

## VIRUS AND HOST FUNCTIONS IN RNA VIRUS REPLICATION

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Our laboratory is studying aspects of the replication and pathology of several viruses, including positive-strand RNA ((+)RNA) viruses and the reverse-transcribing viruses HIV and hepatitis B virus. These studies seek to identify and characterize both virus and host functions required for replication. Host genes required for viral replication are not subject to high frequency viral escape mutations and may be valuable targets for developing effective and possibly broad-spectrum antiviral controls. (+)RNA viruses include numerous pathogens such as hepatitis C virus and the SARS coronavirus. Our 3D electron microscope tomography imaging and other approaches show that (+)RNA virus genome replication occurs in virus-induced, membrane-bounded mini-organelles whose structure, assembly and function share unexpected parallels with the extracellular virions of retroviruses and dsRNA viruses, revealing functional and potentially evolutionary links. Using novel yeast systems and other cells, our systematic, genome-wide analyses show that diverse host genes control (+)RNA virus translation, recruitment of viral RNA templates from translation to replication, chaperone-mediated activation of RNA replication complexes, viral RNA and protein stability, membrane characteristics essential for RNA replication, and additional steps. In other recent studies we found that hepatitis B virus, the major cause of liver cancer, depends on the host multivesicular body pathway for infectious virion release and, with John Young, we showed that the host sulfonation pathway is required at a novel post-entry, nuclear-associated step in HIV replication. We and other collaborators also recently used *Drosophila* cells to conduct a genome-wide RNAi screen for host factors required for the replication of influenza virus, a negative-strand RNA virus. This screen identified over 100 genes whose suppression significantly inhibited influenza virus replication and/or gene expression at diverse steps. The relevance to mammalian cells was illustrated by testing a subset of the genes identified. The results showed, e.g., that *ATP6V0D1*, *COX6A1* and *NXF1* have varied, key functions in the replication of H5N1 and H1N1 influenza A viruses in human HEK293 cells. Thus, these findings identify a large number of potential host gene targets for influenza virus therapy and control.