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Therapeutic Applications of Stem Cells for Cerebral Palsy

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Abstract

Cerebral palsy (CP) is an umbrella term that describes the consequences of brain injury during the neonatal period or postnatal period. Symptoms can range in severity but typically include muscular issues, cognitive impairment, and seizures. During the neonatal periods, the cause of brain injury is generally unknown. However, one of the primary known causes of CP is hypoxic ischemia (H/I). There is no cure for CP, and patients tend to rely on medication and or surgical procedures for symptom management. Recently stem cells have been an essential topic of therapeutic agents for CP due to their regenerative properties and the potential to restore motor and cognitive function. This article will discuss the various types of stem cells being studied for potential CP treatments and animal and clinical trials results.

Keywords

Mesenchymal; Adipose; Embryonic; Induced pluripotent stem cells

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Introduction

Cerebral palsy (CP) is an umbrella term for a collection of neuromotor disorders that typically occurs due to injury to the developing brain. Damage may occur in the prenatal stages of pregnancy or the early prenatal period. There are several causes of brain injury during these critical developmental periods, including stroke and premature birth, and one of the most common causes is hypoxia-ischemia H/I. In addition to the known causes, many CP cases result from damage prenatally due to unknown reasons. The predominant clinical manifestation of CP is damage to the periventricular white matter (PWM). Thus, CP is one of the most prevalent causes of adolescent disability [1-4]. However, most cases of CP occur during the prenatal period and have an unknown cause. The patient's symptoms vary drastically from muscle spasms, seizures, cognitive impairments, and orthopedic complications. Clinicians have various methods of classifying CP. Typically CP can be broken up further into subtypes spastic, ataxic, dyskinetic which are the predominant neurological signs [4,5].

The clinical management for CP is limited to physical therapy, Botox, and orthopedic surgery. In severe cases, patients may need round-the-clock care [6]. CP is incurable, and patients often struggle to maintain a decent quality of life. Patients often experience secondary conditions due to complications with CP. Currently, there is no cure for CP. This review will use stem cells as a potential therapeutic option for CP. Recently stem cells have been an essential topic in the treatment of CP due to their regenerative properties and the potential to restore motor function. This article will discuss the various types of stem cells being studied for potential CP treatments and animal and clinical trials results. The types of stem cells currently under research as potential therapeutics for CP include mesenchymal (MSC), neural (NSC), embryonic (ESC), and induced pluripotent stem cells (IPSCs). Each type of stem cell offers various attractive characteristics that could help regenerate CNS tissue, ultimately restoring some functionality and mitigating symptoms.

Pathology

Injury to the developing brain can lead to clinical manifestation of CP. Damage can result from various insults to the developing brain, including but not limited to inflammation, infection, premature birth, H/I, and genetic disorders [1-4,7]. As a result of these insults, damage to white matter in the CNS typically suffers [1-3,8]. The damage to the white matter leads to problems in posture, cognition, and motor function. These defined causative agents are rare, as in many cases, the causative agent of CP is unknown and occurs during the perinatal period of pregnancy [1,2]. In the study of CP incidence, there is a discrepancy in male to female occurrences. Males appear to be more susceptible to brain injury; the mechanisms are unclear. However, it is suspected that there is a difference in the neuroprotective elements present in the development of males and females [7]. Overall there are several causative agents associated with the development of CP.

CP Stem Cell Therapy

CP is one of the leading causes of pediatric disability occurring worldwide [3,7,9]. Currently, clinicians are limited to medication, physical therapy, and surgeries as a treatment for CP. In addition to the symptoms of CP, patients can often experience a plethora of comorbidities such as infections, seizures,

psychological disorders, etc... [10]. Depending on the severity of the symptoms, patients could require continuous care or multiple procedures to maintain a decent quality of life. With a wide range of symptoms, patients may need to be cared for by several clinicians, from neurologists to psychiatrists, over their lifetime.

