Role of Mechanical cues in the control and guidance of Glioma Progression

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Abstract

Glioblastoma (GBM) represents at present the greatest oncological challenge being one of the most incurable form of brain tumour with very poor prognosis. Evidence suggests that GBM cells sense and respond to gradients of extracellular matrix stiffness -durotaxis- with an increase of its malignant and invasive characteristics. Yet the durotactic role remains ill-defined due to the interference of other compounding stimuli (topographical and chemical) in the design of functional cell culture substrates. To address this problem, we studied the morphology and motility of *in vitro* GBM cells on uniform polydimethilsiloxane (PDMS) substrate with well-defined stiffness gradients that allowed a selected degree of decoupling of the mechanical chemical and topographic cues. To directly characterize the impact of local stiffness on directional migration, cells were imaged and tracked by time-lapse microscopy and tracking software. Preliminary data revealed that different GBM cell lines respond to a stiffness gradient with directed migration to stiffer or softer patterns in a cell type dependant manner. Pharmacological inhibition of non muscle myosin II-based contractility or its upstream regulator ROCK blunts this rigidity-sensitivity. Inhibition of microfilament contraction and polymerization of F-actin was sufficient to inhibit glioblastoma movement but not durotaxis, suggesting that alternative signalling is used to respond to durotactic directional cues. The speed and length of the directional migratory response to stiffness gradients was found to depend on the magnitude of stiffness of the microenvironment encountered by the cell. By isolating external environmental cues and controlling stiffness gradients, we will better understand if a durotactic mechanism has an overall or cancer-specific impact on disease progression.