How to Heal a Broken Heart: Improving the effectiveness of Stem cell Based Cardiovascular Regeneration

Akinwumi Akinkunmi¹, Professor Christian Bach²

Abstract - The aim of this study is to analyze the factors which drive the capabilities of stem cell therapy for cardiovascular regeneration. Using this analysis a more effective and non invasive approach for stem cell therapy is proposed. A model was constructed through analysis of scientific journals in order to create a framework for understanding the relationship between the independent and dependent variables. Furthermore, a hypothesis was derived using this model consisting of four independent factors and one dependent factor. It is difficult to understand the full implication of the study because of ethical issues, and FDA regulations involved with human clinical tests. If this procedure can be implemented in a clinical setting it has the capability to save millions of lives. Due to the high incidence of individuals around the world suffering from cardiovascular disease, this study is another step towards curing the number one killer around the world.

Keywords: Hyperhomocysteinemia, Cardiac Stem Cell, Hydrogel

INTRODUCTION

An exponential growth in the population of patients affected by mortal consequence of cardiovascular diseases have led to an increase in incidence to roughly 1 million patients seeking either bypass surgeries and angioplasty per year worldwide (MERIT-HF, 1999). As a result, these surgeries cause numerous damages to vascular networks, therefore alternatives measure must be discovered to repair theses vessels without applying invasive techniques [1]. This can be accomplished through tissue engineering.

Tissue engineering is the process of creating new functional cells in a damaged area through the use of stem cells, scaffolds and growth factors, but their usage is not required to be concurrent [2]. Therefore, the combination of these three factors will lead to regeneration and integration of functional tissues in the cardiovascular system [3] and [4].

The development of the utilization of stem cell therapy to repair myocardial damage is a field that is attracting much attention [5]. Many different types of stem cells that can differentiate into different cardiovascular lineage have been identified, and each type of stem cell has its advantages and disadvantages. There is experimentally backed evidence that stem cells function in a paracrine manner when transplanted after myocardial infarction, which stimulates cardiovascular regeneration through angiogenesis and vasculogenesis [6].

The resent discovery of endogenous cardiac stem cells is contributing to a better understanding of tissue regeneration within the cardiovascular system [6], [7]. Earlier studies indicate that cardiac stem cells have the capacity to differentiate into endothelial cells, smooth muscle cells and functional cardiomyocytes [8]. Furthermore, a population of cardiac stem cells and progenitor cells have been identified to be directly involved in myocardial regeneration by independent studies [9], [10], [8], [11], [12], [13], [14], [15], giving rise to the notion that exogenous cardiac stem cells will indeed undergo differentiation in a foreign human body [16], [17].

The benefit of cardiac stem cells is that they are highly likely to differentiate into a cardiovascular lineage, while stem cells from other organs such as bone marrow cells are not as committed. Therefore, they are better able to

¹ University of Bridgeport, 163-12 Sayres Ave Jamaica, NY 11433, Akinwumi2013@yahoo.com
² University of Bridgeport, 221 University Ave, Bridgeport, CT 06604, Cbach@bridgeport.edu
replace dead tissue after transplantation (Kajstura et al., 2010[7]. As a result of experiments using rat subjects with myocardial infarction, cardiac stem cells reduced the infarct size and improved cardiac performance [8]

However, a major issue has risen when applying regenerative cardiac stem cells to medicine for the treatment of coronary and peripheral artery disease; this issue is the difficulty of isolating and delivering specific exogenous stem cells to target myocardial repair and also stimulating recruitment of endogenous stem cells. Therefore, increase focus on biotechnology and pharmacological strategies have been adopted to combat these pressing issues. Combining the use of stem cells, biomaterials, and growth factors will improve stem cell implantation and endogenous regeneration of myocardial tissues [18], [2].

**RESEARCH METHOD**

As a research method scientific journals were obtained for the science direct database, which was made available through the University of Bridgeport subscription. With an understanding of the importance of establishing a dependent variable and an independent variable I used the model based method to establish a relationship between the two variables. Information was compiled from numerous journal articles in accordance with the guidelines postulated by LePine and Wilcox-King [19].

