Emergent, collective behaviour of cell groups in long-range biomaterial mechanosensing

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INTRODUCTION

Cells attach to and exert tensile and compressive forces on extracellular matrix (ECM), 'measuring' the resultant deformation that develops. The degree of resistance of an ECM to deformation is dependent on its stiffness. Cells use information obtained in this way to make fundamental decisions in how to move, divide and differentiate. Stiffness is not only dependent of the elastic modulus of the ECM, however, but also on its dimensions. This has the corollary that single cells are able to sense underlying stiff substrata through soft ECMs at low (<10 μm) thicknesses[1]. Here, we hypothesised that groups of cells would be able to deform materials to a greater degree than individual cells, and therefore be able to act collectively to mechanosense underlying substrates or features at greater depths than individual cells.

METHODS

To test this, we fabricated polyacrylamide hydrogels in the range of 1 - 1000 μm in thickness and of 0.5 – 40kPa elastic modulus adhered to glass substrates. Hydrogel surfaces were then covalently modified with ECM proteins, and MG63 cells were plated on hydrogels either at low density or in compact colonies/islands. Cell density, cell aspect, and cell perimeter was measured by microscopy, and hydrogel displacement by time-lapse imaging of hydrogel-embedded fluorescence fiduciary beads.

RESULTS

The spreading of separated, single cells on soft (1kPa) hydrogels increased exponentially as function of decreasing hydrogel thickness, with a half maximal response at ~3.2 μm. Similarly, the spreading of cells within cell islands of defined area (4×10^4 - 4×10^5 μm^2). also increased exponentially as a function of decreasing hydrogel thickness, but with a much greater half-maximal response of 54 μm^2. Depth-sensing was dependent on Rho kinase activity. Hydrogel displacements were greater for colonies vs. single cells and for thick gels *vs.* thin gels.

CONCLUSIONS

These results support the notion that groups of cells act collectively to mechanosense rigid materials beneath elastic hydrogels at greater depths than individual cells. This raises the intriguing possibility that the collective action of cells in tissues such as epithelia may allow cells to sense structures of differing stiffness at comparatively large distances. This has implications in cell patterning and differentiation in development, in tissue healing, and in the design of implanted biomaterials.

REFERENCES

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