Integrated stress response as a means for targeting GBM stem cells

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Glioblastoma multiforme (GBM) is the most prevalent and aggressive form of adult primary brain tumor. Standard of care includes maximal tumor resection followed by temozolomide and radiation therapy. Despite trimodality therapy, these tumors invariably recur. Glioma stem cells (GSCs) have been implicated as a contributing factor in tumor recurrence and therapeutic resistance. Reports in the literature have indicated that activation of the integrated stress response (ISR) may be a promising strategy to target this population of cells. Utilizing a novel ISR-inducing compound that we identified from a cell-based luciferase reporter screen, we tested GSCs’ sensitivity to treatment with this small molecule including both evaluation of differentiation and apoptosis. We found that treatment with this lead compound produced significant effects, such as apoptosis and reduced stemness, in human glioma CSCs through the induction of an integrated stress response.