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Invited review

Viral vectors for therapy of neurologic diseases

Sourav R. Choudhury [a, b], Eloise Hudry [c], Casey A. Maguire [d], Miguel Sena-Esteves [a, b], Xandra O. Breakefield [d, *], Paola Grandi [e]

[a] Department of Neurology, University of Massachusetts Medical School, Worcester, MA 01605, USA
[b] Gene Therapy Center, University of Massachusetts Medical School, Worcester, MA 01605, USA
[c] Alzheimer's Disease Research Unit, Harvard Medical School & Massachusetts General Hospital, Charlestown, MA 02129, USA
[d] Department of Neurology and Center for Molecular Imaging Research, Department of Radiology, Massachusetts General Hospital and NeuroDiscovery Center, Harvard Medical School, Boston, MA 02114, USA
[e] Department of Neurological Surgery, University of Pittsburgh Cancer Institute, Pittsburgh, PA 15219, USA

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ABSTRACT

Neurological disorders – disorders of the brain, spine and associated nerves – are a leading contributor to global disease burden with a shockingly large associated economic cost. Various treatment approaches – pharmaceutical medication, device-based therapy, physiotherapy, surgical intervention, among others – have been explored to alleviate the resulting extent of human suffering. In recent years, gene therapy using viral vectors – encoding a therapeutic gene or inhibitory RNA into a "gutted" viral capsid and supplying it to the nervous system – has emerged as a clinically viable option for therapy of brain disorders. In this Review, we provide an overview of the current state and advances in the field of viral vector-mediated gene therapy for neurological disorders. Vector tools and delivery methods have evolved considerably over recent years, with the goal of providing greater and safer genetic access to the central nervous system. Better etiological understanding of brain disorders has concurrently led to identification of improved therapeutic targets. We focus on the vector technology, as well as preclinical and clinical progress made thus far for brain cancer and various neurodegenerative and neurometabolic disorders, and point out the challenges and limitations that accompany this new medical modality. Finally, we explore the directions that neurological gene therapy is likely to evolve towards in the future.

This article is part of the Special Issue entitled "Beyond small molecules for neurological disorders".

Contents

Abbreviations: AAV, adeno-associated virus; Ad, adenoviral; ALD, adrenoleukodystrophy; AD, Alzheimer's disease; APP, amyloid precursor protein; ALS, amyotrophic lateral sclerosis; APCs, antigen presenting cells; APOE, apolipoprotein E; AADC, aromatic L-amino acid decarboxylase; ARSA, arylsulfatase A; ASPA, aspartoacylase; BBB, blood-brain-barrier; BDNF, brain-derived neurotrophic factor; CD, Canavan's disease; CAR, coxsackie and adenovirus receptor; CNS, central nervous system; CDNF, cerebral dopamine neurotrophic factor; CSF, cerebrospinal fluid; CED, convection-enhanced delivery; CTL, cytotoxic T lymphocyte; DCs, dendritic cells; DRG, dorsal root ganglia; FIX, factor IX; Fah, fumarylacetoacetate hydrolase; GABA, gamma amino-butyric acid; GAN, giant axonal neuropathy; GDNF, glia-derived neurotropic factor; GBM, glioblastoma; GAD, glutamic acid decarboxylase; GCH1, GTP cyclohydrolase I; HSV, herpes simplex virus; HR, homology-directed recombination; HIV, human immunodeficiency virus; HRV2, human rhinovirus type 2; IRDs, inherited retinal dystrophies; ICV, intracerebroventricular; IT, intrathecal; IRES, internal ribosomal entry site; IND, Investigational New Drug; LINCL, late-infantile neuronal ceroid lipofuscinosis; LPD, lipid-encapsulated plasmid DNA; LTR, long terminal repeat; LDL, low density lipoprotein; LSDs, lysosomal storage disorders; MRI, magnetic resonance imaging; MLD, metachromatic leukodystrophy; MoMLV, Moloney murine leukemia virus; MSD, multiple sulfatase deficiency; NAA, N-acetyl aspartate; NGF, nerve growth factor; NF1, neurofibromatosis type 1; NF2, neurofibromatosis type 2; NRTN, neurturin; oHSV, oncolytic herpes simplex virus; OV, oncolytic virus; OTC, ornithine transcarbamylase; PD, Parkinson's disease; Rb, retinoblastoma; RRV, retroviral replicating vector; SFV, Semliki Forest virus; SCID, severe combined immune deficiency; sh, short hairpin; SMA, spinal muscular atrophy; TLRs, Toll-like receptors; TSC1, TSC2, tuberous sclerosis complex type 1 and 2; TH, tyrosine hydroxylase; VTA, ventral tegmental area; VLCFA, very long-chain fatty acids; VSV-G, vesicular stomatitis virus G; X-ALD, X-linked adrenoleukodystrophy; ZFNs, zinc-finger nucleases; 5-FC, 5-fluorocytosine; 5-FU, 5-fluorouracil.

