

# MECHANICAL PROPERTIES OF HUMAN GLIOMAS AND MECHANORESPONSES OF GLIOBLASTOMA CELLS

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## Introduction

The stiffness of tissues, often characterized by their time-dependent elastic properties, is tightly controlled under normal condition and central nervous tissue is among the softest tissue in vertebrates. Changes in tissue and organ stiffness occur during development and are frequently symptoms of diseases such as fibrosis, cardiovascular disease and some forms of cancer. Primary cell isolated from various tissues often respond to changes in the mechanical properties of their substrates, and the range of stiffness over which these responses occur appear to be centred on the elastic modulus of the tissue from which they are derived. Both glial and neuronal cells differ from most other cell types in that they respond *in vitro* to a much lower range of stiffness than cells derived from stiffer organs, with glial cells activating cytoskeletal assembly with increasing stiffness but neuronal cells exhibiting inhibited neurite outgrowth and branching. Here we test the hypotheses that the stiffness of tumors derived from CNS (Central Nervous System) tissue differs from that of normal brain, and that transformed cells derived from such tumors exhibit mechanical responses that differ from those of normal glial cells.

## Results

Figure 1 shows that when the Young's moduli of 7 different human gliomas were measured by indentation, the average values were  $134 \pm 56$  Pa, the range from 90 to 141 Pa, and there was a significant lateral heterogeneity on a sub mm length scale. When probed to different depths ranging from 50 to 500 microns, there is evidence of slight strain stiffening. The magnitudes of these elastic moduli are well within the range of stiffness reported from normal brain, both grey and white matter, suggesting that the local stiffness, measured on a 100 micron to 1 mm length scale is not substantially greater for tumors compared to normal tissues. On the other hand, different classes of immortalized cells derived from

human glioblastoma show substantially different responses to the stiffness of substrates *in vitro*. When cultured on polyacrylamide gels with Young's moduli ranging from 200 Pa to 40 kPa and soft hyaluronic acid gels glioma cells attach and spread differently dependent on substrate stiffness and ECM (Extracellular Matrix) component used as a ligand.

## Discussion

Unlike breast and some other cancers where the stroma and the tumor itself is substantially stiffer than the surrounding normal tissue, the data here suggest that gliomas can arise without a gross change in the macroscopic tissue stiffness. However, the chemical and topographical features of the extracellular environment within gliomas is substantially different from that of normal brains, and some glioblastoma cells exhibit strongly altered response to substrates that contain different ECM components such as fibronectin or collagen 1 that are expressed at low levels in normal CNS but at much higher levels within tumorous.

## Figures

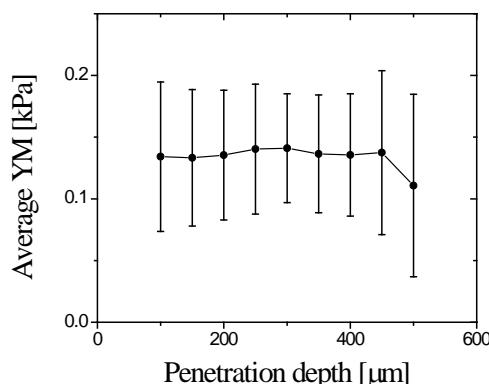


Figure 1: Glioma elastic modulus as a function of penetration depth expressed as a mean  $\pm$  standard deviation.