Main Submission

Gene Therapy: A Strategy for the Treatment of Alzheimer's Disease

Danielle Weber-Adrian

University of Toronto

In 2010, an estimated 35.6 million people worldwide were suffering from dementia[1]. This number is expected to increase, resulting in a global disease burden of 115[4]. million people by 2050[1]. Alzheimer's disease (AD) is the most common form of dementia, and is characterized by memory loss[2], gross atrophy of the brain, and the accumulation of both intraneuronal tau protein aggregates and extracellular amyloid-β protein[3]. Gene therapy allows for therapeutic treatment through the continuous expression of a transgene, and is currently under clinical investigation for a variety of neurological diseases including AD[4]. Gene therapy has two main delivery conduits: viral vectors and nonviral vectors[5]. However, a challenge in AD treatment with gene therapy is the delivery of the therapeutic vector into the brain. Systemic delivery from the blood is hindered by the presence of the blood brain barrier (BBB), which prevents passive diffusion of ~98% of small molecule drugs and limits the passage of gene therapy vectors[6]. This short review will cover current delivery strategies for overcoming the BBB along with a sample of genes that have been investigated as AD therapeutics.

Invasive delivery requires surgical administration of a therapeutic into the brain through trans-cranial injection, either into the parenchyma or intracerebroventricular space[6]. Intracerebroventricular injection allows for delivery to the entire central nervous system through circulation in the cerebrospinal fluid (CSF); however, this limits delivery in areas of the brain with less CSF exposure, and cannot target delivery to specific brain regions. Additionally, the rate of efflux from the brain into the CSF is much higher than the diffusion rate from the CSF into the brain[6]. Parenchymal injections mediate targeted delivery to specific brain regions, but this technique is associated with risks of surgical complications[6].

Despite these limitations, direct injection provides the only AD-related gene therapy clinical experience to date. As most cases of AD are attributed to idiopathic causes, as opposed to genetic predisposition, gene-mediated therapeutic strategies typically focus on neuroprotection and repair.[7] Thus far, there have been two clinical trials investigating gene therapy for the treatment of AD[8]. Both trials have investigated delivery of neurotrophic growth factor (NGF), which has been shown to prevent cholinergic neuron degeneration[8]. This is of relevance to AD since memory impairment has been directly correlated with degeneration of cholinergic neurons[9]. The phase I results of a clinical trial using intracranial delivery of NGF-expressing fibroblasts showed a reduction in the rate of cognitive decline[8]. A phase II trial using a viral vector to deliver NGF to the basal forebrain is currently underway[8]. Other gene-mediated targets for the treatment of AD in preclinical models have included brain-derived neurotrophic factor (BDNF), fibroblast growth factor 2 (FGF2), and anti-inflammatory cytokine interleukin-4 (IL-4)[7,8]. BDNF gene therapy has been shown to restore spatial memory performance in AD model rodents, partially rescue age-associated changes in gene expression, and prevent neuronal cell death when delivered prior to surgically-induced brain lesions[8]. FGF2 gene therapy directed to the hippocampus has also shown improvement in spatial learning, enhanced clearance of amyloid-β fibrils, and increased neurogenesis in an AD mouse model[8]. Lastly, IL-4 gene delivery to the hippocampus improved spatial learning and increased neurogenesis, while decreasing hypertrophy, nonspecific activation of glial cells, and amyloid β deposition[8]. Although these therapeutics show potential for the treatment of AD, the safety of gene delivery to the brain could be enhanced by a non-surgical distribution method.

Non-invasive techniques for delivery to the brain, which do not require transporter-mediated delivery across the BBB, include intranasal delivery, chemical disruption of the BBB, and localized permeabilization of the BBB with

focused ultrasound[6,10]. Intranasal delivery bypasses the BBB by delivering the drug through the submucus space of the nose directly into the CSF. However, this technique is restricted in volume (≤100 µL) and associated with the same limitations as intracerebroventricular delivery[6]. Chemical mediated BBB disruption causes global permeabilization of the BBB, but is largely associated with leakage of toxic plasma proteins into the central nervous system[6]. Lastly, MRI-guided focused ultrasound treatment allows for transient and localized BBB permeabilization, and has been shown to mediate targeted gene delivery to the brain in a mouse model[10]. While promising, this technique has yet to be used in a clinical context. Additionally, non-invasive methods for gene delivery to the brain face the challenge of curtailing gene expression in non-target organs after systemic delivery, which could result in side effects.

In conclusion, preclinical and clinical investigations in gene therapy for AD show promise, and suggest that gene therapy could surpass the limitations of traditional pharmacology by providing treatment in a sustained manner. Future studies will hopefully lead to success in clinical trials, as well as progress in developing safer methods for therapeutic delivery. ■

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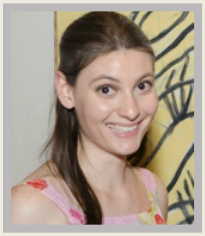

Danielle Weber-Adrian

Danielle Weber-Adrian completed her B.Sc. in Biochemistry at the University of Waterloo, and is currently a PhD candidate in the Department of Laboratory Medicine and Pathobiology at the University of Toronto. Danielle's academic passion is neurodegenerative disease research, and her PhD thesis focuses on gene therapy-based strategies for the treatment of Alzheimer's disease. Her research is conducted at the Sunnybrook Research Institute (http://sunnybrook.ca/research/content/?page=sri-groups-brain-home).