proceedings

Abstract

Cell Entry by Quasi-Enveloped and Naked Hepatoviruses †

Stanley M. Lemon

Lineberger Comprehensive Cancer Center, Departments of Medicine and Microbiology & Immunology, The University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7292, USA; smlemon@med.unc.edu

† Presented at Viruses 2020—Novel Concepts in Virology, Barcelona, Spain, 5–7 February 2020.

Published: 11 June 2020

Abstract: Hepatoviruses are unusual picornaviruses, distinct genetically and structurally from other members of the *Picornaviridae*, exclusively hepatotropic, and released from infected cells without lysis in small membranous vesicles resembling exosomes. These quasi-enveloped virions (eHAV) are infectious and the only form of virus found circulating in blood during acute infection. By contrast, naked virions (nHAV) are shed in feces, having been stripped of membranes by bile salts during passage from the liver through the biliary system. nHAV is exceptionally stable, promoting efficient inter-host transmission through the environment, whereas the membranes cloaking quasi-enveloped eHAV virions protect the virus from neutralizing antibodies, facilitating stealthy spread of infection in newly infected hosts. Since quasi-enveloped eHAV lacks virus-encoded surface proteins, its mechanism of cell entry has been enigmatic. Previous studies in our laboratory have shown that both virion types are internalized primarily by clathrin- and dynamin-dependent endocytosis, facilitated by integrin β_1, followed by trafficking through early Rab-5A$^+$ and late Rab-7a$^+$ endosomes. eHAV undergoes further ALIX-dependent trafficking to LAMP1$^+$ lysosomes where the quasi-envelope is enzymatically degraded. Although TIM1 (HAVCR) was reported many years ago to be a receptor for HAV, it is not essential for infection with either virion type and acts only to facilitate eHAV entry by binding phosphatidylserine on its surface. While late steps in entry remain uncertain, recent studies in our laboratory indicate that both virion types require a ganglioside within the late endolysosome to initiate transfer of the viral RNA to the cytoplasm to initiate replication. Ganglioside GD1a appears most active in facilitating cell entry, and binds to the capsid optimally at the low pH of endolysosomes Remarkably, neither virion type requires PLA2G16 for infection, although this phospholipase is essential for successful transfer of the RNA genome of many other picornaviruses to the cytoplasm. This, and other unusual features of HAV, including the fact that the assembly of capsid pentamers is driven by the C-terminal pX domain of VP1 rather than VP4, and the exceptional stability of the capsid, greatest at the low pH of endolysosomes, suggest an atypical mechanism for HAV uncoating and genome release.