Stem cells have much to offer as a therapeutic option for CP. Applications of stem cells in patients aim to restore cognitive and motor functions via cell differentiation and proliferation into neurons and glial cell lines and release supportive elements. The application of stem cells can be a great aid in symptom management. Different cells have various appealing features to offer in regeneration and maintenance of the CNS microenvironment [5]. In CP, lesions and scarring occur primarily in the periventricular areas of the brain. However, some lesions occur in gray matter and the corticospinal tract [3,4] (Figure 1).

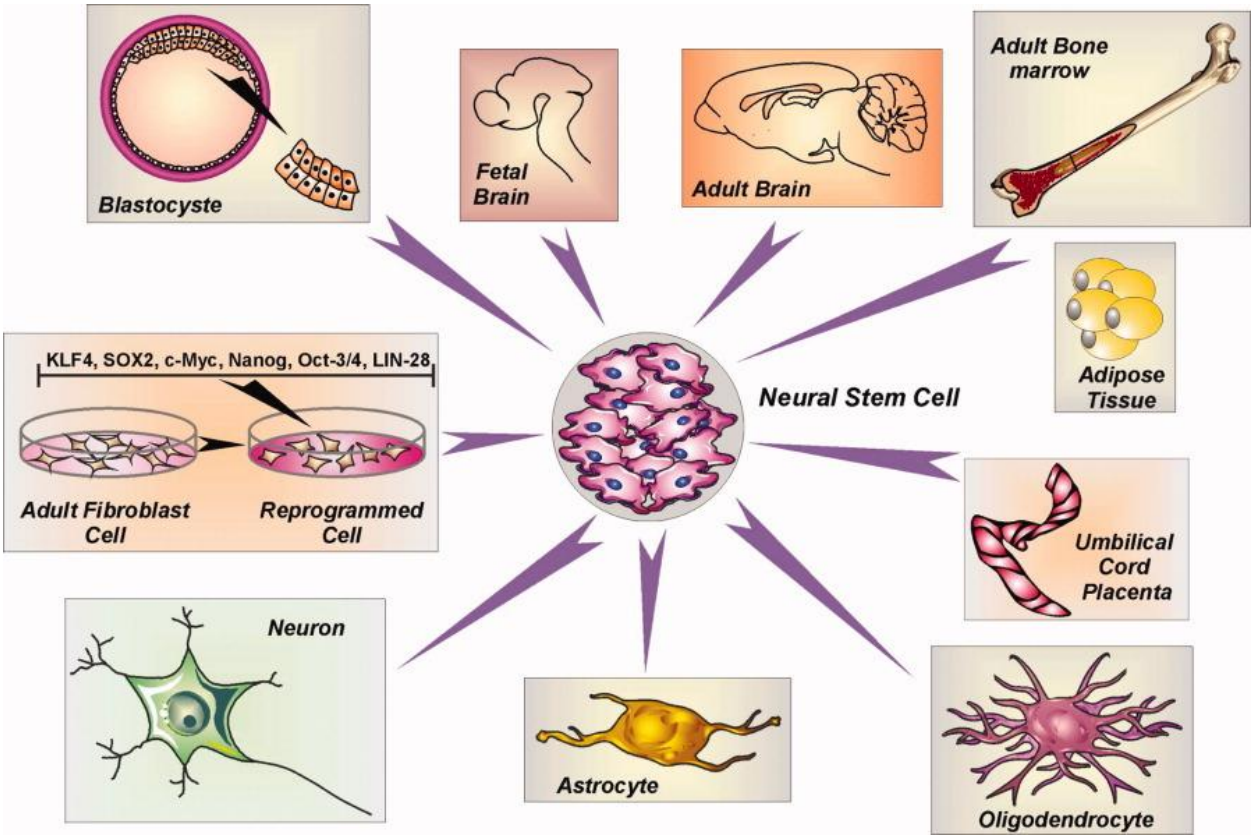

Figure 1: Derivation and differentiation of neural stem cells [3].

