Changing Region on AAV-PHP.eB Brings Negative Effects on Human AAVR Binding

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Adeno-associated virus (AAV) 9 and its variants are promising vectors for gene therapy to treat neurological diseases. The clinical uses of AAV9 along with its variants are leveraged by the discovery of their blood brain barrier (BBB) penetrating character. The entry of AAV-PHP.eB is mediated mainly by adeno-associated virus receptor (AAVR), which contains 5 polycystic kidney disease (PKD) repeat domains. I determined the cryo-EM structures of the AAV-PHP.eB, an AAV9 based variant with enhanced transduction in central and peripheral nervous system, alone or in complex with AAVR. These structures reveal the molecular details of their AAVR recognition, the PKD2 of AAVR binds AAV-PHP.eB virions at between 3-fold protrusion and 2/5-fold wall. Amino acid residues on capsids of AAV-PHP.eB and AAVR are also found, which include the engineered residues on AAV-PHP.eB. I further discuss the discrepancy of conformational changes of AAV9 and AAV-PHP.eB capsids upon AAVR binding, explaining the problem why changing region on AAV-PHP.eB brings negative effects on AAVR binding. This project provides a foundation to the design of more efficient AAV vectors with central nervous system tropism.

Awards Won:
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