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Modern Stem Cell Therapy of Cardiac and Neurodegenerative Disorders: Pluses and Minuses

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Abstract:
Stem cell therapy is used for the treatment of many diseases like diabetes, ischemia, Parkinson's disease, cardiac and neurodegenerative diseases. Stem cells can be differentiated into many new types as they are actually undifferentiated cells. Cardiac disease is a life-threatening disorder. Any type of injury to heart muscles increase risk factors for myocardial infarction. Studies indicate that different stem cells are used for the improvement of ventricular function by transplantation. New cardiac tissue cannot be formed but transplanted stem cells have paracrine effects that may be limited by teratoma formation. The brain has a specific formation of substitution connection to the confined and compact action of neuronal stem cells respectively. This demonstrates nervous abnormality and series of neurodegenerative infections that shows a critical civil issue of our inhabitants. So, competitive analysis is motivated using stem cell therapy as a key. Then comparisons of different studies for the treatment of different individuals who are suffering from neurodegenerative diseases are done. Different actions are taken that show aims for the charge of NP afflicted individuals. This review sums up the current scenario of stem cell therapy in Cardiac and Neurodegenerative disorders.

Keywords: Stem cells, neurodegenerative pathologies, stem cell therapy, cardiac disorders.

INTRODUCTION

In multicellular organisms, stem cells are undifferentiated cells which have the ability to form different type of cells by the process of differentiation. Stem cells can be classified on the basis of origin, the potential of differentiation and cell surface markers (Ali *et al.*, 2016). Two types of stem cells are found in humans that are embryonic and adult stem cells. These undifferentiated stem cells can be grown under artificial environment and are used for many medical therapies e.g. Bone marrow transplantation (Tuch, 2006). Stem cells have two properties; self-renewal and potency. Stem cell therapy is used to get rid of various disorders. Research is being done to cure different diseases such as neurodegenerative and heart problems. It is used for treatment of different types of cancer (Karanes *et al.*, 2008). Healthy brain cells contain neural stem cells which induce neuroprotection to brain. Stem cell therapy is also used for treatment of myocardial infarction by forming heart muscles, stimulating growth of new blood vessels (Androutsellis-Theotokis *et al.*, 2006).

Cardiovascular diseases lead to death. Acute and chronic injury results in loss of cardiac tissue. Recent therapies reduce the risk of cardiovascular disorders by remodeling it. Different stem cells transplantation in cardiac muscles after ischemic injury will be helpful. When stem cells are transplanted in heart muscles then they exert paracrine effect. Studies showed that adult heart has more potential for in vivo therapy with stem cells, it improves healing of cardiac muscles.

Myocardial Infarction and Ischaemia

It starts many events like injury leading to scar, loss of structural integrity, glycolysis stop, ATP loss, lactic acid accumulation leading to less pH, failure of ATPase pump, resulting in apoptosis. As the cell death starts, phagocytosis occurs and muscle walls decrease, only a scar remains (Frangogiannis, 2008). Increasing oxygen demand limits ischaemic burden to prevent scar and enhance myocardial function. Discovery of proliferation capacity and plasticity of various stem cells act as a potential therapy.

Embryonic stem cells (ES cells or ESCs)

ESCs are obtained in undifferentiated form from human and mouse (inner mass of blastocyst), differentiate as embryoid bodies then cultured in media and go to differentiated state in specialized cell types which is cardiomyocyte (Doetschman *et al.*, 1985; Odorico *et al.*, 2001). The cells implanted in any organ show repairing cardiac tissue after injury. It results in long term survival and differentiation.

But first, it has a risk of teratoma formation. It can be benign or malignant. The second issue affects immunity. ESCs have human leukocyte antigen (HLA), that arises graft rejection and increase immune suppression. Studies trying to solve this problem by regenerating inducible pluripotent stem cells (ips).

Basal stem cells (BSCs)

The cells differentiate into cardiomyocytes in the culture and help in the treatment of cardiac diseases, also improves ventricular function and regeneration of cardiac cells (Kamihata *et al.*, 2001). Transplant of these stem cells decreased infarct scar size and improves ventricular ejection function.

Mesenchymal stem cells (MSCs)

These cells are separated from hematopoietic stem cells and differentiated into osteoblasts and adipocytes that differentiate in vitro into cardiomyocytes and showed cardiac repair and regeneration. They are less immunogenic and it reduces need for immune suppression. Studies on mice with post-infarct mice showed reduction in infarct size and improves ventricular function (Tomita *et al.*, 1999). The difficulty arises due to their higher differentiation capacity.

