Controlling Mesenchyme Tissue Remodeling via Spatial Arrangement of Mechanical Constraint

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Statement of Purpose: Tissue remodeling processes in normal development or disease progression strongly depend on the biomechanical properties of bulk tissues and mechanobiological responses of individual cells. By integrating biological tissues with engineered materials and designed structures, numerous efforts have been devoted to elucidating the relationship between tissue remodeling and fundamental biophysics. Despite these previous efforts, it is still elusive how tissue remodeling process evolves with different patterns of mechanical constraint. To address this, we created an *in vitro* tissue model from the mesenchymal stromal cells derived from human induced pluripotent stem cells (**hiPSC-MSCs**) using fabricated devices with different spatial arrangements of standing posts would influence the progression of tissue remodeling. Furthermore, we integrated a computational model based on volumetric contraction to predict the deformation across the constrained tissues. By tightly coupling tissue fabrication and multiscale modeling, this experimental-computational integrated model would shed light on tissue mechanics and morphological evolution under different designs of mechanical constraints.

Methods: The PDMS devices with different spatial arrangements of standing posts were generated from 3D-printed ABS molds and coated with 10% Pluronic Acid. hiPSC-MSCs were used to generate 3D mesenchymal tissue constructs around the standing posts. In this study, we primarily focused on two geometric designs of the tissue constructs: triangular shape with 3 standing posts and square shape with 4 standing posts. For each geometric design, we changed the side length of the tissue constructs (6 mm or 8 mm). Moreover, we imposed a center post for each design to study how it would affect the distribution of mechanical constraint and the progression of tissue remodeling. To simulate the morphogenetic evolution of tissue remodeling, we used a bulk contraction model with a time-dependent free-energy function to predict the stress distribution and the corresponding tissue deformation represented by gap and deflection. To model the maximal tissue contractility with fully developed stress fibers, the bulk contraction modulus of the tissue is fixed, while the elastic moduli are relaxed due to the viscoelastic behaviors of biological tissues.

Results: To characterize the tissue remodeling, two parameters of gap and deflection were measured from mesenchymal tissue constructs every two days for 11 days (**Fig. 1a**). The gap is defined as the distance between the furthest tip of the expanded loop to the post center and the deflection is defined as the distance between the tissue's outer edge and the geometric center. For the triangular tissue designs with different post distances and insertion of center post, we observed that the tissues of 8 mm side length without a center post had significant gap elongation as early as Day 3, while tissues of 8 mm with center post only showed an increase of gap starting Day 7. For 6 mm side length, the tissues without a center post showed an increase of gap starting Day 7, while the gap for the tissues with a center post remained relatively consistent over 11 days. Tissue compaction induced a decrease of deflection for all the tissues, but the tissues without center posts showed a faster decreasing trend, comparing to their counterparts with center posts respectively. This indicated that the insertion of a center post could alter the mechanical stress distribution and enhance the tissue stability during remodeling processes. Our simulations were able to reproduce the morphogenetic evolution of the tissue remodeling and mechanical stress distribution within the tissues that led to the gap extension and tissue compaction (**Fig. 1b**). The trend of gap extension and deflection compaction from the simulation results was consistent with the experimental results observed from the tissues with different designs. We also found that square tissue shape would lead to more prominent tissue remodeling with larger gap extension and deflection compaction.

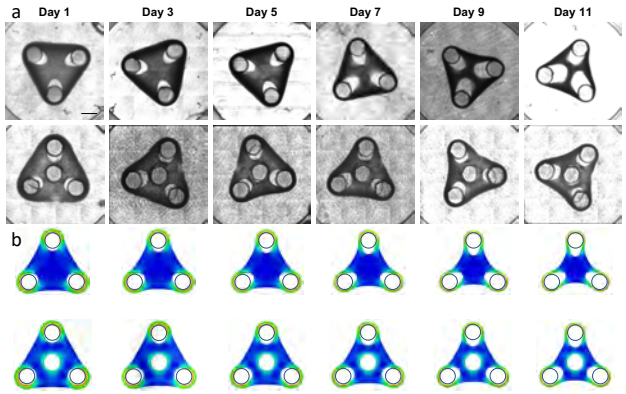

Figure 1. *(a) Experimental model and (b) computational model of mesenchymal tissue remodeling of triangular shape with and without a center post.*

Conclusions: We established an *in vitro* mesenchymal tissue model based on hiPSC-MSCs to study the tissue morphological evolution under the mechanical constraints. Meanwhile, we also developed a computational model to predict the stress distribution and the corresponding tissue deformation. This experimental-computational integrated model can be considered as a promising initiative for future mechanistic understanding of the relationship between mechanical design and tissue stability, which could possibly provide design rationale for tissue fabrication and manufacturing.