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Capsid Structural Transitions Associated with Uncoating and Nuclear Entry of Human Parvovirus B19

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During cell entry, the metastable parvovirus capsid undergoes a program of sequential rearrangements/modifications to ensure the delivery of the viral genome into the nucleus of host cells. These transitions and the cell factors that trigger them remain largely unknown. By using cell fractionation and antibodies against different capsid epitopes, we have followed changes in the capsid conformation of human parvovirus B19V (B19V) along the entry pathway. Upon binding to susceptible cells, the VP1 unique region (VP1u) become accessible. In the acidic endosomes, the PLA_2 region remains stable at the capsid surface, however the N-terminus of the VP1u becomes again inaccessible. Following endosomal escape, the incoming capsids are phosphorylated, and the viral genome is externalized but remains tightly associated to the assembled capsid. Only the phosphorylated capsids with accessible genomes are imported into the nucleus via dynein-mediated transport. In their uncoated conformation, the incoming capsids support *in vitro* complementary-strand synthesis without the need for capsid disassembly. Taken together, our studies reveal a sequence of capsid structural transitions triggered by specific cellular factors resulting in the uncoating of the incoming capsids in the cytosol. The capsids with accessible genomes enter the nucleus in a conformation that supports complementary-strand synthesis.