IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
July 2019 Vol.:15, Issue:4

Prominent Stem Cell Types Used in Cardiovascular and Parkinson's Disease: A Review

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Sabari Nath K.F.[1]*

[1]Sreekrishna College of Pharmacy and Research Centre, Parassala, Kerala, India.

Submission: 21 June 2019
Accepted: 27 June 2019
Published: 30 July 2019

HUMAN JOURNALS
www.ijppr.humanjournals.com

Keywords: Prominent Stem Cell, Cardiovascular, Parkinson's Disease

ABSTRACT

Regenerative medicine is one of the most innovative branch of medical research. The most striking form of research was made in stem cell therapy. It laid the framework of application of cell based therapies that could be used to cure diseases. The regenerative capabilities of stem cells could be useful for diseases such as cardiovascular disease and Parkinson's disease. However, there is still no general consensus regarding the type of stem cell that could be used for tissue regeneration. This promising ability of stem cells has made stem cell therapy an advanced and new-fangled scientific research field. The regenerative aspect of stem cells have prompted researchers to explore its potential applications in damaged and diseased tissues. So, the application of novel stem cell therapies could achieve ambitious aim of effective regenerative medicine for diseases such as cardiovascular diseases and Parkinson's disease. But the major conundrum of stem cell research is associated with the use of a particular cell type that can harness the expected regeneration of desired tissue. There is still no general consensus regarding the type of stem cell that can instigate the regeneration of tissues. This review provides a general overview about the most prominent cell types that can be used in regenerative medicine associated with cardiovascular and Parkinson's disease. Moreover, this review highlights the advantages as well as disadvantages of each cell type.

INTRODUCTION

Stem cells can simply be defined as immature cells that has the ability to self renew and regenerate into different cell types. Stem cells exist both in embryos as well as in adult cells. The differentiation potential of stem cells are the basis of stem cell research. Stem cells play a crucial role in homeostasis and tissue repair. During an injury, a stem cell will undergo cell division and, turns into a daughter cell and a progenitor cell. Progenitor cells are the intermediate type of cells that exist between the undifferentiated stem cells and fully differentiated cells. So, progenitor cells only give rise to a specific type of cell. With each step in differentiation, a stem cell reduces its ability to differentiate. Based on the differentiation potential, a stem cell can be called as totipotent, pluripotent, multipotent and unipotent stem cells. Totipotent stem cells are capable of dividing and differentiating into a whole organism. It is the stem cell with highest differentiation potency. Pluripotent stem cells (PSCs) form cells of all germ layers but not extraembryonic structures, such as the placenta. Multipotent stem cells have an even narrower spectrum of differentiation. They can only form cells of specific lineages. Unipotent stem cells are the ones which have least differentiation potency as they can only form one type of cell. So the type of stem cell used for regenerative medicine is of immense importance as it is the differentiation potency of the stem cell that helps in tissue grafting.

CARDIOVASCULAR DISEASES

Cardiovascular diseases remains as one of the most dominant factors of mortality worldwide. They are the leading of cause of death in India. Cardiovascular diseases include various disorders affecting the heart and blood vessels: coronary heart disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis, Ischaemic heart disease, stroke and pulmonary embolism. Among these, Ischaemic heart disease and stroke are the major causes of more than 80 percentage of cardiovascular disease related deaths. Despite having various pharmacological and surgical interventions, cardiovascular diseases still remains as a major factor of mortality as none of the current treatment strategies can regenerate heart tissue. Stem cell therapy has the potential to revolutionize the conventional methods of treatments associated with cardiac disorders.

