A Cardiac Patch for Delivering Therapeutic Stem Cells to the Heart Following Myocardial Infarction

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Abstract

While medical practices have evolved tremendously on the immediate aftermath of a myocardial infarction (MI), there are no techniques currently administered to slow, cease or reverse the negative side effects of an occluded artery. Previous work has demonstrated that the extent of myocardiocyte cell death and subsequent scar formation following MI can be decreased by the administration of "survival signals", such as those secreted by mesenchymal stem cells, to the damaged myocardium. While the therapeutic effects of such factors have been documented, the difficulty lies in the ability to maintain a constant flux of secretion factors to the site of damage. We have engineered a hydrogel construct optimized to release survival signals from encapsulated stem cells directly to the myocardium to reduce the tissue degradation associated with MI's.

Hydrogel patches composed of a combination of poly(ethylene glycol) (PEGDA) and methacrylic alginate (MA) have been engineered to support cell viability and initiate a neovascularization response in egg membrane assays. With possible beneficial properties shown *in vitro*, an *in vivo* approach has been taken to test the efficacy and possible treatment of ischemia in the heart. We have adopted a mouse MI model to test the efficacy of a cell encapsulated hydrogel patch on the survival of cardiac tissue following ischemia. To maintain patch adhesion to the heart surface, we have developed a biocompatible glue that ensures long term patch-to-tissue interactions. Work is currently underway to test the efficacy of encapsulated mesenchymal stem cells in aiding in tissue healing and preventing tissue degradation using a combination of cardiomyocyte co-culturing techniques, echocardiogram measurements, and histological testing.

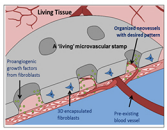

Figure 1: Factors produced by cells encapsulated within the hydrogel patch impact the surrounding tissue in a targeted manner. Proangiogenic growth factors concentrate in engineered "wells" within the patch, directing angiogenesis at the site of the wells.

Methods

Murine MI Model

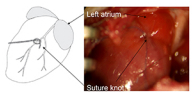

Figure 2: Murine myocardial infarction model on 8wk old C57BL/6J mice. Suture is placed just below and to the right of the left atrium to block the flow through the left anterior descending artery (LAD). Successful ligation can be noted as a lightening of the myocardial tissue due to occlusion of blood flow.

Hydrogel Fabrication

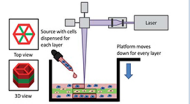

Figure 3: Schematic representation of the Stereolithography Apparatus' (SLA) bottoms-up approach to cell encapsulation through photopolymerization. The SLA allows us to control the patterning and encapsulation of cells on a layer-by-layer basis.

Results

Cell Encapsulation

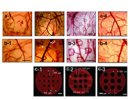

Figure 4: Formation of patterned neovessels on chick chorioallantoic membrane formed under PEGMA patches with microchannel diameters of 0 (a-1), 300 (a-2), 500 (a-3) and 1000 μm (a-4) and further magnified (b1-4). Pictures of hydrogel stamp with microchannels varied from 300, 500 and 1000 μm (c 1-3)[1]

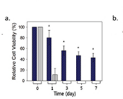

Figure 5: Fibroblast cells were encapsulated in either PEGDA-MA (blue) or PEGDA (grey) hydrogels and their viability (a) and VEGF secretion (b) were measured. Cells remained viable and actively secreting angiogenic growth factors for up to one week within the engineered patch[2]

Assessment of LAD Ligation

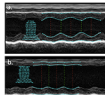

Figure 6: Scar tissue and ventricle thinning are indicative of successful LAD ligation. Ultrasound images of left ventricular beating before (a) and after (b) LAD occlusion. A decrease in heart wall movement can clearly be seen post-infarction. Masson's Trichrome staining 1wk post-surgery (c) display wall thinning and scar tissue deposition (blue), indications of necrotic tissue due to lack of blood flow to the area. Percent change in ejection fraction (EF), calculated as the change in EF 1wk post-surgery as a fraction of the measured EF prior to surgery, show a marked decrease in heart function in mice who underwent LAD ligation.

Patch Adhesion

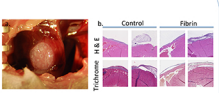

Figure 7: Hydrogel constructs were transferred to the surface of the heart wall to test the ability of the patch to remain at the desired site for an extended period of time (a). Patch adherence alone proved unsuccessful, necessitating the need for a biocompatible glue. A formulation of fibrinogen and thrombin was placed on top of the hydrogel and the animal was sutured closed. Histological analysis at 1wk showed the retention of the patch on the heart surface in animals that received the glue, but none on the control animals (b).

Future Work

Preliminary tests still need to be done with the BMSC's to ensure their protective capabilities. These include determining their:

1) Secretion profile of encapsulated cells both in hypoxic and normoxic conditions
2) Protective effects through co-culture studies with a mouse cardiomyocyte cell line (HL-1)
3) Angiogenic capabilities via the chick chorioallantoic membrane assay

Once these studies are performed, all necessary pieces will be in place for implementation of a BMSC encapsulated hydrogel patch to test its ability to secrete beneficial soluble factors, decrease damage caused by a myocardial infarction, and promote angiogenesis to ischemic heart tissue.

Acknowledgments and References

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2. Chan V, Zorlutuna P, Jeong JH, Kong H, Bashir R. Three-dimensional photopatterning of hydrogels using stereolithography for long-term cell encapsulation. Lab on a chip. 2010;10(16):2062-70.