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Research review paper

Development of hybrid viral vectors for gene therapy

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ABSTRACT

Adenoviral, retroviral/lentiviral, adeno-associated viral, and herpesviral vectors are the major viral vectors used in gene therapy. Compared with non-viral methods, viruses are highly-evolved, natural delivery agents for genetic materials. Despite their remarkable transduction efficiency, both clinical trials and laboratory experiments have suggested that viral vectors have inherent shortcomings for gene therapy, including limited loading capacity, immunogenicity, genotoxicity, and failure to support long-term adequate transgenic expression. One of the key issues in viral gene therapy is the state of the delivered genetic material in transduced cells. To address genotoxicity and improve the therapeutic transgene expression profile, construction of hybrid vectors have recently been developed. By adding new abilities or replacing certain undesirable elements, novel hybrid viral vectors are expected to outperform their conventional counterparts with improved safety and enhanced therapeutic efficacy. This review provides a comprehensive summary of current achievements in hybrid viral vector development and their impact on the field of gene therapy.

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Abbreviations: AAV, adeno-associated viral vector; AAVS1, adeno-associated virus integration site 1; ADA, adenosine deaminase; AdV, adenoviral vector; CAR, Coxsackie-adenovirus receptor; CBD, chromatin-binding domain; CCR5, the chemokine (C–C motif) receptor 5 gene; DBD, DNA-binding domain; DMD, Duchenne muscular dystrophy; DSB, double-strand break; EBNA1, Epstein–Barr virus nuclear antigen 1 protein; EBV, Epstein–Barr virus; FIX, coagulation factor IX; FR, the family of repeats of EBV; FV, foamy virus; HAC, human artificial chromosome; HMGB1, high-mobility group DNA-binding protein-1; HR, homologous recombination; HSV, herpes simplex viral vector; IDLV, integration-defective lentiviral vector; IDRV, integration-defective retroviral vector; IR, inverted repeat; ITR, inverted terminal repeat; LCA, Leber congenital amaurosis; LEDGF, lens epithelium-derived growth factor; LMO2, LIM domain only 2; LTR, long terminal repeat; LV, lentiviral vector; MMLV, Moloney murine leukemia virus; MLV, murine leukemia virus; MOI, multiplicity of infection; p5IEE, p5 integration efficiency element; RGD, arginine–glycine–aspartate motif; RNP, ribonucleoprotein particle; RT, retrotransposition; RV, retroviral vector; S/MARs, scaffold/matrix attachment regions; SB, Sleeping Beauty transposition; SCID, severe combined immunodeficiency; ZFD, zinc-finger domain; ZFN, zinc-finger nuclease.

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1. Introduction

The knowledge that certain diseases can be attributed to defects in DNA has led naturally to the development of therapies that deliver functional genes into patients to compensate for altered or abolished functions (Friedmann and Roblin, 1972). This therapeutic gene transfer process is called gene therapy. The first approved gene therapy trial was performed in the USA in 1990 when two patients with adenosine deaminase (ADA) deficiency were treated *via* a mouse-derived retroviral vector (RV) encoding a functional ADA gene (Miller, 1992). Following this, recombinant adenoviral vectors (rAdVs) (Crystal et al., 1994), recombinant adeno-associated viral vectors (rAAVs) (Flotte et al., 1996), and lentiviral vectors (LVs) (Levine et al., 2006) entered clinical trials. Due to its unique ability to infect neural cells, herpes simplex viral vectors (HSVs) have also been tested for delivery of genes, and the first human trial using HSV to treat chronic pain began enrolling subjects in December, 2008 (Wolfe et al., 2009).

Two great breakthroughs in gene therapy were achieved at the beginning of the 21st century. In 2000, a French group led by Alain Fischer reported the impressive improvement of the immune function of two children with X-linked severe combined immunodeficiency (SCID) after receiving a reinfusion of bone marrow cells modified by a murine retroviral vector (Cavazzana-Calvo et al., 2000). In 2002, Claudio Bordignon's group reported another trial on ADA-SCID using a similar bone marrow transplantation method, but included additional non-myeloablative conditioning steps to enrich for genetically corrected cells (Aiuti et al., 2002). In the follow-up report in 2009, this study demonstrated that out of 10 patients receiving ADA gene therapy, eight had excellent immune reconstitution without taking polyethylene glycol-modified bovine adenosine deaminase (PEG-ADA) drugs (Aiuti et al., 2009). Another encouraging breakthrough came in 2008 and 2009 when three independent phase I/II trials using rAAV serotype 2 to treat 30 patients with Leber congenital amaurosis (LCA) type 2 improved visual functions in the majority of treated eyes, as was summarized in a most recent review article (Colella and Auricchio, 2012). A recently published paper reported the use of rAAV to transfer human coagulation factor IX (FIX) into six patients with severe hemophilia. A single dose of intravenous rAAV resulted in enhanced FIX expression and improved clotting in all patients (Nathwani et al., 2011).

