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Emergent dynamics of cardiomyocyte clusters on deformable polymeric substrates

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ABSTRACT

Contractile dynamics of primary cardiomyocyte clusters is studied by culturing them on deformable thin polymeric films. The cell clusters beat and generate sufficient forces to deform the substrates out of plane. Over time, the clusters reorient their force dipoles along the direction of maximum compliance. This suggests that the cells are capable of sensing substrate deformations through a mechanosensitive feedback mechanism and dynamically reorganizing themselves.

In recent years, cardiomyocytes have emerged as a popular choice for bioactuators for powering biological machines consisting of soft polymeric scaffolds at the micro and macro scales [1–7]. This is owing to their unique ability to generate spontaneous, synchronous contractions consuming only glucose as their primary energy source [8]. Most of the biological machine designs reported in the literature use cardiomyocytes conjugated with biocompatible soft polymers like polydimethylsiloxane (PDMS) and hydrogels to produce some form of locomotion by converting chemical energy of the cardiomyocytes to mechanical energy. The mode of locomotion may vary, but the fundamental mechanism that these biological machines exploit to achieve locomotion stems from cell substrate interactions leading to large deformations of the substrates (relative to the cell size). However, the effect of such large scale, dynamic deformation of the substrates on the cellular and cluster level organization of the cardiomyocytes remains elusive.

It is known that cardiomyocytes are mechanosensitive to their local environment and are capable of sensing the substrate elasticity, among other mechanical factors, to remodel and reorganize their internal structures [9]. For example, cardiomyocytes generate highest force when cultured on hydrogel substrates mimicking the elasticity (∼10 kPa) of the heart tissue. The sarcomere alignment and beating frequency of cardiomyocytes are also influenced by substrate stiffness [10–13]. When cultured on polymeric micropillar substrates, the cells generated higher contraction forces on stiffer pillars at the expense of contraction rates. The sarcomere lengths and z-band widths also increase with stiffness [14].

Mechanical microenvironment plays an important role in the modulation of the adhesion structures of cardiomyocytes with substrates. The size and frequency of adhesion sites increase in response to externally applied stretch and cell contractility [15–18]. Force is estimated to be about 15 nN per focal adhesion site, and the net force dipole per cell is about 200–500 nN [19,20]. When cultivated on soft, flexible silicone membranes, the cells generate pleat like wrinkles with a spacing of 1.9 μm. The observed pleats align with the z-disks of the cells [21].

The aforementioned observations of cardiomyocyte mechanosensitivity to their local microenvironment raise the possibility that the large dynamic deformations of the biological machines may induce cellular reorganization in

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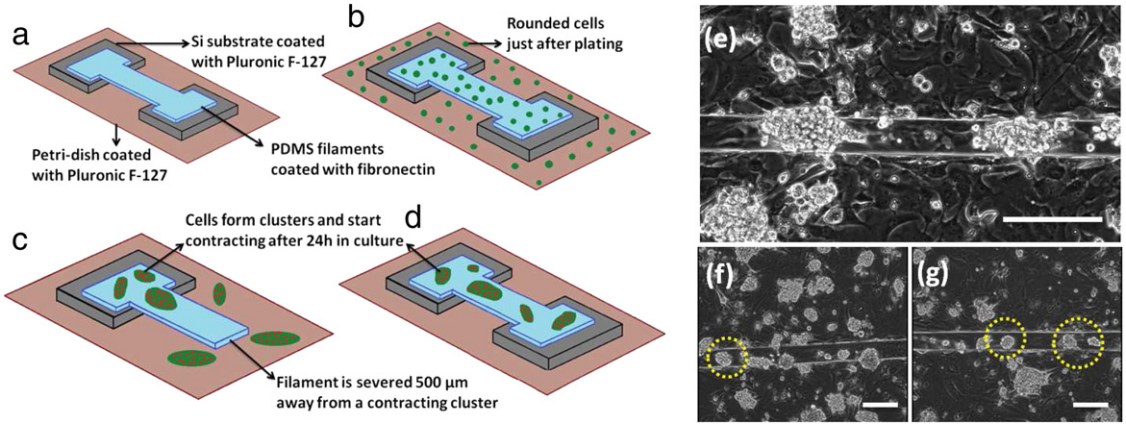

Fig. 1. Experimental platform to study cell-substrate dynamic feedback. (a) Initial configuration of the fibronectin functionalized filament on the substrate before cell plating. (b) Primary cardiomyocyte cells from neonatal rats are plated on the filaments. (c) The filament is severed μm away from a contracting cardiomyocyte cluster at the base of the cantilever after 24 h of cell plating. (d) Filament fixed at both ends. (e) Cardiomyocyte clusters on a narrow filament (30 μm wide). (f–g) Cell clusters on wide filaments (90 μm wide). Cell clusters are well within the width of the filament. (Scale bar: 100 μm).

