Review Article

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Insights in Stem Cells

2015
Vol. 1 No. 1: 5

Combination Cell Therapy: A New Approach for Stem Cell Therapy

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Citation: Hosseini SM, Shirazi K, Gholami M, et al. Combination Cell Therapy: A New Approach for Stem Cell Therapy. Insights Stem Cells. 2015, 1:1.

Abstract

Stroke is one of the leading causes of morbidity and disability. There is no definite treatment for brain stroke. Stem cell therapy is useful for treating brain stroke. Mesenchymal stem cells and neural stem cells can be used to treat stroke. In this review, we explained the benefits of mesenchymal stem cells and neural stem cells for stem cell therapy and the advantages of combination stem cell therapy due to different features of these stem cells.

Keywords: Cell therapy; Stem cells; Stroke

Received: October 28, 2015; **Accepted:** November 24, 2015; **Published:** November 30, 2015

Introduction

Stroke is the second most important death cause after ischemic heart disease [1]. To this day, there is no definite treatment for brain stroke [2]. Stroke is mostly caused by sudden occlusion of brain arteries by an embolism or a thrombosis; this will result in a decrease in brain blood flow and consequently a shortage in oxygen and glucose [3]. Cerebral ischemia causes inflammation and oxidative stress which can result in secondary damage and an excessive amount of apoptosis that is not a direct result of the hypo-perfusion but it affects neurogenesis [4,5]. Stroke leads to different pathologies and is the 6th common cause for reducing disability adjusted life years [6]. A major factor of apoptosis initiation is the activation of caspase-3, which can trigger the apoptosis cascade [7]. Caspases are the most important group of cytokines involved in apoptosis; and caspase-3 is the activated death protease that catalyzes the definite cleavage of many important cellular proteins [8]. Stem cell therapy has opened a new horizon for treating neurodegenerative diseases due to regenerative capacity and anti-inflammatory effects of stem cells.

Mesenchymal stem cells

Mesenchymal stem cells (MSCs) could be isolated from different sources such as bone marrow, adipose tissue and Wharton's jelly [9,10]. MSCs could be used in stem cell therapies because of their anti-inflammatory effects and their ability to reduce apoptosis and their role in protection against oxidative stress. MSCs exert their anti-inflammatory effects via attenuating inflammatory cytokines such as TNF-α (tumor necrosis factor α), IL-17, IL-23, IL-1β ,P-IκB-α, P-IKKβ, p53 protein and increasing the expression of TGF-β,IκB-α,and Bcl-2 which result in modulation of the inflammation [11,12]. Furthermore, locally transplanted MSCs could reduce the level of IL-6 and (IL)-1β and increase IL-10; these effects of MSCs result in diminishing the inflammation [13]. This decrease in inflammation could lead to differentiation of the neural stem cells and it may help neural stem cells to regenerate damaged area of ischemic brain [14]. MSCs through enhancing Bcl-2 gene expression and decreasing the by-products of lipid peroxidation, could reduce apoptosis and oxidative stress [15]. As we showed in our study, the administration of MSCs reduce caspase-3 activity; meaning a reduction in apoptosis. Mesenchymal stem cell therapy can significantly diminish cerebral infarct volume, reduce apoptosis and caspase-3 activity, and thereby improve neurological function [16,17]. MSCs might make some neural regenerations by secreting some neuro-trophic factors (cytokines) including basic fibroblast growth factor (bFGF), endothelial growth factor (EGF), brain derived

neuro-trophic factor (BDNF), vascular endothelial growth factor (VEGF), GDNF, PDGF [18-21].

Neural stem cells

Neural stem cells (NSCs) could be isolated from the sub-ventricular zone (SVZ) of the lateral ventricles, the sub granular zone (SGZ) of the hippocampus dentate gyrus (DG) in the adult, and the ganglionic eminence in the embryo [22-24] and human breast-milk stem cells [25]. Neural stem cells (NSCs) could be used in cell therapies for they can promote angiogenesis via secreting VEGF and neurogenesis after cerebral ischemia [26]. NSCs are capable to protect cells against apoptosis by decreasing the level of caspase-3 activity and increasing Bcl-2 [27,28]. NSCs could show bystander effect, meaning they can exert direct neuroprotection effects through neutralization of free radicals, inflammatory cytokines, excitotoxins, lipases peroxidases and other toxic metabolites that are released following an ischemic event [29]. NSCs can show immunomodulatory actions by a down-regulating inflammatory T cells and macrophages within inflamed areas of the ischemic brain [30-36]. The most important characteristic of NSCs could be their ability to promote regeneration due to their capability to differentiate into three neural lineage cells (neurons, oligodendrocytes and astrocytes). NSCs can differentiate into diverse neuronal subtypes like cholinergic, serotonergic and GABAergic neurons, as well as into striatal neurons expressing substance P and DARPP32 [37]. Furthermore, NSCs might be able to suppress the adverse glial activation in the brain after stroke; they could make neurogenesis faster and more feasible [38]. NSCs as well as MSCs can diminish inflammation in the infracted area by repressing COX-2 [39] **(Table 1).**

Conclusion

Both mesenchymal stem cells and neural stem cells can improve neurological function and reduce brain lesions after brain stroke. Each stem cell type (MSCs and NSCs) has synergic effects on the other and they can benefit each other in cell therapy. Therefore, combination stem cell therapy is more efficient for recovering after brain stroke [16]. We showed that the optimal time for transplantation of MSCs is 12 hours after ischemic stroke [17]. In conclusion, administration of MSCs in acute phase after cerebral ischemia might be helpful due to the secretion of the neurotrophic cytokines, neuroprotection, anti-oxidant, and anti-inflammatory effects of MSCs. We take advantage of NSCs ability in neural regeneration in subacute phase after MSCs make the microenvironment suitable.

Table 1 Stem Cell therapy and its role.

Type of stem cell therapy	Advantages	Most important role
Mesenchymal stem cell (MSC)	• Reducing apoptosis and oxidative stressthrough enhancing Bcl-2 gene expression, reducing Caspase-3 activityand decreasing the by-products of lipid peroxidation[15] • Making neural regenerations by secretingbFGF, EGF, BDNF, VEGF, GDNF, PDGF[18-21]	• Anti-inflammatory effects via attenuating inflammatory cytokines such as TNF-α , IL-6 , IL-17, IL-23, IL-1β ,P-IκB-α, P-IKKβ, p53 protein and increasing the expression of TGF-β,IκB-α, IL-10 and Bcl-2[11-13]
Neural stem cell (NSC)	• Angiogenesis via secreting VEGF[26] • Anti-apoptotic effect bydecreasing the level of Caspase-3 and increasing Bcl-2 [27,28] • Direct neuroprotecting effects through neutralization of free radicals, inflammatory cytokines, excitotoxins, lipases peroxidases[29] • Immunomodulatory actions by downregulating inflammatory T cells and macrophages[30-36] • Diminishing inflammation in the infracted area by repressing COX-2[40]	• Promoting regeneration and neurogenesis due to their ability to differentiate into three neural lineage cells (neurons, oligodendrocytes and astrocytes) [26,37,38]
Combination of NSCs and MSCs	• Synerginc effects of both MSCs and NSCs [16]	• Acute phase: anti-inflammatory effects of MSCs • Sub-acute phase: neural regeneration ability of NSCs

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