Defining the role of nuclear envelope stress in glioblastoma

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Glioblastoma (GBM) is the most common and aggressive primary brain tumor, with a median survival of only 15 months after diagnosis and no cure. A key challenge in treating GBM is its heterogeneity, as glioma stem-like cells (GSCs) can self-renew, change phenotype, and interact with the surrounding tumor microenvironment. While intensive GBM research has revealed a variety of molecular alterations, less attention has been given to the altered biophysical properties. Yet, GSCs experience vastly different mechanical forces than their non-transformed counterparts. We and others have found that these forces cause nuclear envelope (NE) stress, disrupting cell homeostasis, and triggering DNA damage and inflammation. To understand the impact of NE stress on GBM aggressiveness, we are now investigating how GSCs respond to mechanically induced NE stress and to what extent their vulnerability to NE stress correlates with cell state plasticity. To do so, we have first documented the levels of crucial NE stress regulators such as lamins in a panel of patient-derived GSCs. This revealed that the level of Lamin A/C was the highest in a more aggressive GSC cell line. Next we have implemented a mechanical compression paradigm, which we calibrated with astrocytoma cell lines stably expressing two NE stress reporters (BAF and cGAS). We found that both reporters mobilize rapidly to NE lesions, but demonstrate distinct dissolution kinetics. We also found that depleting A-type lamins sensitizes cells to significant NE stress at a moderate confinement level, underscoring their significance. Subsequently, we are evaluating the impact of mechanical confinement on NE stress in the panel of GSCs and exploiting the reporter system for in-depth proteomics analysis to unveil putative novel NE stress regulators. This way, we intend to increase our understanding of GBM pathology progression and contribute insights that could open novel therapeutic avenues for this devastating disease.