Stem Cell Therapy for Treatment of Epilepsy

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Abstract- Epilepsy as one of the most common neurological disorders affects more than 50 million people worldwide with a higher prevalence rate in low-income countries. Excessive electrical discharges in neurons following neural cell damage or loss cause recurrent seizures. One of the most common and difficult to treat types of epilepsy is temporal lobe epilepsy (TLE) which results from hippocampal sclerosis. Nowadays, similar to other diseases, epilepsy also is a candidate for treatment with different types of stem cells. Various stem cell types were used for treatment of epilepsy in basic and experimental researches. Two major roles of stem cell therapy in epilepsy are prophylaxis against chronic epilepsy and amelioration cognitive function after the occurrence of TLE. Several animal studies have supported the use of these cells for treating drug-resistant TLE. Although stem cell therapy seems like a promising approach for treatment of epilepsy in the future however, there are some serious safety and ethical concerns that are needed to be eliminated before clinical application.

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Introduction

Epilepsy is a common neurological disorder, particularly in low-income countries (1). It is identified as one of the most prevalent neurological disorders with neural cell damage or loss. Consequently, excessive electrical discharges in neurons results in recurrent seizures. One of the most common types of epilepsy is temporal lobe epilepsy (TLE) which is the most difficult to treat and associated with a previous brain injury such as trauma, tumor, status epilepticus (SE), meningo-encephalitis, etc. (1-4). Usually, TLE results from hippocampal sclerosis that is characterized by neural cells loss and damage in the hippocampus (5). Epilepsy affects more than 50 million people Worldwide (4). Its lifetime prevalence varied from 1.5 to 14.0 per 1000 in the world (6). While, burden of epilepsy in low-income countries is more than twice in high-income countries, probably because of a higher incidence of risk factors (1). Some studies reported that the rate among developing countries is similar to developed countries (7). In Iran as a developing country, frequency of epilepsy is estimated to be 1.8% in the general population and it is more common among females, unemployed, and higher educational level (8).

Common treatments of epilepsy are predominantly symptomatic, and no effective therapy is available to prevent epileptogenesis (9). Beside the beneficial effects of various treatments for epilepsy, they have some limitations. For example, long term use of antiepileptic drugs can induce undesirable side effects. On the other hand, they have several considerable therapeutic effects on children with refractory epilepsy but, unfortunately, are insufficient for adults (4,5,10-13). Additionally, current pharmacotherapy of epilepsy is largely limited to seizure suppression as a symptomatic treatment approach which has minimum effects on prevention of epileptogenesis or disease progression. Therefore,

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around 30% of all epilepsies (particularly TLE) are refractory to anti epileptic drugs (3). Accordingly, interventional and surgical treatment has performed to eliminate the seizure-generating. Although surgical therapy can improve seizure in most intractable TLE cases, it is limited to less than 50% of patients (4,14). Furthermore, surgical treatment is an invasive procedure with various adverse effects such as brain damage. Hence, Investigators have tried to introduce alternative treatments with more efficacies in prevention of epileptogenesis, targeting underlying factors, and with no adverse effects (3,14-16). One of the novels promising treatments is (stem) cell therapy which is a candidate for treatment of neurological disorders including parkinson's disease, multiple sclerosis, epilepsy, etc. (10,14). Epilepsy is associated with underlying factors such as loss in specific cells in the brain which can be replaced with stem cell transplantation and provide endogeneous factors to prevent epileptogenesis (5,10,17,18). Rather, stem cells have some considerable advantages over existing therapies for epilepsy. For instance, they can be directed to epileptogenesis areas (5).

Stem cell-based approach to epilepsy

Stem cells are immortal cells with self-renewal potency that can generate different cell types. There various stem cell sources such as embryonic, fetal and adult tissues are available (5,19). Nowadays, stem cell research and therapy is an interesting area for investigators and also clinicians. Similar to other diseases, neurological disorders such as stroke, spinal cord injury (20-22), and epilepsy are candidates for treatment with different types of stem cell. At first, cellular therapy for epilepsy has focused on TLE (5).