* Corresponding author. Molecular Neurogenetics Unit, Massachusetts General Hospital-East, 13th Street, Building 149, Charlestown, MA 02129, USA.
E-mail addresses: sourav.rc@gmail.com (S.R. Choudhury), ehudry@mgh.harvard.edu (E. Hudry), cmaguire@mgh.harvard.edu (C.A. Maguire), miguel.esteves@umassmed.edu (M. Sena-Esteves), breakefield@hms.harvard.edu (X.O. Breakefield), pag24@pitt.edu (P. Grandi).

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1. Introduction

Gene therapy is becoming a viable option for clinical intervention largely due to the success and safety of the current generation of virus-based vectors (Naldini, 2015; Maguire et al., 2014). In general viral vectors have proven more efficient at gene delivery *in vivo* than synthetic nanoparticle and liposome vectors, and in most diseases the goal is to transduce as many affected cells as possible. Within the nervous system, phase 1/2 clinical trials have shown benefit for several neurologic diseases involving replacement of defective genes. This includes: restoration of vision, at least for an extended period, in Leber's congenital amaurosis using adeno-associated virus (AAV) vectors (Pierce and Bennett, 2015); curtailment of further brain neurodegeneration in the brain in metachromatic leukodystrophy (MLD) (Biffi et al., 2013) and adrenoleukodystrophy (ALD) (Cartier and Aubourg, 2010) using *ex vivo* genetic modification of hematopoietic stem cells with lentivirus vectors; and safety for oncolytic vectors in clinical trials (Piccioni and Kesari, 2013). Success has also been reported in blocking human immunodeficiency virus (HIV) infection in a single individual using *ex vivo* gene editing of autologous CD4 T cells to disrupt the viral receptor gene *CCR5* (Tebas et al., 2014).

It is no wonder that viruses have led the field in gene therapy, as they have evolved to deliver their genes efficiently, in the form of RNA or DNA into mammalian cells. In many cases their aim is to replicate in and kill the host cell in the process, as in the case of adenovirus and herpes simplex virus (HSV). In other cases they may be non-pathogenic such as AAV, or may either become latent in the host cell for long periods (e.g. HSV in trigeminal neurons) or integrate into the host cell genome at different sites as with retrovirus and lentivirus. Viruses have evolved very efficient mechanisms to deliver their genome into cells (Fig. 1). In the case of HSV and retrovirus/lentivirus their genome is carried within a proteinaceous capsid surrounded by a lipid membrane envelope. This envelope can efficiently fuse with the plasma membrane of the cell delivering its contents directly into the cytoplasm with subsequent release of nucleic acids from the capsid, and either conversion to DNA (in the case of retro/lentivirus vectors) or delivery of DNA (in the case of HSV) into the cell nucleus. Other viruses, such as AAV and adenovirus, have a proteinaceous capsid that is taken up by endocytosis and have evolved ingenious means to escape the endosome/lysosome compartment to deliver the viral DNA to the nucleus. By “gutting” the virus of its own genes and just retaining the packaging signals, one can package viral vectors in culture using viral genes in *trans* for replication and virus structure and generate an efficient delivery vehicle for the transgene of interest with no viral genes.

As in pharmacology, it is a therapeutic advantage if the cause of the disease (target) is known, as in monogenic hereditary diseases. For these diseases, gene therapy strategies using viral vectors include gene replacement by bringing in a normal copy of a defective gene using AAV vectors which establish themselves as stable “episomes” in the cell nucleus, and lentivirus vectors which integrate transgenes into the genome. Both AAV and lentivirus vectors are capable of infecting dividing and non-dividing cells, but the latter are a better choice for permanent modification of dividing cell populations as genomic integration ensures the progeny generated from the primary target cell is also genetically modified. These same vectors can be used to deliver siRNAs (shRNAs)/miRNAs that can downregulate a dominant-negative mutant mRNA/protein, sometimes also decreasing copies of the normal mRNA. This is combined with delivery of a replacement gene that contains “silent” mutations, making the mRNA resistant to cleavage by the RNAi molecule (Mao et al., 2012; Li et al., 2011a; Mueller et al., 2012). In the future with CRISPR or other gene editing technology (Mussolino and Cathomen, 2012) combined with viral vectors, it should be possible to correct gene defects in recessively inherited diseases and to eliminate mutant genes in dominantly inherited diseases in mammalian brain (Swiech et al., 2015). For diseases of unknown etiology, strategies have evolved to deliver neurotrophic factors, neurotransmitters, compensatory proteins, and selectively toxic proteins into the brain.

Some general principles of intervention are becoming clear. 1) *Treat early*. Excluding prenatal gene therapy, which is not considered ethical at this stage, and given that most neurologic diseases have progressive sequelae, it is best to begin treatment as early as possible. For example, for spinal muscular atrophy (SMA) in which motor neurons are lost leading to death within months for some babies, AAV gene replacement is being tested in babies 2–9 months of age (https://clinicaltrials.gov/ct2/show/NCT02122952). In MLD and ALD where gene therapy can arrest neurodegeneration, it is important to treat before extensive damage to the brain has already occurred (Biffi et al., 2013; Cartier et al., 2009). 2) *Too much has to be okay*. With the current generation of promoters, the levels of