CLOSING THE GAP BETWEEN
TISSUE STRUCTURE- FUNCTION RELATIONSHIPS

by

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ABSTRACT

The majority of human diseases occur at the tissue level of cellular organization, but there is an information gap in understanding how tissue structure relates to tissue function, inhibiting disease diagnosis and cures. The current understanding of tissue structure-function relationships primarily describes interactions between individual tissue components, including cells and the extracellular matrix, but fails to quantify cooperative group dynamics between the elements of a tissue. We hypothesize that cells within a tissue work as a community, recognizing and responding to specific, quantifiable, structural, and physical spatial cues in order to perform collaborative tissue functions. This project attempts a more global understanding of tissue structure-function relationships by utilizing an interdisciplinary approach with two juxtaposing *in-vitro* model systems. The first model utilizes computer science graph theory to quantify the unique three-dimensional spatial organizations formed by normal cells with well established functions, versus corresponding cancer disease-states where tissue function has failed, in a collagen-I *in-vitro* tissue construct. The second model combines molecular and biomedical engineering techniques to explore tissue development by functionally undefined mesenchymal stem cells during differentiation, where we induced cell structure reorganization with PI3K inhibition causing a reciprocal change to the microenvironment which then further altered cellular functions. The first model, explored in specific aim one, yields distinct metric profiles identifying the compactness, clustering and uniformity of three-dimensional cellular organizations as quantifiable, global aspects of tissue structure necessary to differentiate between unique health states and tissue types. The second model, utilized in specific aim two, provides quantitative results describing the influence of the cyclical relationship between mesenchymal stem cell structure and the extracellular environment on mesenchymal stem cell differentiation and revealed a role for PI3K in regulating that relationship. The unique global approach to elucidating tissue-structure function relationships in this project collectively provide quantitative support that cells within a tissue act as a community to accomplish functional goals.