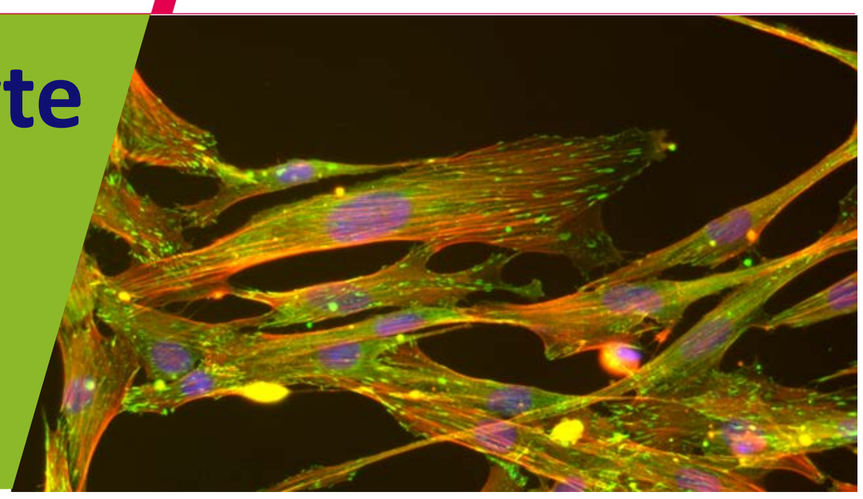
Cell-matrix interactions in cardiomyocyte progenitor cells upon cyclic strain

Cell-matrix interactions in cardiomyocyte progenitor cells upon cyclic strain

A. Mauretti, C. Sahlgren, F. Baaijens, C. Bouten

Eindhoven University of Technology, Eindhoven, The Netherlands



Introduction

After myocardial infarction (MI), the contractility of the heart is severely compromised, and scar tissue is formed. Human cardiomyocyte progenitor cells (CMPCs) injected in the injured myocardium have potential to replace death cardiomyocytes and repair the damaged heart [1;3]. Integration of the transplanted cells in the host tissue and their response to the biomechanical stimuli provided by the heart are crucial for a good outcome of the therapy. The development of focal adhesions (FAs) and actomyosin stress fibers (the **mechanosome**) allows cells to respond upon mechanical stimulation [1;2]. The key to transplanted CMPC integration and functioning in the heart might reside in mechanosome development and CMPC ability to respond to mechanical cues. Here we study the mechanosome of undifferentiated and predifferentiated CMPCs, and their response upon cyclic strain.

Methods

Cardiomyogenic differentiation of human L9TB CMPCs was induced by biochemical stimulation for 14 days (predifferentiated CMPCs) [3;4]. Uniaxial cyclic strain with 10% strain and 0.5Hz was applied to undifferentiated (undiff) and predifferentiated (prediff) CMPCs seeded on collagen IV-coated Bioflex membranes for 48h (Figure 1). Static samples were used as control.

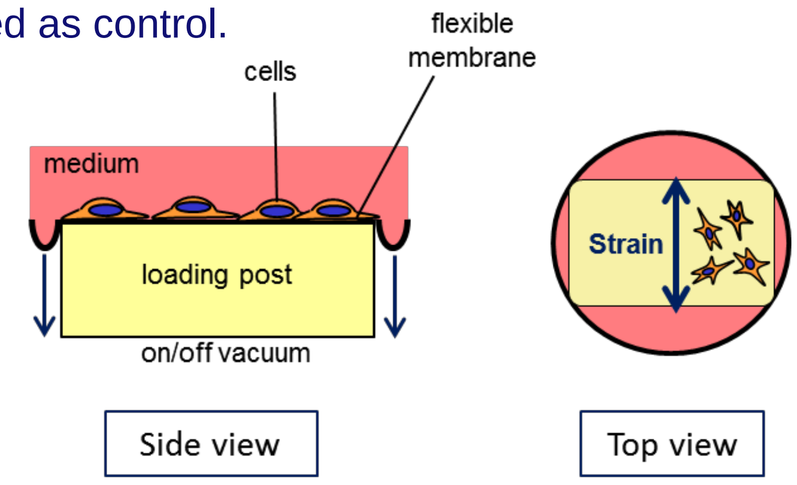


Figure 1: Experimental setup. Cyclic strain was applied with the FlexCell system.