The journals were chosen on the basis of their ability to convey past research, current accomplishments and future opportunities in the field of Vascular tissue repair [19] p.507. In this research I combine literature reviews to examine the impact of different factors on the efficacy of vascular regeneration. The model developed here shows that there are different factors that are detrimental to the regeneration of vascular tissues while others stimulate.

Using the interpretive paradigm I present a detailed description of each factor and present their effect on vascular regeneration [20] p. 615. Therefore provide a comprehensive understanding of the advantages and detriment of each factor to the effectiveness of stem cell driven regeneration of the cardiovascular system.

![Factors That Influence The Effectiveness of stem cells](image-url)
Repairing Vascular tissue

Replacing lost cells with stem cells, which are cells that are yet to differentiate into a particular function, can repair vascular tissue. Stem cell driven regenerative medicine is an area of medicine that is firmly on the rise. Therefore in order to regulate this field “The Food and Drug Agency (FDA, USA) recently recommends that preclinical studies of cardiovascular regenerative medicine should include evidence of biological activity (e.g. proof-of-concept of effective neovascularisation and/or cardiomyogenesis), dose–response (e.g., effect of variation in cell number on the magnitude of cardiac repair and function) and durability of response (e.g., persistence of the therapeutic effect on late ventricular remodeling)” [21].

Considering that cardiovascular disease is considered to be the most lethal in the world, vascular tissue repair has seen much advancement in recent years. Previous postulations have now been amended, for example hearts were previously believed to be unable to regenerate, but the discovery of indigenous cardiac stem cells has rescinded this misconception. With a shift from solely research to advances in marketability of stem cell research after its progression to clinical trials it is clear that companies are beginning to realize the commercial profitability in the field of cardiovascular regeneration.

Hyperhomocysteinemia

Hyperhomocysteinemia (HHcy) is a medical condition caused by genetic mutation and nutritional deficiencies and characterized by a presence of high levels of homocysteine in the blood. Homocysteine is a metabolic by product of methionine a non-essential amino acid (Figure 1). The increase of homocysteine in the blood stream increases the possibility of endothelial injury. Although the mechanism of its effect on the homing of stem cells are yet unclear, it is considered to be an independent risk factor for coronary artery disease and it affects 5 to 7% of the human population.

Studies have shown that high levels of HHcy hinder the ability of endothelial progenitor cells to differentiate in vivo, as well as their capability to adhere and migrate to ischemic areas [22]. HHcy has also been shown to inhibit the ability of stem cell growth factors to recruit stem cells, therefore preventing the migration of stem cell for vascular repair.

Levels of homocysteine can be regulated by the increase or decrease of folic acid and vitamin B6 and B12. As a result, supplements of folic acid and vitamin B6 and B12 have been used to delay the occurrence of vascular disease in effected children [23].
Figure 1: This figure shows the homocysteine metabolic pathway of methionine. Methionine is converted into S-adenosylmethionine, which is then transformed into S-adenosylhomocystein and homocysteine. This homocysteine can now enter into one of two cycles the folic acid and vitamin B12 dependant cycle or the Vitamin B6 dependent pathway. Through these pathways the cysteine generated can be used in protein synthesis and glutathione production [24].

Growth Factor

Growth factors can either be a protein or a steroid hormone. There are many varieties of growth factors resulting in a common effect on the regeneration of the cardiovascular system. Growth factors act as a mediator and examples of growth factors are vascular endothelial growth factors (VEGF), basic fibroblast growth factor (bFGF), and insulin like growth factor (IGF).

Improvement of cell differentiation through the application of growth factors can be achieved through direct injection. For example, the direct injection of VEGF can be used to specifically regulate blood vessel during angiogenesis, this can be used to stimulate endothelial progenitor cell migration to the infarcted area [25], [26]. Stem cells such as bone marrow mononuclear cells have also been shown to synthesize and release VEGF and bFGF, therefore stimulating the multiplication and maturation of adjacent endothelial cells. The combination of stem cells and growth factors has the capacity to increase the potency of each, hence accelerates regeneration and improve function during angiogenesis. The capabilities of stem cells in the infarcted area are very minimal in the absence of growth factors, furthermore the ability of growth factor are optimized when functioning in the presence of other growth factors in-vivo. For example, the VEGF has the capability to induce bFGF and vice versa, while a neutralization of FGF inhibits VEGF induced angiogenesis. Therefore sequential delivery of growth factors is the most optimal approach to creating an environment for vascular myocytes to regenerate [27].

