

Genetic reassortment among hantaviruses - consequences for virus pathogenicity

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Introduction

A number of RNA viruses, among them influenza- and hantaviruses, are transmitted from animal reservoirs to humans. The two virus families possess segmented RNA genomes of negative polarity. It is well known that genetic reassortment processes between influenza virus genome segments are the cause of dramatic changes in antigenicity and virulence of these viruses in their hosts (1). For hantaviruses, these processes have yet to be studied.

Human infections by different hantavirus types can lead to disease with case fatalities between <1% and 50% (2). Dobrava virus (DOBV) is a recently discovered and medically important European hantavirus species. Three genetic variants of DOBV have been found in three different rodent hosts (DOBV-Aa in *Apodemus agrarius*, DOBV-Af in *A. flavicollis*, DOBV-Ap in *A. ponticus*). Whereas clinical courses caused by DOBV-Aa infections are rather mild (<1% case fatalities), infections by DOBV-Ap lead to moderate (5% case fatalities) and by DOBV-Af to severe human disease with case fatalities of up to 12% (3).

Hantavirus genomes consist of three single-stranded (ss) RNA segments of negative polarity; S, M, and L, encoding nucleocapsid protein, glycoproteins, and RNA polymerase, resp. So far, no reverse genetics system is available. It is still unknown which genetic make-up of the viral genome is responsible for the different virulence of the respective virus types and how genetic reassortment can influence the interaction between virus and host.

Since the three Dobrava viruses are genetically highly related but exhibit significantly different virulence in the human host, it is worthy to study the presumably differential modulation of host defense functions. Moreover, *in vitro* generated virus reassortants can help to understand the significance of genetic exchange processes on the virus pathogenicity and to allocate virulence markers to one of the segments of the virus genome.

Work hypothesis

The contribution of single genome segments to the hantavirus pathogenicity and the induction or inhibition of cellular components of host defence can be defined by comparative functional analysis of host cells infected by parental viruses and their reassortants.

Highly strain-specific interactions between RNA, nucleocapsid protein, and RNA polymerase are involved in the intracellular virus replication and maturation.

Proposed thesis topics:

- (1) Modulation of cellular defense mechanisms by hantaviruses of high *versus* low virulence
- (2) Specific interactions of genome and protein components in the intracellular replication and maturation of hantaviruses