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Review Article

Parkinson's disease: cell therapy vs. gene therapy

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Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disease, manifesting as a characteristic movement disorder with a number of additional non-motor features. The pathological hallmark of PD is the presence of intra-neuronal aggregates of a-synuclein (Lewy bodies). The movement disorder of PD occurs largely due to loss of dopaminergic neurons of the substantia nigra, resulting in striatal dopamine depletion. There are currently no proven disease modifying treatments for PD, with management options consisting mainly of dopaminergic drugs, and in a limited number of patients, deep brain stimulation. Long-term use of established dopaminergic therapies for PD results in significant adverse effects, and there is therefore a requirement to develop better means of restoring striatal dopamine, as well as treatments that are able to slow progression of the disease. A number of exciting treatments have yielded promising results in pre-clinical and early clinical trials, and it now seems likely that the landscape for the management of PD will change dramatically in the short to medium term future. Here, we discuss the promising regenerative cell based and gene therapies, designed to treat the dopaminergic aspects of PD whilst limiting adverse effects, as well as novel approaches to reducing a-synuclein pathology.

Keywords: Parkinson's Disease, Cell Therapy, Gene therapy, Levodopa therapy, α-synuclein, Regenerative therapies, Stem cells

Abbreviations: PD: Parkinson's Disease; ALS: Amyotrophic Lateral Sclerosis; SN: Substantia Nigra; L-Dopa: L-Dihydroxyphenylalanine; Mao-B: Monoamino oxidase-B; COMT: Catechol-o-methyl-transferase; iPSCs: Induced Pluripotent Stem Cells; PARK1: Gene which code for alpha-synuclein (SNCA); DJ1: Protein deglycase DJ-1, also known as Parkinson disease protein 7; LRRK2 : Leucine-Rich Repeat Kinase 2; MAPT: Microtubule-Associated Protein *Tau;* NMS: Non-Motor Symptoms; PINK1: PTEN-Induced Putative Kinase 1;

Introduction

Parkinson's disease (PD) is typically known with a characteristic of movement disorder, consisting of bradykinesia, rigidity, rest tremor and postural instability [1]. Additionally, depression, anxiety, sleep abnormalities, constipation, and cognitive decline with dementia, all the non-motor impairment disturbs the patient's quality of life [2]. The movement disorder of PD occurs in part due to the selective loss of dopaminergic neurons of the substantia nigra pars compacta, resulting in depletion of dopamine in the striatum. Non-motor impairment predominantly occurs due to more widespread neurodegeneration, affecting the cortex and a number of brainstem regions [1,3]. Dopaminergic loss also has wider effects, including on sleep and cognition [4]. This neural cell loss generally has been thought due to aging, toxicity, or external assults, etc.

Abnormal intra-neuronal aggregates of α-synuclein, termed Lewy bodies and Lewy neuritis, however, have been found in PD brain [5]. These things can happen due to SNCA mutations, duplications, or triplications, and therefore may be the cause of autosomal dominant familial PD, a genetic reason can be argued [6]. Levodopa was introduced in 1960s, as a therapeutic regiment for PD. However, this is a palliative treatment, and chronic use of levodopa may result in significant adverse effects [1,7]. In this review, we will discuss the merits and demerits of cell therapy and gene therapy for PD.

To treat PD, the aims are:

1. Restoration of Dopamine deficits that occurs due to the loss of dopaminergic neural cells. This could be done by supplying the dopamine substrate L-DOPA from outside, or by blocking the breakdown of DOPA inside the brain.
2. Using the help of viral gene delivery method one can provide gene(s) responsible for Dopamine productions, like TH (Tyrosine Hydroxylase); dopamine–aromatic amine decarboxylase (AADC).
3. Repairment of the genes that cause the agglutination of α-synuclein or supply the genes that clears the agglutinated α-synuclein. These agglutinated synuclein is believed to cause the cell death. However, only 14-16% PD cases are believed to be gene related.

Gene Therapy

The revolution in genetic research in Parkinson's disease has started in 1997. For the first time, though exceedingly rare, an autosomal dominant mutation (termed PARK1) responsible for the protein alpha-synuclein (SNCA) aggregation leading to cellular dysfunction and toxicity [5,8]. By 2016, at least eight monogenic causes for PD are known [9]. The autosomal dominant forms relate either to a mutation of alpha-synuclein or to LRRK2, whereas autosomal recessive forms (PARK2, PINK1, DJ1) cause mitochondrial dysfunction [10]. Increased levels of SNCA impairs Nurr1 function, thus hampering the effect of GDNF and other members of growth factors ligands. In a paper, Oh et al. (2015) reported the effect of AAV-mediated overexpression of Nurr1 and its co-transcription factor Foxa2 in the midbrain of a MPTP-mouse model [11]. They could rescue 69% of the neurons to the injection site, including a large amount of striatal fibers, as well as detect a decrease of the pro-inflammatory cytokines IL-1 and iNOS. Also, by expressing Nurr1 and Foxa2 in conjunction with GDNF or NRTN it is possible that the GFL may be efficient in PD therapy [12].

