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Multivesicular bodies and the hepatitis E virus life cycle – more than just release?

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A peculiar feature of the hepatitis E virus (HEV) is its reliance on endosomes for its release. This route, mediated by MVBs, can be targeted by drugs, yet little is known about viral replication. The latter is mediated via the viral polyprotein pORF1 comprising seven domains. Neither its putative proteolytical processing nor its subcellular localization is fully clarified. Here, we aim to decipher the latter with respect to subcellular structures associated to the viral replicase. These may be targeted to counteract viral replication.
When expressed ectopically, pORF1 accumulated in vesicular structures within the endosomal system. The localization to CD63-positive structure was most pronounced and an association to the MVB-resident viral protein pORF3 was observed. Expression of the polyprotein's seven subdomains Met (methyltransferase), Y, PCP (papain-like cysteine-protease), HVR (hypervariable region), X, Hel (helicase) and RdRp (RNA-dependent RNA-polymerase) revealed that PCP is the only domain localizing like the full-length protein. A PCP-deficient pORF1 mutant lost its naïve association to MVBs. Strikingly, both pORF1 and PCP alone displayed release into the extracellular space via exosomes.
In summary, pORF1 localizes to MVBs in a PCP-dependent manner and is released via exosomes. This advances understanding of the viral life cycle leading to rational drug-design, as replication and release could be coupled, which may even indicate capsid-independent spread.

Keywords

HEV, pORF1, multivesicular bodies, exosomes, replication

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Junior Scientist Status

Yes, I am a Junior Scientist.

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