Biomimetic In Vitro Model of Human Cardiac Replacement Fibrosis: a Preclinical Testing Platform to assess the Safety and Target Efficiency of Precision Nanomedicine for Cardiac Regeneration

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Cardiovascular diseases are the leading cause of mortality globally. Myocardial infarction (MI) leads to the irreversible loss of cardiomyocytes (CMs) and the development of dysfunctional and stiff fibrotic tissue [1, 2]. Scarring includes cardiac fibroblasts (CFs) activation into myofibroblasts (MyoFs) and over-deposition of fibrotic extracellular matrix (ECM), mainly composed by fibronectin (F) and type I collagen (C1). Recently, novel microRNAs (miRNAs) with the ability to induce direct reprogramming of CFs into CMs [1] or proliferation of CMs [3] have emerged for potential use in cardiac regeneration. However, their translation into therapies requires safe and efficient nanocarriers for cell-targeted miRNA delivery. The availability of in vitro models recapitulating the in vivo-like tissue complexity is fundamental for optimizing precision nanomedicine.

In this work, a novel in vitro model of human cardiac replacement fibrosis was prepared, by culturing CFs in biomimetic scaffolds with randomly-oriented nanofibrous structure, fabricated by electrospinning of polycaprolactone (PCL) solution, followed by surface-functionalization with human C1 and F, to mimic structure and composition of pathological cardiac ECM [4]. Coated scaffolds showed similar surface stiffness (measured by AFM) as cardiac fibrotic ECM. Scaffold biomimicry induced myofibroblast activation and the deposition of fibrotic ECM in 7 days. The model was exploited to test the efficiency for CFs-to-CMs direct reprogramming of novel polymer-lipid hybrid nanoparticles, surface functionalized with a specific antibody (F_H-NPs) and loaded with reprogramming miRNAs ("miRcombo"). F_H-NP testing in the model demonstrated their superior internalization, transfection and direct reprogramming efficiency, respect to control unfunctionalized hybrid nanoparticles and commercial transfection agents.

In conclusion, the herein developed model efficiently replicated human cardiac replacement fibrosis, for use as a robust platform for preclinical testing of therapies in nonanimal models. In the future, CF co-culture with suitable CM proportions will allow the optimization of precision nanomedicine in a more complex in vivo-like cardiac microenvironment.

References:

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