

Abstract

A Sensitive Yellow Fever Virus Entry Reporter Identifies Valosin-Containing Protein (VCP/p97) as an Essential Host Factor for Flavivirus Uncoating [†]

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Abstract: Flaviviruses are enveloped, arthropod-borne, positive-strand RNA viruses that cause significant human disease. While the basic mechanisms of flavivirus entry and fusion are understood, little is known about the postfusion events that precede RNA replication, such as nucleocapsid disassembly. We recently developed a sensitive, conditionally replication-defective yellow fever virus (YFV) entry reporter to quantitatively monitor the translation of incoming virus particle-delivered genomes. We validated that viral gene expression can be neutralized by YFV-specific antisera and requires known pathways of flavivirus entry; however, as expected, gene expression from the defective reporter virus was insensitive to a small molecule inhibitor of YFV RNA replication. The initial round of viral gene expression was also shown to require: (i) cellular ubiquitylation, consistent with recent findings that dengue virus capsid protein must be ubiquitylated in order for nucleocapsid uncoating to occur, and (ii) valosin-containing protein (VCP)/p97, a cellular ATPase that unfolds and extracts ubiquitylated client proteins from large macromolecular complexes. RNA transfection and washout experiments showed that VCP/p97 functions at a postfusion, pretranslation step in YFV entry. Together, these data support a critical role for VCP/p97 in the disassembly of incoming flavivirus nucleocapsids during a postfusion step in virus entry.

Keywords: flavivirus; nucleocapsid; uncoating; viral entry; ubiquitin; VCP/p97



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