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Role of Stem Cells in Cerebral Infarction

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Review Article

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Abstract

Cerebral ischemia which may lead to brain tissue damage is one of the leading causes of mortality and physical disability in the world. Transplantation of stem cells has been proposed to be one of the effective therapies for a number of neurological disorders. The ability of stem cells to differentiate into various cells has been explored so that these cells can be beneficial for the use in regenerative therapy. Mesenchymal stem cells which have the ability to promote neurogenesis are currently the promising donor cells for the cure of cerebral infarction. These cells have been reported to show functional proliferation of neurons as well as inhibiting neuronal apoptosis. Exogenous stem cells from various sources can generate neural cells and strengthen the synaptic connection after cerebral infarction. Among all the stem cells, bone marrow derived mesenchymal cell transplantation has been shown to be effective in the treatment of cerebral ischemia. Besides transplantation of stem cells, endogenous enhancement of neural stem cells can also promote neurogenesis. Since neural stem cells are located in the subventricular zones and in the hippocampus of the brain, proper stimulation of these area could enhance neurogenesis in vivo. Both P13k pathway and electrical stimulation are synergistically required to overcome the acute and chronic phases of cerebral infarction. Therefore, sufficient clinical trials should be done to obtain evidence so that stem cell therapy can be used for regenerative therapy in future as these cells have shown remarkable potential in the regeneration of functional neurons.

Keywords: Cerebral Infarction; Mesenchymal Stem Cells; Exogenous Stem Cell Transplantation; Endogenous Enhancement Of Stem Cells; Neurogenesis; Regenerative Therapy

Abbreviations: ESCs: Embryonic Stem Cells; iPSCs: induced Pluripotent Stem Cells; IS: ischemic stroke; BIA: brain infarct area; rTMS: Repetitive transcranial magnetic stimulation.

Introduction

Cerebrovascular disease, which is the third most common cause of death in the world after heart disease and cancer have almost found its therapeutic solution.

Stem cells have been said to have profound effect in the prevention of extension of cerebral infarction. It is believed that these cells are capable of replacing damaged cells and thus many diseases can be cured. Cerebral infarction occurs due to focal brain necrosis which is caused by partial or complete blood loss resulting in decrease cerebral perfusion. Major cause of cerebral infarction is thromboembolism. Since cerebral infarction is a life threatening disease, it is of crucial importance to conduct researches on role of stem cells in neurogenesis.

Besides surgical decompression, the only currently available treatment is recombinant tissue plasminogen activator (t-PA) [1]. This t-PA is only applicable to use within three hours of onset of ischemia and the results can only be observed if it is given within 90 minutes [2]. One of the drawbacks of this t-PA is a narrow time window and thus it is mainly used in emergency room. Due to this, alternative treatments for example by using stem cells have been discovered.

Neural stem cells (NSC) were discovered in humans in the region of the brain called the hippocampus which was known to be the area involved in the formation of memories and in the subventricular zones [3]. Many clinical studies have been carried out to investigate the potential application of the two primary approaches in the treatment of cerebral infarction. First approach is by exogenous stem cell transplantation from multiple sources that can generate neuronal cells with functional synaptic connection in the infarcted area [4]. The second approach is by enhancement of endogenous stem cell transplantation which is less invasive compared to the latter [5].

Besides, some studies said that non-neuronal stem cells also have the ability to differentiate into neural tissues. For example embryonic stem cells and adult stem cells also known as somatic stem cells. Recently, studies regarding somatic stem cells transplantation have confirmed to be efficient for the repair of neuronal diseases due to trophic factors that are secreted by these cells [6]. It has also been shown that pre-activated and disaggregated shape-changed platelets (PreDSCP) and human embryonic stem cell-derived exosomes (hESC-Exo) treatments can reduce brain-infarct area (BIA) in rat with preservation of neurological function following acute ischemic stroke (AIS) induced by left middle-cerebral artery occlusion [7] .The stem cells are used because they have remarkable potential of self-renewal and multipotency properties. They are also capable of migrating into the areas of injury and secrete neuroprotective compounds apart from generating variety of functional cell types. These properties are beneficial in later time points when conventional medical therapies would no longer be effective.

Even though stem cell therapy has been successful in the treatment of cerebral diseases in animal models, there is still no evidence of success in clinical trials. Therefore, the purpose of this study is to explore the role of stem cells in cerebral infarction and the effectiveness as well as the safety measures of stem cell therapy so that it can be used as regenerative therapy for neuronal diseases in future.

Cerebral Infarction

Neurons are the functional unit of the central nervous system. They have a unique ability to receive, store and transmit information. Neurons of different types in various locations have distinct properties including their roles, neurotransmitters used, metabolic requirements and their level of excitability in a given time. Since neurons are permanent cells which cannot undergo cell division, destruction of even a small number of neurons for a specific function may leave an individual with neurological deficit.