The replacement of damaged or lost cells and also substitution of physiological mediators may represent two major mechanisms underlying therapeutic effects of transplanted stem cells into the patient with refractory epilepsy. Meanwhile, trans-differentiation, cell fusion, producing trophic factors or cytokines, and even activating endogenous neural stem cells are several bases of stem cells therapeutic effects (15). Different types of stem cells were considered for treatment of epilepsy as basic researches or future clinical trials. The purpose of this review is a brief evaluation of common types of stem cells that were studied in the field of epilepsy.

Embryonic stem cells

Embryonic stem cells (ESCs) are pluripotent cells with self-renewal potency that can be derived from the inner cell mass (ICM) of blastocysts and have the ability of differentiation into different cell types of three germ layers. Several studies reported considerable advantages of ESCs-based approach in the neurological disorders (23,24). Hence, ESCs are candidate as a therapeutic approach to various clinical diseases and consequently they have created tremendous hopes in the regenerative medicine arena. For instance, in neurodegenerative diseases, ESCs have introduced a new opportunity to substitute damaged neural cells with the normal stem cells. Therefore, ESCs with self-renewal and differentiation capacity can be used for research and therapy in the area of neurology (25). They also can be differentiated to neural progenitor cells or functional neurons and glial cells after transplantation (23,26). Moreover, ESCs can be expanded in vitro and highly purified generation of neural progenitor cells is easily accessible. In epilepsy, damaged or lost neurons could be replaced with ESCs as well their inhibitory mediators such as γ-aminobutyric acid (GABA) used to inhibit the seizure and reduce excitability in chronic epilepsy (23). An interesting study showed that after transplantation of neural progenitor cells (differentiated from ESCs) into the hippocampi of mice model of status epilepticus they differentiated to mature neurons (27). These results suggest that there is a compatible environment with differentiation of progenitor cells in damaged brain in chronic epilepsy that can provide the base of novel cellular therapies for the treatment of epilepsy. Although, ESCs have unlimited potential of self-renewal and differentiation to neural precursors, they could arise ethical and safety concerns (25). Therefore, these concerns and risks associated with ESCs such as tumor formation need to be realized and decreased before implementing in clinical transplantation trials. On the other hand, more investigations are needed to elucidate long-term survival and probable adverse effects of transplanted cells in neurodegenerative disorders including epilepsy (28).

Fetal stem cells

Fetal neural stem cells demonstrate a strong differentiation and integration potential following transplantation into central nervous system. They are investigated experimentally in various neurological disorders, in particular in clinical trials for spinal cord injury, stroke and pediatric metabolic disorders that are expanded ex vivo before transplantation in human or animal models. As GABA has a fundamental effect on reducing excitability in epilepsy and also inhibiting

seizure (23), transplantation of GABA-producing cells into the brain has been examined in various models of epilepsy particularly, in TLE. The role of loss of GABA-ergic cells supports the feasibility of cellular therapy in epilepsy. Several studies have examined injection of GABA-producing cells in different parts of the brain for instance, substantia nigra, hippocampus and dentate gyrus in epilepsy models. They hypothesized that increasing GABA as a neurotransmitter seems to decrease seizure susceptibility and treat epilepsy (5). Accordingly, in another study, GABA-ergic cells injected into the hippocampus of adult rats, differentiated into various types of inhibitory interneurons and reduced the frequency of seizures significantly. Other studies showed that transplantation of fetal neural stem cells into the hippocampi in epileptic rat can reduce the motor and severe convulsive seizure (29). A surprising study was performed by Baraban *et al.*, who injected fetal neural precursor cells to treat seizures in a genetically modified model of epilepsy and showed a reduction of electrographic seizures. Their result indicated that in a generalized genetic model of epilepsy, the therapeutic effect of transplanted cells resulted from a mechanism in the brain to control seizure activity (30). Intravenous transplantation of fetal neural stem cells also was examined and showed a significant reduction in spontaneous motor seizure frequency and severity (31). Moreover, other studies showed that the transplantation of hippocampal precursor cells considerably could help to improve learning and memory deficits associated with status epilepticus (4). Despite several advantages of fetal stem cells and their promising effects on treatment of epileptic animal models, serious ethical concerns similar to ESCs present. Therefore, investigators should overcome all ethical obstacles. More studies also are needed to confirm the safety of fetal progenitor cells transplantation.

