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Injectable and protease-degradable hydrogel for siRNA sequestration and triggered delivery to the heart

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Abstract:

Injectable hydrogels have significant therapeutic potential for treatment of myocardial infarction (MI) through tissue bulking and local drug delivery, particularly for small interfering RNAs (siRNAs). As siRNA targets are identified as potential treatments for MI, hydrogels may bolster efficacy through local and sustained release. Here, we designed an injectable hydrogel to respond to local upregulation in proteolytic activity after MI to erode and release siRNA against MMP2 (siMMP2), a target implicated in deleterious remodeling. Specifically, hyaluronic acid (HA) was modified with hydrazides or aldehydes and mixed to form shear-thinning and self-healing hydrogels through dynamic hydrazone bonds and with peptide crosslinkers that degrade in response to protease activity. HA was further modified with β-cyclodextrin to sequester cholesterol-modified siRNA, limiting passive diffusion. Hydrogels eroded in response to proteases and released active siRNA that knocked down MMP2 in primary cardiac fibroblasts. In a rat model of MI, hydrogels delivering siMMP2 attenuated hydrogel erosion by ~46% at 4 weeks when compared to hydrogels delivering control siRNA, ultimately improving myocardial thickness in the infarct. Delivery of the siMMP2 hydrogel led to significant functional improvements, including increased ejection fraction (27%, 66%), stroke volume (32%, 120%), and cardiac output (20%, 128%) when compared to hydrogels with control siRNAs or saline injection alone, respectively. This report demonstrates the utility of biomaterial-based RNA delivery systems for cardiac applications.

Keywords: siRNA, myocardial infarction, hydrogel, matrix metalloprotease

1. Introduction