



# Karolinska Institutet

**Department of Microbiology, Tumor and Cell Biology,  
Karolinska Institutet, and The Swedish Institute for Infectious  
Disease Control, Stockholm, Sweden**

## Pathogenesis of an emerging pathogen – Crimean-Congo Hemorrhagic Fever virus

**AKADEMISK AVHANDLING**

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## **ABSTRACT**

Epithelial cells represent the first barrier to viral infection and the site of viral entry and release is often intimately connected with viral spread and pathogenesis. The plasma membrane of epithelial cells is polarized into an apical and basolateral domain separated by tight junctions (TJs). TJs also regulate paracellular permeability and can cause leakage upon deregulation.

The key players underlying VHF pathogenesis are believed to be endothelial cells (ECs) and immune cells. Generally ECs can be targeted either directly by viral infection and/or indirectly by soluble mediators released from infected immune cells leading to the observed hemorrhage and vascular permeability.

The main aims of this thesis were to study the direct and indirect effect of viral replication on epithelial and immune cells as a possible contribution to CCHF molecular pathogenesis.

By studying the site of entry and release in polarized epithelial cells, we showed the entry and release of CCHFV to be preferentially basolateral. We studied the transepithelial electrical resistance (TER) over infected epithelial cells, and showed that CCHFV replication has no direct effect on epithelial permeability. Furthermore, we observed no effect of CCHFV on the localization of the TJ proteins occludin and ZO-1 in epithelial cells. Interestingly, CCHFV does directly activate ECs upon infection as shown by upregulation of intercellular adhesion molecule 1 (ICAM-1) release of IL-6 and IL-8 and most importantly increased adhesion of leukocytes.

The finding that the increased vascular permeability and hemorrhage is most likely not caused by CCHFV induced TJ disassembly suggests that other cells are likely to be, at least partly, involved in pathogenesis and we therefore focused on the contribution of immune cells to pathogenesis. We showed that only monocyte-derived dendritic cells (moDCs) could be productively infected by CCHFV and that infection was followed by the release of tumor necrosis factor (TNF), IL-6 and IL-10. Interestingly, conditioned media from CCHFV-infected moDCs activated ECs as indicated by enhanced intercellular adhesion molecule 1 (ICAM-1) expression. This effect was shown to be dependent on TNF.

The work presented in this thesis provides an insight into the direct and indirect interplay between epithelial cells and immune cells and provides data that could be used for further studies into the underlying mechanisms of CCHF pathogenesis. Importantly understanding the mechanisms behind CCHF pathogenesis is most likely needed for the future development of specific treatments and/or vaccines against CCHFV.

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