One prominent concern for viral gene therapy is safety, especially where administration of viral vectors into patients can elicit unexpected immune responses (Somia and Verma, 2000). The first person to die as the result of a clinical gene therapy trial suffered from massive immune responses triggered by the infusion of rAdV into the liver (Wilson, 2009). Another safety concern is insertional mutagenesis. Integrating viral vectors, such as RVs, could potentially activate or disrupt nearby genes after transgene integration. In clinical trials for treatment of X-linked SCID, five out of the 20 patients eventually developed leukemia, and four out of these five patients had the activation of proto-oncogene, LIM domain 2 (LMO2), by the viral long terminal repeat (Dave et al., 2009).

Viral vectors are being constantly engineered to reduce their toxicity and to improve their therapeutic effects. Recently, a novel trend in viral vector development is the creation of hybrid vectors (Clement et al., 2009; de Silva and Bowers, 2011; Glauser et al., 2006; Hausl et al., 2011; Lam and Breakefield, 2000; Mitani and Kubo, 2002; Muther et al., 2009; Oehmig et al., 2004; Zhang et al., 2009). Although "hybrid vector" has been used to refer to a large array of novel vectors, in this review, hybrid vectors are defined as chimeric vectors composed of elements from two or more viruses or vectors combined with other protein or genetic components. Here, we mainly discuss those combinations that alter the state of the delivered vector genome in the infected cells, leading to prolonged transgene expression or safer transgene integration. This review provides an overview of hybrid vector technology developed for adenoviral, retroviral/lentiviral, adeno-associated viral, and herpesviral vectors.

2. Hybrid adenoviral vectors

Around 25% of all gene therapy trials are currently based on AdVs, making them the most clinically used vector (Edelstein et al., 2007). The detailed description of adenovirus structure and life cycle has been reviewed elsewhere (McConnell and Imperiale, 2004), and the schematic outlines of viral structure, wild-type and recombinant virus genomes, and the infection process for AdV are shown in Fig. 1. Briefly, adenoviruses are non-enveloped viruses with a double-stranded DNA genome, around 36 kb in size. The two termini of the adenovirus genome are inverted terminal repeats (ITRs) and the genome can produce over 50 proteins after extensive splicing. The adenoviral genome is packaged in an icosahedral protein capsid, with fiber proteins projecting from the capsid. Recombinant AdVs are constructed by inserting a transgene expression unit into the adenovirus genome, and the most advanced third-generation gutless AdVs retain only *cis*-acting elements essential for virus packaging. Gutless AdVs are less toxic due to the absence of viral protein expression, and can accommodate insertion of foreign DNA up to approximately 36 kb (Alba et al., 2005). AdVs can deliver genes to both dividing and non-dividing cells. For the majority of adenovirus species, excluding species B and several serotypes from species D, the cell receptor, Coxsackie-adenovirus receptor (CAR) is the major binding site for the fiber protein (Hall et al., 2010). The binding of the arginine–glycine–aspartate (RGD) motif in the virus capsid to the cellular integrin receptor is also essential for efficient virus internalization. AdVs enter the cellular cytoplasm *via* clathrin-mediated endocytosis and are ultimately transported to the nucleus through the nuclear pore, where the association of the AdV genome with nuclear matrix initiates the transcription. Within host nuclei, AdV DNA seldom integrates into cell genome (Harui et al., 1999) and transgene expression gradually declines (Ehrhardt et al., 2003).

2.1. Adenoviral/retroviral hybrid vectors

To address the decline of transgene expression from episomal AdV DNA, incorporation of chromosome integration systems into AdV has been suggested. One system, based on the addition of retroviral integration machinery (including foamy virus [spumavirus]) into AdV, is called AdV/RV hybrid, which maintains the appealing attributes of AdV for *in vivo* gene delivery and of RV for long-term transgene expression.

Currently, two methods have been established to generate AdV/RV. The first method is based on the *in situ* generation of RV by inserting