An Injectable and Thermosensitive Hydrogel Capable of Delivering TGF-β Receptor II Inhibitor to Control Cardiac Fibrosis

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Statement of Purpose: Cardiovascular disease is the leading cause of death in the US. Myocardial infarction (MI) is a major cardiovascular disease that affects more than 8 million Americans. Within the first week following MI, cardiac fibroblasts start to turn into myofibroblasts. This is mediated by TGFβ pathway where the upregulated TGFβ binds to TGFβ receptors, especially TGFβ receptor IIs (TGFβRIIs) on the cardiac fibroblast surface. Myofibroblasts initially deposit ECM to strengthen the injured heart tissue and minimizes tissue dilation. However, later excessive accumulation of ECM results in progressive formation of fibrotic scar. The scar tissue not only disrupts normal myocardial structure but also increases stiffness of the heart and significantly contributes to cardiac dysfunction [1]. Additionally, the stiff scar tissue drives surrounding healthy heart tissue to be damaged due to unmatched stiffness [2]. These events finally result in heart failure, a disease that affects about 5.7 million people in the US, and causes 20% and 50% of patients die within 1 and 5 years, respectively [3]. The objective of this study is to develop a drug release system that can be delivered into hearts to sustainedly release TGFβRII inhibitor (GFI) to block TGFβ pathway-induced cardiac myofibroblast formation.

Methods: An injectable and thermosensitive hydrogel was synthesized to serve as carrier for TGFβRII inhibitor. The hydrogel was based on N-isopropylacrylamide (NIPAAm), acrylate-polylacitde (APLA) and 2-hydroxyethyl methacrylate (HEMA), and was synthesized through free radical polymerization. Hydrogel thermal transition temperature was measured using DSC. Hydrogel solution injectability was tested by injecting a 20% hydrogel solution through a 26 gauge needle at 4°C. Peptide ECGLLPVGRPDRNVWRWLCK was used as GFI. The peptide was encapsulated in the 20% hydrogel solution. Peptide release kinetics was determined at 37°C using PBS as release medium. The efficacy of peptide in blocking TGFβRIIs was tested after adding the peptide to the cultured cardiac fibroblasts followed by immunohistological analysis.

Results: The synthesized hydrogel exhibited thermal transition temperature around room temperature. A 20% hydrogel solution can be readily injected through a 26 gauge needle at 4°C. The peptide can be sustainedly released from the hydrogel during a 28-day release period (Figure 1). The release kinetics was dependent on the peptide loading, and addition of chondrotin sulfate and heparin addition. The amount of released peptide was significantly increased when increasing the peptide loading and use of chondrotin sulfate (CS) and heparin (HP). MTT assay demonstrated that the released peptide did not affect cardiac fibroblast growth. Immunohistological analysis showed that the peptide can completely block TGFβRIIs on cardiac fibroblasts (Figure 2).

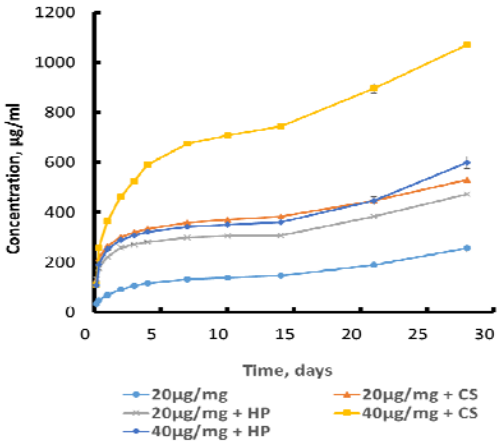

Figure 1. GFI Release kinetics during 28 days period. Note: 20μg/mg means 20μg peptide powder to 1mg dry hydrogel polymer

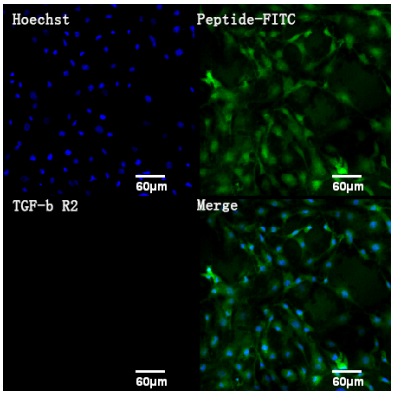

Figure 2. The addition of GFI peptide restricts the expression of TGFβRII

Conclusions: A drug delivery system based on an injectable and thermosensitive hydrogel, and TGFβRII blocking peptide was developed to attenuate cardiac fibrosis. The peptide can be continuously released from the hydrogel for 4 weeks. Future work will focus on in vivo evaluation of the efficacy of developed system.

References:

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[2]Chaanine AH. Circ Heart Fail. 2013 May;6(3):572-83
[3] Rosamond W. Circulation. 2007;115:E69-E171.