**New Therapies For Glioblastoma: A Focus On Metabolism**

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**Research**

Gliomas are the most common type of primary brain tumours that mainly arise from glial cells and the degree of malignancy is categorised on the World Health Organization (WHO) grading system scale from I to IV. Grade I tumours are benign and can be cured with surgical resection. Grade II tumours are low-grade malignancies, but early diffuse infiltration of the surrounding brain renders them incurable by surgery and grade III tumours exhibit increased anaplasia and proliferation over grade II tumours, with a median survival in patients of 3.5 to 5 years. Grade IV tumours (also called glioblastoma or glioblastoma multiforme (GBM)) exhibit more advanced features of malignancy and aggressively infiltrate the brain.

Surgical resection, followed by post-operative radiotherapy and the chemotherapeutic temozolomide is the standard of care for glioblastoma patients. However, the overall prognosis for glioblastoma patients remains very poor with a median survival of only 15 months and a 5-year survival of only 10%. Many strategies over the last 2 decades have been pursued to improve the survival outcomes of these patients, with the most common being the addition of newer agents to the backbone of surgery and the chemo-radiation protocol. To date, none of these agents have shown additional benefit. A major problem is that the definitive drivers of glioblastoma progression have not been completely discovered.

**Outcome**

Alterations of metabolic activities support the malignant properties of cancer cells; however, the role of lipid metabolism in primary brain cancer biology has received relatively little attention. We have now generated a genetic model of glioblastoma to understand how specific alterations in lipid accumulation can lead to the pathogenesis of this disease. Our finding demonstrates that glioblastoma cells utilize differences in metabolic processes driven from fats (called lipids) allowing tumour cells to advantageously grow at greater rates to normal brain cells. Secondly, we investigated the relationship between hypoxia and lipid metabolism in glioblastoma. Hypoxia develops very early during tumour establishment due to an inadequate blood supply around the tumour. Hypoxia is regarded as a major determinant of tumour aggressiveness because it induces remodelling of the metabolic landscape, promotes progression and causes therapeutic resistance. Our results suggest that products of lipid breakdown are an important fuel source required to meet the biosynthetic and bioenergetic demands of malignant growth during hypoxia. This represents an important conceptual advance, as currently there is scarce understanding of the pathways that sustain the high metabolic demands imposed on glioblastoma cells during hypoxia. Importantly, we have also identified two agents that are capable of inhibiting these lipids driven metabolic processes. We therefore aim to test these agents to determine whether they can inhibit glioblastoma progression in animal model. Overall, our data shows that glioblastoma cells have unique lipid metabolic dependence that can be exploited for therapeutic gain.

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