The Efficacy of Gene Therapies in Curing Neurodegenerative Diseases, specifically, Parkinson's Disease

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Abstract

Gene therapy has been proven to be promising in curing diseases due to its ability to deliver potentially life-long therapeutic effects without the need for repeated administration. However, limited research has been conducted on the lack of biomarkers and clinical parameters that predict therapeutic efficacy. To fill this gap in research, this review paper will explore the efficacy of gene therapies in curing neurodegenerative diseases–specifically Parkinson's Disease–by analysing, comparing, and contrasting the methodologies and results of two studies conducted to further explore this topic. In the first study, researchers used fluorodeoxyglucose (FDG) positron emission tomography (PET) to determine if gene therapy would be an effective measure for motor improvement in people with Parkinson's disease through metabolic activity. They did this by having 12 patients participate in an open-label safety and tolerability study of unilateral stereotaxic infusion of STN AAV-GAD (Feigin et al., 2007). Similarly, in the second study, researchers used PET scans and the UPDRS scale in order to determine if gene therapy would be an effective measure for motor improvement in people with Parkinson's disease through AADC expression. Resembling the structure of the first study, 10 patients received bilateral putanimal infusions, instead with AAV2-hAADC (Mittermeyer et al., 2012). Both studies found that gene therapy had significant positive impacts on activity in different regions of the brain, hence proving that gene therapy is indeed efficate in managing–not curing, at the moment–Parkinson's disease. However, further studies are needed to clarify the relationship between changes in metabolic activity and objective treatment-specific efficacy outcomes, which could create or perfect existing treatments for not just Parkinson's disease, but all neurodegenerative diseases.

Introduction

Gene therapy involves the transplantation of normal genes into cells in place of missing or defective ones in order to correct diseases. By delivering a copy of a therapeutic gene to affected cells, the product encoded by that gene (mRNA and/or proteins) will be continuously synthesized within the cell, resulting in therapeutic effects (Martier & Konstantinova, 2020).

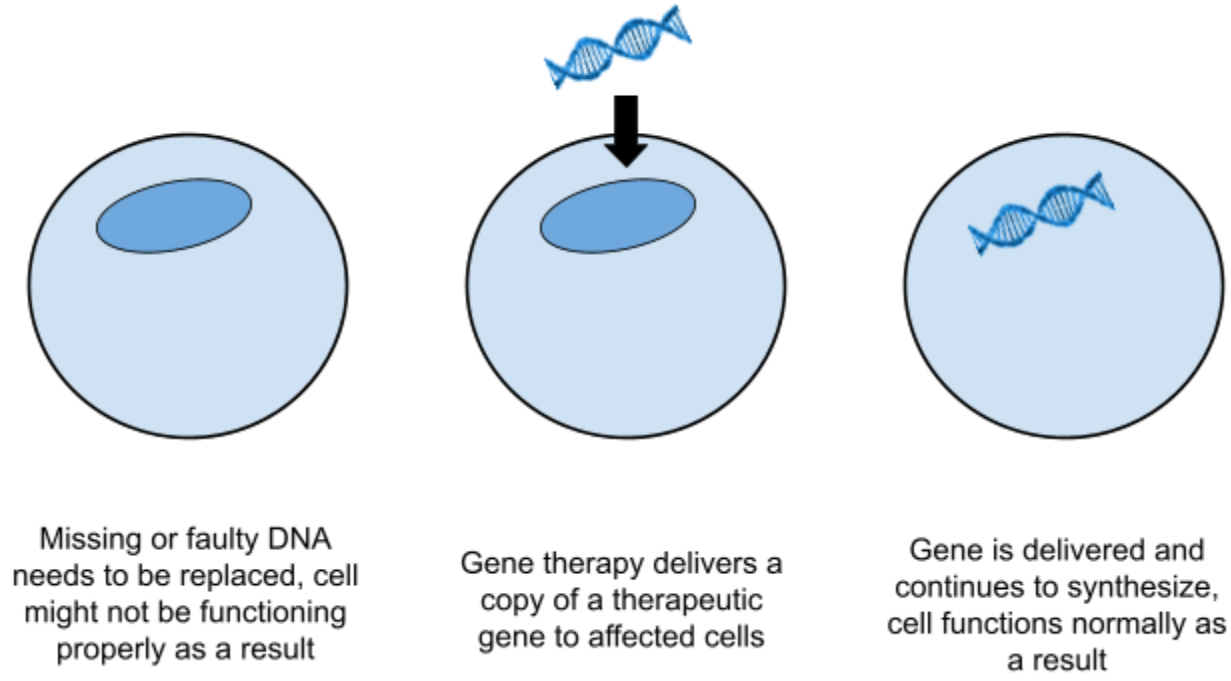

Figure 1: This figure shows how gene therapy works to correct a malfunctioning cell. Missing or fault DNA that is causing the cell to malfunction is replaced by a therapeutic gene by a mode of gene therapy, which results in the continuous synthesis of the new gene in the cell and correct functionality of the cell.

Gene therapy is widely used because it is a single, long-lasting intervention strategy; instead of having to use multiple doses to achieve positive effects, gene therapy is able to cross the blood-brain barrier well, which makes it an effective treatment that needs not be repeated multiple times. In addition, it is unique in its ability to specifically and precisely target the cause of the appearance

of a disease, including those of neurodegenerative diseases which affect the central nervous system and ultimately lead to neurodegeneration. Coupling this with its ability to deliver potentially life-long therapeutic effects without the need for repeated administration, people who suffer from neurodegenerative diseases have the potential to be cured forever with gene therapy. For example, various studies have shown that gene therapy delivering glutamic acid decarboxylase (GAD)–an enzyme that allows for the detection of antibodies against it–is known to have therapeutic effects in patients with Parkinson's disease (PD)–a neurodegenerative disease. However, limited research has been conducted on gene therapy's limited choice of delivery methods, and the lack of reliable biomarkers and clinical parameters that predict therapeutic efficacy or the rate of disease progression. To fill this gap in research, this review paper will explore the efficacy of gene therapies in curing neurodegenerative diseases–specifically Parkinson's Disease–by analysing, comparing, and contrasting the methodologies and results of two studies conducted to further explore this topic.

