Enterovirus-A71 exploits RAB11 to recruit chaperones for virus morphogenesis

Ng, Q.Y., *et al*. *J Biomed Sci*. 2024; *31*: 65.

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Background: Enterovirus A71 (EV-A71) is a major etiological agent of Hand, Foot, and Mouth Disease (HFMD), with increasing association with severe neurological complications in children. Despite its clinical significance, effective antiviral therapies remain lacking, primarily due to limited understanding of the virus-host interactions that facilitate EV-A71 replication and morphogenesis. Membrane trafficking pathways, often hijacked by viruses, are particularly underexplored in EV-A71 infection.

Objective: This study aims to identify host membrane trafficking proteins essential for EV-A71 infection and to determine how the small GTPase RAB11A contributes to the viral life cycle.

Results: A targeted siRNA screen of 112 membrane trafficking genes identified RAB11A as a prominent host factor required for efficient EV-A71 replication in motor neuron NSC34 cells. *RAB11A*-knockdown significantly reduced viral titers without inducing cytotoxicity. RAB11A and its isoform RAB11B functioned redundantly and were exploited by diverse EV-A71 genogroups and Coxsackievirus A16, indicating a conserved role in enteroviral infections. Functional assays demonstrated that RAB11A/B does not participate in early infection steps such as viral entry, genome replication, or internal ribosome entry site (IRES)-mediated translation. Instead, siRNA knockdown reduced the ratio of infectious viral particles to viral RNA and increased the VP0: VP2 ratio, indicating a block in provirion maturation—a step involving VP0 cleavage into VP2 and VP4. RAB11A interacted with both structural (VP1, VP2) and non-structural (3C, 3D) viral proteins at replication organelles. However, confocal imaging comparison with dominant negative (S25N) and constitutive (Q70L) mutants revealed that the GTPase activity of RAB11A was dispensable for infection. Mass spectrometry of RAB11A immunoprecipitated showed a significant shift in its host interactome during infection, with chaperones—particularly CCT8 of the TRiC/CCT complex—emerging as dominant binding partners. Silencing *CCT8* impaired virion maturation and reduced viral titers, confirming its pro-viral role.

Conclusion: This study uncovers a novel role for RAB11A in the EV-A71 life cycle, independent of its canonical GTPase-mediated trafficking function. Instead, RAB11A acts as a scaffold to recruit host chaperones essential for virion maturation, providing new insights into EV-A71 pathogenesis and potential therapeutic targets.