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COMPRESSION STIFFENING OF BRAIN AND ITS EFFECT ON MECHANOSENSING BY GLIOMA CELLS

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The stiffness of tissues, often characterized by their time-dependent elastic properties, is tightly controlled under normal condition and central nervous system tissue is among the softest tissues. Changes in tissue and organ stiffness occur in some physiological conditions and are frequently symptoms of diseases such as fibrosis, cardiovascular disease and many forms of cancer. Primary cells 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 limited to the tissue elastic modulus from which they are derived. Our goal was to test the hypotheses that the stiffness of tumors derived from CNS 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. Unlike breast and some other cancers where the stroma and the tumor itself is substantially stiffer than the surrounding normal tissue, our data suggest that gliomas can arise without a gross change in the macroscopic tissue stiffness when measured at low strains without compression. However, both normal brain and glioma samples stiffen with compression, but not in elongation and increased shear strains. 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 grown on soft polyacrylamide and hyaluronic acid gels. This outcome supports the hypothesis that compression stiffening, which might occur with increased vascularization and interstitial pressure gradients that are characteristic of tumors, effectively stiffens the environment of glioma cells, and that *in situ*, the elastic resistance these cells sense might be sufficient to trigger the same responses that are activated *in vitro* by increased substrate stiffness.