Perspective of the Stem Cell therapy in Cardiovascular Disease

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Abstract: Stem cells are population of immature tissue precursor cells that is capable of self-renewal and provision of replacement cells for many tissues. The regenerative cardiovascular medicine to use stem cell therapy that is a novel approach is feasible, safe and potentially beneficial in patient with cardiovascular disease. Recent clinical results have shown the feasibility of adult autologous cell therapy in acute myocardial infarction in humans. Stem cell therapy represents a fascinating new approach for the management of heart diseases. The conclusion of the research and clinical trial on the stem cell transplantation in different heart disease have been obtained exciting results of treatment, the results bode well for the myocardial regeneration by using human stem cells in the future.
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1. Introduction

In 1968, doctors performed the first successful bone marrow transplant. Subsequent to 1968, there was a new scientific filed- Regenerative cardiovascular medicine producing in the frontline of 21st-century health care. The regenerative cardiovascular medicine to use stem cell therapy that is a novel approach is feasible, safe and potentially beneficial in patient with cardiovascular disease (this article focus the heart disease). However, the more 40 years developing history of the stem cell on the research and clinical trial have been past, why is there not a complete procedure to be fit to use stem cell to treat cardiovascular? There are two reasons below that affect the Stem cell therapy in cardiovascular disease: The reason one is the stem cell research that has been highly controversial due to the ethical issues concerned with the culture and use of stem cells derived from human embryos; But aside from the ethical issues are not the subject of this article, the another reason that need a good communication of the research, clinical and patient with the basic theory on the stem cell therapy.

2. What are stem cells?

Stem cells are population of immature tissue precursor cells that is capable of self-renewal and provision of replacement cells for many tissues. In the other words, stem cells are unspecialized cells that have two defining properties: the ability to differentiate into other cells and the ability to self-regenerate.

The ability to differentiate is the potential to develop into other cell types. A totipotent stem cell (e.g. fertilized egg) can develop into all cell types including the embryonic membranes. A pleuripotent stem cell can develop into cells from all three germinal layers (e.g cells from the inner cell mass). Other cells can be oligopotent, bipotent or unipotent depending on their ability to develop into few, two or one other cell types.

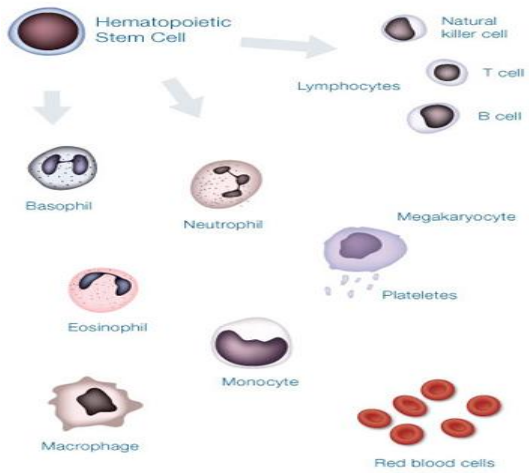

Fig. 1 Differentiation of Stem Cell

Self-regeneration is the ability of stem cells to divide and produce more stem cells. During early development, the cell division is symmetrical i.e. each cell divides to gives rise to daughter cells each with the same potential. Later in development, the cell divides asymmetrically with one of the daughter cells produced also a stem cell and the other a more differentiated cell (Fig. 2).

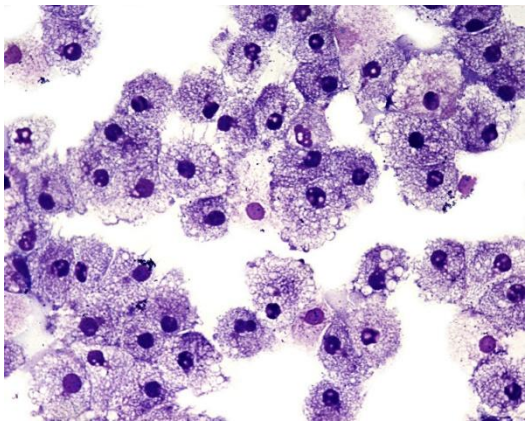

Fig. 2 Cells Self-Regenerative

3. What is the Regenerative Cardiovascular Medicine?

Like what the described above, the Self-regenerative and differentiate are the two major aspects of Stem cells that are different another somatic cells. The research and developing of the Stem cell created a novel medical field that was called Regenerative Medicine. The concept of Regenerative Cardiovascular Medicine is using the body's own stem cells and growth factors to repair tissues which might become a reality as new basic science works and initial clinical experiences have "teamed-up" in an effort to develop alternative therapeutic strategies to treat the diseased myocardium.

