ANISOTROPIC AUXETIC CARDIAC PATCH WITH MODULATED CELL ADHESION AND INFLAMMATORY BEHAVIOUR TO SUPPORT EPICARDIAL THERAPIES

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Introduction

Anisotropic structure of the heart are the key players modulating the cardiac performance. However, after myocardial infarction (MI) and formation of myocardial ischemia, these characteristics varies drastically which could terminate to heart failure. Epicardial restraint constructs such as cardiac patch are a new class cardiac therapy [1]. Cardiac patch of the future should be able to mimic the sophisticated mechanical anisotropic characteristics. 3D-printed synthetic biopolymers are suitable candidate due to their facile tailor ability with adequate mechanics [2]. However, their hydrophobicity and the absence of particular cell recognition sites needs to be improved for a successful regeneration. In this study auxetic (Aux) designs integrated in to the patch to simulate an anisotropic behavior via precise 3D printing bow-tie microstructures. To tackle the limited cell adhesion affinity, we utilized human placenta chorion derived extracellular matrix (hpcECM) as a coating to improve cell proliferation and the acceptance of these therapeutic patches in regions of local tissue damage.

Method

Various printing parameters (pressure, temperature, flow rate, digital coding, needle size) were optimized. Morphological and mechanical behavior of the patches (AuxPCL, AuxPCL-hpcECM) were studied via SEM, tensile tests and nano indentation. Roughness and wettability of the patches were studied. Various cell types such as human umbilical vein endothelial cells (HUVEC), endothelial progenitor cells (EPC), H9C2 cardiomyoblasts and human fibroblasts (HFF) were utilized to identify the biocompatibility, hemocompatibility and the role of hpcECM on proliferation and maturation/differentiation of cells via XTT, live dead, hemolysis and clot formation assays at various time points. Furthermore, expression of pro-inflammatory (CD80, CCR7, IL-1a & TNF-a) and anti-inflammatory (CD163, CD206& IL-10) macrophage and cytokine markers were assessed via PCR.

Results

Optimized printing parameters resulted in production of reproducible scaffolds with good structural integrity and pore size of (~0.2 mm^2). Tensile tests showed a clear anisotropic stiffness-ratio with ultimate strain of 7-20%; close to the range of physiological deformations of the myocardium (15-22%). Nano indentation confirmed softer and more elastic micro-environment in the present of hpcECM. A significant increase of initial cell attachment/differentiation (H9C2, HUVECs, HFF cells) mediated by hpcECM coated PCL constructs which led to a more mature cells (EPC, H9C2 cells) were observed. Patches were hemocompatibility with a low hemolysis rate. Pro-inflammatory gene expressions were showed in all groups at 24 and specifically after 72 hours followed by a significant reduction after 1 week. Immunomodulatory effect of the patches was validated.

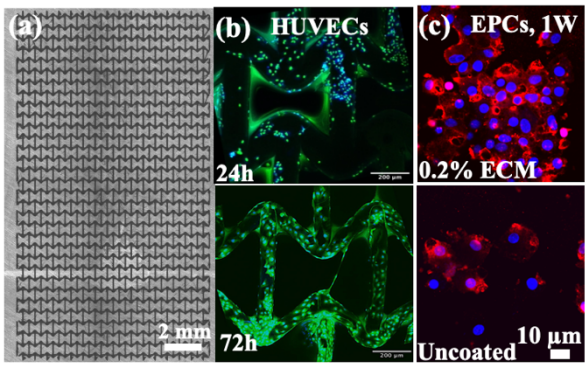

Figure 1: (a) AuxPCL patch, (b) HUVECs proliferation (c) Role of hpcECM on EPCs adhesion and maturation (Prom1 staining)

Discussion

High resolution 3D printed patch showed promising results for the use of this mechanically tunable biomaterial in cardiac tissue engineering with positive hemocompatibility and immunomodulatory characteristics. Furthermore, hpcECM is capable of providing cells an extracellular matrix based platform with higher cell affinity promoting the proliferation, attachment and cellular metabolic activity of the cells.

References

1. Bar et al., Front. Bioeng. Biotechnol., 8:2020.
2. N. R. Richbourg et al., J Tissue Eng Regen Med., 13:8,2019.

Acknowledgements

This work was partially supported by Ludwig Boltzmann Institute for Cardiovascular Research.