Bone marrow derived mesenchymal stem cells (BM- MSCs)

Human mesenchymal stem cells are non-haematopoietic multipotent stem cells which has the capability to differentiate into osteocytes, adipocytes and chondrocytes. Both small and large animal studies of these cells showed promising results. Orlic et al were among the first to show an improvement in cardiac function after intramyocardial injection of BM-derived mesenchymal stem cells into female mice in an acute myocardial model.[1] That study shows the successful differentiation of BM-derived stem cells into cardiomyocytes, endothelial cells, smooth muscle cells, and vascular structures in the infarcted region of the heart. Another small animal study by Kudo M et al also showed significant engraftment of the MSCs and its differentiation into cardiomyocytes. [2] The infarct size as well as the number of cardiomyocytes were significantly improved. In large porcine model study by Amado LC et al, demonstrated that allogenic MSCs can be delivered via injection, to a region of damaged myocardium where it was engrafted successfully. [3] These engrafted MSCs dramatically reduced the extent of necrotic myocardium and promote the regeneration of new, contractile myocardium along the subendocardial surface of the myocardial infarction.

Karantalis et al demonstrated that the intramyocardial injection of MSCs in patients undergoing CABG reduced scar size and improved tissue perfusion as well as regional function predominantly at the site of injection. [4] These findings are consistent with other studies of cell-based therapy in the setting of cardiac surgery, in which there was an increases in left ventricular ejection fraction and decrease of scar tissue.[5]

Cardiac stem and progenitor cells

Cardiac stem cells are cells which are residing within the heart in a limited number. They give rise to cardiac progenitor cells which migrate to the site of injury when a need for repair arises. But these cells will get depleted during large infarction occurring to the heart. Beltrami et al conducted the landmark study on an adult rat, discovering the presence of self-renewing c-Kit$^+$ cells in the adult heart, able to differentiate into cardiomyocytes, endothelial cells and smooth muscle cells and to support the regeneration of injured heart tissue. [6] Oskouei BN et al study compared the differentiation potential of cardiac stem cells with that of bone marrow derived mesenchymal stem cells.[7] The major finding of that particular study was that, human fetal heart-derived c-kit$^+$ cardiac stem cells attenuate cardiac remodeling, decrease infarct size, improve left ventricular function, and differentiate into blood vessels and myocardium

with greater potency than bone marrow-derived MSCs. Furthermore, a systemic analysis by Zwetsloot PP et al which include 80 preclinical studies revealed significant improvement of ejection fraction in preclinical animal models of myocardial infarction compared with placebo.

In 2011, the phase 1 clinical trial (SCIPIO) was conducted and its data revealed that the intracoronary infusion of autologous cardiac stem cells was effective in improving left ventricular systolic function and reducing infarct size in patients with heart failure after myocardial infarction. [9] However this particular article was retracted later. Another phase 1 clinical trial (CADUCEUS) showed reduction in scar mass and no patients died. But there was no changes in end-diastolic volume, end-systolic volume, and left ventricular ejection fraction between the patient and control group. [10] Ishigami et al conducted the phase 2 of clinical trials (PERSEUS) in 2017, which showed the improvement of ventricular function as well as growth in cardiosphere derived cells treated patients. The study also reports improved heart failure status, somatic growth and quality of life in patients. [12] So, even though phase 2 PERSEUS trial reported a much better result than the CADUCEUS trial.

Embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs)

Embryonic stem cells are stem cells which are derived from the inner cell mass of the blastocyst and they can differentiate into all three of the germ layers (endoderm, ectoderm and mesoderm). Induced pluripotent stem cells are the type of stem cells which can be derived from adult cells.In 2006, the land mark study was conducted by Takahashi and Yamanaka, reported the generation of pluripotent stem cells from mouse fibroblasts tissue.[13] 1 year later, they generated human iPSCs from human fibroblasts. [14] Both embryonic stem cells and induced pluripotent stem cells have shown promising results in animal models. Kawamura M et al used.

