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Injectable self-healing hydrogel delivering microRNAs-loaded nanocarriers as a promising advanced therapy for cardiac regeneration

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INTRODUCTION: Cardiovascular diseases are the leading cause of death worldwide. Myocardial infarction (MI) causes the irreversible loss of cardiomyocytes and the formation of a dysfunctional scar tissue, leading to heart failure [1]. Recently, the delivery of microRNAs (miRNAs) able to induce direct cell reprogramming (DR) has emerged as a new option for in situ myocardial regeneration. Previously, we have demonstrated that transient transfection of human adult cardiac fibroblasts (AHCFs) with four microRNA mimics ("miRcombo") using commercial Dharmafect (DF) triggers DR into induced cardiomyocytes (iCMs) in vitro [1]. In this work, we designed safe and efficient nanocarriers for in situ DR of AHCFs into iCMs [2] and injectable self-healing hydrogels for their local administration.
METHODS: Lipoplexes based on a cationic and a helper lipid containing miRNA (LPs/miRNA) were prepared and surface coated with natural or synthetic polymers (NPs/miRNA) and thoroughly characterized physico-chemically. AHCFs were transiently treated with NPs/miRNA vs. LPs/miRNA and DF/miRNA and their viability, miRNA uptake and transfection efficiency were assessed. Hydrogels (HYDs) were prepared through Schiff base reaction of alginate dialdehyde (ADA) [3] and chemically-modified gelatin (GEL-C) and thoroughly characterized. In vitro release kinetics of particles loaded with siRNA-Cy5 embedded into HYD was analyzed. The ability of free and released particles to induce miRcombo-mediated direct reprogramming in vitro was analyzed. Biodistribution was assessed by in vivo trials in infarcted mouse models after intracardiac injection.
RESULTS: NPs/miRNA showed higher miRNA encapsulation efficiency (99% vs. 64%) and biocompatibility (100% vs. 50-60%), and similar cell transfection efficiency compared to commercial DF/miRNA control. LPs/miRcombo and NPs/miRcombo increased in vitro direct reprogramming efficiency respect to DF/miRcombo. Selected HYD showed injectability, cell adhesion ability, biomimetic stiffness, and proper stability. NPs/miRNA showed superior stability and could be delivered through the injectable HYD. Mouse trials showed improved heart biodistribution with NPs-loaded HYD.
DISCUSSION & CONCLUSIONS: LPs/miRNA were efficient and safe but unstable, hence they were suitable for in vitro transfection, only. Novel NPs/miRNA (patented) were efficient, safe and stable when embedded in HYD. Injectable self-healing HYD improved local retention in vivo. NPs/miRNA allowed surface functionalization for cell-targeted delivery.
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