruses) because they replicate both within ticks and vertebrate hosts. Next generation sequencing techniques, however, have revealed a much larger diversity of viruses in ticks that are not amenable to isolation by traditional techniques like cell culture and suckling mice inoculation [10,11••]. Many of these viruses may prove to be tick-specific viruses similar to the recent discovery of insect-specific viruses within mosquitoes [12]. TBVs that cause human and animal disease appear to represent a small fraction of the tick virome. The remainder of this review will focus on the transmission and evolution of members of the family *Flaviviridae* because they represent the best studied and well-characterized TBVs to

Table 1

Select tick-borne viruses listed by virus family

Family	Characteristics[a]	Virus	Geographic location	Disease	Tick vectors[b]
Flaviviridae	Enveloped, spherical, ssRNA(+)	Tick-Borne Encephalitis	Europe, Northern Asia	Encephalitis (humans)	*Ix. ricinus*, *Ix. persulcatus*
		Powassan	North America, Russia	Encephalitis (humans)	*Ix. cookei*, *Ix. scapularis*
		Louping Ill	Great Britain, Ireland	Encephalitis (sheep)	*Ix. ricinus*
		Kyasanur Forest Disease	India	Hemorrhagic fever (humans)	*Ha. spinigera*
		Omsk Hemorrhagic Fever	Russia	Hemorrhagic fever (humans)	*De. reticulatus*
Bunyaviridae	Enveloped, spherical, segmented ssRNA(−)	Crimean-Congo Hemorrhagic Fever	Africa, Asia, southern Europe	Hemorrhagic fever (humans)	*Hy. marginatum*, *De. marginatus*
		Nairobi Sheep Disease	Africa	Fever, diarrhea (sheep, goats)	*Rh. appendiculatus*
		Huaiyangshan	East Asia	Hemorrhagic fever (humans)	*Ha. longicornis*
		Heartland	Central United States	Hemorrhagic fever (humans)	*Am. americanum*
Orthomyxoviridae	Enveloped, spherical, segmented ssRNA(−)	Bourbon	Central United States	Hemorrhagic fever (humans)	Unknown
Rhabdoviridae	Enveloped, bullet-shaped, ssRNA(−)	Sawgrass	Eastern United States	Unknown	*De. variabilis*
Reoviridae	Non-enveloped, icosahedral, dsRNA	Colorado Tick Fever	Western United States	Fever (humans)	*De. andersoni*
Asfarviridae	Enveloped, icosahedral, dsDNA	African Swine Fever	Africa, southern Europe, Caucasus region	Fever (pigs)	*Or. moubata*, *Or. erraticus*

[a] ssRNA(+): single-stranded positive-sense RNA; ssRNA(−): single-stranded negative-sense RNA; dsRNA: double-stranded RNA,
[b] Am.: Amblyomma; De.: Dermacentor; *Ix.*: *Ixodes*; *Ha.*: *Haemaphysalis*; *Hy.*: *Hyalomma*; *Or.*: *Ornithodoros*; *Rh*: *Rhipicephalus*.

date. However, it is worth noting that ticks also transmit segmented viruses (*Bunyaviridae* and *Orthomyxoviridae*) that may evolve by segment reassortment in addition to random mutation. Evidence for genetic reassortment has been inferred for CCHFV with variable mutation rates between segments and possible genetic recombination within segments [13].

The family *Flaviviridae*, genus *Flavivirus* represents a diverse group of viruses and includes a number of important mosquito-borne and tick-borne pathogens such as dengue virus, TBEV, West Nile virus (WNV) and Zika virus. These viruses are approximately 40–50 nm in diameter and consist of a host-cell derived lipid bilayer membrane surrounding a nucleocapsid core containing a single strand of positive-sense RNA. By phylogenetic analysis, flaviviruses cluster into groups defined by the arthropod vector: mosquito-borne, tick-borne, no known vector, and insect-specific flaviviruses [14,15]. The tick-borne flaviviruses may be further subdivided into the mammalian and seabird associated groups, and Kadam virus that forms a third evolutionary lineage (Figure 1) [16•]. Tick-borne flaviviruses known to cause disease in humans and domestic animals are all members of the tick-borne encephalitis sero-complex and include TBEV, louping ill virus (LIV), Omsk hemorrhagic fever virus, Kyasanur Forest Disease virus (KFDV), and POWV. The designation of these viruses was historically based on clinical symptoms, geography, and serological criteria; however, genetic analyses do not support some species assignments. Grard *et al.* proposed taxonomic changes that involved synonymizing LIV and other sheep and goat encephalitis viruses with eastern and western TBEV into a single species — TBEV [16•]. In addition, Alkhurma hemorrhagic fever virus is considered a subtype of KFDV [17] and Deer tick virus (DTV) is recognized as a subtype of POWV [18,19].

Virus transmission by tick vectors

Both *Argasidae* (soft-ticks) and *Ixodidae* (hard-ticks) can transmit viruses; however, the vast majority of TBVs of human and agricultural importance are transmitted by hard-ticks [20]. Hard-ticks have three distinct life-stages; larvae, nymph and adults with each stage dependent on