hiPS-CM-sheet transplantation technique in order to transfer iPSCs to the infarcted myocardial region in a porcine model. [15] The hiPS- CM sheet was able to produce improved cardiac performance, angiogenesis, and an attenuated left ventricular remodelling.Chong JJ et al study was able to produce human ESC-derived cardiomyocytes in macaques. [17] More than one billion ESCs were delivered via intramyocardial route to generate extensive remuscalarization of infarcted heart. Promising preclinical studies of ESCs lead to the initiation of phase 1 clinical trial in 2017 (ESCORT). [18]6 ischaemic heart failure patients

who were included in the ESCORT trial showed improved left ventricular ejection fraction and only one patient died early in the trial due to cell unrelated comorbidities. Despite promising results, both ESCs and iPSCs are associated with teratoma formation.[19, 20]Furthermore, genomic instabilities has been reported in iPSC lines which are resulting from pre-existing variation on the parent cell.[21]

PARKINSON'S DISEASE

Parkinsonism is a nuerodegenerative disease characterized by the deficiency of dopamine. It mainly affects the basal ganglia of the central nervous system, causing tremor, rigidity, bradykinesia, gait disturbances and postural instability. Since ageing is a risk factor associated with Parkinson's, prevalence of Parkinson's disease is expected to increase in the coming decades. Till date, none of the pharmacological as well as surgical interventions associated with the disease, can completely cure the disease. This is because of the lack of treatment strategies that can actually bring back the degenerating dopaminergic terminals. So, stem cell therapy possesses the potential to provide better therapeutic results as they have the ability to differentiate as well as self renew.

Human fetal ventral mesencephalon (FVM)

FVM tissue obtained from aborted fetuses were the most prominent source of dopaminergic cell source in the 1980s and 1990s. Following promising preclinical studies, first clinical trial was conducted by OlleLindvall et al.[22] But it showed only modest clinical improvements for the 2 patients involved. Later studies with higher patient population showed significantly better results. [23, 24]Freeman TB et al study involved 4 Parkinson's patients had fetal nigral transplantations. Grafts were bilaterally implanted into the post commissural putamen using 3 to 4 donors per side with a gestational age of 6 1/2 to 9 weeks post conception. All of the patients involved experienced clinical benefits.[24] Another study by Brundin P et al had bilateral human embryonic mesencephalic tissue transplantation in 5 Parkinson's patients. All of the patients experienced symptomatic relief and had proper graft survival. One key feature of this particular study was the usage of the lipid peroxidation inhibitor tirilazadmesylate which was used to increase graft survival rate. [23]

Embryonic stem cells (ESCs)

ESCs treated animal models have shown improvements in Parkinson's disease. [25]M. Acquarone et al study used mitomycin treated ESCs on a mouse model and produced significant improvement in motor function and reduced akinesia without tumor formation.[25] Despite behavioral recovery after transplantation of ESCs-derived neural cells in animal models, little is known about the mechanisms underlying graft function in this study.[25]Another important discovery associated with the embryonic stem cells is regarding the ESC derived nueral cell grafts. A retrospective study by Kirkeby Aet al analysed 500 grafts to identify factors that determined a successful ESC graft outcome.[26] It was found that the grafts containing a high content of tyrosine hydroxilase-positive cells were seen in those grafts that were enriched for neural progenitor cells expressing markers found in the caudal midbrain. Further investigations needs to be done to reach conclusive evidence regarding the potential of ESCs.

Nueral stem cells (NSCs)

Nueral stem cells are cells which are capable of differentiating into group of nueral sub cell types such as neurons, astrocytes and oligodendrocytes. One of the major advantages of the NSCs is that, the preliminary studies revealed that it can differentiate into dopaminergic neurons, make the host microenvironment optimal for survival of grafts and can induce behavioural recovery.[27, 28]One major study on nueral stem cells was done by X. Deng et al in 2013.[29] In that particular study, glial-derived neurotrophic factor (GDNF) was co transplanted along with NSCs and fetal dopaminergic neurons improved the graft survival and promote the differentiation of NSCs into dopaminergic neurons at the transplantation site.[29] They obtained a much higher differentiation rate compared to other studies. [30] Glial-derived neurotrophic factor is a protein that is encoded by the GDNF gene. It is a prominent protein which is involved in promoting the differentiation of the dopaminergic neurons. The X. Deng et al study proposed that, the promising results that they got was because of the GDNF gene overexpression and its cooperative interactions with the NSCs and dopaminergic neurons. Recently, a phase I study of transplantation of NSCs for PD patients was reported from Turkey. [31]Lenglige et al study involved 21 patients who had NSC transplantations from ESCs improved motor functions without any significant adverse effects.

