Cyclic strain anisotropy regulates valvular interstitial cell phenotype and tissue remodeling in three-dimensional culture

Russell A. Gould, Karen Chin, Thom P. Santisakultarm, Amanda Dropkin, Jennifer M. Richards, Chris B. Schaffer, Jonathan T. Butcher

Department of Biomedical Engineering, Cornell University, Ithaca, NY 14850, USA

1. Introduction

Planar connective tissues such as the diaphragm, pericardium, and valve leaflets perform critical biomechanical functions under cyclic mechanical loading [1,2]. These tissues have evolved complex multidirectional collagenous fiber orientations that result in anisotropic mechanical properties ideally suited to their local microenvironment. Resident tissue fibroblasts continuously repair and remodel their tissue microenvironment in response to these mechanical cues, including secreting and/or degrading extracellular matrix proteins, releasing soluble growth factors, and reorganizing cell–cell/cell–matrix adhesive interactions [3,4]. Fibroblasts transition between a quiescent synthetic phenotype, characterized by homoeostatic matrix turnover, to activated contractile myofibroblasts that change the underlying matrix mechanics and/or composition depending on the remodeling state of the tissue [5]. For example, during wound closure and fibrosis/scar formation, myofibroblasts elevate expression of contractile proteins and generate traction forces that create mechanical tension to pull matrix fibers together [6]. Heart valve leaflets are exposed to arguably the most demanding mechanical environment in the body, yet interstitial fibroblasts thrive and mediate significant matrix remodeling [7,8]. Mechanical microenvironmental cues therefore provide strong inductive signals regulating tissue homeostasis and remodeling, but how they mediate healthy instead of pathological tissue remodeling remains poorly understood.

Mechanistic understanding of fibroblast-mediated tissue remodeling has advanced considerably with the aid of engineered tissue models that enable testing of molecular, cellular, and tissue scale mechanisms within a well-defined, repeatable, and physiologically relevant microenvironment [9]. Fibroblasts in anchored three-dimensional (3-D) hydrogels develop mechanical tension leading to increased expression of contractile proteins, enhanced matrix synthesis, and release of growth factors such as transforming growth factor-beta (TGFβ), while fibroblasts in free-floating unstrained gels remain quiescent [10]. More recently, bioreactors have been developed to apply specific mechanical strain parameters uniformly to specimens so as to isolate the underlying signaling mechanisms [11]. For example, cyclic stretching of fibroblasts