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The Structure of the Transferrin Receptor:Canine Parvovirus Complex Reveals how the Interactions Control Viral Host Range

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Canine parvovirus (CPV) and closely related viruses infects dogs and other carnivores, and can cause acute hemorrhagic enteritis, myocarditis and cerebella disease. Those viruses utilize the transferrin receptor type-1 (TfR) to bind, enter and infect target cells, and species-specific binding to TfR controls viral host range. The interaction between CPV and TfR has been extensively studied by mutational and biochemical analyses, identifying functional sites controlling infection and host range, but a useful structural analysis of the CPV-TfR complex has not been possible. Here we reveal the virus-receptor interaction at a high-resolution by incubating CPV capsids with TfR isolated from black-backed jackal and using cryo-EM single particle analysis accompanied by a state-of-art instrumentation and technology. An icosahedral 3D reconstruction allowed us to build an atomic model of the capsid. Symmetry-mismatch reconstruction and localized reconstruction methods revealed the asymmetric structure of the CPV-TfR complex and identified the interacting surface and precise binding residues on both molecules. The purified TfR in the structure was in the form of complexes with transferrin (Tf), likely derived from cell culture media. Analysis of different complexes showed up to twelve TfR-Tf complex molecules bound per capsid, and each interaction varied slightly for the binding angle between CPV and TfR and the binding residues. Our results provide a structural explanation for the previous genetic studies, and provide important new insights into the host range control and variation of these parvoviruses associated with new pandemics in dogs.