The most common cerebrovascular diseases are ischemia, embolism, and hypertensive intraparenchymal hemorrhage and rupture aneurysm. Stroke is the clinical presentation that applies to all these conditions. There are two types of ischemia namely global ischemia and focal cerebral ischemia. Global ischemia occurs when there is generalized reduction of cerebral perfusion as in cardiac arrest. On the other hand, focal cerebral ischemia occurs following a reduction or cessation of blood flow to a localized area of the brain due to embolic or thrombotic arterial occlusion. The outcome of cerebral ischemia is cerebral infarction. Survival of brain tissues at risk depends on the presence of collateral circulation, the duration of ischemia and the rapidity of blood flow reduction to the particular area in the brain. Metabolic depletion of energy due to ischemia can result in inappropriate release of neurotransmitters such as glutamate which leads to cell damage due to excessive influx of calcium ions through NMDA-type glutamate receptors. This results in free radical regeneration and mitochondrial injury which leads to cell death or infarction mostly through necrosis.

Cerebral infarction may occur due to in situ thrombosis, embolism or various forms of vasculitis. Majority of thrombotic occlusions are due to atherosclerosis. The most common sites for thrombosis to

occur are at the carotid bifurcation, the origin of middle cerebral artery and either end of the basilar artery. Cardiac mural thrombi are among the most common source of embolism to the brain. Internal carotid artery is frequently affected in this case. Cerebral infarction can be classified into hemorrhagic infarction and lacunar infarction. Hemorrhagic infarcts are characterized by multiple, sometimes confluent, petechial hemorrhages associated with embolic events. The hemorrhage occurs due to secondary leakage of blood from the collateral vessels or through dissolution of intravascular occlusive material which causes the infarcted area to be reperfused. Lacunar infarcts are small lake like spaces which occur in deeper parts of the brain such as basal ganglia, thalamus, white matter and the brain stem. They are caused by occlusion of deep penetrating branches of major cerebral arteries and are particularly common in hypertension and diabetes patients who are associated with severe atherosclerosis of small vessel disease [8].

Stem Cell Therapies

The only currently available successful treatment for cerebral infarction in acute phase is administration of tissue plasminogen activator (t-PA) [9] but patients who survive the acute phase suffer from permanent hemiparesis in the chronic phase. This highlights the need for regenerative medicine in future treatment of cerebral diseases. Stem cell population which can be found in the subventicular zones and hippocampus in the brain may represent a potential repair mechanism after injury. Stem cells are capable of replacing damaged cells due to disease or injury through cell replacement therapy [10]. Many different types of stem cells can be cultured and transplanted such as embryonic stem cells, neural stem cells, mesenchymal stem cells, induced pluripotent stem cells and hematopoietic stem cells.

The replacement can be done either by in vitro differentiation of stem cells into the desired cell type followed by transplantation of the differentiated cells into the affected region [11] or by direct transplantation of stem cells followed by spontaneous in vivo differentiation of stem cells into the needed cell types [12]. Neurogenesis in response to brain injury may also occur spontaneously in some areas in the brain but this is not sufficient to allow complete recovery of the damaged area [13]. Apart from cell replacement therapy, it has been found that stem cells appear to show potent tropism for injury. They are attracted to the injured area and may secrete trophic factors that can promote survival of the damaged cells [14]. Two primary approaches that are used in the treatment of cerebral infarction are exogenous stem cell therapies and enhancement of endogenous stem cells.

Exogenous Stem Cell Transplantation

Transplantation of stem cells is one of the most established strategies. However, transplantation of these untreated cells without treatment is not useful for regeneration of neural tissues as they cannot survive and differentiate into neurons in the recepient's neural tissues. Therefore, before transplantation, addition of neurotrophic factors such as fibroblast growth factor eight is required for neuronal differentiation of the transplanted neural stem/progenitor cells. Embryonic Stem Cells (ESCs) and induced Pluripotent Stem Cells (iPSCs) can give rise to different types of neurons both in vitro and after intracerebral transplantation as they are pluripotent in nature [15]. It has also been reported that mesenchymal and ectodermal stem cells have the capability for neuronal differentiation. Examples of mesenchymal cells are bone marrow mesenchymal stem cells and adipose derived mesenchymal stem cells whereas ectodermal stem cells are neural stem cells. Recent studies have shown that transplantation of mesenchymal cells have reduced the expression of the axon inhibitors such as Nogo- A MAG and OMgp. Besides, these cells also inhibit neuronal apoptosis and decrease Caspase- 3 and increase Bcl -2 protein expression levels. These two mechanisms have been said to promote functional recovery of the central nervous system after cerebral ischemia but it is yet to be confirmed. In addition, mesenchymal stem cells are also capable of secreting growth factors including nerve growth factors, brain derived neurotrophic growth factors and glioma derived neurotropic factors [16]. To add to the inhibition of neural apoptosis, exogenous neural growth factors also play an important role in neuronal plasticity and regenerative potential [17]. Brain derived neurotrophic factors are capable of inducing neurite out growth [18] while glioma derived neurotrophic factors can prevent neuronal death after brain injury [19,20]. Further it has also been revealed that bone marrow derived mesenchymal cells can promote recovery of the central nervous system after cerebral ischemia by decreasing the expression of myelin associated inhibitors and by inhibiting neuronal apoptosis [21].

