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From Symptom Relief to Disease Treatment: A Review of Stem Cell Therapy Development for Parkinson's Disease

Hanbo Dong

Biochemical Engineering Department, University College London, London, UK
dhb0425@163.com

Abstract: *In the past, the treatments of some diseases only focused on the relief of the symptoms due to technological limitations. Take Parkinson's Disease (PD) for example, it is caused by the damage of specific neuron cells resulting in the loss of striatal dopamine. The traditional treatments were the direct replenishment of the missing substance by exogenous drugs or identical substances. This clearly does not stop the progression of the disease, as the loss of specific cells cannot be regenerated. In this case, the discovery of stem cells with potency of regeneration and differentiation have provided a new way to cure the damage of specific cells. The feasibility of differentiating stem cells into specific cells as a therapy has been demonstrated by many studies and significant progress has been made. This paper reviews the development of therapies for PD from levodopa to stem cell therapy over the last decades and discusses the currently known risks for stem cell therapy with potential solutions.*

Keywords: *Parkinson's Disease, Treatment Evolution, Stem Cell, Stem Cell Therapy, Pluripotent Stem Cell*

1. Introduction

1.1. Parkinson's Disease

Parkinson's disease (PD) is a neurodegenerative disorder. Clinical symptoms in people with PD are usually tremor, rigidity and slow movements [1]. By 2016, more than 6 million people around the world were affected by PD [2], which has a significant negative impact on human society [3]. As the second most common neurodegenerative disease, the prevalence of PD increases significantly as population age increases [4], meaning that the burden of PD on society will increase as the population ages [5]. Lewy bodies and the loss of dopaminergic neurons in substantia nigra compacta are considered as the typical pathological features. These may result from a complex interplay of abnormal aggregation of α-synaptic proteins, synaptic transport issues and neuroinflammation [6,7]. The loss of dopaminergic neuronal cells leads to a decrease in striatal dopamine and a consequent imbalance in the direct and indirect pathways through the basal ganglia, resulting in motor retardation in patients [3].

1.2. Stem Cell

Stem cells have an unlimited capacity for self-renewal and the potency to differentiate into other cell types [8]. In the past, depending on their origin, stem cells derived from blastocysts were named as embryonic stem cells (ESC) and had the potential in differentiation of any cell types. While adult or somatic stem cells have a finite differentiate ability and are derived from adult tissues, mainly bone marrow, but are also found in the placenta, cord blood and fetal tissue [9]. New research findings have given rise to controversy over these terms. A previous study proved human somatic cells could be reprogrammed back to the embryonic state by using four transcription factors, Klf4, c-Myc, Sox2 and Oct4 [10]. Therefore, a more accurate classification would be to divide the stem cells into two main types based on their potency, multipotent stem sell (MSC) and pluripotent stem cell (PSC) [9]. PSCs, including ESCs and reprogrammed somatic induced pluripotent stem cells (iPSCs), can proliferate indefinitely and differentiate into three germ layers of cells [11]. MSCs are relatively less pluripotent, but still have the flexibility to become progenitor cells of a particular germ layer or one or two cell types of a particular tissue [9]. Currently, both stem cell applications are in clinical trials [11-13], but this article reviews mainly PSC therapies and the risks.

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2. Traditional Treatment for PD

2.1. Levodopa

Among the several pharmacological treatments for PD, it has long been argued that the most effective one is the direct replenishment of the missing striatal dopamine [14]. Levodopa, the precursor of dopamine, is the typical drug for this treatment as it can effectively cross the blood-brain barrier and be metabolized to dopamine in the small intestine [15]. Although the use of levodopa can reduce symptoms such as motor retardation in patients, the progression of the disease cannot be stopped. It has been shown that the effects of levodopa decline over time, leading to the need for patients to increase the dose and frequency of administration [16]. Patients using levodopa are also at risk of a variety of complications such as dyskinesia and freezing episodes [17].

