CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP100437

Project Title:
Can glioblastoma growth be suppressed by targeting glutamine metabolism?

Award Mechanism:
High Impact/High Risk

Principal Investigator:
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Entity:
The University of Texas Southwestern Medical Center

Lay Summary:

Glioblastoma (GBM) affects 14,000 Americans annually and is the deadliest primary brain malignancy. Survival statistics are dismal, with an average life expectancy of only 14.5 months despite maximal therapy with surgical resection, radiation and temozolomide. This underscores a desperate need for novel therapeutic strategies. Attacking tumor metabolism has outstanding therapeutic potential because tumorigenesis requires specific metabolic activities to drive cell growth. This metabolic 'transformation' is triggered by mutations in tumor suppressors and oncogenes, suggesting that targeting tumor metabolism will be effective and well-tolerated. Through extensive study of the metabolism of GBM cells, we identified a new pathway involving the amino acid glutamine. This pathway is critical for the growth of GBM cells in culture, and we have identified the enzymes and transporters responsible for maintaining its activity. We hypothesize that glutamine metabolism is also required for GBM growth in animal models of cancer and in humans. We will study GBM metabolism in an "orthotopic" mouse model, in which human tumor tissue is implanted into the mouse brain. Then, tumor cells will be modified genetically to selectively impair individual steps of the glutamine metabolic pathway, and these modified cells will be implanted into new mice to test their ability to form tumors. We hope to identify specific enzymes that can be targeted to slow tumor growth and to prolong the survival of the mice. We anticipate that these studies will improve our understanding of the metabolism of tumorigenesis and will identify novel therapeutic targets for GBM. If this work is successful, we will plan future studies to identify pharmacological inhibitors of the key metabolic steps, with the hope of translating these findings into clinical studies.