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Abstract

ER-Shaping Atlastin Proteins Act as Central Hubs to Promote Flavivirus Replication and Virion Assembly †

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Abstract: Members of the *Flavivirus* genus rely extensively on the host cell endomembrane network to generate complex membranous replication organelles (ROs) that facilitate viral genome replication and the production of virus particles. For dengue virus and Zika virus, these ROs included vesicles which are formed through membrane invagination into the endoplasmic reticulum (ER) lumen, termed invaginated vesicles or vesicle packets (VPs), as well as large areas of bundled smooth ER, termed convoluted membranes. Though the morphology of these virus-induced membrane structures has been well characterized, the viral and host constituents that make up flaviviral ROs are still poorly understood. Here, we identified a subset of ER resident proteins (atlastins), normally required for maintaining ER tubule networks, as critical host factors for flavivirus infection. Specific changes in atlastin (ATL) levels had dichotomous effects on flaviviruses with ATL2 depletion, leading to replication organelle defects and ATL3 depletion to changes in viral assembly/release pathways. These different depletion phenotypes allowed us to exploit virus infection to characterize non-conserved functional domains between the three atlastin paralogues. Additionally, we established the ATL interactome and show how it is reprogrammed upon viral infection. Screening of specific ATL interactors confirmed non-redundant ATL functions and identified a role for ATL3 in vesicle trafficking. Our data demonstrate that ATLs are central host factors that coordinate the ER network and shape the ER during flavivirus infection.

Keywords: Flavivirus; dengue virus; Zika virus; atlastin; virus replication organelle; ER membrane structure; membrane fusion; vesicle transport; virus-host interactions