The Regenerative Medicine-Regenerative Cardiovascular Medicine births brought a great revolution in the medicine history. Because the Regenerative Cardiovascular births, many patients suffered from cardiovascular disease were away from the suffering to have the normal life, and may patients also were away from dead to obtain relive. And Because the Regenerative Cardiovascular Medicine births, there are some cardiovascular disease are ongoing to be a goodbye plan and have a good trip of no cardiovascular disease in human life.

4. Do the Cardiovascular Disease is cured by Stem Cells transplantation?

The Cardiovascular Disease have been recognized a serious disease on human health body since having the human medicine. But, there were many cardiovascular disease patients to be dead from the not enough knowledge and treatment approach. The modern molecular biologic technical come out after another that reveal some etiology and mechanism of Cardiovascular Disease. So,the cardiovascular disease treatment have been occurring a bigger developing, the doctors and research scientist have been created many approach to cured some patients suffered from the cardiovascular disease with the etiology of mechanism and dynamic reasons. But aside from the cardiovascular disease occurred by mechanism and dynamic reasons, there are many cardiovascular disease with the myocardium tissue, cell and blood vessel damaged by the reasons of ischemic, myocardial infarction and etc, which couldn't be cured by removing the mechanism and dynamic reason, and can't also cured by any pharmaceuticals.

It would be a good approach for treating the heart disease by studying the strategy and tactics in the stem cell transplantation.

5. The Cardiovascular Disease being away from Human should be the Results of current Research and the Clinical Practice

5.1. The heart angiogenesis related with the stem cell transplantation

Endothelial cells alone can initiate the formation and sprouting of endothelium-lined channels, namely angiogenesis, in response to a physiological or pathological stimulus. Peri-endothelial cells are required for vascular maturation. Recruitment of smooth muscle cells provides these vessels with essential viscoelastic and vasomotor properties and enables accommodating the changing needs in tissue perfusion. This later stage is called arteriogenesis and has a major role in collateral growth.

Endothelial progenitor cells could be isolated from peripheral blood and/or bone marrow and showed incorporation into sites of physiological and pathological neovascularization in vivo after either systemic injection or using direct intramyocardial transplantation.

In contrast to differentiated endothelial cells, transplantation of progenitor cells successfully enhanced vascular development by in situ differentiation and proliferation within ischemic organs.8 On the basis of these findings, the beneficial property of endothelial progenitor cells is attractive for angiogenic cellular interventions and as cell-mediated vehicles for gene therapy applications targeting regeneration of ischemic tissue and of failing hearts.

5.2. Heart Muscle related Stem Cell Differentiation and Self-regenerative

The transplant cells of primarily noncardiac origin, such as human bone marrow-derived mononuclear cells containing human stem cells that is the principal aim on the heart disease curing. These cells may operate as a precursor of heart muscle tissue and of coronary blood vessel cells.

The Human bone marrow contains hematopoietic (1% to 2%) and mesenchymal stem cells (<0.05%).

Both types of stem cells may contribute to heart muscle repair. Hematopoietic stem cells are progenitor cells for many types of cells, eg, endothelial cells, which may also differentiate to heart muscle cells.

Mesenchymal stem cells are progenitor cells for types of cells such as heart muscle cells, as well as for a variety of cells of noncardiac concern. Recent results in mouse experiments suggest the potency of extracardiac progenitor cells for transdifferentiation into new cardiomyocytes after acute experimental myocardial infarction.A experimental provided that the bone marrow cells cultured with 5-azacytidine differentiated into cardiac-likeheart muscle cells, as well as for a variety of cells of noncardiac concern.

Thus, there is growing evidence for a repair function of extracardiac cells, eg, from bone marrow in the case of cardiac lesion and the necessity of myocardial healing, although these results are not unanimously approved.

5.3. Milieu-Dependent Differentiation and Enhanced Environment after Stem cell transplantation

5.3.1. The fate of Stem Cell is guided by the engraft environment to become the aim tissue

Normal growth and ultimate stem cell fate depend on engraftment in an appropriate "niche." Studies from several species demonstrate that bone marrow-derived stem cells are stem cells for various mesenchymal tissues. The cells are therefore not simply stromal precursors, but precursors of peripheral tissues, such as heart muscle. Nonetheless, the mechanisms by which the local milieu influences stem cell differentiation are as yet undetermined. Thus, it seems that the fate of bone marrow stem cells is determined by the environment in which they engraft rather than by an intrinsically programmed fate.

