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Characterization of pH-Dependent Structural Changes in Adeno-Associated Virus by Cryo-Electron Microscopy and 3D Image Reconstruction

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Adeno-associated virus (AAV) is a non-enveloped, icosahedral virus packaging a single-stranded DNA genome, and in recent years has garnered significant research interest for use as a human gene therapy vector due to its non-pathogenic nature. AAV expresses three overlapping structural proteins: VP1, VP2, and VP3, which assemble into a T=1 capsid (protein shell) at an approximate ratio of 1:1:10 ratio, and can package and deliver therapeutic transgenes to numerous cell types. However, little is known about the biology and biochemistry of how these viruses traffic through the endosomal/lysosomal pathway after receptor attachment and how this can affect the efficiency of transgene expression. Acidification in this pathway is essential for AAV infection, including the activation of a PLA2 enzyme encoded within their minor VP1 and localized inside of the capsid until required to function. Previous work from our lab has shown that AAV capsid VPs experience autolytic processing but complementary structural information is incomplete. Towards filling this gap, the structure of AAV serotype 2 (AAV2) has been determined by cryo-electron microscopy and 3D image reconstructions at the pH conditions experienced in the extracellular space, early endosome, late endosome, and lysosome, pH 7.4, 6.0, 5.5, and 4.0, respectively, to ~3.8 Å resolution. At this resolution, the amino acid side-chains were interpretable for the C-terminal ~520 residues of the VP3 common region, similar to previous reports for other AAVs and parvovirus capsids. The structures show surface loop re-arrangements concomitant with drop in pH while the core VP structure remains unchanged. We also show that capsid thermal stability increases with decreasing pH conditions. The functional implications of these observations will be discussed, especially within the context of the AAV life cycle and gene therapy vector design.