In vitro and in vivo gene therapy vector evolution via multispecies interbreeding and retargeting of adeno-associated viruses.

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Public Summary:

Scientific Abstract:
Adeno-associated virus (AAV) serotypes differ broadly in transduction efficacies and tissue tropisms and thus hold enormous potential as vectors for human gene therapy. In reality, however, their use in patients is restricted by prevalent anti-AAV immunity or by their inadequate performance in specific targets, exemplified by the AAV type 2 (AAV-2) prototype in the liver. Here, we attempted to merge desirable qualities of multiple natural AAV isolates by an adapted DNA family shuffling technology to create a complex library of hybrid capsids from eight different wild-type viruses. Selection on primary or transformed human hepatocytes yielded pools of hybrids from five of the starting serotypes: 2, 4, 5, 8, and 9. More stringent selection with pooled human antisera (intravenous immunoglobulin [IVIG]) then led to the selection of a single type 2/type 8/type 9 chimera, AAV-DJ, distinguished from its closest natural relative (AAV-2) by 60 capsid amino acids. Recombinant AAV-DJ vectors outperformed eight standard AAV serotypes in culture and greatly surpassed AAV-2 in livers of naive and IVIG-immunized mice. A heparin binding domain in AAV-DJ was found to limit biodistribution to the liver (and a few other tissues) and to affect vector dose response and antibody neutralization. Moreover, we report the first successful in vivo biopanning of AAV capsids by using a new AAV-DJ-derived viral peptide display library. Two peptides enriched after serial passaging in mouse lungs mediated the retargeting of AAV-DJ vectors to distinct alveolar cells. Our study validates DNA family shuffling and viral peptide display as two powerful and compatible approaches to the molecular evolution of novel AAV vectors for human gene therapy applications.

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