Endothelial progenitor cells (EPCs)

These bone-marrow-derived cells reach the site of injury and proliferate and incorporate in microvasculature. They can be recognized by markers on surface. In case of any injury, they separate from bone marrow stem cells and burn cancer or myocardial infarction (Jujo *et al.*, 2008). Studies are being carried out to enhance its mobilization towards injured site. It improves the functioning of the left ventricle in both types of ischemia and inhibits fibrosis.

Barriers include heterogeneity of cell population, SC and EPCs pool of these cells is less in persons having cardiac ischemia, hypercholesterolemia, and diabetes (Vasa *et al.*, 2001).

Myoblasts

These are sources of stem cells and used for cardiac repair. They are inside the basal membrane of muscles and stimulated to proliferate in any case of injury or disease. Further, it is differentiated into ESCs and cause teratoma formation (Murry *et al.*, 1996). It has improved ventricular function and decreased remodeling because of matrix breakdown. These cells do not fully differentiate into cardiomyocytes in vivo.

Barriers include increased arrhythmic events and these cells go towards myoblasts instead of cardiomyocytes after differentiation (Reinecke *et al.*, 2002).

Cancer stem cells (CSCs)

It is considered as a post-mitotic organ for the discovery of male cardiomyocytes and endothelial cells in donor female cardiac tissue transplanted in male recipient (Quaini *et al.*, 2002). There are certain dyes on stem cells when heart was stained, it shows a pool of SP cells. These SP cells differentiate into cardiomyocytes. Cells that express stem cells factor c-Kit located in heart in small clusters have regenerative potential and increased ventricular function. Stem cells express Sca-1^{+}, it home to myocardium and differentiate into cardiomyocytes. Cardiac progenitors from mouse cells are taken by digestive cardio sphere which differentiates into cardiomyocytes and smooth muscle cells.

Recent studies trying to improve their migration and number of cells to injured areas in ischemia showed that all cells differentiate to cardiomyocytes. These are origin of new cells in stressed myocardium and homeostasis of organ. These stem cells had shortage of regeneration ability in severe damage and undergo apoptosis. Stem cell pool diminishes with aging.

Paracrine effects in stem cells

Along with improved ventricular function, these stem cells infused into mature cardiovascular cells to give cardioprotective effects after transplantation. The differentiated Cardiomyocytes have favorable paracrine effects in injured myocardium prevent apoptosis and promote healing. These cells promote tissue recovery and decrease infarct size (Kupatt *et al.*, 2005). These progenitor cells have different effects, involving wound healing, prevent from apoptosis and reduce fibrosis.

Stem cells as innovative drugs in neurodegenerative diseases

Stem cells in the brain were discovered in 1965 by Altman and Das and its presence is well organized (Altman and Das, 1965). Stem cells present in the brain of humans and mammals are called neural stem cells (NSC) (Zhao *et al.*, 2008). Quiescent and active stem cells are present in brain. NSCs is regulated due to changes in the microenvironment of niches (Cavallucci *et al.*, 2016). The proliferative rate has been detected in the subventricular zone (SVZ), then the subgranular zone (SGZ) in rodents (Curtis *et al.*, 2012). Neurogenesis occurs in early childhood. Negative results on cortical neuronal proliferation in adults employ 14C detector of DNA duplication because of limited sensitivity of technique used (Gould, 2007). NSCs are present in nervous system but

their regenerative ability is limited in adults, it reveals to repair injuries of nervous system, neurodegenerative pathologies (NPs), Parkinson's disease (PD), Alzheimer's disease (AD) and Huntington's diseases (HD) (Kumar *et al.*, 2017; Pramanik *et al.*, 2017).

Pathophysiology of these diseases is still unclear. The researchers focus on regenerative medicines as a solution. Stem cell therapy has been conducted on animal models for preclinical studies (Girlovanu *et al.*, 2015). Alternative therapeutic approaches are metformin, natural anti-oxidants and physical exercise (Markowicz-Piasecka *et al.*, 2017; Ramos *et al.*, 2017). Stem cells are used to process the progression of these diseases. Cell-based therapy (clinical application) for some human pathologies. Various cellular types are MSCs, ESCs, and organ-specific stem cells based on cell therapy. NSCs are studied as therapeutic NP agents. These are identified by combination of molecules including nestin, neural nuclei microtubule-associated protein 2 and other biomarkers (Reekmans *et al.*, 2012).