The third major discovery was the fact that 3-7% of patients with idiopathic PD carry a heterozygous mutation for the gene glucocerebrosidase A. Genome-wide association studies have confirmed—besides the role of alpha-synuclein—the importance of the microtubule-associated protein tau (MAPT) in the etiopathogenesis of PD. Furthermore, at least 28 genetic risk (susceptibility) factors have been identified, and it is likely that this number will further increase [9]. However, there are some concerns which limits the gene therapy for PD. In fact, the therapy is irreversible, and in most cases, uncontrollable. Opto- and chemogenetics, in contrast, can be applied when necessary and side effects may therefore be less. Genome editing mutations in several genes have been associated with both familial- and sporadic PD, including parkin, LRRK2, SNCA, PINK1, DJ-1, VPS35, DNAJC13, CHCHD2 [8]. Several of these mutations potentially influence neuroplasticity, immunomodulation, endosomal sorting, autophagy and mitochondrial function linked to the development of PD, are able to induce double-stranded DNA-breaks and cause familial parkinsonism [13-20]. However, editing of those genes for therapeutic purposes, as of yet, not approved by any ethics committee.

Cell Therapy

Cell replacement therapy for PD with dopaminergic (DA) neurons, is considered to be the most promising candidate for restoring nigrostriatal DA transmission [21]. Ongoing research in people with Parkinson's disease is attempting to transplant modified cells, including induced pluripotent stem cells (iPSCs) into the right part of the brain. The study shows that astrocytes, a type of cell that supports other brain cells and is not affected in Parkinson's, could be turned into dopamine-producing cells inside the brain [22,23]. However, many problems like propensity to form teratomas and also ethical issues, which are associated with this approach limit their uses clinically [24-26].

Embryonic stem cells (ESCs) although have been shown to be successfully induced to differentiate into DA neurons *in vitro* [22,23,27], many problems like propensity to form teratomas and also ethical issues, limit their uses clinically [24, 25].

Midbrain-derived hNSCs may be more intended to differentiate into DA neurons, however, clinical application has been hindered due to the lack of sufficient midbrain tissues. In addition, midbrain-derived hNSCs lose their proliferative property and multipotency for differentiation in long term cultures [24]. Human neural stem cells (hNSCs) isolated from fetal forebrains can be expanded in cultures for more than a year without losing their multipotency to differentiate into neurons and glial cells [24]. However, forebrain-derived hNSCs appear to hardly differentiate into functional DA neurons, lacking the capacity to release dopamine, compared to midbrain-derived hNSCs, which limited their therapeutic application in PD.

Since the issue is to supply Dopamine in the SN region in PD patients, implantation of melanocytes was another thought. The melanocyte is a neural crest originated cell and specific for melanin synthesis in the skin from Tyrosine by a rate-limiting enzyme Tyrosinase (EC 1.14.18.1; aminophenol monooxygenase) [28]. Some studies have shown that induced expression of Tyrosinase into Tyrosine Hydroxylase (TH) null mice can reverse the PD symptoms in them [29,30]. Taken together, a therapeutic potential of cell transplantation of melanocytes in patients with Parkinson's disease can be understood. However, Melanocytes do not have Dopamine scavenging system, like Dopamine Transporter (DAT), Mono-amino-oxidase B (MAO-B), and Catecholamine Transferase (COMT), therefore they cannot maintain the physiological level of the Dopamine in the synaptic cleft and ultimately may cause the same problem as happens with the levodopa therapy, like Dyskinesis and motor neuron defect [31,32].

Another cell type that can be considered to evaluate their potentiality of using as a therapeutic regiment to treat PD patients is human neural stem cells (hNSCs). hNSC contains Tyrosine hydroxylase (TH) that catalyzes the initial, rate-limiting step in the biosynthesis of catecholamines, including DA, noradrenaline, and adrenaline [33]. The most important physiological aspect of functional hNSCs, as we see in our experiments, that they not only have the capability to synthesize DA but also release DA in response to substrate (DOPA)-induced condition than those obtained in control groups. These cells also express DAT (Dopamine

Transporter), another marker for mature and functional DA neurons, plays a key role in terminating dopaminergic signaling by catabolizing any excess DA which is neurotoxic also, to DOPAC, 3,4-Dihydroxyphenylacetic acid [34].

Therefore, hNSCs being equipped with DA production, release, and its breakdown, can efficiently control the physiologic level of DA in the synaptic cleft can be a better choice over any other [35]. However, hNSCs is a slow growing cell and senesce after a few passages rendering a low level of supply for treatment. Attempts are going to develop in our lab a natural cell modification method by cell-cell interaction to increase the growth potential and survival length of hNSCs along with its DA-ergic quality, (In Progress).

Discussions and Conclusions

In summary, owing to the advances in the field of internal medicine and the surgical disciplines, patients with PD can live longer. However, with increasing age and duration of PD, increased risk to fall and to incur fractures—and other non-motor symptoms (NMS) appear. These NMSs include autonomic dysfunctions, sleep impairment, pain syndromes, and neuropsychiatric symptoms, including depression, impulse control disorders, hallucinations, and cognitive impairment, and many other associated problems, for example, orthopedic syndromes, diabetes mellitus and metabolic syndrome, heart failure, and stroke [36,37].

