MATRIX STIFFNESS-TGF-B1 INTERPLAY REGULATES CARDIAC FIBROBLAST CONTRACTILITY

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Introduction

After myocardial infarction, cardiac fibroblasts adopt a myofibroblast phenotype that is characterized by elevated cell-generated contractile forces [1]. This increase in contractile forces contributes to activation of latent matrix-embedded TGF-β, increased wall stress, and fibroblast-to-myofibroblast transition, thereby promoting fibrosis, cardiac dysfunction, and heart failure [2-4].
Fibroblast contractility is regulated by the level of TGF-β1 and the degree of matrix stiffness, which are typically increased in the infarcted heart [5-6], yet it remains incompletely understood how these cues collectively influence cardiac fibroblast contractility. Here, we therefore investigated how TGF-β1 signaling and matrix stiffness collectively regulate cardiac fibroblast contractility.

Methods

Cardiac fibroblasts were obtained by successfully differentiating human pluripotent stem cells (hPSCs), which was verified using qPCR and immunostainings. These hPSC-derived cardiac fibroblasts were seeded on polyacrylamide (PAA) gels of different stiffness, ranging from healthy (~15 kPa) to infarcted (~100 kPa) myocardium, and stimulated with TGF-β1 or a TGF-β inhibitor (SB431542). After 24 hours on gels, cell-generated contractile forces were measured using traction force microscopy.

Results

Cardiac fibroblasts exerted contractile forces on the PAA gels which increased in magnitude with matrix stiffness (Figure 1). Additionally, we found that matrix stiffness regulated TGF-β1 responsiveness, resulting distinct mechanical behavior between TGF-β1 stimulated or inhibited cardiac fibroblasts in a specific range of matrix stiffness.

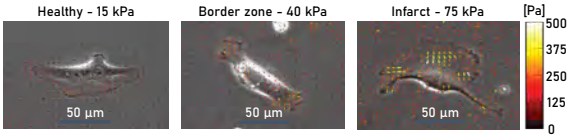

Figure 1: Representative overlays of traction force vectors on phase contrast images of cardiac fibroblasts (TGF-β1 stimulated) on PAA gels of different stiffness.

Discussion

The mechanical environment of the heart is crucial for its function, which is reflected by the detrimental effects that increased fibroblast contractility has on cardiac function [2-4]. Understanding how cardiac fibroblast contractility is regulated is therefore a crucial step to develop novel therapies to treat cardiac fibrosis. While the individual roles of TGF-β1 and matrix stiffness in regulating fibroblast contractility have been recognized [5], our findings show that an interplay exists between these cues. Our current efforts are aimed at identifying the underlying mechanism that links matrix stiffness to the TGF-β pathway.

References

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