Differentiation and the mechanosome

Prediff CMPCs developed mature FAs and actin stress fibers (the mechanosome) 24h after seeding. Undiff cells showed immature FAs, and no stress fibers were present (Figure 2). Cardiomyogenic differentiation is thus needed for the mechanosome development in CMPCs.

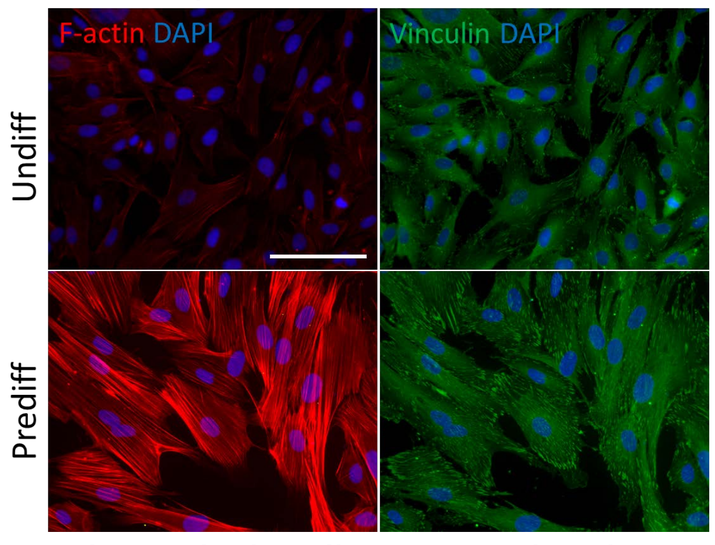


Figure 2: F-actin and vinculin expression in undiff and prediff CMPCs 24h after seeding on collagen IV-coated cover glasses. Scale bar 100 µm.