5.3.2.The engraft tissue functional activity enhance the transdifferentiation of Stem Cell transplantation

It is the final poupose for the stem cell transplantation to promote the transplanted stem cells differentiating to cardiomyocytes. Therefore, enhancement of functional activity of the specific organ's niche for heart muscle, eg, by positive inotropic (pharmacologic augmentation of contractility) or by positive chronotropic stimuli (heart rate increase by exercise), may promote and intensify the transdifferentiation of bone marrow-derived stem cells to the cardiomyocyte phenotype. After an injury, eg, myocardial infarction, or a cellular damage, eg, in severe pressure or volume overload of the heart, specific factors, including cytokines, stem cell factor, and various growth factors, that stimulate cell replication and substitution in the injured tissue are released by the surrounding cells. In addition, transplanted stem cells, differentiating to cardiomyocytes, become indistinguishable over time from the surroundin cardiomyocytes, and they begin to express the contractile proteins specific for striated heart muscle, including desmin, a-myosin, heavy chain, a-actinin, and phospholamban at levels that are the same as in the host cardiomyocytes. This transdifferentiation process is more pronounced in injured tissue than in healthy organs and may be intensified when the heart as the recipient organ contributes to its enhanced environment by high chronotropic and inotropic activity.

Thus, regionally large concentrations of stem cells and increased mechanical activity of the recipient heart muscle may provide a favorable environment for successful engraftment of stem cells after cardiac injury.

5.4. The targeted and regional administration and stem cells transplantation should be preferred that are the first of success

In regional heart muscle disease, as in myocardial infarction, selective cell delivery by intracoronary catheterization techniques leads to an effective accumulation and concentration of cells within the infarcted zone. This can be realized in humans with bone marrow-derived cells.With intracoronary administration, all cells must pass the infarct and peri-infarct tissue during the immediate first passage. Accordingly, with the intracoronary procedure, the infarct tissue can be enriched with the maximum available number of cells at all times. Further developments of catheterization systems for various clinical studies are needed.

5.5. Stem Cells transplantation for heart disease therapy: A Joint Clinical and Experimental Approach

The Cardiac lesions may be multifactorial and include myocardial infarction, myocarditis, cardiomyopathy or cardiac remodeling due to severe pressure, and volume overload. It is uncertain whether the same therapeutic approach and the same type of cells will be suitable for all of these different diseases. However, organ repair by stem cells represents a general biological mechanism. Thus, it will be one of the future tasks to find the most practical and specific way of evolving and targeting the healing potency of stem cells for selected cardiovascular diseases.

5.6. Detection of Transplanted Stem Cell

The transplanted cell or cell population is a single unit in a complex biological network of other cells. An important clinical problem will be the

identification and localization of transplanted autologous stem cells within the injured area of the heart. Therefore, for both localization and fate mapping of stem cells within the target organ, specific cell markers are desirable.

How to detect the if the stem cell success or not? It will be lot work to be doing in the future.

6. The source of the Stem Cells is the critical in Regenerative Cardiovascular Medicine

6.1. Embryonic stem cells

The number of stem cells present in an adult is far fewer than the number seen in early development because most of the stem cells have differentiated and multiplied. This makes it extremely difficult to isolate stem cells from an adult organism, which is why scientists hope to use embryonic stem cells for therapy because embryonic stem cells are much easier to obtain. But the ethical problems have been hard point for a long time

6.2. Adult Stem Cells

Ethical problems for adult autologous stem cells do not exist, and although much experimental work remains to be done, their clinical relevance and therapeutic benefit in heart disease have recently been seen well.

6.3. Cord blood stem cells

Cord blood, from the umbilical cord, was believed to be an alternate source of hematopoietic stem cells; however, it is impossible to obtain sufficient numbers of stem cells from most cord blood collections to engraft an adult of average weight. Development continues on techniques to increase the number of these cells ex vivo. Cord blood contains both hematopoietic and non-hematopoietic stem cells.

7. Conclusion

Cardiovascular disease is a leading cause of death worldwide killing 17 million people each year, especially due to heart attack and stroke. In the United States, heart disease is the number one cause of death. The high rate of mortality associated with heart diseases is the inability to repair damaged tissue due to the full differentiation of heart tissue. Interruption of blood supply to the tissue causes infarction of the myocardium and death of myocardiocytes.

Recent clinical results have shown the feasibility of adult autologous cell therapy in acute myocardial infarction in humans. Stem cell therapy represents a fascinating new approach for the management of heart diseases. However, many unresolved questions about experimental and clinical cardiology are still open for future research, especially many basic problems concerning, among others. With regard to the clinical practicability, ethical problems, and hazards of immunogenity, actual and future research will focus preferably on adult stem cells, whereas research on embryonic stem cells may emerge presumably into comparable clinical relevance in several years.

The conclusion of the research and clinical trial on the stem cell transplantation in different heart disease have been obtained exciting results of treatment, the results bode well for the myocardial regeneration by using human stem cells in the future. The cardiovascular disease might be cured by Stem Cell transplantation for a not long time.

