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Injectable Myocardial Matrix as a Scaffold for Myocardial Tissue Engineering

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Abstract—**Current injectable materials utilized in myocardial tissue engineering have been borrowed from other tissue engineering applications and have not been specifically designed for the myocardium. We have recently tested the feasibility of using an injectable form of myocardial extracellular matrix that would provide cardiac specific matrix cues as well as be amenable to minimally invasive delivery. We have demonstrated that this material self-assembles in vivo to form a nanofibrous scaffold, which supports the infiltration of neovasculature. We have also demonstrated that this material may be delivered minimally invasively through a catheter.**

I. Introduction

Despite recent advances in tissue engineering, heart failure following a myocardial infarction (MI) continues to be the leading cause of death in the United States, with end-stage heart failure patients still relying on donor hearts. Several alternatives to total heart transplantation have been examined, including angiogenic therapies, cell transplantation, and material based treatments, such as LV restraints and tissue engineering approaches. *In situ* cardiac tissue engineering is an attractive approach, since potential therapies could be delivered minimally invasively. Injectable biomaterials for cardiac tissue engineering, such as collagen [1, 2], Matrigel [3, 4], alginate [5], self-assembling peptides [6], and chitosan [7], have been explored as potential treatments, both cellular and acellular, for MI. However, none of these materials have been specifically designed for the heart, nor do they mimic the structure and chemical make up of the natural myocardial extracellular matrix (ECM). Providing cells with the correct environmental cues is essential to the success of a tissue engineering approach [8-10]. Therefore, we sought to examine the feasibility of using an injectable form of myocardial matrix, which would provide cardiac specific cues for myocardial repair.

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II. Methods

A. Preparation of myocardial matrix

Hearts were harvested from pigs, approximately 30-45 kg, and the ventricular tissues was cut into pieces of about 2 mm in thickness. The tissue was briefly rinsed with deionized water and then stirred in 1% (wt/vol) sodium dodecyl sulfate (SDS) in phosphate buffered saline (PBS) for 4-5 days, until the tissue was decellularized. The tissue was then stirred in 1% (vol/vol) Triton X-100 for 30 min for final cell removal. Finally, decellularized cardiac tissue was stirred overnight in deionized water to ensure removal of detergents. After lyophilizing, the matrix was milled into a fine powder (Fig. 1a), and solubilized similarly to a previous report on bladder matrix [11].

B. In vitro characterization

The myocardial matrix was characterized by SDS-PAGE, and glycosaminoglycan content was characterized with the Blyscan assay. The matrix was also neutralized, and brought up to 37°C to form a gel (Fig. 1b). Gel structure was then analyzed with scanning electron microscopy (Fig. 1c).

C. In vivo application

Neutralized myocardial matrix was injected into the left ventricular free wall of rats, and the presence of neovasculature was examined at 11 days post-injection. The ability to be injected

through the Myostar catheter (Cordis) was tested both in *vitro* (Fig. 2a) and in a pig model of myocardial infarction (Fig. 2b).

III. RESULTS

We have successfully demonstrated the ability of the solubilized myocardial matrix to form a nanofibrous gel at physiologic temperature *in vitro* and *in situ*, with a complexity that mimics the native ECM, and the ability of the matrix to promote vascular cell infiltration *in vivo*. In addition, we have shown the clinical potential of this material for minimally invasive delivery, by pushing the solubilized material through a 27 gauge Myostar catheter in a pig model.

IV. CONCLUSION

We have demonstrated the feasibility of utilizing an injectable form of myocardial matrix as a scaffold for myocardial tissue engineering. This material may facilitate both acellular and cellular treatments for MI and heart failure.

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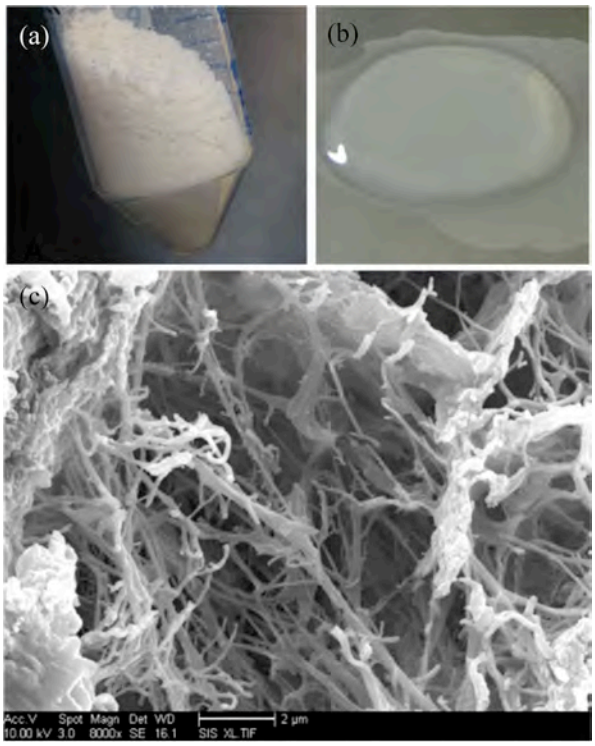

Fig. 1. *In vitro* characterization of the decellularized myocardial matrix. (a) lyophilized powder, (b) gel, (c) Scanning electron micrograph, revealing nanofibrous structure.

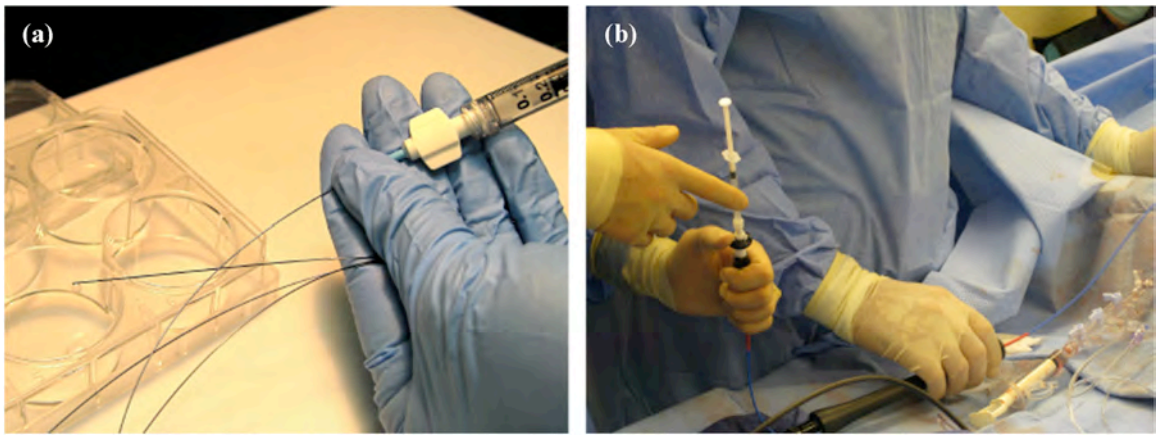

Fig. 2. Myocardial matrix being pushed through a 27 gauge Cordis cathéter (a) *in vitro* and (b) in a porcine myocardial infarction model.