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IDENTIFICATION AND CHARACTERIZATION OF HOST FACTORS INVOLVED IN ORTHOFLAVIVIRUS INFECTION

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Akademisk avhandling

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Abstract
Orthoflaviviruses are arthropod borne single stranded RNA viruses that cause mild to severe illness in humans, affecting millions of people each year with no antivirals currently available. This viral genus includes viruses such as tick-borne encephalitis virus (TBEV), West Nile virus (WNV) and Zika virus (ZIKV). Orthoflavivirus have their own viral proteins, yet like other viruses they also recruit and utilize several cellular proteins to fulfill their life cycle. While some of these host factors have been identified or characterized, most of them remain unknow. In this thesis, I have used different tools to identify and characterize novel proteins involved in orthoflavivirus infection.

Understanding the function of cellular proteins in the viral life cycle is important to comprehend the disease mechanism of the virus and to develop antivirals that target these. In the first part, we implemented proteomic phage display (ProP-PD) to identify short linear motif (SLIM) interaction between viral and cellular proteins, and this method identified Polyadenylate-binding protein 1 (PABP1) as a pro viral factor for many RNA viruses. In the second part of this thesis, we identified proteins involved in TBEV infection by performing an ascorbate peroxidase (APEX) 2-screen to identify proteins found in the vicinity of TBEV NS4B. Using this approach we identified Acyl-CoA Binding Domain Containing 3 (ACBD3). This protein is found in close proximity of TBEV NS4B affecting both viral replication and assembly in TBEV and Langat virus (LGTV) infection, by modifying the trafficking between the endoplasmic reticulum (ER) and Golgi.

In the third part of the thesis, we explored the role of the nucleoporins (NUPs) in orthoflavivirus infection. NUPs are the building blocks of the nuclear pore complex, which is the complex responsible for the transport of RNA and proteins between the nucleus and cytoplasm. By implementing a variety of different molecular biology techniques, we identified NUP153 and NUP98 to be of importance in the viral life cycle. We observed that during orthoflavivirus infection, NUP153 and NUP98 are upregulated and recruited from the nucleus to the cytosolic region where they bind viral RNA (vRNA). We found that NUP153 regulates viral translation, while NUP98 is important for viral replication, showing the importance and different functions of this protein family in orthoflavivirus infection.

Furthermore, in this thesis we also evaluated the use of peptides to block these specific virus-host protein interactions as potential antivirals. We show that peptides targeting and binding to PABP1 and NUP98 are antivirally active against several orthoflaviviruses. Taken together, the findings presented in this thesis have led to a better understanding of specific host factors required for the viral life cycle. This knowledge can be used in the development of new antivirals.

Keywords
Orthoflavivirus, TBEV, Host Factors, Nuclear pore complex, RNA-binding Proteins, NUP98, NUP153, ACBD3, PABP1

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