Matrix Elasticity Directs Stem Cell Fates – How Deeply Can Cells Feel?

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Abstract— **Cells make a number of key decisions by actively applying forces to the objects that they 'touch'. Naive mesenchymal stem cells (MSCs) from human bone marrow will be shown to specify lineage and commit to phenotypes with extreme sensitivity to tissue level elasticity. Soft matrices that mimic brain appear neurogenic, stiffer matrices that mimic muscle are myogenic, and comparatively rigid matrices that mimic collagenous bone prove osteogenic. Inhibition of the motor protein myosin blocks all elasticity directed lineage specification. While the results have significant implications for understanding physical effects of the in vivo microenvironment around cells and also for use of materials in biological studies and therapeutic applications of stem cells, they raise additional questions such as how far cells can feel. This question is addressed with MSCs and a series of gels of controlled thickness, with the results showing that cells probe microns into matrix.**

Keywords— **stem cells, matrix, elasticity, forces, differentiation.**

I. Introduction

Cellular organization within a multicellular organism requires a cell to assess its relative location, taking in multiple cues from its microenvironment. Given that extracellular matrix (ECM) consists of the most abundant proteins in animals and contributes structure and elasticity to tissues, ECM scaffolds likely provide key physical cues to tissue cells extending to processes such as stem cell differentiation [1]. In vivo, fibrous characteristics of ECM may be less prominent and less important than cell-scale elasticity: a cell engages ECM and actively probes it, sensing in deformation the elastic resistance that seems to characterize different tissues. Deformations propagate into the ECM and nearby cells but like the proverbial princess who feels a pea placed many mattresses below, the cell possesses feedback and recognition mechanisms that also establish how far a cell can feel. Initial experiments and computational modeling of cell and matrix mechanics lend insight into the sub-cellular sensitivity, propagating into the deformable nucleus [2] and manifested in molecular transitions detected by novel Mass Spectrometry methods [3]. Continuity of deformation from matrix into the cell and further into the cytoskeleton-caged and linked nucleus suggests mechanisms to directly modeulate processes such as differentiation of stem cells.

II. Methods and results

Cells feel their physical environment by applying traction stresses to matrix and then sensing mechanical response(s) at the cell-matrix interface. The propagation of deformations into elastic and homogeneous media is relatively long range, decaying as the inverse of the distance from the force source, but cells might not be very sensitive to much of the displacement field that they genereate. For thin gel substrates affixed to an underlying rigid substrate, the long range propagation of displacements will be affected. If the cells feel matrix displacements, then one would predict very different responses for cells on thin versus thick substrates.

The spread area of a cell is a simple morphological metric of cell state and can be used to identify the critical thickness of a compliant matrix at which cells start to feel a rigid substrate that is hidden beneath the cell. In general, cells spread more and generate more stress (prestress or tension) on matrices with higher E. A thin gel matrix on rigid glass is expected to be effectively stiffer than a thick version of the same matrix. The first study that aimed to assess how deep cells feel showed that smooth muscle cells do not change spread area when plated on either 5 μm or 70 μm thick polyacrylamide gels [2], but subsequent work with MSCs showed that cell spreading on matrices softer than $E \sim 5$ kPa is larger on sub-micron thin gels than on thicker substrate [1]. Differences in cell morphology extend into the cell to the nucleus, with increasingly distinctive nuclear changes with soft substrates thinner than a few microns. Ongoing transcript profiling studies are beginning to correlate changes in the expression of nuclear envelope and cytoskeletal genes with nuclear morphology, suggesting mechanical linkage and transduction processes.

III. Conclusions

The experimental results to date thus show that mechanosensitivity – at least in depth perception by cells – is limited to sub-cellular length scales. Ultimately, even if one's cells are not of royal descent, they seem to feel the difference not only between stiff or soft but also thick or thin matrix surroundings.

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