Thus, the therapeutic need is not only to treat the motor and non-motor complications of the PD patient but also to repair their cognitive defects. Furthermore, identification and determination of a primary endpoint of clinical neuroprotective effect is also a challenge [38-40]. Till now, gene therapy has reached clinical trials on the basis of improving the treatments that target motor symptoms, however gene therapy is less effective when compared to "cell replacement therapy" (CRT). Further, only 10 to 14% of PD are related to the genetic defect. Considering the majority of PD cases, CRT seems to be the best choice provided right selection of the cells can be done based on their proliferative potential, ability to differentiate, and DA-ergic efficiency. NSCs being equipped with DA synthesis and its breakdown to maintain the physiologic level of DA in the synaptic cleft, can be a better choice over any other. These cells will be a need-based supplier of DOPA but will not produce any neural tube defects like long term DOPA therapy as these cells have DA scavenging systems, like Dopamine Transporter (DAT) and monoamino oxidase B enzyme [35]. However, hNSC, since a slow growing cell and senesce after a few passages, it needs some modifications to increase their growth potential and survival length,

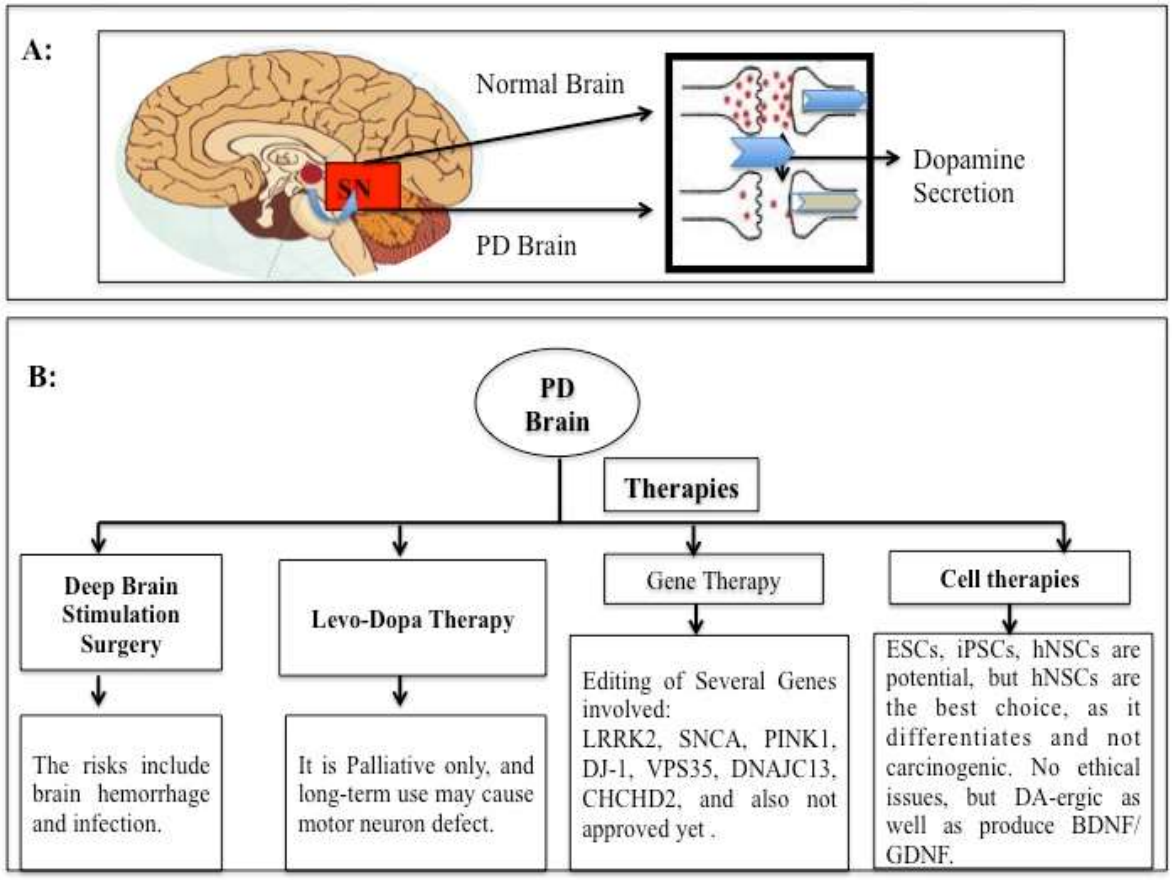

Figure 1: Schematic diagram of Parkinson's disease and it's therapeutic options.

along with their DA-ergic quality. A Schematic diagram has shown in Figure 1 to depict the therapeutic options for Parkinson's disease where cell therapy is the best option to choose.

Cell-Cell interaction, a method for cell modifications was well known now-a-days, and described elsewhere [41,42]. We are presently attempting towards that strategy to improve the growth potential and survival length of hNSCs along with their capabilities to produce Dopamine and BDNF/GDNF.

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Authors Contribution

All the authors contributed equally.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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