Biomaterials

Inefficiencies and high incidence of death of inserted stem cells into the vascular system has prompted an examination of injection techniques of stem cells, which have been deemed insufficient. This has led to the development of biomaterial that can assist in the delivery of such cells to the infarcted areas. Biomaterials can be used to promote revascularization, modulate inflammation of extracellular environment, and act as vehicles to focus cells in vascular tissue regeneration. As biomaterial engineers have concluded, the stem cell environment is vital to its survival, therefore biomaterials are made to mimic the extracellular matrix of the cardiac cells and texture of the vascular muscles [28], and there are many different types of biomaterials. One such biomaterial is hydrogels, and it has many advantages.

Hydrogels can be prepared using natural or synthetic hydrophilic and biodegradable polymers such as collagen, fibrin, alginate, and peptides [29]. Hydrogels are advantageous because the can easily be manipulated, which allows for greater control over stem cell differentiation by permitting the generation of a chemical gradient for cell guidance. Hydrogels are valued above scaffolds (another form of biomaterials) because they can form gels in-vivo after injection directly to the infarcted area.

Biomaterials are beneficial because they can create a three-dimensional tissue environment in-vivo. Furthermore, they can be used to control the inflammation in the infarcted area, allowing for easier migration of stem cells; also they can be used to guide the release of growth factors and cytokines to maximize the result of stem cell activities. Perhaps their best advantage is that they can easily be reproduced.

Age

Age is a factor that has a great impact on the ability of stem cells to perform their function in-vivo [30], and an understanding of its impact will help in determining the best regenerative approach in different age groups. A 2002 study [30] demonstrated that "young, but not old, bone marrow stem cells incorporated into neovasculature and restored cardiac angiogenic functions [31]. This is true for transplanted stem cells but even more detrimental to resident progenitor stem cells. The unfavorable effect is due to the influence age has on the extracellular matrix in the region of injury in addition to accumulation of oxidative damage, loss of replication ability, and most crucially telomere shortening. The association of telomere shortening with an arrest of cell cycle suggests that with age the ability of resident progenitor cells to replicate diminishes, because the phenotype of short telomeres will be passed down to the daughters during the cell cycle. This is a result of the natural aging process that promotes impairment of the regulatory mechanisms used to control cardiovascular repair, and may lead to cell apoptosis.
With increase in age there are fewer numbers of cardiac stem cells and cardiac progenitor cells, and an increase in cell cycle arrest due to damage to DNA that leads to fewer proliferations. Furthermore, age causes changes to the extracellular matrix of the infarcted area by inducing inflammation that reduces mobility, fibrosis, and oxidative stress. Consequently, this is a disadvantageous environment for the optimum functionality of the stem cells.

**Importance of Model**

When applying stem cell therapy to regenerate the cardiovascular system there are several factors to consider, this model presents such factors. Scientists are mystified by the minimal retention of stem cells after implantation and the low levels of differentiation during therapy. Therefore we hypothesize that addressing these factors before and during application of stem cells will improve the efficacy and retention of the cells.

**Conclusion**

In conclusion, regardless of the immense advancements that have occurred in the field of cardiovascular regeneration, vascular disease remains the leading cause of mortality in the world. As stem cell therapy is the best alternative to invasive surgeries it is important to understand the factors which affect the function of these cells in-vivo.

After analyzing these factors I conclude that the best treatment should account for these factors, therefore making the treatment more personalized. The benefits of these more personalized medicine is that stem cells will have a longer life span in-vivo because you can minimize immune response against the stem cell, consequently increasing the probability of differentiation. Hence, my argument supports the use of growth factors and biomaterials in to improve the effectiveness of stem cells drive therapy for vascular tissue regeneration.

**REFERENCES**