

Integrin beta 1 facilitates non-enveloped hepatitis E virus cell entry through the recycling endosome

Info

PUBLISHED DATE JOURNAL
2025-06-26 Nature Communications

LINK
<https://doi.org/10.1038/s41467-025-61071-y>

Authors

Rebecca Fu Paula Jordan Zoe Engels
Jasmin Alara Weihs Josias Mürle Huanting Chi
Sebastian Burbano de Lara Barbara Helm
Mara Klöhn Jungen Hu Andrew Freistaedter
Tobias Boettler Marco Binder **Ursula Klingmüller**
Eike Steinmann Pierre-Yves Lozach
Thibault Tubiana Stanley M. Lemon
Viet Loan Dao Thi

Abstract

Hepatitis E virus (HEV) is a major cause of acute hepatitis and mainly transmitted faecal-orally. HEV particles present in faeces are naked (nHEV), whereas those found in the blood are quasi-enveloped (eHEV) with a cell-derived lipid membrane. Despite its global health impact, the cellular life cycle of HEV remains poorly understood, particularly regarding the mechanisms of viral entry into host cells. To address this knowledge gap, we develop a high content RNA-FISH-based imaging assay that allows for the investigation of the entry pathways of both naked and quasi-enveloped HEV particles. Surprisingly, we find that integrin $\alpha 3$, previously implicated in nHEV cell entry, is not expressed in the cell types that are most permissive for HEV infection. Instead, we identify integrin $\beta 1$ (ITGB1) pairing with different α -integrins as the key player mediating nHEV cell entry. Our results indicate that the interaction of nHEV with ITGB1 facilitates entry through Rab11-positive recycling endosomes. In contrast, eHEV particles do not interact with ITGB1 and enter cells using a classical endocytic route via Rab5a-positive early endosomes. The entry of both types of HEV particles requires endosomal acidification and proteolytic cleavage by lysosomal cathepsins, which ultimately results in delivery of the HEV genome to the cytoplasm.