

The Glioblastoma Multiforme Brain Tumor Research Grant

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Identification of therapeutic targets in glioblastoma stem cells

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Abstract

The vast majority of glioblastoma (GBM) patients will develop tumor recurrence despite being treated with near-total resection and postoperative radiation/chemo therapy. However, the molecular mechanisms underlying persistent tumorigenesis and treatment resistance are still poorly understood. Laboratory evidence indicates that GBM tumors contain a small population of CD133+ neural stem-like cells capable of initiating and repopulating tumors in animals; therefore, these so-called GBM stem cells are likely to be responsible for brain cancer recurrence. We **aim to** identify the functional marker(s) specific to GBM stem cells that potentially can serve as therapeutic target(s). To carry out this goal, we have established a culture system that allows for retrieving expandable CD133+ GBM stem cells from primary human GBM cell cultures. We have validated the identity of these cultured CD133+ GBM cells by demonstrating their ability to form CD133+ spheres in culture and to initiate tumor formation in mouse brains in vivo. In contrast, autologous CD133- GBM cells showed no tumorigenic potential. To identify GBM stem cell-specific genes, we will perform comparative analysis of genome-wide transcription profiles of CD133+ GBM cells relative to autologous CD133- GBM cells. Genes that are overexpressed in CD133+ GBM cells, but not expressed by autologous CD133- GBM cells, will be selected as candidate genes. The list of candidate genes will be further refined by selecting those genes that are shared by all tumorigenic CD133+ GBM cells derived from multiple patients. To validate the function of candidate genes in CD133+ GBM stem cells, we will use a short hairpin RNA (shRNA)-based cell microarray for high-throughput loss-of-function screens mediated by the silencing of targeted candidate genes. If a defined shRNA that knockdowns a particular gene expression has led to the suppression of sphere formation of CD133+GBM cells, animal experiments will be performed to further verify the efficacy of gene-targeted loss of tumor-initiating ability. We **anticipate 6-8 months** for identifying the candidate genes specific to GBM stem cells in vitro, and **another 6-8 months** for completion of the final verification of gene function in vivo.