Structural Characterization of Emerging Human Protoparvoviruses

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Recent advances in DNA sequencing technology have led to the discovery of several new members of the *Proparvovirus* genus capable of infecting humans: bufaviruses 1 to 3 (BuV1-BuV3), cutavirus (CuV), and tusavirus (TuV). These viruses were found in different tissues, including the gastro-intestinal tract and cutaneous malignant melanoma lesions. The viral capsid plays a central role in the infection of these cells since it mediates the attachment of the virus to specific receptors on the target cells as well as protection of the genome enroute to the nucleus for uncoating and replication. We determined the capsid structures for these emerging viruses to assist in functional characterization and the development of strategies to control virus infection using cryo-electron microscopy and image reconstruction in the 2.6 to 3.0 Å resolution range. The resolution of the maps enabled the atomic assignment of the amino acids of the major capsid protein, VP3. These viruses, which display different tissue tropisms and sequence identities share common capsid features with other parvoviruses including depressions at the icosahedral 2-fold and surrounding the 5-fold symmetry axes, protrusions at or surrounding the 3-fold axes, and a channel at the 5-fold axes. Furthermore, the overall VP2 structure topology of these viruses are highly similar, with the core being completely superposable. The differences are localized to surface loops, in previously defined common variable regions, which have been shown to be involved in receptor binding, cellular trafficking, transcription, and antigenic reactivity. These protoparvoviruse display the most outwardly extended 5-fold channels among the human parvoviruses and display capsid surface similarities to the animal protoparvoviruses such as CPV and MVM. These structures provide a 3D platform for functional annotation of these pathogens that will help to understand their disease mechanisms on a molecular level towards the development of therapeutics.