2.2. Cell Transplantation

Another therapy is the treatment of dopaminergic neuronal loss in specific regions through cell transplantation. Since the 1980s, transplantation of fetal ventral midbrain (FVM) tissue, which contains the progenitor cells of dopaminergic neurons, has been considered an effective surgical treatment [18]. Since the first FVM transplantation in Lund, Sweden, in 1987 with positive results [19], a dozen more patients have undergone transplantation in the 1990s [20-22]. The results of surgery are variable but generally positive [23, 24], and long-term monitoring has shown that the grafts continue to have a significant positive effect on patients after twenty years [25]. However, one of the limitations of using FVM tissue is the issue of cell origin. Grafts from fetuses raise ethical issues [26]. At the same time, individual differences in the origin of the cells have caused problems such as unstable clinical efficacy and safety issues [27, 28]. Therefore, regardless of the small-scale clinical results of FVM transplantation therapy, the source issue makes it impossible to meet the treatment requirements of a large number of patients with advanced PD [29].

3. Stem Cell Therapy for PD

FVM transplantation proved the feasibility of cell therapy for PD, but the source issues led to the need to find alternative sources of cells. In this case, Stem cells were considered a renewable source of cell transplantation therapy due to their differentiation and proliferation properties. Stem cell-based therapies have developed rapidly in the last two decades.

3.1 ESC Therapy

In 2004, hESs were successfully differentiated into midbrain dopamine neurons in vitro by using the neuroinductive properties of stromal feeder cells. Up to 79% of the differentiated neurons expressed rate-limiting enzymes in dopamine synthesis and key markers of normal midbrain dopamine neurons [30]. In the same year, an experiment in which hESC-derived neural progenitor cells were implanted in rats with PD showed positive results, demonstrating the long-term survival of the grafts and the improvement in rat's partial behaviours from transplantation [31]. Subsequent pre-clinical studies have yielded further positive results. Muramatsu et al. transplanted neural stem cells derived from crab-eating macaque ESCs into the putamen of neurotoxin-injured crab-eating macaque. The release of dopamine was monitored, demonstrating the feasibility of ESC therapy in a primate model [32]. Furthermore, hESC-derived dopamine neurons were subjected to comprehensive preclinical validation. The potency experiments demonstrated that the derived neurons had similar functional potency to dopamine neurons derived from FVM [33, 34].

3.2 IPSC Therapy

Several years after iPSC was first generated, neural progenitor cells differentiated from rhesus iPSC were successfully transplanted into the brains of hemiparkinsonian rhesus macaque and survived for up to six months. The grafts differentiated dopamine neurons in the brain without causing severe inflammation or immune rejection [35]. Two years later, a study achieved survival of crab-eating macaque autologous iPSC-derived grafts for up to two years [36]. These positive results in non-human primate models have underpinned the development of subsequent iPSC therapies. A study in 2020 showed autologous human iPSC have been successfully differentiated into midbrain dopaminergic progenitor

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cells and transplanted into the brains of patients. The clinical results demonstrated the patients sustained benefited over 24 months from transplantation and a 6% reduction in levodopa equivalents. Also, prior to clinical use, neurons derived from these progenitor cells demonstrated the dopamine-secreting capacity of dopaminergic neurons in vitro and showed similar functional efficacy to FVM-derived tissue in animal models. No immunosuppressive agents were used throughout the treatment period [37]. Despite the lack of controls in this experiment requiring further study, such exciting and positive results have significantly supported for the development of stem cell therapies in the future. Currently, therapies based on different types of PSC are being developed in several countries and many are already in the clinical trials [12].

4. Current Risks and Potential Solutions

However, there are still some challenges associated with stem cell therapy compared to pharmacological treatments. Apart from the well-known high cost of using autologous iPSC and the ethical issues of using ESC [38], two main challenges and some latest solutions using biochemical engineering techniques will be discussed.

4.1 Immune Rejection

At first, immunologic constraints of PSC transplantation are a serious challenge, which are one of the most significant hurdles PSC treatment [39]. Allelic discrepancies between the graft and the host trigger immune rejection, resulting in histocompatibility antigens. ABO blood-group antigens, human leukocyte antigen (HLA) antigens, and major/minor histocompatibility complex antigens are the three types of transplant antigens to consider [40]. Early research suggested that long-term or even whole-life immunosuppression would be necessary after transplantation if the stem cell derivative does not match patient's major histocompatibility complex [41]. Although iPSC reprogrammed from patient cells can be autologously transplanted to reduce immune rejection [42], this approach is largely limited by its cost, time consumption and high tumourigenicity [43]. Immune rejection is also obvious when using allogeneic iPSC for lower cost [44].

