



Characterizing important flavivirus-host interactions:

Replication, assembly, restriction factors,
and vaccine development

av

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Abstract

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The genus *Flavivirus* (family *Flaviviridae*) consists of important zoonotic viruses that cause morbidity and mortality worldwide. These viruses are enveloped and have a positive-sense single-stranded RNA genome encoding a polyprotein. Cleavages of the polyprotein by host and viral proteases result in individual viral proteins, including the structural capsid (C), pre-membrane (prM), envelope (E) proteins, and seven nonstructural proteins. Removal of the C-prM-E genes in the flavivirus genome results in replicons that can replicate in transfected cells but do not generate infectious virus particles. The replicon can be co-expressed with the C-prM-E genes in trans, resulting in packaging of the replicon and generation of replicon virus-like particles (RVPs).

During cellular infection, various host proteins are employed, supporting multiple stages of the virus life cycle. In this thesis, we identified and characterized functions of the host lunapark protein and two members of the Endosomal Sorting Complexes Required for Transport Machinery – ALIX and CHMP4A. We also revealed how the host proteins were recruited by virus proteins during infection.

To counteract the virus infection, virus-infected cells can express antiviral proteins. We demonstrated the antiviral mechanism of interferon-stimulated gene (ISG) 15 and the E3 ligase for ISG15 conjugation HERC5, which degrades ALIX and CHMP4A, indirectly targets virus infection. Furthermore, using proteomic screening, we identified tripartite motif-containing proteins (TRIM) – TRIM21 and TRIM14 – as restriction factors to Langkat virus and Zika virus.

We also established and characterized an RVP production system based on the West Nile virus (WNV) Kunjin strain. The system was used as a vector to express antigens from Ebola virus (EBOV), which can potentially be developed as a vaccine platform against WNV and EBOV.

Keywords: Flaviviruses, virus-host cell interaction, lunapark, ESCRT, ALIX, CHMP4A, ISG15, TRIMs, replicon virus-like particles, vaccine

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