Methodology

In the first study, researchers used FDG PET imaging to determine if gene therapy would be an effective measure for motor improvement in people with Parkinson's disease through metabolic activity. In order to do so, 12 patients–aged 58 years old on average–with Parkinson's disease–stage 3 or greater–participated in an open-label safety and tolerability study of unilateral stereotaxic infusion of STN AAV-GAD for advanced disease, similar to other past studies. (Fukuda, 2001).

Participants were divided into three equal dosing groups: low, medium, high, and all received the same final injection volume of 50 µl. Efficacy measures included the Unified Parkinson's Disease Rating Scale (UPDRS), scales of activities of daily living (ADL), neuropsychological testing, and PET imaging with 18F-fluorodeoxyglucose. PET scans were performed with repeat imaging at 6 and 12 months after gene therapy and changes in regional metabolism after surgery were assessed across three time points, with activity at each time point bering measured within a spherical volume-of-interest of 4mm. Additionally, metabolic images were processed using SPM5 running on Matlab 6.5. To determine whether changes in network activity differed for the operated and unoperated hemispheres across the three time points, a two-way RMANOVA was performed for each of the two networks, which included time and hemisphere as two within-subject variables (Feigin et al., 2007). Similar to the first study, in the second study, researchers used PET scans and the UPDRS scale in order to determine if gene therapy would be an effective measure for motor improvement in people with Parkinson's disease through AADC expression. The second study followed a structure almost identical to that of the first; 10 patients–aged 64 on average and with stage 3 or 4 Parkinson's disease–received bilateral putanimal infusions of AAV2-hAADC after being separated in either a high or low dosage group. PET scans were performed for evaluation of AADC expression one to ten days before and one to six months after gene therapy using a Siemens 3D acquisition PET scanner. Additionally, the subjects were evaluated with the UPDRS scale at the same time when the PET scans were administered (Mittermeyer et al., 2012).

Results and Discussion

From the first study, after unilateral gene therapy, researchers observed a significant reduction in metabolism in the thalamus, involving the ventrolateral and mediodorsal nuclei. The analysis also

revealed a significant metabolic increase after surgery in the ipsilateral primary motor region, which extended into the adjacent lateral premotor cortex, both of these results meaning that there was objective evidence of a therapeutic response subsequent to the intervention. Additionally, after gene therapy, there was a significant difference in the time course of PDRP activity across the two hemispheres; in the unoperated hemisphere, network activity increased continuously over the 12 months after surgery. By contrast, in the operated hemisphere, a decline in network activity was evident during the first 6 months, which matches what other studies have said (Trošt et al., 2005). Over the subsequent 6 months, network activity on this side increased alongside analogous values on the unoperated side. The time course of PDRP indicated that higher doses of AAV-GAD therapy would results in a better metabolic response, hence proving that gene therapy had a positive result on metabolic activity nevertheless (Feigin et al., 2007). In the second study, researchers found that AAV2 targets striatal interneurons do not degenerate in idiopathic PD from the PET scans, leading them to conclude that gene transfer in PD patients is permanent.

Additionally, they observed no progressive degeneration of dopaminergic neurons in the MPTP model beyond that occurring with the acute intoxication with MPTP, which led them to believe that the reduction of FMT-PET signal in patients treated with AAV2-hAADC reflected ongoing neurodegeneration rather than loss of AADC expression, meaning that the AADC gene therapy was effective in aiding with Parkinson's disease, which is similar to what similar studies obtained (Hadaczek et al. 2010). Moreover, the UPDRS showed a great improvement within the first 12 months, which was most likely due to a placebo effect as it displayed a slow deterioration in subsequent years. Although, patients demonstrated a variety of adverse effects during the course

of the study including upper respiratory infections, incisional tenderness, and more, however, this was expected by the researchers (Mittermeyer et al., 2012).

Conclusion

Gene therapy has been proven to be promising in curing diseases due to its ability to deliver potentially life-long therapeutic effects without the need for repeated administration, hence the reason for two studies seeking to find the efficacy of gene therapy in curing neurodegenerative diseases, specifically Parkinson's disease. The first study observed significant improvements in both regional and network-related metabolic activity after unilateral STN AAV-GAD gene therapy for PD, which was consistent with the results of other therapeutic interventions for PD such as drugs and surgical intervention (Feigin et al., 2007). Additionally, the second study found that AAV2-mediated gene transfer appeared to be permanent and was altered little by the ongoing neurodegenerative process (Mittermeyer et al., 2012). Hence, both studies found that gene therapy was indeed effective in managing Parkinson's disease, which could possibly be applied to the management of other similar neurodegenerative diseases such as Alzheimer's Disease in future studies, which affects more than 6.5 million Americans older than 65 years old per year (Alzheimer's & Dementia, 2022). Furthermore, employing the PET scanning technique that both studies used will help clarify the relationship between changes in metabolic activity and objective treatment-specific efficacy outcomes if similar studies are conducted in the future, which could be done by increasing the volumes and doses of the bilateral injections. The findings from these studies can then be used to create or perfect already-existing treatments for those suffering from not only Parkinson's disease, but anyone who has a neurodegenerative disease, which would help more than 50 million Americans per year.

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