Inducing anisotropy in 3D cardiac microtissues to improve cell and tissue function

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materials-driven regeneration

Introduction

The human myocardium is a mechanically active tissue typified by its anisotropic organization of cells and extracellular matrix. Upon injury, two main events alter the myocardium, leading to failing of the heart (Figure 1):

1) A loss of beating cardiomyocytes, resulting in compromised contraction force,
2) Disruption of the highly organized anisotropic structure, resulting in impaired coordinated contraction and compromised differentiation, matrix production, and mechanotransduction of resident and newly injected cardiac cells.

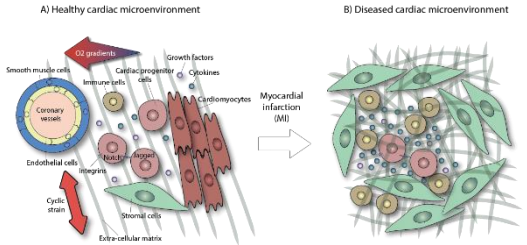

Figure 1: Schematic representation of the healthy (left) and diseased (right) myocardial micro-environment consisting of cardiomyocytes (red), cardiac fibroblasts (green) and supporting cell types. Mauretti et al., *Stem Cell Int*, 2017.

Research Aim

In this study, we propose three-dimensional (3D) isotropic cardiac microtissues as an *in vitro* disease model to understand the effect of organization on myocardial function and develop methods to restore myocardial anisotropy *in vivo*.

The research aims are:

- Investigate the influence of inducing anisotropy on cell (local) and tissue (global) function
- Study the mechanical forces playing a role during the transition from isotropic to anisotropic tissue (computational)

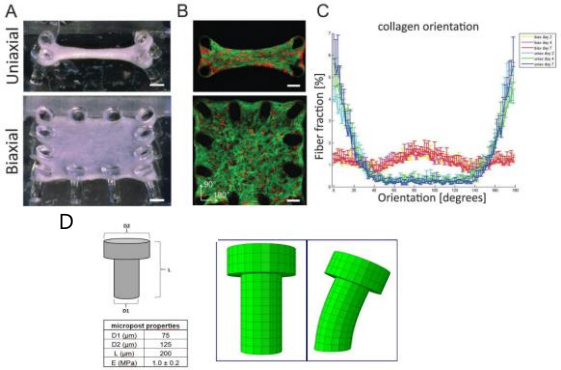

Figure 2: μTUG system with uniaxial or biaxial constraints to manipulate tissue organization and quantify tissue contractility. v. Spreeuwel et al., *Int Biol*, 2014.

Approach

hiPSC-derived cardiomyocytes (hiPSC-CMs) and cardiac fibroblasts (cFBs) are encapsulated in cardiac microtissues, composed of collagen I and Matrigel, and biaxially constrained between flexible micropillars to induce isotropic tissue organization and allow quantification of tissue contractility. Upon isotropic tissue formation, mechanical manipulation of the micropillars results in uniaxial constrained tissues, initiating tissue remodeling towards an anisotropic structure (Figure 3).

Using this approach, we can study how inducing anisotropy alters the phenotype and function of cardiac tissue. Moreover, we can model the mechanical forces that play a role during this transition.

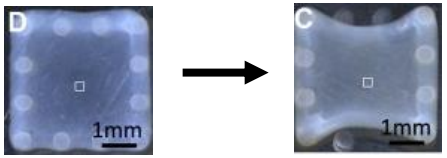

Figure 3: manipulation of mechanical constraints to induce anisotropic cell organization and matrix remodeling. Obbink-Huizer et al., *Biom Mod Mech*, 2014.

Conclusion In this study we present a 3D myocardial disease model that includes the loss of organization upon injury, an aspect often overlooked. With this model, we aim to gain insights on how we achieve anisotropic organization in the injured myocardium to aid cardiac regenerative therapies.

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