The use of immunosuppressive drugs can leave patients vulnerable to infection and compromise the effectiveness of treatment [45]. Many alternatives are available to avoid the use of immunosuppressants and to counteract the immune response after transplantation. Firstly, one study reported a method to inactivate the HLA gene in the PSC using gene editing technology [46]. By eliminating the beta 2-microglobluin (B2M) gene, HLA-A, HLA-B, and HLA-C, can be rendered inactive [10]. In addition, although PSC treatment is immunologically rejected by the human body, MSCs have strong immunomodulatory characteristics as they can affect the quantity and function of cells in the immune system [47]. Since MSCs only act locally at the graft site, Srivastava et al. proposed co-transplantation of iPSC derivatives with allogeneic MSCs in order to reduce immune resistance and improve graft survival [48]. It suggests MSC is useful for reducing immune rejection and can avoid non-specificity, which is better than using immunosuppression. The feasibility of this approach was demonstrated by recent findings that the ratio of CD8 and CD4 was reduced by co-transplanted MSC [49].

4.2 Tumourigenicity

On the other hand, the use of pluripotent stem cell transplantation faces the risk of tumorigenesis. Andrews et al. suggests that cancer cells and PSCs have cellular and genetic similarities as PSCs are continuously proliferating [50]. In this case, there are three possible causes of tumours [11]. Firstly, the unlimited proliferative capacity of pluripotent stem cells is a double-edged sword, because those stem cells that are not differentiated will continue to proliferate after implantation, which raises the risk of teratomas [11]. A research shows that teratomas are observed when PSC are implanted into rodents [51]. Consequently, teratomas or tumours may emerge if undifferentiated cells exist in the final product of hPSC differentiation. Secondly, during the culture of PSC in vitro, mutations and chromosomal abnormalities may occur, leading to a risk of tumourigenesis [52]. Therefore, genomic abnormalities may occur in long-term PSC culture, including massive chromosome duplication and deletions and point mutations [53,54]. In the absence of tumour suppressor genes, the culture products of PSC may become tumourigenic [52]. The third situation is for transplants using iPSC, where Iida et al. and Nori et al. found that the differentiation products of iPSC were tumorigenic even though all undifferentiated cells had been removed [55, 56]. One of the main reasons for this is the tumorigenicity of Yamanaka factors [57], such as Klf4 and cMyc, which are mutated genes in human cancers [11].

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In order to reduce the tumourigenic risk of stem cell therapies, stem cell must be efficiently differentiated and purified using efficient purification methods, i.e. screening out those cells that are undifferentiated and preventing them from being transplanted into the body. The potential of Fluorescence-activated cell sorting (FASC) to purify stem cell differentiation products is brilliant, as it isolates individual cells with a purity and efficiency of over 95% [58-60]. FACS is a kind of flow cytometry used in biochemical engineering, which can fluorescently label target cells and impart an electrical charge to droplets. When a droplet passes between two charged plates, the droplet and the cells within it are separated according to the charge they have been given [61]. In addition, the highly proliferative capacity of stem cells should be limited. Early studies have focused on the intracellular telomerase that consists of two subunits, the protein subunit hTERT and the RNA subunit hTR and suggested that it relates to the proliferative capacity of human cells [62 -64]. Liu et al. proposed to inactivate telomerase by hTERT knockout, thereby limiting the proliferative capacity of ESCs [51]. In the absence of telomerase activity, each division of a cell results in shortening of its telomeres [65]. When telomeres shorten below a certain level, DNA is damaged as a result [66]. Cell apoptosis is induced as PSC is very sensitive to DNA damage [67].

5. Conclusion

The large number of people suffering from PD places a huge burden on society, resulting in an increasing demand for therapies to stop the disease progress. The ability of stem cells to proliferate and differentiate offers a promising new approach to treat the specific diseased tissue of PD. Although levodopa remains the dominant treatment for PD, many stem cell therapies for PD have begun early clinical trials. The two main risks of using stem cells for treatment, immune rejection and tumourigenicity, are discussed. Potential solutions include the use of gene editing, stem cell co-transplantation, FASC purification and hTERT knockout. These techniques have achieved positive results in research, but the feasibility of using them in large-scale production still needs to be determined.

This article reviews the evolution of treatment from early management of PD symptoms through drugs to autologous stem cell therapy through iPSC. In the future, more research should focus on the efficacy of stem cell therapies for PD in large-scale trials and the application of new technologies to address the risks of stem cell therapies.

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