CONCLUSION

The current studies of stem cell types associated with cardiovascular and Parkinson's disease reveals that, there is still a large scope for research remaining.Among cardiovascular stem cell types, cardiac stem and progenitor cells were the ones which showed promising results as they showed significant clinical improvements in phase 2 of the clinical trials. Both iPSCs and ESCs have been associated with teratoma formation and studies associated with mesenchymal stem cells hasn't been done on a larger scale. In the case of stem cell types used for Parkinson's disease, no studies have been done on a larger scale. Among the cell types, from these preliminary studies, NSCs are the ones which is showing desirable results as the survival rate of their grafts are high and differentiation rate was much more compared to other studies. Another advantage of the NSCs were its ability to make the host environment optimal for host survival. However, none of these studies provide conclusive evidence. So, all of these stem cell types reveals a need of better understanding of molecular mechanisms and further research strategies need to be initiated to completely utilise these cells achieve the desired therapeutic results.

REFERENCES

1. Orlic D, Kajstura J, Chimenti S, Jakoniuk I, Anderson SM, Li B, Pickel J, McKay R, Nadal-Ginard B, Bodine DM, Leri A, Anversa P. Bone marrow cells regenerate infarcted myocardium.**Nature**. 2001; *410*:701–705. doi: 10.1038/35070587.

2. Kudo M, Wang Y, Wani MA, Xu M, Ayub A, Ashraf M. Implantation of bone marrow stem cells reduces the infarction and fibrosis in ischemic mouse heart.JMol Cell Cardiol. 2003; *35*:1113–1119.

3. Amado LC, Saliaris AP, Schuleri KH, St John M, Xie JS, Cattaneo S, Durand DJ, Fitton T, Kuang JQ, Stewart G, Lehrke S, Baumgartner WW, Martin BJ, Heldman AW, Hare JM. Cardiac repair with intramyocardial injection of allogeneic mesenchymal stem cells after myocardial infarction.**ProcNatl** AcadSci USA. 2005; *102*:11474–11479. doi: 10.1073/pnas.0504388102

4. Karantalis V, DiFede DL, Gerstenblith G, Pham S, Symes J, Zambrano JP, Fishman J, Pattany P, McNiece I, Conte J, Schulman S, Wu K, Shah A, Breton E, Davis-Sproul J, Schwarz R, Feigenbaum G, Mushtaq M, Suncion VY, Lardo AC, et al.: Autologous mesenchymal stem cells produce concordant improvements in regional function, tissue perfusion, and fibrotic burden when administered to patients undergoing coronary artery bypass grafting: The Prospective Randomized Study of Mesenchymal Stem Cell Therapy in Patients Undergoing Cardiac Surgery (PROMETHEUS) trial. Circ Res 2014; 114: 1302–1310.

5. Patel AN, Geffner L, Vina RF, Saslavsky J, Urschel HC, Kormos R, Benetti F. Surgical treatment for congestive heart failure with autologous adult stem cell transplantation: a prospective randomized study. **J** Thorac Cardiovasc Surg. 2005; *130*:1631–1638.

6. Beltrami AP, Barlucchi L, Torella D, Baker M, Limana F, Chimenti S, Kasahara H, Rota M, Musso E, Urbanek K, Leri A, Kajstura J, Nadal-Ginard B, Anversa P: Adult cardiac stem cells are multipotent and support myocardial regeneration. Cell 2003; 114: 763–776.