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References

1. Choudry FA, Mathur A.: Stem cell therapy in cardiology. Regen Med. 2011 Nov;6 (6 Suppl): 17-23.
2. Bernal A, San Martín N, Fernández M, Covarello D, Molla F, Soldo A, Latini R, Cossu G, Gálvez BG. L-selectin and SDF-1 enhance the migration of mouse and human cardiac mesoangioblasts. Cell Death Differ. 2012 Feb;19(2):345-55. doi: 10.1038/cdd.2011.110. Epub 2011 Aug 26
3. Vassalli G, Moccetti T.: Cardiac repair with allogeneic mesenchymal stem cells after myocardial infarction. Swiss Med Wkly. 2011 May 23; 141: w13209. doi: 10.4414/smw.2011.13209.
4. Trounson A, Thakar RG, Lomax G, Gibbons D. Clinical trials for stem cell therapies. BMC Med. 2011 May 10;9:52.
5. Sturzu AC, Wu SM. Developmental and regenerative biology of multipotent cardiovascular progenitor cells. Circ Res. 2011 Feb 4;108(3):353-64.
6. Van Linthout S, Savvatis K, Miteva K, Peng J, Ringe J, Warstat K, Schmidt-Lucke C, Sittinger M, Schultheiss HP, Tschöpe C.: Mesenchymal stem cells improve murine acute coxsackievirus B3-induced myocarditis. Eur Heart J. 2011 Sep;32(17):2168-78. Epub 2010 Dec 22.
7. Dib N, Khawaja H, Varner S, McCarthy M, Campbell A: Cell therapy for cardiovascular disease: a comparison of methods of delivery. J Cardiovasc Transl Res. 2011 Apr;4(2):177-81. Epub 2010 Dec 23.

8. Hosoda T.: C-kit-positive cardiac stem cells and myocardial regeneration.. Am J Cardiovasc Dis. 2012;2(1):58-67. Epub 2011 Dec 15.
9. Mackie AR, Losordo DW.: CD34-positive stem cells: in the treatment of heart and vascular disease in human beings. Tex Heart Inst J. 2011;38(5):474-85.
10. Aggarwal R, Lu J, Pompili VJ, Das H: Hematopoietic stem cells: transcriptional regulation, ex vivo expansion and clinical application**.** Curr Mol Med. 2012 Jan; 12(1):34-49.
11. Carvalho G, Rassi S, Bastos JM, Câmara SS.: Asymptomatic coronary artery disease in chagasic patients with heart failure: prevalence and risk factors. Arq Bras Cardiol. 2011 Nov; 97(5):408-12. Epub 2011 Oct 21.
12. Kehat I, Kenyagin-Karsenti D, Snir M, et al. Human embryonic stem cells can differentiate into myocytes with structural and functional properties of cardiomyocytes. J Clin Invest. 2001; 108: 407–414.
13. Epstein SE, Fuchs S, Zhou YF, et al. Therapeutic interventions for enhancing collateral development by administration of growth factors: basic principles, early results and potential hazards. Cardiovasc Res. 2001;49: 532–542.
14. George B.: Regulations and guidelines governing stem cell based products: Clinical considerations. Perspect Clin Res. 2011 Jul;2(3):94-9.
15, Wong RS.: Mesenchymal stem cells: angels or demons? J Biomed Biotechnol. 2011; 2011:459510. Epub 2011 Jul 24.
16. Mingliang R, Bo Z, Zhengguo W. Stem cells for cardiac repair: status, mechanisms, and new strategies. Stem Cells Int. 2011;2011:310928. Epub 2011 Jun 15.
17. Park JH, Yoon JY, Ko SM, Jin SA, Kim JH, Cho CH, Kim JM, Lee JH, Choi SW, Seong IW, Jeong JO.: Endothelial progenitor cell transplantation decreases lymphangiogenesis and adverse myocardial remodeling in a mouse model of acute myocardial infarction. Exp Mol Med. 2011 Aug 31;43(8):479-85.
18. Vassalli G, Moccetti T.: Cardiac repair with allogeneic mesenchymal stem cells after myocardial infarction. Swiss Med Wkly. 2011 May 23; 141: w13209. doi: 10.4414/smw.2011.13209.
19. Zhang Y, Wang D, Chen M, Yang B, Zhang F, Cao K.: Intramyocardial transplantation of undifferentiated rat induced pluripotent stem cells causes tumorigenesis in the heart. PLoS One. 2011 Apr 28;6(4):e19012.
20. Jezierska-Woźniak K, Mystkowska D, Tutas A, Jurkowski MK.: Stem cells as therapy for cardiac disease - a review. Folia Histochem Cytobiol. 2011; 49(1):13-25.

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