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Department of Microbiology, Tumor and Cell Biology

Hantaviruses – from interferons to development of an *in vitro* model

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ABSTRACT

Hantaviruses can cause hemorrhagic fever with renal syndrome (HFRS) and hantavirus cardiopulmonary syndrome (HCPS), two severe diseases that often are associated with a deadly outcome as there is no cure. The natural hosts of hantaviruses are rodents and insectivores, which are believed to harbor the virus asymptomatically. The pathogenesis in humans is unclear, but increased vascular leakage and affected endothelial cells, possibly due to rigorous and unhampered immune responses, are hallmarks of HFRS and HCPS. Interferons (IFNs) are part of the innate immunity and mediate production of antiviral molecules but can also modulate the adaptive immune responses against infections. In an attempt to increase the knowledge about pathogenesis in humans, we aimed to understand the interactions between hantaviruses and the IFN-response and provide tools to investigate the potential differences in innate immune regulation between human cells and cells from a natural hantavirus host.

Our results in paper I indicate that hantaviruses can interfere with induction of innate immune responses in patients and inhibit the antiviral effect of all types of IFNs. We observed that serum levels of IFN-α and -β were unaltered in Puumala virus (PUUV)-infected patients while the level of the more recently discovered IFN-λ was decreased during the acute phase of the disease. IFN-λ was shown to inhibit replication of the prototype hantavirus Hantaan (HTNV) but to a lesser extent than IFN-α, -β or -γ. The function of STAT1, a protein that is crucial for IFN signalling, was inhibited in HTNV infected cells.

In paper II, we observed that a hantavirus infection could induce IFN-λ specifically, without inducing IFN-α or -β. This has never been described before, and has taught us more about the complexity of IFN induction.

In paper III, we described both mutations and substantial phenotypical differences in two PUUV isolates compared to each other and to their parental strain. These results imply that we might study spontaneous mutations rather than true differences between hantaviruses when we use cell culture propagated viruses.

Due to lack of host-specific tools, not much is known about the responses to infection in natural hantavirus hosts. In paper IV, we describe the development of an *in vitro* model (vole embryonic fibroblasts, VEFs) for studies of bank vole borne viruses and induction of innate antiviral reactions in response to infection. This model will be a valuable tool for future studies of how PUUV and other zoonotic viruses harbored by bank voles affect cells from their natural host compared to human cells. Also, wild type PUUV was shown to infect VEFs, indicating that cells from natural hosts might be a way of isolation and propagation of hantaviruses.

In conclusion, the results included in this thesis contribute to an increased knowledge about hantaviruses and their interactions with human and natural host cells. This knowledge, combined with future studies will hopefully lead to a better understanding of hantavirus pathogenesis and ultimately result in a cure.

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