7. Oskouei BN, Lamirault G, Joseph C, Treuer AV, Landa S, Da Silva J, Hatzistergos K, Dauer M, Balkan W, McNiece I, Hare JM. Increased potency of cardiac stem cells compared with bone marrow mesenchymal stem cells in cardiac repair. Stem Cells Transl Med. 2012; *1*:116–124. doi: 10.5966/sctm.2011-0015

8. Zwetsloot PP, Vegh AMD, Jansen Of Lorkeers SJ, van Hout GPJ, Currie GL, Sena ES, Gremmels H, Buikema JW, Goumans MJ, Macleod MR, Doevendans PA, Chamuleau SAJ, Sluijter JPG: Cardiac Stem Cell Treatment in Myocardial Infarction: A Systematic Review and Meta-Analysis of Preclinical Studies. Circ Res 2016; 118: 1223–1232.
9. Bolli R, Chugh AR, D'Amario D, Loughran JH, Stoddard MF, Ikram S, Beache GM, Wagner SG, Leri A, Hosoda T, Sanada F, Elmore JB, Goichberg P, Cappetta D, Solankhi NK, Fahsah I, Rokosh DG, Slaughter MS, Kajstura J, Anversa P: Cardiac stem cells in patients with ischaemic cardiomyopathy (SCIPIO): Initial results of a randomised phase 1 trial. The Lancet 2011; 378: 1847–1857.
10. Makkar RR, Smith RR, Cheng K, Malliaras K, Thomson LEJ, Berman D, Czer LSC, Marbán L, Mendizabal A, Johnston PV, Russell SD, Schuleri KH, Lardo AC, Gerstenblith G, Marbán E: Intracoronary cardiosphere derived cells for heart regeneration after myocardial infarction (CADUCEUS): A prospective, randomised phase 1 trial. The Lancet 2012; 379: 895–904.
11. Makkar RR, Smith RR, Cheng K, Malliaras K, Thomson LEJ, Berman D, Czer LSC, Marbán L, Mendizabal A, Johnston PV, Russell SD, Schuleri KH, Lardo AC, Gerstenblith G, Marbán E: Intracoronary cardiosphere derived cells for heart regeneration after myocardial infarction (CADUCEUS): A prospective, randomised phase 1 trial. The Lancet 2012; 379: 895–904
12. Ishigami S, Ohtsuki S, Eitoku T, Ousaka D, Kondo M, Kurita Y, Hirai K, Fukushima Y, Baba K, Goto T, Horio N, Kobayashi J, Kuroko Y, Kotani Y, Arai S, Iwasaki T, Sato S, Kasahara S, Sano S, Oh H: Intracoronary Cardiac Progenitor Cells in Single Ventricle Physiology: The PERSEUS (Cardiac Progenitor Cell Infusion to Treat Univentricular Heart Disease) Randomized Phase 2 Trial. Circ Res 2017; 120: 1162–1173.
13. Takahashi K, Yamanaka S: Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 2006; 126: 663–676.
14. Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, Yamanaka S: Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell 2007; 131: 861–872.
15. Kawamura M, Miyagawa S, Miki K, Saito A, Fukushima S, Higuchi T, Kawamura T, Kuratani T, Daimon T, Shimizu T, Okano T, Sawa Y. Feasibility, safety, and therapeutic efficacy of human induced pluripotent stem cell-derived cardiomyocyte sheets in a porcine ischemic cardiomyopathy model.**Circulation**. 2012; *126*:S29–S37. doi: 10.1161/CIRCULATIONAHA.111.084343.
16. Chong JJ, Yang X, Don CW, et al. Human embryonic-stem-cell-derived cardiomyocytes regenerate non-human primate hearts. **Nature**. 2014; *510*:273–277. doi: 10.1038/nature13233.
17. Chong JJ, Yang X, Don CW, et al. Human embryonic-stem-cell-derived cardiomyocytes regenerate non-human primate hearts. **Nature**. 2014; *510*:273–277. doi: 10.1038/nature13233.
18. Philippe Menasché, ValérieVanneaux, Albert Hagège, Bernard Cholley, Gerard Tachdjian, Lucie Tosca, Jean-HuguesTrouvin, Jean-RochFabreguettes, Hélène Blons, Reem Al-Daccak, OnnikAgbulut, Eric Tartour, Michel Desnos, and JérômeLarghero. Human Embryonic Stem Cell-derived Cardiac Progenitors for Heart Failure. One-year Results of the ESCORT Trial. Circulation. 2017;136: A14798.
19. Kooreman NG, Wu JC. Tumorigenicity of pluripotent stem cells: biological insights from molecular imaging. J R Soc Interface. 2010;7(Suppl 6): S753–63.
20. Nussbaum J, Minami E, Laflamme MA, Virag JAI, Ware CB, Masino A, Muskheli V, Pabon L, Reinecke H, Murry CE: Transplantation of undifferentiated murine embryonic stem cells in the heart: teratoma formation and immune response. FASEB J 2007; 21: 1345–1357.
21. Yoshihara M, Hayashizaki Y, Murakawa Y: Genomic Instability of iPSCs: Challenges Towards Their Clinical Applications. Stem Cell Rev 2016.
22. Lindvall O, Rehncrona S, Brundin P, Gustavii B, Astedt B, Widner H, et al. Human fetal dopamine neurons grafted into the striatum in two patients with severe Parkinson's disease. A detailed account of methodology and a 6-month follow-up. Arch Neurol. 1989;46(6):615–31.
23. Brundin P, Pogarell O, Hagell P, Piccini P, Widner H, Schrag A, et al. Bilateral caudate and putamen grafts of embryonic mesencephalic tissue treated with lazaroids in Parkinson's disease. Brain. 2000; 123(Pt 7):1380–90.
24. Freeman TB, Olanow CW, Hauser RA, Nauert GM, Smith DA, Borlongan CV, et al. Bilateral fetalnigral transplantation into the postcommissural putamen in Parkinson's disease. Ann Neurol. 1995;38(3):379–88.

