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Potential importance of error catastrophe to the development of antiviral strategies for hantaviruses

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Abstract

Hantaviruses represent an important and growing source of disease emergence in both established and developing countries. The New World hantaviruses have been touted as potential biological weapons because of their lethality to humans and high infectivity as an aerosol. It is also important to acknowledge the threat that hantaviruses can represent to US troops that operate in a foreign territory endemic for hantavirus infection, as was demonstrated in the Korean War. Effective vaccines, immunotherapeutics and antivirals for the prophylaxis or treatment of hantaviral infections are not available. Recent evidence that hantaviruses are prone to error catastrophe opens the door to the development of new therapeutic strategies. Possible future directions for applying lethal mutagenesis as a strategy for the development of novel and more effective antiviral therapies for treatment of hantavirus infections are discussed.

Keywords: Error catastrophe; Antiviral strategies; Hantaviruses

1. Introduction

Hantavirus is one of five genera in the family Bunyaviridae, which also includes *Bunyavirus*, *Nairovirus*, *Phlebovirus* and *Uukuvirus* (Schmaljohn and Dalrymple, 1983; Schmaljohn and Hooper, 2001). The Bunyaviridae are geographically and ecologically varied and include etiologic agents for many serious human diseases (Beaty and Calisher, 1991). Hantaviruses differ from the other genera in that they are enzootic viruses of wild rodents rather than arthropod vectors (Hjelle and Yates, 2001). Furthermore, they cause persistent infections without apparent disease symptoms in their natural hosts (Yanagihara et al., 1985; Netski et al., 1999; Meyer and Schmaljohn, 2000a, 2000b; Botten et al., 2003). Although, the exact mechanism of transmission from rodents to humans is unknown, inhalation of aerosolized virus from rodent excreta is thought to be the main route of transmission to humans (Lee et al., 1981; Tsai, 1987). Hantaviruses are globally distributed (Schmaljohn and Hjelle, 1997) and several members of the genus cause deadly human illnesses such as hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS) (Table 1) (Hjelle et al., 1995; Peters et al., 1999). Old World hantaviruses are responsible for HFRS mainly in Asia and Europe, whereas New World hantaviruses are responsible for HPS in the Americas (Schmaljohn and Hjelle, 1997; Peters et al., 1999).

Hantaviruses are enveloped, spherical, negative-strand RNA viruses with a tripartite, segmented genome composed of S (small), M (medium) and L (large) RNAs (Fig. 1, Schmaljohn and Hooper, 2001). These segments encode the nucleocapsid or N protein, two glycoproteins, G1 and G2, and the RNA dependent RNA polymerase (RdRp), respectively. The viral RdRp mediates both the replication of the genomic and anti-genomic viral RNAs and the transcription of viral mRNAs in the cytoplasm (Fig. 2); however, little is known regarding the biochemical or molecular steps, including the role of cellular proteins, in these processes

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Table 1
Representative pathogenic hantaviruses, their clinical syndromes, disease distribution and mortality rates

Pathogens	Disease	Distribution	Mortality rate (%)
Hantaan virus, HTNV	HFRS (severe)	Asia	5–10
Dobrava virus, DOBV	HFRS (severe)	Europe (Balkans)	5–10
Seoul virus, SEOV	HFRS (moderate)	Southeast Asia and worldwide	1–2
Puumala virus, PUUV	HFRS (mild)	Northern and Central Europe	<1
Sin Nombre virus, SNV	HPS (severe)	North America	>40
Bayou virus, BAYV	HPS (renal variant)	North America (Unites States)	>40
Andes virus, ANDV	HPS (severe)	South America (Argentina, Chile)	>40

(Jonsson and Schmaljohn, 2001). The apparent fidelity of the replication process can be inferred from sequence analysis of virus populations in wild rodents and cell culture (Plyusnin et al., 1994, 1995, 1996; Lundkvist et al., 1997; Feuer et al., 1999; Severson et al., 2003). The deduced mutation frequency, approximately 10^{-3} to 10^{-4} from these studies, appears to be similar to the frequency for other RNA viruses in this respect (Drake and Holland, 1999). Hence, hantaviruses form quasispecies populations in nature and in cell culture (Eigen, 1996). These characteristics found in hantavirus and other RNA viruses suggest that they replicate near an error threshold (Domingo and Holland, 1994). This hypothesis suggests that any increase in the intrinsic mutation rate would drive the virus into a nonproductive infection due to a "meltdown" of the viral sequence information. These heterogeneous and dynamic aspects of RNA virus populations should stand as important considerations in the design of antiviral drug therapies (Domingo et al., 1997; Crotty and Andino, 2002; Eigen, 2002). Hence, strategies to design and develop antiviral drugs that could drive virus replication into error catastrophe should be considered. In the following, we will briefly review hantavirus disease and current approaches to the treatment of hantavirus infection. This background will provide a platform to discuss the transition of hantavirus into error catastrophe and the impact this may have on the design of effective therapeutics based on this paradigm.

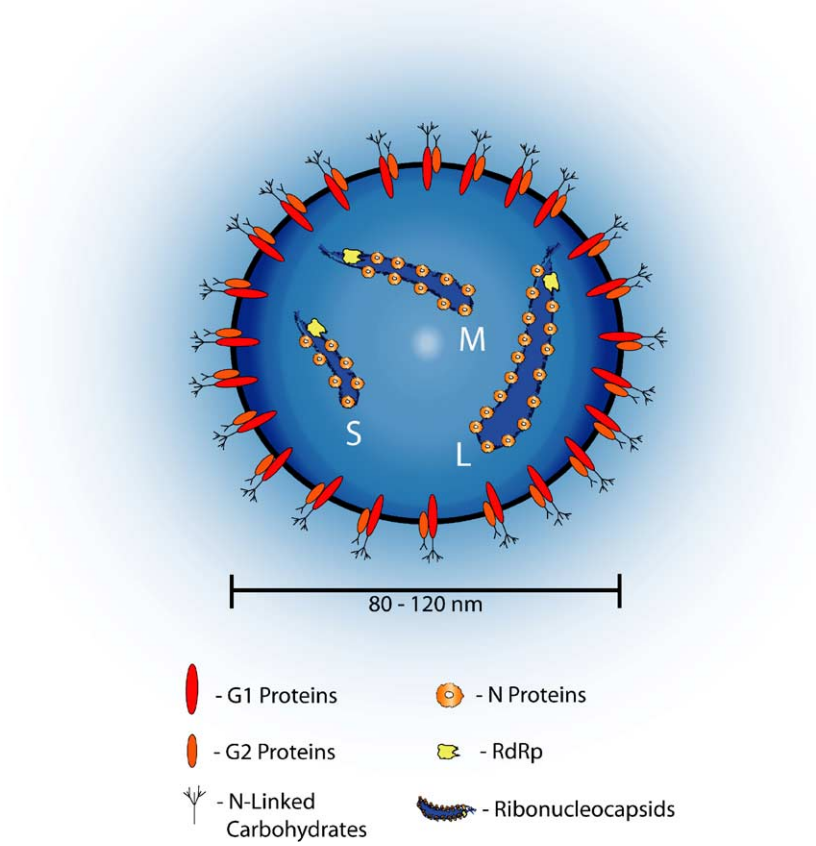

Fig. 1. Cartoon illustration of cross section of a hantavirus virion. The virion's lipid membrane is derived from the Golgi and contains the cotranslationally processed glycoproteins, G1 and G2. Internally the genomic viral RNAs are complexed with N protein, and possibly the RdRp, to form ribonucleocapsid structures (illustration courtesy of Steven J. Plane).