Matrix Mechanics Modulate Cancer Plasticity

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Metastasis is the primary cause of cancer morbidity and mortality. High phenotypic heterogeneity and plasticity occurring in many cancer types are major contributing factors to tumour progression and metastatic spread. The tumor microenvironment (TME) consists of a complex assortment of multiple cell types and extracellular matrices, driving dynamic changes of phenotypic and molecular cell states. Model systems that mimic aspects of the TME are useful tools for probing signal transduction underlying disease progression.

Here, we show how mimicking the biophysical and biochemical attributes of the TME in spatially addressable *in vitro* models can be used to better probe cancer plasticity. Hydrogel micropatterning was utilised to coordinate substrate-cancer cell interactions, where confinement and stiffness trigger partitioning of different cell types in ways that mimic organisation *in vivo*. We have further developed mechanically tuneable 3D bioengineered tumour matrices to study the spatial organisation and dynamic phenotypic changes that are related to tumour growth and invasion processes.

Our results show that matrix stiffness and architecture differentially regulate plasticity in different cancer models. Our 3D matrices allow for precise and modular control of ECM properties and replicate the intricate mechanics-plasticity interactions observed in 2D.

The fabrication of multiple aspects of the TME allows better control over features responsible for progression, thereby providing improved tools for fundamental studies and drug development.