Ectodermal Derived Stem Cells

Neural Stem Cell (NSC) Transplantation: Since it is difficult to obtained neural stem cells in the subventricular zones and hippocampus, allogenic transplantation of human NSCs has been performed.

NSCs can differentiate into neurons, oligodendrocytes, astrocytes and even endothelium. But actual results in preclinical studies have been varied. Several studies have shown that NSCs can clearly survive after transplantation and have tendency to migrate towards the infarcted area. Most studies have not observed changes in the infarct size after NSC transplantation [2]. Recently, it was established that co-injection of neural stem cells and IFN-γ can improve therapeutic outcomes in ischemic stroke model. Pro-inflammatory cytokine feature of IFN-γ has the potential to protect stem cell population during inflammatory response, as well as encourages neurogenesis of stem cells. The most important finding of this study is that IFN-γ did not hinder with the proliferation of neural stem cells (NSCs) in vitro but induced remarkable levels of neuronal differentiation significantly superior to those of other four cytokines brain-derived neurotrophic factor (BDNF) , Vascular endothelial growth factor (VEGF) ,transforming growth factor beta(TGF-β) and (insulin like growth factor-1) IGF-1. Besides, additional neurological benefits and significantly increased in neurogenesis in vivo were also seen by co-treatment with IFN-γ and NSCs as compared with NSC transplantation alone [22].

Dental pulp stem cells: These cells are promising donor cells for neuronal regenerative therapy because they are actually neural crest derived cells [23]. They can differentiate into neurons. It has been reported that transplantation of these cells can induce endogenous axon proliferation [24] and they can also differentiate into functional active neurons in a favorable environment [25].

Mesenchymal Derived Stem Cells

Bone Marrow Mesenchymal Stem Cells: Bone marrow mesenchymal stem cells have also been reported to be able to differentiate into neural tissues besides bone, cartilage and adipose tissue. Transplantation of these cells has been done for cerebral infarction via intravenous transfusion [26]. Some of them are capable to penetrate the blood brain barrier but these cells have low survival rate and unable to function as neurons. One of the advantages of using these cells is, even though they cannot differentiate into neurons, they can still secrete neutrotrophic factors which may have effects on neural tissue repair. The results of clinical trials using human autologous bone marrow derived mesenchymal stem cells for ischemic brain disease have appeared to be safe and it also showed improvement of the disease [27].

Adipose tissue derived mesenchymal cells: Besides, adipose tissue derived mesenchymal cells can also be used for exogenous stem cell transplantation. These cells can differentiate into motor neuron like cells in the presence of retinoic acid and sonic hedgehog. The clinical application of these cells in animal models and in humans is still limited [28]. Although the effect is limited but these cells can be of therapeutic use as they can secrete trophic factors such as vascular endothelial growth factor and hepatocyte growth factor which can contribute to the repair of ischemic brain tissue [29].

Embryonic Stem Cells and Induced Pluripotent Stem Cells

Embryonic Stem Cells and induced Pluripotent Stem Cells can generateLong-term self-renewing neuroepithelial-like stem cells (lt-NESCs) which are capable in differentiating into stable neuronal and glial cells with hindbrain specification [30]. Improvements were seen in general neurological score [31] because of cell implantation observed in the desired site. Besides, these stem cells have the ability to reduce secondary damage after stroke. In rodent stroke models, iPSC derived neuronal precursor cells transplantation showed reduced overall damage and tissue loss in the ischemic hemisphere, with transplantation within days of the stroke and even in the first week after stroke [32,33]. Before transplantation of the cells, availability of the cells, immune response, ethical concerns in using embryonic stem cells must be addressed [34] and the possibility of tumor formation must be taken into consideration when embryonic and induced pluripotent stem cells are used [35,36].

