Herpes Simplex Virus 1 Protein ICP0 through Host Protein CIN85 Evades Antiviral Responses

Sarah Lasnier*, Rabina Saud*, Sreenath Muraleedharan Suma*, Kim Foster-Lemieur*, Maria Kalamvoki, Ph.D.
*Authors have equally contributed to these studies.
The University of Kansas Medical Center, Department of Microbiology, Molecular Genetics and Immunology

Received Aug. 28, 2025; Accepted for publication Sept. 10, 2025; Published online Sept. 10, 2025
https://doi.org/10.17161/kjm.vol18.24435

Introduction. HSV-1 has infected 70% of the world population. The virus establishes lifelong reservoirs in neurons but occasionally is reactivated causing a variety of diseases. HSV-1 has evolved strategies to counteract antiviral responses, and the Infected Cell Protein 0 (ICP0) plays a fundamental role in this process. Early in infection, ICP0 localizes to the nucleus where it enables viral gene expression. Virus replication triggers translocation of ICP0 to the cytoplasm where its function remains unknown. ICP0 interacts with the adaptor protein CIN85, which has a major role in surface receptor endocytosis, and protein sorting.

Methods. To investigate the ICP0/CIN85 interaction we developed a virus, lacking the 244-277 aa of ICP0 that mediates binding to CIN85. We analyzed ICP0/CIN85 colocalization by immunofluorescence. Using a targeted approach, we identified other cargo localizing to the ICP0/CIN85 structures. We determined the fate of this cargo by analyzing the content of extracellular vesicles. Finally, we evaluated the ability of this virus to evade antiviral responses.

Results. As opposed to wild type virus, in ICP0 delta244-277 infections, ICP0 did not colocalize with CIN85 in vesicles. ICP0/CIN85 vesicles are chimeric composed of early and late endosomal markers, as well as autophagosome, and innate immunity components. Cargo associated with the CIN85 vesicles is exocytosed, in an ICP0-dependent manner. ICP0 delta244-277 virus failed to evade antiviral responses and displayed reduced virus yields.

Conclusions. Cytoplasmic ICP0 associates with CIN85 and determines endosome and EV proteome content. Exocytosis of the ICP0/CIN85 vesicle content likely represents a novel immunoevasion mechanism of HSV-1.

Support: *NIAID R01AI162784, F31AI186315, NIGMS P20GM130448, NIH S10 OD 023625, NIH S10 OD032207*