Cardiac Tissue Regeneration Methods: A Literature Review

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ABSTRACT: Individuals who experience severe trauma can often experience loss of tissue function and disability due to deficient cardiac muscle regeneration. The long-term goal of this work is to develop an advanced implantable system with defined physical and biochemical signals that supports muscle growth. Lack of proper vascularization is the main issue that the highlighted experiments are trying to incorporate [4]. **The objective of this ongoing project is to identify in vitro and in vivo methods that supports muscle growth and efficient vascularization.** Vascularization of the inactive cardiac tissue will promote regular organ function. Methods performed in the past incorporate both in vitro and in vivo strategies that use a variety of different approaches. Different culture conditions are currently being investigated to observe how physical and biochemical signals affect the production of muscle fibers and blood vessel formation. A challenge facing this type of tissue engineering is the construction of a scaffold that is biocompatible and can be safely implanted into a rat or human [4]. Improving vascularization methods can provide cardiac regeneration therapy for patients.

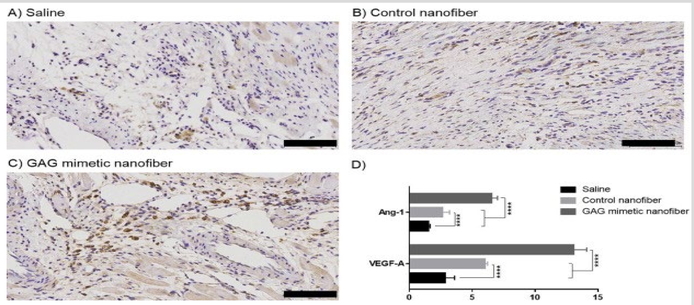
INTRODUCTION:

- Without proper vascular networks within the heart, transportation of blood and other nutrients to tissues in the body would not occur.
- After myocardial infarction (MI), the cardiac tissue has suffered damage to its own vascular network and must be repaired in order to return to normal function [4].
- A properly controlled cell environment that is equipped with a functional matrix can promote vascularization of cardiac tissue. These include biomaterial, non-scaffold cellular and hybrid methods [4].
- Tissue engineering is a promising field to further advance cardiovascular regeneration systems and methods. Cell viability and behavior must remain preserved when using any engineered method.

IN VITRO METHODS:

1. Protein scaffold

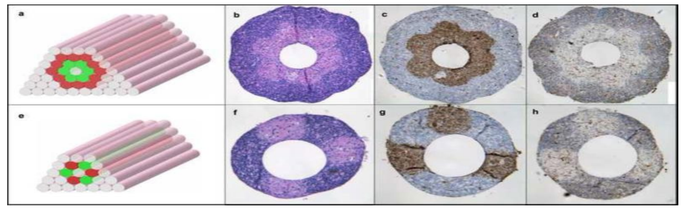
- GAG mimetic peptide nanofiber protein scaffold.
- The fibers were able to bind to the following growth factors: VEGF, hepatocyte growth factor (HGF) and fibroblast growth factor-2 (FGF-2).
- H9C2 cells were derived from embryonic rat ventricles.
- Viability of H9C2 cells cultured on GAG mimetic nanofibers for 24 hours and the GAG system was biocompatible with H9C2 cells.
- These nanofibers increased vasculature of VEGF-A and Ang1 [8].



1. Representative immunostained images of VEGF in both saline, Control nanofiber and GAG mimetic nanofiber treated tissues and Cardiac tissue gene expression analysis of VEGF-A and Ang-1 [8].

2. Scaffold free tubular grafts

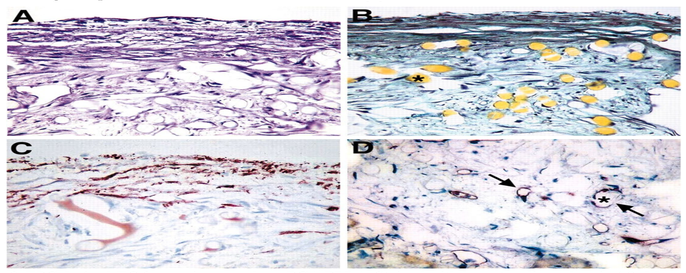
- Constructs small diameter multi-layered tubular vascular grafts.
- The flexible nature of the tube diameter allowed for the construction of branched macrovascular structures.
- Chinese Hamster Ovary (CHO) cells, Human umbilical vein smooth muscle cells (HUVSMCs) and Human skin fibroblasts (HSFs) were morphed into cylinder shapes
- This method proved to use fabrication technology that can be reliable and scalable [6].



2. Design template for tubular structures for cell lines[6].

3. Biodegradable scaffold

- Polyglycolic acid-poly-l-lactic acid (PGA-PLLA) is a known biocompatible and biodegradable polymer.
- Human umbilical cord blood was used to extract CD34+/CD133+ cells.
- Cells were cultured with VEGF, basic fibroblast growth factor, epidermal growth factor, and insulin-like growth factor I growth factors.
- The EPC- derived EC were seeded with human smooth muscle cells (SMC) onto PGA-PLLA, after 6 days there was an addition of an endothelial monolayer [9].

