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INTRODUCTION

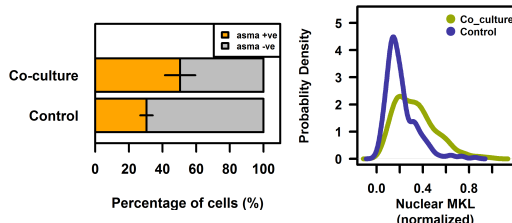
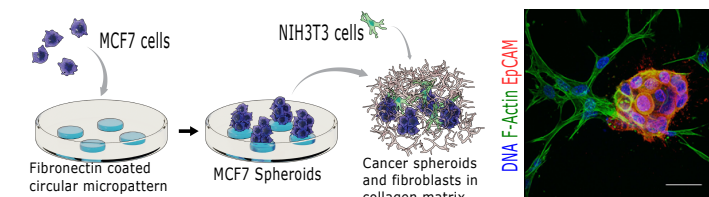
Fibroblasts are a heterogeneous group of cells comprising of subpopulations that have been found to be activated in the tumor microenvironment. These activated fibroblasts, often characterized by high expression levels of alpha-Smooth Muscle Actin (α SMA), are important regulators of tumor initiation and growth. Factors that modulate to such selective activation are not understood.

OBJECTIVE

Recent studies have suggested that the cellular perception of environmental signals are modulated by cell geometry^[1-2].

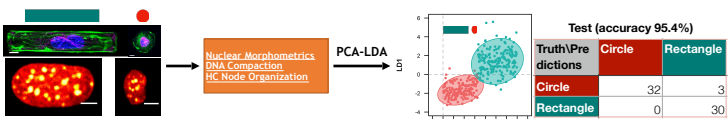
We aim to study the contribution of the intrinsic cell geometric heterogeneity in modulating the nuclear mechanotransduction of signals from the microenvironment, resulting in their selective activation of fibroblasts in the presence of cancer cells.

FIBROBLAST ACTIVATION IN 3D CO-CULTURE MATRIX

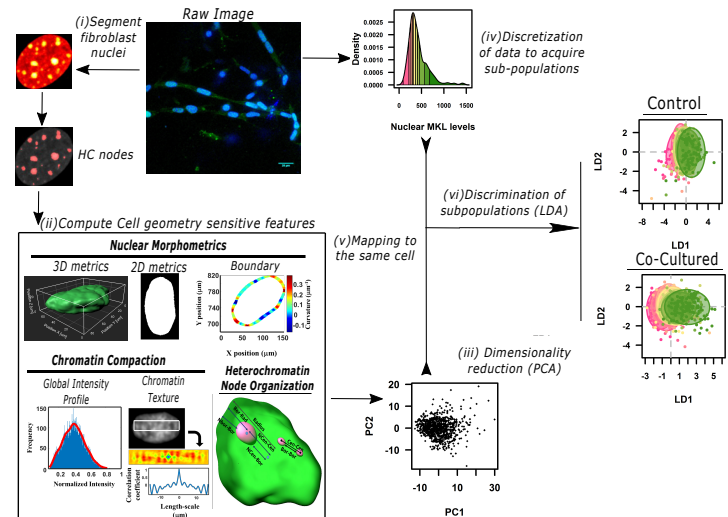


In the co-culture system there is increased TGF-beta signaling in fibroblast cells

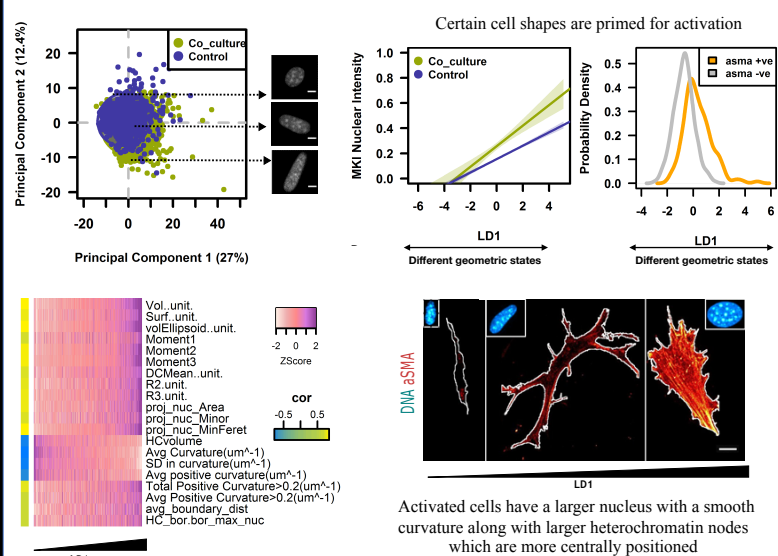
MAPPING CELL SHAPE TO ACTIVATION LEVELS



Nuclear morphometrics and internal chromatin organizational features are sensitive to and predictive of cell geometry

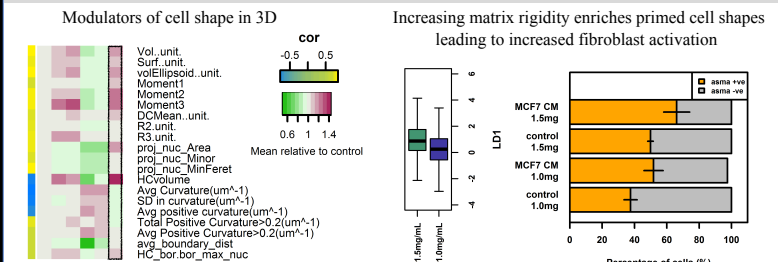


FIBROBLAST ACTIVATION IS COUPLED TO CELL SHAPE

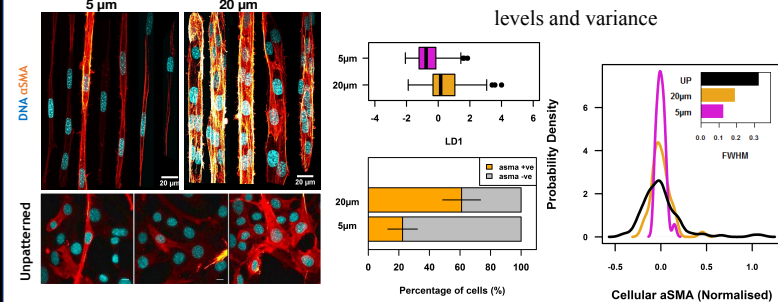


Activated cells have a larger nucleus with a smooth curvature along with larger heterochromatin nodes which are more centrally positioned

TUNING ACTIVATION BY CONTROLLING CELL SHAPE

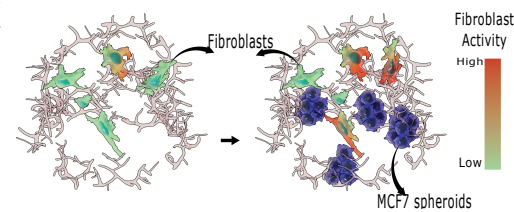


Controlling cell geometric heterogeneity allows control of fibroblast activation levels and variance



CONCLUSION

The nuclear enrichment of MKL, a TGF-beta effector transcription factor, is modulated by cell geometry. Such cell geometry dependent nuclear signaling leads to the selective activation (increased protein expression levels of α SMA), a target gene of MKL, in the presence of cancer cells.



Our study presents a framework for studying single cell heterogeneity and highlights the importance of the geometric state of fibroblasts in the interpretation of environmental signals.

REFERENCES AND FUNDING

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