



Contribution ID: 247

Type: Oral presentation

A novel trans-Golgi-associated egress pathway of ORF3-deficient hepatitis E virus preserves quasi-envelopment in human hepatoma cells

Tuesday, October 14, 2025 9:55 AM (15 minutes)

Hepatitis E virus (HEV) normally exits host cells as quasi-enveloped particles by exploiting multivesicular bodies (MVBs), a process mediated by the accessory protein pORF3. To investigate the functional relevance of this pathway, an ORF3-deficient genotype 3c mutant (HEV Δ ORF3) was generated and analyzed in two human cell lines: hepatoma-derived PLC/PRF/5 and lung carcinoma-derived A549/D3 cells. While HEV Δ ORF3 reached wild-type levels of extracellular RNA in PLC/PRF/5 cells, it showed markedly impaired replication in A549/D3 cells, highlighting a strong cell-type dependency in the ability to compensate for the loss of pORF3. Despite reduced infectivity, virions from PLC/PRF/5 cells retained a quasi-envelope, as shown by gradient centrifugation, electron microscopy, and neutralization assays requiring detergent treatment. Confocal imaging revealed altered intracellular trafficking in HEV Δ ORF3-infected PLC/PRF/5 cells: pORF2 localization shifted from the MVB marker CD63 to the trans-Golgi marker TGN46. This switch was also reflected in virion composition, with TGN46 enriched in HEV Δ ORF3 particles. These findings identify an alternative, Golgi-associated egress route in hepatoma cells PLC/PRF/5 that preserves quasi-envelopment in the absence of pORF3. Given HEV's zoonotic potential and its ability to cross species barriers, identifying alternative release mechanisms is crucial for assessing host adaptation and transmission dynamics in the One Health context.

Keywords

Viral hepatitis, exosomes, Hepatitis E virus, viral egress, MVBs, quasi-envelopment, trans-Golgi network, viral life cycle

Registration ID

OHS25-89

Professional Status of the Speaker

Postdoc

Junior Scientist Status

Yes, I am a Junior Scientist.

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Session Classification: Session 6: Emerging Pathogens II

