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IN VITRO MODELS OF HUMAN PATHOLOGICAL CARDIAC TISSUE VIA BIOARTIFICIAL SCAFFOLDS / Chiono, Valeria; Zoso, Alice; Spedicati, Mattia; Ruocco, Gerardina; Carmagnola, Irene. - STAMPA. - (2019). ((Intervento presentato al convegno Advanced Cell Therapies and Tissue Engineering tenutosi a Milan (Italy) nel November 14-16, 2019.

Availability:
This version is available at: 11583/2798934 since: 2020-02-28T15:22:15Z

Publisher:
Ospedale San Raffaele and Nature

Published
DOI:

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21 December 2022

Flash Talk - Also Poster # 14

IN VITRO MODELS OF HUMAN PATHOLOGICAL CARDIAC TISSUE VIA BIOARTIFICIAL SCAFFOLDS

Valeria Chiono[1,2,3], Alice Zoso[1,2,3], Mattia Spedicati 1,2, Gerardina Ruoccoi 1,2, Irene Carmagnola1,2[3]

[1] Department of Mechanical and Aerospace Engineering, Politecnico di Torino, Turin, Italy ,[2] POLITO Biomedlab, Politecnico di Torino, Turin, Italy ,[3] Interuniversity Center for the promotion of the 3Rs principles in teaching and research, Italy

Background Myocardial infarction causes the loss of billions of cardiomyocytes and the remodelling of local extracellular matrix (ECM), leading to the progressive formation of a stiff fibrotic tissue mainly populated by cardiac fibroblasts. *In vitro* models of human pathological cardiac tissue able to closely reproduce post-infarct microenvironment could greatly improve preclinical experimentation on human heart, providing predictive tools to study new therapies. In this work, the structure and composition of bi- and three-dimensional scaffolds were tailored to obtain models of human pathological cardiac tissue with different thicknesses and severity degrees.

Methods electrospinning (Linari Engineering) and fused-deposition modelling (Rokit Invivo) to obtain 2D and 3D scaffolds, respectively processed Polycaprolactone (PCL). Gelatin (G) was grafted on scaffold surface through a mussel-inspired approach based on two steps: (i) 3, 4-Dihydroxy-D, L-phenylalanine (DOPA) polymerisation on PCL surface; (ii) incubation in G solution. After each functionalization step, physicochemical, morphological and mechanical characterizations were performed. Cardiac fibroblasts isolated from human ventricle (HCFs, PromoCell) were cultured on the scaffolds at a density of 7x104 cells/cm2, and their adhesion, proliferation and protein expression were analysed.

Results SEM analysis showed that 2D electrospun membranes consisted of a nanofiber network free of defects, while a reproducible interconnected porous structure was obtained for 3D scaffolds. QCM-D, ATR-FTIR and XPS analyses confirmed successful surface modification after each step, while the amount of grafted G was quantified by a colorimetric assay. Mechanical and thermal properties of scaffolds did not vary after functionalization. HCFs cultured on G grafted scaffolds showed better attachment and proliferation compared to non-functionalized scaffolds. The expression of fibroblast markers (α-SMA, DDR2) and secretion of typical cardiac ECM proteins (Fibronectin, Laminin, Tenascin and Collagen IV) were confirmed by immunofluorescence and western blot analysis.

Conclusions 2D and 3D bioartificial scaffolds supported long-term HCF culture, and their composition and structure affected HCF markers and protein deposition. In the future, new therapies will be tested in vitro using such constructs. This project has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme grant agreement No 772168.