25. M. Acquarone, T. M. de Melo, F. Meireles et al., “Mitomycin-treated undifferentiated embryonic stem cells as a safe and effective therapeutic strategy in a mouse model of Parkinson's disease,” Frontiers in Cellular Neuroscience, vol. 9, article 97, 2015.
26. Kirkeby A, Nolbrant S, Tiklova K, Heuer A, Kee N, Cardoso T, et al. Predictive markers guide differentiation to improve graft outcome in clinical translation of hESC-Based therapy for Parkinson’s disease. Cell Stem Cell. 2017;20(1):135–48.
27. J. N. Le Grand, L. Gonzalez-Cano, M. A. Pavlou, and J. C. Schwamborn, “Neural stem cells in Parkinson's disease: a role for neurogenesis defects in onset and progression,” Cellular and Molecular Life Sciences, vol. 72, no. 4, pp. 773–797, 2015.
28. Moukhles H, Amalric M, Nieoullon A, Daszuta A (1994) Behavioural recovery of rats grafted with dopamine cells after partial striatal dopaminergic depletion in a conditioned reaction-time task. Neuroscience 63(1): 73–84.
29. X. Deng, Y. Liang, H. Lu et al., “Co-transplantation of GDNF-overexpressing neural stem cells and fetal dopaminergic neurons mitigates motorsymptoms in a rat model of Parkinson’s disease,” PLoS ONE, vol. 8, no. 12, Article ID e80880, 2013.
30. Jin G, Tan X, Tian M, Qin J, Zhu H, et al. (2005) The controlled differentiation of human neural stem cells into TH-immunoreactive (ir) neurons in vitro. NeurosciLett 386(2): 105–110.
31. Lige L, Zengmin T. Transplantation of neural precursor cells in the treatment of Parkinson disease: an efficacy and safety analysis. Turk Neurosurg. 2016;26(3):378–383.