Mesenchymal Stem Cells

MSCs are a promising candidate for CP therapy for a plethora of reasons. MSCs can be derived from several tissue types, including bone marrow-derived (BMSC), adipose tissue (AMSC), and umbilical cord blood (USB-MSC). Overall, MSCs are one of the best options simply because of their ability to differentiate and proliferate into several cell types and modulate immune system responses [11,12]. Several clinical trials have had excellent results given the intensive study and testing of MSCs in several neurological diseases.

Clinical Trials & Animal Trials

It is important to note that some variations of MSCs have not been studied as extensively due to ethical reasons, derivation methods, and the potential for rejection. In these trials, several aspects of patient symptoms are assessed, including gross motor movement, language ability, and the number of lesions. The gross motor improvements are typically measured by the Gross Motor Function Classification System (GMFCS). At the same time, language is generally assessed with the language development quotient (LDQ) [13,14]. In the clinical application of MSCs, the overall goal is for differentiation of cells, symptom reduction, and mitigation of immune responses. As stated previously, MSCs can be derived from different tissues and have varying properties. In the case of BMSCs, the study of autologous BMSC transplants is very appealing due to their ability to restore tissues and immune regulation.

In a clinical trial, researchers applied autologous BMSCs that had been observed with neural stem cell-like derivation *in vitro*. The cells were administered to CP patients with transplantation to the subarachnoid space via spinal tap following retrieval and *in vitro* differentiation. The results indicated that some patients gradually improved their gross motor abilities and language use based on the GMFCS and LDQ assessments [13]. In a similar clinical trial, HUC-MSCS were chosen due to their immunosuppression and ease of access. The cells were administered to pediatric patients via intravenous injection over a select time frame. This study also yielded significant improvements in patient gross motor ability and cognitive functions. Another exciting aspect of this study was measuring cerebral metabolic activity; precisely, the uptake of ^{18} F-fludeoxyglucose (^{18}F-FDG) with PET/CT scanning. There was a noticeable uptick in cerebral metabolic activity in the patients that received stem cells and a decrease in periventricular inflammation [2].

Overall, the use of MSCs as a therapeutic option for CP is becoming more appealing with good results from trials. More effort should be directed to the exact mechanism in which MSCs aid in improving the symptoms of CP. Furthermore, there are still areas of concern in applying MSCs, such as the potential for tumorigenesis and immune rejection. Patients may experience side effects such as nausea, vomiting, and intracranial pressure [11,12]. MSCs appear to be an excellent option for transplantation and improving patient symptoms [14]. Continuous research is needed to ensure the safety and efficacy of cell transplantation.

Neural Stem Cells

Neural stem cells (NSCs) or neural progenitor cells are derived from CNS tissue of fetal specimens. NSCs have an edge on other stem cell types in that they have committed to the differentiation into neuronal cell lines. NSCs can mitigate the immune response of the recipient as well as potentially secrete some trophic factors [15]. One of the main issues of NSCs is the ethical issues when it comes to harvesting. NSCs are derived primarily from aborted fetal CNS tissue. This moral issue also presents challenges to properly studying NSCs and fully understanding their properties [16].

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Clinical & Animal Trials

Clinical trials with NSCs have taken place and have yielded some promising results. A clinical trial conducted administered NSCs to pediatric patients with severe CP cells were administered via injection into the lateral ventricles. The results of this trial were improvements in the gross motor movements of pediatric patients. It was also noted that there was an increase in motor development following the procedure [17]. Hypoxia-ischemia (H/I) is one of the causes of CP, and it occurs during the perinatal period of pregnancy. In a rat model of H/I researchers suspected the NSCs have a role in regenerating damaged nervous tissue and exhibit stem cell-like properties under the stressful conditions of H/I. The results of this study show that there are increases in factors that induce the cell-like behavior from the subventricular zone and an increase in multipotent neurospheres from H/I models. The increased multipotency of the neurospheres suggests that neural progenitor cells have undergone a shift to multipotency [18]. Rodent models of CP following the delivery of NSCs have displayed the ability to home to damaged areas and proliferation of microglia and neurogenesis, resulting in some restoration of function [3]. NSCs are a promising therapeutic option for CP. Several studies, both clinical and animal, display good results. However, while NSCs do have some immunomodulatory properties, there is the risk of rejection following administration. Also, the potential for the formation of tumors is still a risk that must be assessed [3,18].

