Catheter-deliverable, Thermal and pH Responsive Hydrogels for Delivery of Cardiac Progenitor Cells into Infarcted Hearts

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Statement of Purpose: Myocardial infarction (MI) affects more than 8 million people in the US. MI causes massive cell death, resulting in a decrease in heart function. Stem cell therapy has been considered as a promising approach to regenerate the lost cells [1]. A clinically attractive strategy to deliver stem cells into the infarcted hearts is to use a minimally invasive catheter procedure [2]. However, delivery of stem cells in saline solution results in extremely low cell retention, because the low viscosity saline solution cannot efficiently hold the cells in the beating heart tissue. We hypothesized that using thermosensitive hydrogels as stem cell carriers can significantly improve the cell retention, as these hydrogels quickly solidify once being delivered into the heart, thus can be retained in the heart. However, thermosensitive gels cannot be delivered directly by the catheter because they form solid gels in the catheter at 37°C. In this work, we developed a family of thermal and pH-sensitive hydrogels that do not solidify at pH 8.0 at 37°C, but solidify at pH 6.5-6.8, typical pH range at the infarct area. These hydrogels therefore can be delivered into infarcted hearts by catheter. Interestingly, the hydrogels can even stimulate the cardiac differentiation of a type of cardiac progenitor cell - cardiosphere-derived cell (CDC).

Methods: The hydrogel polymers were synthesized by copolymerization of N-propylacrylamide (NIPAAm), propylacrylic acid (PAA), poly(ethylene glycol) methyl ether methacrylate (MA-PEG) and biodegradable macromer 2-hydroxyethyl methacrylate-co-oligo(trimethylene carbonate) (HEMA-oTMC). The feed ratio of NIPAAm, PAA, MA-PEG and HEMA-oTMC was 87/6/5/2 (EG1), 84/6/7/3 (EG2) and 86/6/5/3 (EG3), respectively. The hydrogel polymers were dissolved in PBS, and the pH was adjusted to 8.0. The injectability was tested using Abbott Voyage catheter (inner diameter 0.2 mm) at 37°C. Gelation temperatures of the hydrogel solutions were determined by DSC under pH 6.5 and 7.4, respectively. CDCs were encapsulated in the hydrogels at a density of 10 million/ml. After 7 days of culture, dsDNA content (for live cells) was quantified. Cardiac differentiation was characterized by real-time PCR and immunohistochemistry [3].

Results: Structure of the hydrogel polymers was verified by 1H-NMR. Polymer composition was consistent with the monomer feed ratio. All of the hydrogel solutions were injectable through the catheter at pH 8.0, and formed solid gels at pH 6.5 (infarcted tissue). The hydrogel solutions had gelation temperatures higher than 37°C at pH 8.0, and lower than 37°C at pH 6.5. The hydrogels were biocompatible as CDCs maintained their cell number in the hydrogels. CDCs in the EG1 and EG2 hydrogels differentiated into cardiac lineage. At the mRNA level, the expressions of cTnT and CACNA1c were significantly upregulated. At the protein level, the differentiated cells expressed cTnI and connexin 43 (CX43) (Figure 1).

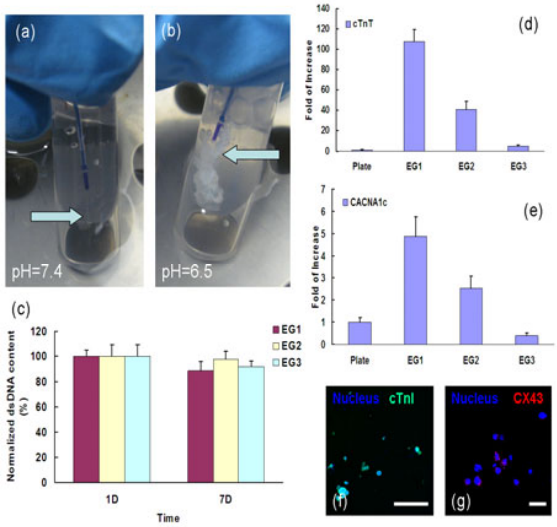

Figure 1. (a) & (b) Flow/gelation at different pH at 37°C; (c) dsDNA contents of cells in hydrogels; (d) & (e) Expressions of early cardiac markers cTnT and CACNA1c; (f) & (g) immuno-fluorescence of early cardiac proteins for CDCs in hydrogels.

Conclusions: A family of thermo- and pH- sensitive hydrogels has been synthesized. The hydrogel solutions were able to inject through a minimally invasive catheter. The hydrogels were biocompatible and can stimulate cardiac progenitor cells differentiate into cardiac lineage. These results demonstrated that the developed hydrogels can be promising stem cell carriers for cardiac cell therapy.

References:

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