Self-healing and injectable alginate-based hydrogel for microRNA delivery to promote cardiac regeneration after myocardial infarction

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Abstract

Cardiac regeneration after myocardial infarction (MI) represents a worldwide clinical challenge due to the scarce regenerative properties of heart tissue. Recently, our group demonstrated the *in vitro* direct cell reprogramming (DR) of human adult cardiac fibroblasts (AHCFs) into induced cardiomyocytes using a combination of four micro-RNA (miRNA) mimics, termed "miRcombo"[1], showing potential for *in situ* myocardial regeneration. To achieve a safe and effective administration of miRcombo *in vivo*, we designed polymer-based nanoparticles (NPs) characterized by increased *in vitro* DR efficiency compared to commercial transfection agents. The aim of this work was to develop an injectable hydrogel able to allow *in situ* delivery and local retention of the miRNA-loaded NPs within the fibrotic scar tissue. Alginate (Alg) was selected for the hydrogel development since Alg-based systems are currently being investigated in clinical trials for MI treatment. To improve Alg degradability and cell-adhesive properties, we blended the polymer with alginate dialdehyde (ADA)[2], an Alg oxidised form, and a chemically-modified gelatin (Gel-M). Double-crosslinked hydrogels (D-HYD) were successfully optimized, combining chemical (ADA/Gel-M Schiff base) and physical crosslinking (Alg/calcium ions) to achieve cardiac-like viscoelastic properties, injectability and self-healing features and good cytocompatibility *in vitro*. NPs incapsulating a model fluorescent oligonucleotide, Cy5-siRNA, could be successfully embedded within the D-HYD matrix and a complete and gradual release of Cy5-siRNA was achieved in 14 days. *In vitro* DR experiments with AHCFs are currently under investigation.

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References

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