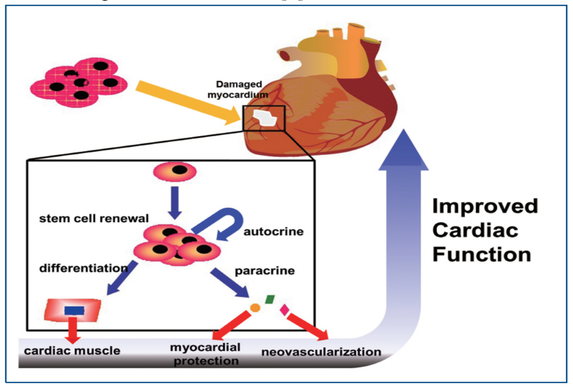


3. EPC derived-EC form microvessels on PGA-PLLA. Stained with hematoxylin and eosin (*A*), Movat pentachrome (*B*), anti-α-SMA (*C*), or anti-CD31 (*D*). PGA-PLLA fibers appear yellow (* in *B*) when subjected to Movat pentachrome staining procedure. Microvessels (arrows) lined with CD31$^+$ cells are shown in *D*. PGA-PLLA fibers are shown in some microvessel lumens (* in *D*) [9].

IN VIVO METHODS:

1. Transplantation of stem cells

- Bone marrow mesenchymal stem cells (BMSC) injection in vivo is treated to the cardiac site.
- BMSC were mixed with heparin and filtered before implantation.
- BMSCs have the highest capability to adhere to the patient's vessel wall at the infarcted area after balloon deflation.
- It had taken the stem cells a total of 1 week to express myocardial genes. It was found though that the best possible time for implantation of BMSC is 7 to 14 days after acute myocardial infarction.
- The study demonstrated BMSCs improve cardiac function and remolding of the left ventricle [1].



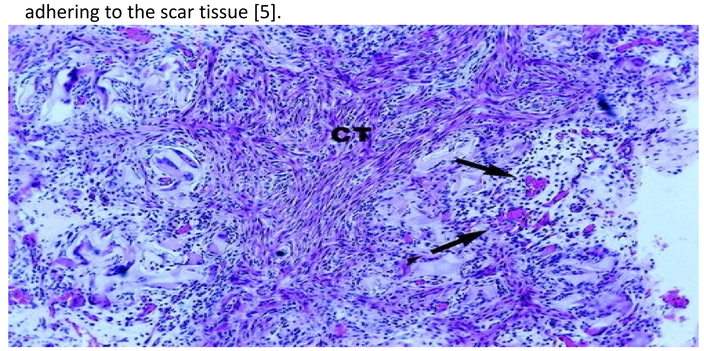
1. Schematic representation of the mechanisms of stem cells involved in heart repair.
Feng Y, Wang Y, Cao N, Yang H, Wang Y. Progenitor/stem cell transplantation for repair of myocardial infarction: Hype or hope? Ann Palliat Med 2012;1(1):65-77. DOI: 10.3978/j.issn.2224-5820.2012.04.01

2. Injectable Hydrogel

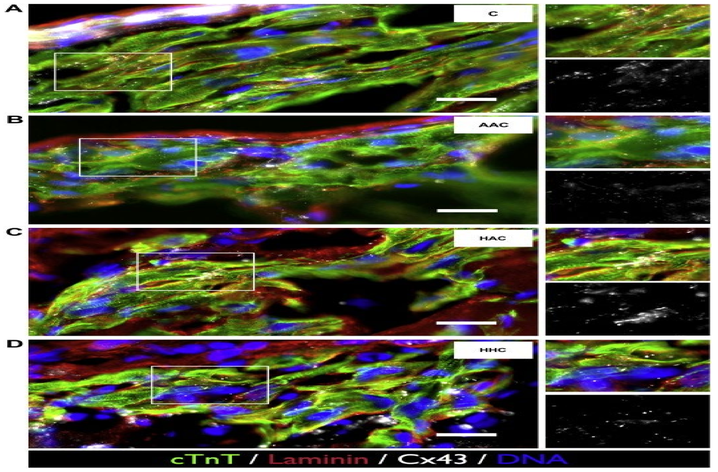
- Aldehyde and hydrazide-derivatives enable covalent hydrazine cross-linking of polysaccharides with the presence of myocytes.
- The hydrogels resemble natural extracellular matrices. They contained pores on their structures and visible network structure.
- Addition of collagen type 1 helped in contractile tissue production.
- Neonatal rat heart cells were seeded for the in-situ experiment.
- The blending of alginate and hyaluronic acid created a more flexible system.
- This hydrogel system can be used for further investigation when used for cardiac muscle reconstruction [2].

3. Cell seeded graft

- Male inbred Lewis rats had undergone left ventricular myocardial scar generation.
- Rats were split into three groups, implantation of seeded graft, unseeded graft, and a sham operation.
- Cells were obtained from the rats that received the graft. The graft was then sutured to the scar after three weeks.
- The grafts were observed to be beating after 7 days post implantation, the density of the cells were greater.
- The previously placed Gelfoam mesh was partially absorbed, and the graft was adhering to the scar tissue [5].



3. Photomicrographs of cell-seeded grafts implanted into subcutaneous tissue of adult rats for 5 weeks [5].



2. Hydrogel-based bioartificial cardiac tissue consists of longitudinally arranged cardiomyocytes with distinct morphology [2].

DISCUSSION/CONCLUSION:

Many methods either in vitro or in vivo use either a scaffold-based or cell therapy method in order to create a proper matrix for cell viability. Methods outlined here often work both in vitro and in vivo environments to test the same method. Notably, the use of stem cells seem to be a popular choice of cell line to use with different methods. Also, in vitro experiments will likely use natural growth factors in hopes to have these cells differentiate into viable cardiomyocytes and function in regenerated cardiac tissue. More research and experimentation must be conducted on the previously mentioned experiments in order to have more conclusive and reproducible ways of cardiac tissue regeneration.

CHALLENGES/FUTURE WORK:

The continuing challenge of these experiments is to construct strategies that promote vascularization, meaning to design bioactive scaffolds to meet the composition of the myocardial structure. Many research states that coculturing cells will most likely be incorporated in future experiments. Testing different types of polymers is also a possibility [5].

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