Green injectable pectin-based hydrogels for controlled release of EVs for cardiac fibrosis treatment

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Introduction

Cardiac fibrosis is a maladaptive remodeling of the myocardium, which progression is still poorly understood. Current treatments are unable to revert fibrosis and restore cardiac functionality. The local delivery of cell-derived extracellular vesicles (EVs) with cardioprotective and anti-fibrotic effects is promising to enhance myocardial repair. Injectable self-healing hydrogels are minimally invasive systems serving as depots for controlled release of therapeutics [1].
In this work, hydrogels based on pectin derived from fruit-processing industry waste were designed as sustainable and versatile systems for the controlled release of human amniotic fluid-derived stem cells (hAFSCs) EVs as a treatment for cardiac fibrosis [2]. EVs-hydrogel drug delivery systems (DDS) were characterized and tested in vitro with human cardiac fibroblasts (HCF) and H9c2 rat myoblasts.

Materials and Methods

To develop injectable pectin-based hydrogels, oxidized pectin (PDA) was synthesized with 2.5 and 5% oxidation degrees (PDA_2.5 and PDA_5), to introduce aldehyde groups and was then blended with modified gelatin (G-m) able to react with aldehyde moieties in PDA, obtaining chemically crosslinked hydrogels. PDA/G-m hydrogel composition was optimized by analyzing rheological properties, stability in physiological conditions and cell cytocompatibility and adhesion of HCFs and H9c2, as well as their injectable behavior. hAFSCs-EVs were provided from University of Genoa, and their effect on HCFs preliminarily evaluated by 2D cell tests. Tests on EVs release from EVs-PDA/G-m hydrogels were performed using microfluidic chips for next testing in beating human cardiac fibrotic tissue in a chip model.

Results

The oxidation degrees of pectin (PDA_2.5 and PDA_5) were confirmed using a colorimetric assay. Rheological analysis, stability studies and in vitro biocompatibility and cell adhesion tests allowed the selection of injectable PDA/G-m hydrogel compositions. Hydrogels showed in vitro cytocompatibility and HCFs/H9c2 adhesion as well as the ability to enable EV controlled release for prolonged functionality.

Discussion

This study developed sustainable PDA/G-m hydrogels for safe and effective controlled release of EVs in situ. Pectin was selected as green biomaterial for hydrogel design, while functionalized gelatin was added to impart cell bioactivity. Hydrogels were chemically crosslinked through Schiff base reaction, showing tunable mechanical properties, injectability, biocompatibility and capability to sustain HCF spreading. The effect of controlled release of hAFSCs-EVs from hydrogels is under testing in human cardiac fibrosis on a chip model.

Conclusions

This work developed DDS based on injectable PDA/G-m hydrogels as a promising platform for in situ delivery of hAFSCs-EVs for the treatment of cardiac fibrosis. Future research will focus on the characterization of the cardioprotective and anti-fibrotic effects of released EVs.

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References

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