Mode of stem cell delivery

There are few stem cell delivery methods namely intraparenchymal transplantation, intravenous administration and intraarterial administration. The number of survival of the transplanted stem cells depends on the methods used which in turn affect the recovery from cerebral infarction. The best method used to deliver a large amount of stem cells in the ischemic area is by using intraparenchymal transplantation. This is an invasive method. Intravenous administration unlike in intraparenchymal transplantation is a non-invasive method. But in this method, the desired stem cells will normally end up in the liver and lungs leaving a small fraction of stem cells surviving in the ischemic penumbra [37]. On the other hand, intraarterial administration via a micro-catheter to the ischemic penumbra can be performed in a clinical situation in which this method is

expected to be less invasive as compared to intraparenchymal transplantation.

Enhancement of Endogenous Stem Cell Therapy

Role of PI3K pathway

Another approach that is less invasive compared to exogenous stem cell transplantation is enhancement of endogenous stem cells. Activation of phosphatidylinositide 3-kinase pathway (PI3K) in the subventricular zones and hippocampus after cerebral infarction could enhance endogenous neurogenesis. PI3K pathway helps in cell proliferation, growth, differentiation and migration of endogenous neural stem cells [38]. The role PI3K pathway in differentiation of NSCs is contradicted because some studies have suggested that this pathway is not required for the differentiation of NSCs [39]. Many studies have shown that activation of this pathway helps to protect the neurons and brain from ischemic injury. For instance, several neurotrophic factors such as brain derived neurotrophic factor and fibroblast growth factor [40]. Protects the brain after ischemic injury through activation of PI3K pathway. Besides, migration of NSCs is enhanced by the activation of receptor tyrosine kinase ErbB4 which leads to activation of PI3K pathway. Activation of PI3k pathway by erythropoietin produces matrix metalloproteinase which could also enhance the migration of NSCs to the infarcted area [41]. This study has been supported by the finding that matrix metalloproteinase inhibitors cause reduction in neuroblasts migration in the area of ischemic injury [42]. The studies stated above indicate that appropriate activation of P13K pathway may be beneficial in preventing brain cell damage after stroke.

Role of Electrical and Repetitive Transcranial Stimulation

Electrical stimulation and repetitive transcranial magnetic stimulation can also be used to enhance endogenous neurogenesis. Deep brain stimulation of the anterior nucleus of the thalamus can enhance the presence of endogenous NSCs in the hippocampal dentate gyrus which leads to enhancement of neurogenesis. Electrical stimulation in rat models during acute phase of cerebral infarction has shown increase in cerebral perfusion, reduction in infarct volume and behavioral recovery. The neuroprotective effect was derived from PI3K pathway [43]. During chronic phase of cerebral infarction, electrical stimulation of the striatum has shown proliferation, migration, and neuronal differentiation of endogenous NSCs in the subventricular zone. Transcranial direct current stimulation has been performed on animal models, which is thought to strengthen synaptic connection [44-52]. Besides vagus nerve stimulation in ischemic patients and rat models have shown behavioral recovery and reduction in the size of infarct. Repetitive transcranial magnetic stimulation (rTMS) is commonly used compared to electrical stimulation because patient can avoid surgery that is required for electrode transplantation. Overall, electrical stimulation has been shown to be effective in both acute and chronic phase of cerebral infarction.

Role of Pre-activated and Disaggregated Shape-Changed Platelets (PreDSCP) and human embryonic stem cell-derived exosomes (hESC-Exo)

Administrations of PreD-SCP and hESC-Exo have shown to reduce brain infarct area (BIA) and neurological deficits in rats after acute ischemic stroke (IS). The therapeutic neurological outcomes were achieved mainly through inhibition of inflammation, oxidative stress, and cellular apoptosis as well as enhancing angiogenesis. Besides, another fascinating finding was preservation of the integrity of neurons and myelin sheath that may account for improvement in neurological function in rats after IS. The most remarkable finding in this study is that the neurological function was notably improved by day 3. Increase expressions of angiogenesis biomarkers (i.e., at molecularcellular levels) in IS animals were also noted after receiving hESCExo/PreD-SCP treatments compared to those animals that have not received the treatment [7].

Conclusion

Stem cells have shown to be very effective in the treatment of cerebral infarction. These cells are capable of differentiating into various functional neuronal cells in addition to migrating and secreting neuroprotective compounds in the areas of injury. Currently, somatic stem cells are the most promising cells that can be used to treat cerebral infarction. Exogenous transplantation of stem cells and enhancement of endogenous stem cells have also shown to promote neurogenesis in the infarcted areas. Despite lack of evidences of success in clinical trials, stem cells show tremendous potential that these cells can be used as regenerative medicine in future. However, the tumour formation with stem cell administration warrants necessary precaution. Further, long-term studies are indicated to strengthen the positive effects of stem cell therapy in cerebral infarction.

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