CMPC response upon cyclic strain

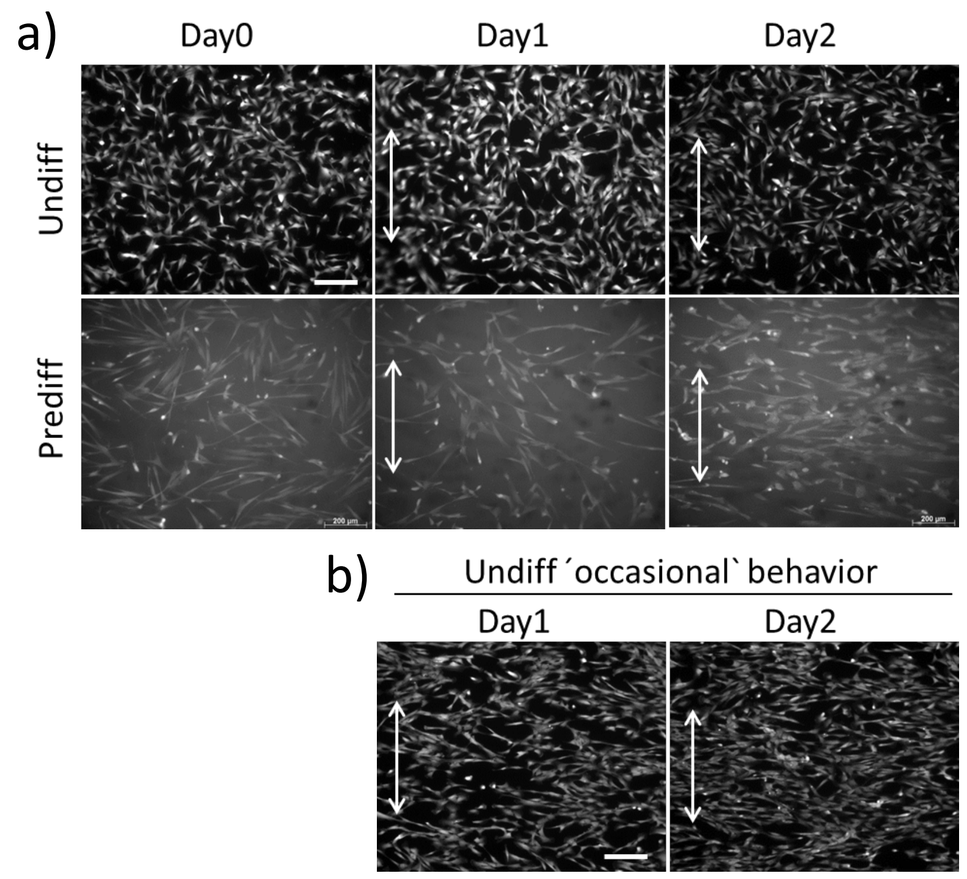


Figure 3: a) After one day of applied cyclic strain (Day1), both undiff and prediff cells mainly kept a random orientation. After two days of straining (Day2), prediff CMPCs showed a main orientation perpendicular to the strain direction (strain avoidance), whereas undiff CMPCs displayed the same behavior as Day1. **b)** Occasionally, undiff CMPCs showed strain avoidance at Day1, depending on their localization in the well plate, and maintained the same behavior at Day2. Scale bar 200µm.

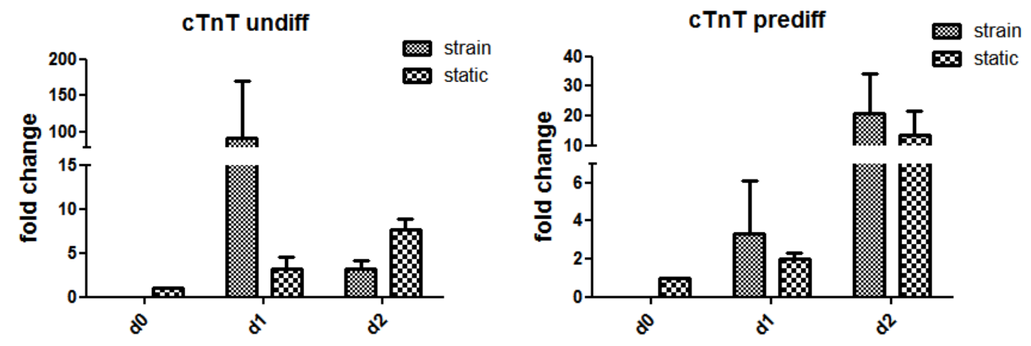


Figure 4: Upregulation of the late cardiac gene cTnT after one day of strain in undiff CMPCs suggests that cyclic strain might induce CMPC differentiation. Strain-induced differentiation might be responsible for the occasional cell alignment in response to mechanical loading.

Conclusions and future outlook

Our results indicate that human CMPCs are able to sense and respond to external mechanical cues only when cardiomyogenic differentiation is biochemically induced, thanks to the mechanosome development that follows differentiation. The occasional strain avoidance displayed by undifferentiated CMPCs might be due to strain-induced differentiation. This 2D study represents a first step toward future experiments in 3D, niche-like environments.

/Department of Biomedical Engineering

References:

[1] Pijnappels DA et al., Ann. N.Y. Acad. Sci. 2010;1188:7-14
[2] Kanchanawong P at el., Nature 2010;468:580-586
[3] Smits AM et al., Nature Protocols 2009;4(2):232-243
[4] Bax N, Marion MH et al., JMCC 2012;53:497–508