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3D Melt-fabricated bio-hybrid scaffolds for the *in vitro* modelling of human cardiac fibrosis.

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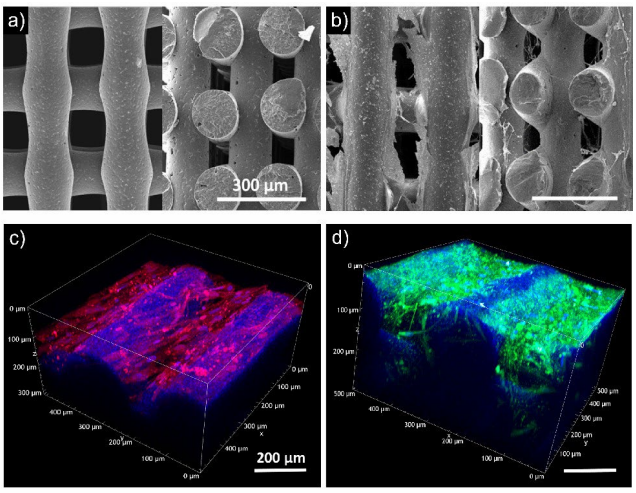
Abstract

Myocardial infarction causes cardiomyocytes loss, and extracellular matrix (ECM) remodelling, resulting in a scar tissue mainly populated by cardiac fibroblasts, rich in collagens (Type I, II, IV) and stiffer [1]. Following the 3Rs principle, *in vitro* models of human cardiac post-infarct tissue may improve preclinical validation of new therapies for cardiac regeneration. This work focused on the design of bioartificial scaffolds providing support and mechanical stimuli for adult human cardiac fibroblasts (AHCFs) adhesion and activation into myofibroblasts to develop *in vitro* models of cardiac fibrosis. 3D polycaprolactone (Mw=43.000 Da, PCL) scaffolds with interconnected porosities were fabricated by melt extrusion additive manufacturing (MEAM) (Figure 1a) and, functionalized with type A Gelatin (G), exploiting mussel-inspired pre-coating. G grafting and its stability was confirmed by QCM-D analysis and by static contact angle measurement respectively. G coating improved long-term culture of AHCFs (up to 21 days) and, combined with PCL stiffness, stimulated fibrotic ECM deposition, as confirmed by SEM (Figure 1b) and two photon excitation fluorescence (TPEF) images (Figure 1c, 1d). The expression of myofibroblast markers (α-SMA) and the secretion of fibrotic ECM proteins (Fibronectin, Laminin, Tenascin and Collagen I, II and IV) by immunofluorescence analysis confirmed the engineering of a fibrotic tissue [2]. As a step forward to this work and previous literature [3], stretchable PCL wavy meshes were designed and fabricated by MEAM, and then embedded into AHCFs-cellularized GelMA hydrogels. Such structures provided mechanical resistance and biomimetic composition, sustaining long-term dynamic testing. PCL mesh geometry was designed by structural and FEM analyses. AHCFs morphology and distribution were analyzed by immunofluorescence analysis after 14 days culture time, confirming the successful development of human cardiac fibrotic tissue. Both works confirmed that mechanical stiffness affects AHCFs behaviour triggering their fibrotic activation. Models will be validated by testing drugs with well-know effect on human cardiac fibrotic tissue.



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