An Injectable and Thermosensitive Hydrogel Capable of Delivering Matrix Metalloproteinases 2 Inhibitor to Control Myocardial Remodeling

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Statement of Purpose: Myocardial infarction (MI) is a major cause of death in the U.S. After MI, structural alterations (remodeling) occurs [1]. The upregulated matrix metalloproteinases (MMPs) degrade cardiac ECM [3], leading to a decrease in wall thickness. In severe cases, this causes cardiac rupture [2]. To control cardiac ECM degradation, MMP inhibitors (MMPIs) such as doxycycline and o-phenanthroline have been delivered systemically to decrease MMP bioactivity [4]. However, systemic delivery experiences limited efficacy as the dosage allocated to heart is low. In addition, high dosage of MMPI may have toxic effect. In this study, a non-toxic peptide based MMPI was encapsulated in a hydrogel to explore the effect of controlled release of MMPI on the decrease of cardiac ECM degradation.

Methods: An injectable and thermosensitive hydrogel was synthesized to serve as a carrier for MMPI. The hydrogel was based on N-isopropylacrylamide (NIPAAm), acrylate-polylacitde (APLA) and 2-hydroxyethyl methacrylate (HEMA). Hydrogel thermal transition temperature was determined by DSC. Hydrogel solution injectability was tested by injecting a 4°C, 20% hydrogel solution through a 26-gauge needle. The peptide CTTHWGFTLC(FITC) was used as a MMPI. The MMPI release kinetics was determined at 37°C using PBS as release medium. Bioactivity of the released MMPI was evaluated using fluorogenic resonance energy transfer (FRET) peptide substrate. To evaluate the efficacy of MMPI delivery in control cardiac ECM degradation, the hydrogel encapsulated with MMPI was injected into infarcted rat hearts. The heart tissues were harvested after 4 weeks of implantation. Wall thickness as well as collagen composition of the infarcted hearts was evaluated.

Results: APLA hydrogel demonstrated a thermal transition temperature around room temperature. The hydrogel solution (20%, w/v) was injectable through a 26 gauge needle at 4°C. The MMPI can be continuously released from the hydrogel during a 28-day release period (**Figure 1**). The release kinetics was dependent on the peptide loading, and addition of chondroitin sulfate (CS) and heparin. The amount of released peptide was significantly increased when increasing the peptide loading and use of CS and heparin (HP). The released MMPI remained bioactive **(Figure 1)**. The ratio of wall thickness (infarcted area/healthy area) in the MMPI treated group was much higher (77.8±12.7%), than that of the MI group (25.8±3.7%). The Picrosirius red staining (**Figure 3**) demonstrated that more type III collagen was preserved in MMPI treated group.

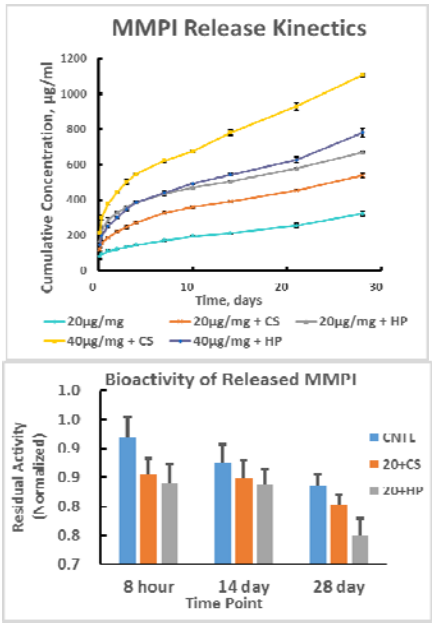

Figure 1. (Upper) MMPI Release kinetics during a 28-day period. 20μg/mg means 20μg peptide powder to 1 mg dry hydrogel polymer; (Lower) Bioactivity of released MMPI at time point 8 hour, 14 and 28 day.

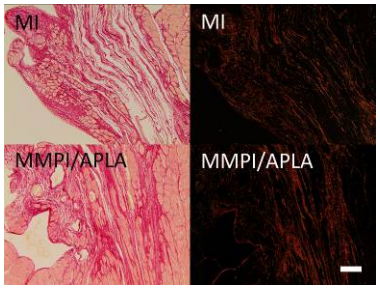

Figure 2. Picrosirius red staining of MI and MMPI treated groups (Scale bar=150 μm).

Conclusions: Controlled release of MMPI injected into infarcted hearts attenuated cardiac ECM degradation. The developed release system has the potential to prevent cardiac rupture after MI.

References:

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