Embryonic Stem Cells

Embryonic stem cells are derived from the inner blastocyst developing embryos and have pluripotency. Pluripotency is a significant advantage due to the possibility of cells differentiating into neurons and glial cells *in vitro* [9, 19]. ESCs can be harvested and given proper treatment to develop into all three germ layers; differentiation can be done *in vitro.* ESCs offer a wide range of versatility in treatment applications of neurodegenerative disorders [13]. In applying ESCs to CP, the goal is to restore some motor and cognitive function to improve the quality of life. ESCs have been studied in animal models and human clinical trials.

Animal & Clinical Trials

In rodent models of CP, the administration of ESC has displayed great results in improving motor function. In a clinical study, HuESCs were administered to CP pediatric patients and delivered intravenously to repair visual impairment. The results of this study were auspicious in that all patients had some form of visual improvements at the end [20]. A significant concern with ESCs persists as several reports of teratoma formation following administration. This is due to the ESCs being able to circumvent the immune system if the cells are administered and undifferentiated. There are efforts to obtain pure cultures of differentiated cells to prevent tumor formation [19].

Induced Pluripotent Stem Cells

Induced-pluripotent stem cells (IPSCs) offer a unique ability in that these are somatic cells that can be harvested from almost any tissue and be reprogrammed to pluripotency. The ability to reprogram cells back to pluripotency is thanks to the 2006 advancement made by Yamanaka and Takahasi [21]. The reprogramming of cells is done by IPSCs, circumventing the ethical issues associated with the ESCs and

NSCs; they also have the ability for autologous transplantation, reducing the probability of an immune response (Jessica Sun, Luigi). IPSCs have tremendous potential. However, there is a risk of teratoma formation up following transplantation.

Animal & Clinical Trials

Several CP animals' models, specifically rodent models, have been tested using IPSCs as a therapeutic option. In one study, the results were quite intriguing. Researchers used the Human derived IPSCs (Hu-IPSCs) astrocytes in a mice model of neonatal hypoxia/ischemia, a common cause of CP. The cells were administered intranasally with the hopes of stimulating oligodendrocyte maturation. The results were that the application of cells was that they do myelinogenesis. The researchers also concluded that applying the cells or the treated media resulted in similar outcomes. There was also a noticeable improvement in behavior (Peng Jiang). In a similar application of IPSCs, researchers once again derived astrocytes. The mouse model used modeled neonatal hypoxia-ischemia (H/I). The results of applying this Hu-IPSC immature astroglia suggest that they help restore some functionality in H/I induced brain injury. The animal models of IPSCs show promising results; however, the risk of tumor formation is still considerable. IPSCs also present an issue in the derivation method as it is challenging to modify a large culture of cells [22,23].

Conclusion

CP continues to be a primary cause of pediatric neurological deficits in conjunction with cognitive impairments. CP is again an umbrella term for several disorders resulting from injury to the developing fetal brain. Some of the primary causes of injury include hypoxia-ischemia (H/I) and premature birth [1,8]. Injuries often cause damage to the white matter regions of the brain leading to clinical symptoms. Treatment of CP is limited to pharmaceuticals, physical therapy, and care teams. Stem cells offer a therapeutic approach to restoring some functionality to CP patients. The goal of stem cell therapy for CP is to improve motor movement/control and cognitive output. Currently, several stem cells types are being researched as therapeutic candidates. These include neural stem cells (NSCs), mesenchymal stem cells (MSCs), embryonic stem cells (ESCs), and induced pluripotent stem cells (IPSCs). Many of these cells have been studied in animal models and clinical studies, each showing promising results [5,10]. The future of stem cell treatment of CP will include more understanding of the mechanisms in which stem cells aid in the recovery of nervous tissue. There must also be an effort to find a viable and reliable source of stem cells. Overall the future of stem cells as an option for treating CP is potential.

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