As early diagnosis of human neurodegenerative disorders is quite difficult, stem cell therapy and gene transfer remain the only options to cope with NPs. Therapy of stem cells may involve the transplant of either neural or mesenchymal cells or embryonic stem cells. Stem cell therapy is used to treat many neurodegenerative disorders, spinal cord injuries, tumors or brain diseases. There are certain limitations associated with stem cell therapy i.e. the use of the most effective or the more suitable stem cells for the grafting, the better understanding of the mechanism that's followed by the stem cells transplantation in order to give the results with better efficacy. Despite the limitations, stem cell therapy is considered to be as effective as to treat neurodegenerative disorders i.e. HD, AD, MS, ALS, and PD. HD was the first neurodegenerative disorder for which the stem cell therapy was first proposed. As a treatment of HD, stem cells or progenitors of neural cells or bone marrow are transplanted, but the result of MSCs transplantation is not clearly evident. So, NSCs transplantation is considered as an effective treatment against HD (Wiatr *et al.*, 2018). However, in the case of MS, the transplantation of MSCs is considered a better option for the treatment as compared to the transplantation of NSCs and HSCs. And for the treatment of ALS, the use of stem cell therapy is still on trials but the transplantation of OECs and iPSCs is reported to be an effective treatment of the disease (Gourronc and Klingelhutz, 2012; Ludolph *et al.*, 2010)

Parkinson's disease

Parkinson's disease is a dopaminergic disorder which is caused by stress, mutations, aging, mitochondrial harm by chemical agents and cerebral hypoxia. The origin of this disease is not clear but different genetic and environmental factors may play important role to cause this disease. Among genetic factors, the mutation occurred in 28 gene as well as the genes which encodes the α-synuclein protein. Insoluble Lewy's bodies accumulated inside the cell. Commonly α-synuclein performs function of the regulation of dopamine. But when mutation reduced the use of dopamine in performing their activity, the remaining released in extracellular membrane. When Lewy's bodies accumulated, it will cause the cell death of dopaminergic.

According to the recent research, in PD patients, α-synuclein bear stress alteration on methionine residues which results in the decrease of hydrophobicity and increase the polarity. All these reasons collectively result in the formation of α-synuclein oligomer. In 1982, it had been seen that some drugs addicted boys were suffered from long-life PD due to the usage of different chemicals like MPTP.

Moreover, it is stated that a link is present between PD and aging because with the aging phenomena endogenous protection depleted and ROS assembles in cell which leads to cell death by damaging the DNA structure or alters the enzymatic reactions that control the main

functions of body like replication (Baba *et al.*, 1998).

In addition, an alluring facet of PD is that to treat this disease only palliative action is used. Only L-DOPA injections are used, their half-life is very small and effective for very short time. Correspondingly, it is agreeable that by the usage of stem cell theory, convert the dopamine into pars compacta of substantia nigra. For this purpose, different kinds of cell lineages may be used. On the other hand, many times replacement of cells is performed being more successful method.

ESCs lineage in Parkinson's disease performs its function in three steps. In first step, dopaminergic neurons are formed in vitro by the differentiation of ESCs in the presence of different stimulators in which the BMP, EGF, and GDNF involved. In second step, induction of the endogenous dopaminergic neurons in the affected animal and check out the recovery signs due to the behavior. Then the cells attain the phenotype of dopaminergic neurons and results in the synaptic markers. This phenomenon has ethical limitations and is not selected in clinical trial in PD patients.

MSCs lineage in Parkinson's disease is used due to the formation of different factors like growth factor, cytokines which are responsible for neural regeneration. It is also involved in different phenomena like apoptosis and tumor necrosis. This lineage has beneficial effects on the PD. The clinical trial is approved for this lineage.

Various stem cells have been extracted and used in vitro for the formation of such chemicals that convert into functional myocardium. Stem cells release various chemicals which enhance such factors by showing paracrine effects in cardiomyocytes formation by inhibiting apoptosis and increase scar formation (Ryzhov *et al.*, 2008). Researchers are trying to improve their culturing process so that more viable stem cells form and their amount increase and can convert to cardiomyocytes and could successfully inoculate into injured tissue. Several attempts are also done to increase cardiac potential for generation of cardiomyocytes.

Stem cell therapy is advantageous for simulating molecular pathways and drug screening (Zhang *et al.*, 2008). However, we can't find the capacity of this therapy to enhance the continence and reprieving the onrush of different diseases, because there is lack of research and equipment. But still there is an observation of great expression that may be useful in further research.

CONCLUSION

Hence it can be concluded that stem cell therapy is trying to increase the regenerative ability of heart and brain cells by improving internal repair that is somewhat similar to that done in the laboratory. Further work is still needed to improve quality of life and decrease mortality rate in cardiac and neurodegenerative patients.

CONFLICT OF INTEREST

All the authors have declared that no conflict of interest exists.

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