How the Non-Enveloped SV40 Penetrates the ER Membrane during Entry

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Biological membranes represent a major barrier during viral infection. While the mechanism by which an enveloped virus breaches the limiting membrane of a host cell is well-characterized, this membrane penetration process is poorly understood for non-enveloped viruses. Indeed, most available insights on membrane transport of non-enveloped viruses are built upon in vitro studies. We established a cell-based assay to probe the molecular mechanism by which the non-enveloped SV40 penetrates the endoplasmic reticulum (ER) membrane to access the cytosol, a critical step in infection. We found that, despite conformational changes imparted on the virus by the ER-resident PDI family proteins, the viral particle nonetheless penetrates the ER membrane as a large and intact viral particle. These results suggest that the ER membrane can accommodate translocation of a large protein complex, possibly through either a sizeable protein channel or the ER membrane bilayer. Strikingly, EM analyses demonstrate that the ER-localized virus displays a hexagonal geometry containing complex protrusions, in contrast to WT virus that contains a near-spherical geometry with no protrusions. The hexagonal viral intermediates with complex protrusions may represent membrane penetration intermediates. Our findings thus illuminate the molecular mechanism by which a non-enveloped virus penetrates the limiting membrane of a host cell during entry.