Cardiac delivery of therapeutics via injectable thermosensitive hydrogels

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Many genes and pathways have been indicated to play essential roles during heart regeneration and manipulation of these pathways using mRNAs or small molecules have been shown to be promising therapeutic strategies. For this, a dual delivery system composed of mRNA polyplexes and micelle-containing thermosensitive hydrogel, previously complexed with CHIR-99201 (GSK3 inhibitor-Wnt agonist), was designed allowing local sustained release of the therapeutics. In this study, the synthesis of mPEG-pDMAEMA copolymer was optimized via RAFT polymerization and this polymer was used as polymeric carrier for mRNA condensation. Condensed mRNA polyplexes showed an average size of 146±11 nm (N/P charge ratio 10) with a positive zeta potential (10.1±0.3 mV). Subsequently, the loading of mRNA polyplexes into a thermosensitive pNIPAM-PEG-pNIPAM (NPN) hydrogel was evaluated to facilitate local and sustained mRNA release. The NPN triblock copolymer synthesized by ATRP polymerization, was used as a carrier for CHIR by forming flower-like micelles, encapsulating the drug via heat-shock procedure. The CHIR-NPN gel was then formulated by increasing the CHIR-NPN polymer content, reaching the final concentration of 20%w/w. After 15 days, NPN placebo hydrogels were fully dissolved while drug-loaded hydrogels exhibited much longer degradation times (54 days). This proves that the presence of CHIR affects the stability of the hydrogel, presumably due to its interaction with the dehydrated pNIPAM blocks. CHIR-loaded gels showed temperature-sensitive behavior with a gel point below 37°C, proving their injectability and *in situ* gelation. In conclusion, the synergistic release of mRNA polyplexes and CHIR-NPN micelles offers a promising therapy for myocardial regeneration.