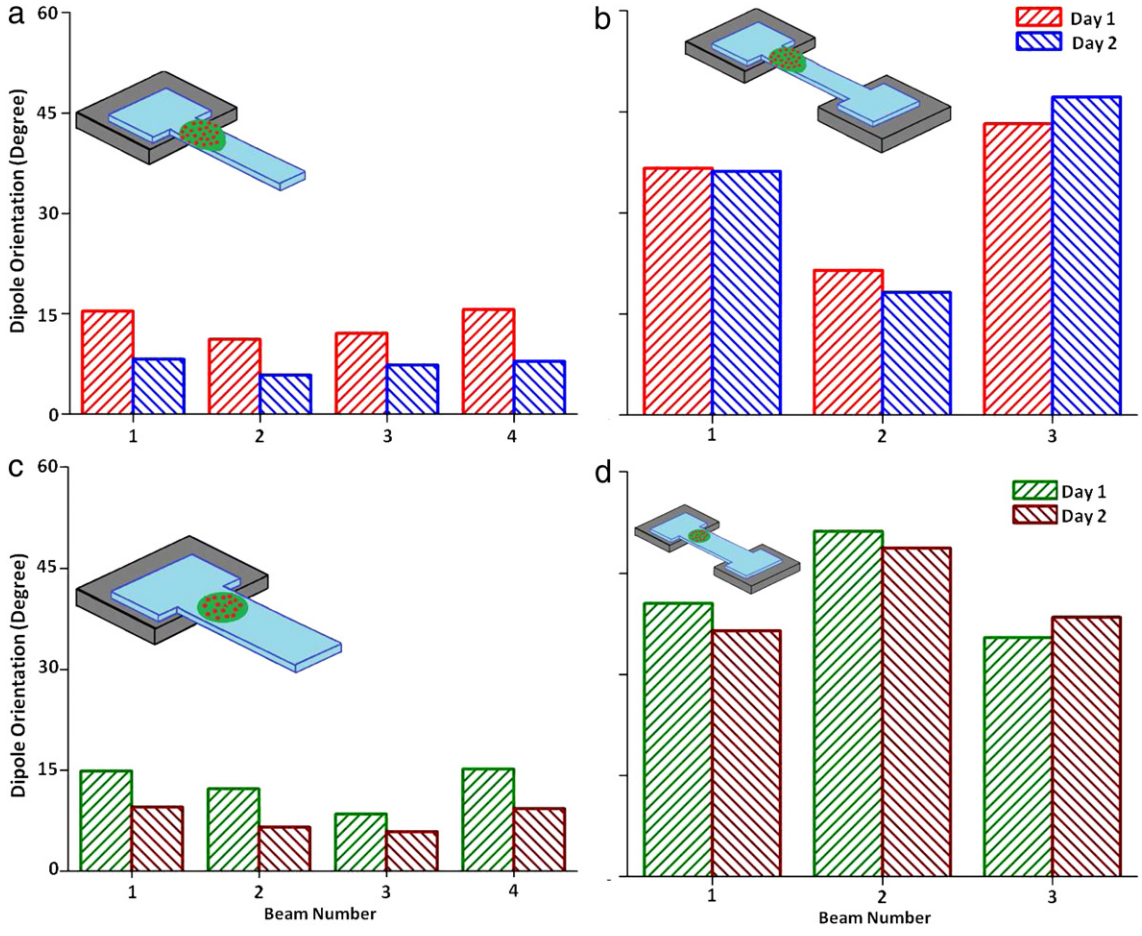

Fig. 2. Directions of contractile dipoles of cell clusters on filaments (see Fig. 1) become biased within 48 h. (a) Contractile force dipole directions of clusters on four different narrow cantilever filaments (free to deform) after 1 and 2 days of release (see Fig. 1). (b) Dipole directions on three different narrow fixed–fixed filaments. (c) Dipole directions on wide cantilever filaments, and (d) wide fixed–fixed filaments.

the contraction dynamics of the cardiomyocyte clusters. The objective of this study is to explore this possibility by plating clusters of cardiomyocytes on deformable film substrates with anisotropic compliance.

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