Induced pluripotent stem cells

The most successes in clinical stem cell transplantation for treatment of various diseases have resulted from adult stem cell therapy which can provide the option of autologous stem cell source with no immunogenicity. This opportunity also is rendered using induced pluripotent stem cells (iPSCs) generated from somatic cells (5). Human iPSCs are candidates for regenerative medicine and tissue engineering (32). Nowadays, using the iPSCs for treatment of neurological disorders is an interesting area of neuroregeneration (33). Novel iPSC technology could produce reprogrammed pluripotent stem cells without using integrating viruses in vitro and has consequently reduced risks of viral episomal vectors (5). More evidences of reprogramming neural stem cells using a single round of transduction are available. Further studies are needed to realize the risks of residual transgene expression and potential neoplasia (34).

Mesenchymal stem cells

Recently, several experimental investigations reported the therapeutic effect of mesenchymal stromal cells (MSCs) in central nervous system disorders such as spinal cord injury, stroke, parkinson's disease, and brain trauma (35-37). Their therapeutic effects seem to result from stimulation of endogenous glial cells or neural stem cells, reduction of apoptosis and degeneration, modulation of inflammatory responses, and self-repair promotion in the brain. Additionally, MSCs arouse neuroprotective properties by releasing neurotrophic factors and immunomodulation (35,38) which can attenuate seizure in epilepsy (5, 39). Human MSCs could be derived from bone marrow and other tissues for instance; adipose tissue, peripheral blood, umbilical cord blood and tissue, *etc* (40). Bone marrow is an easily accessible source and provides an autologous transplantation opportunity with no immunogenicity or ethical limitation in comparison with embryonic or fetal stem cells. However, some crucial questions are needed to be answered by conducting more studies. For example; more studies are needed to confirm therapeutic effect of human MSCs in epilepsy models, clarify long term survival of transplanted MSCs, and elucidate specific differentiation of MSCs and their paracrine therapeutic effects (41).

Discussion

Recently, stem cells have aroused promising hope for treating various neurological disorders includes epilepsy. Two major goals are followed by stem cell therapy for epilepsy. The first one is to use a prophylaxis against chronic epilepsy, and the second one is to ameliorate cognitive function after the occurrence of TLE. It is considered that the fundamental causes of seizure after status epilepticus, stroke, and head trauma are hippocampal degeneration and multiple epileptogenic changes in the hippocampus that could be followed by TLE. Hence, stem cell therapy approaches into the hippocampus showed promising results in ameliorating seizure and cognitive dysfunction in epileptic patients. These cells could be derived from

various sources, including human ESCs, MSCs, and human iPSCs. Several animal studies support the use of progenitor cells for treating drug-resistant TLE (4,42,43). Although iPSCs, ESCs, and fetal stem cells seem like candidates for treatment of epilepsy (5,17,44,45). However, there are several safety and also ethical concerns about using them. Undesirable immunogenesis and tumor formation are two major problems that needed more restrict studies to be eliminated before translating basic and experimental experiences to the clinic (4,17). For instance, researchers have tried to develop new induction technology for generating neurons directly from somatic cells (e.g. fibroblasts) with bypassing ESCs to avoid ethical, technical, and safety concerns (46). Although, induction of pluripotency is an opportunity, but it is far from clinical applications because of some concerns discussed previously. The main problem about the use of iPSCs is a retroviral vector that is applied for induction. Retroviral vector application could result in uncontrolled differentiation and viral contamination. Accordingly, better understanding of migration, differentiation, and survival of the transplanted cells is critical for development of alternative techniques leading to a safer clinical application of iPSCs (5).

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