GEORGETOWN UNIVERSITY
Georgetown University Medical Center
Department of Biochemistry and Molecular & Cellular Biology

The Department of Biochemistry Presents:

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12pm - 1pm

Leveraging synergistic metabolic therapies in glioblastoma: PI3K inhibitors and the ketogenic diet

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Glioblastoma (GBM) remains a poorly treatable disease with high mortality. Targeted therapies have gained interest in this disease, but efficacy is limited by therapeutic resistance, often because of tumor heterogeneity. Phosphoinositide 3-kinase (PI3K) inhibitors represent a strong drug class for GBM, but their use is associated with insulin feedback that reactivates the PI3K pathway and drives therapeutic resistance. Here, we target insulin feedback that is the primary mechanism of PI3K inhibitor-related therapeutic resistance in GBM using the ketogenic diet. We treated patient-derived GBM stem cells with vehicle or the pan-PI3K inhibitor, BKM-120, in conjunction with phenformin to decrease glucose utilization. These cells exhibited 65% less proliferation when exposed to BKM-120 and phenformin. We then treated NOD scid gamma (NSG) mice containing patient-derived GBM xenografts with vehicle or BKM-120 on a regular or ketogenic diet to determine whether reducing insulin feedback increases BKM-120 efficacy. Mice with intracranial GBM xenografts survived longer and grew smaller tumors when treated with BKM-120 on the ketogenic diet than with BKM-120 or the ketogenic diet alone. We measured pro-inflammatory cytokines in GBM cells treated with BKM-120 and phenformin in comparison to vehicle-treated cells to determine their effect on neuro-inflammation. We also applied conditioned medium from GBM cells treated with BKM-120 and phenformin to cortical neurons to measure oxidative stress. We found that phenformin reduced the production of pro-inflammatory cytokines, including TNF-alpha, IFN-gamma, IL-1beta, and IL-6, by BKM-120-treated GBM cells. Cortical neurons treated with conditioned medium from BKM-120- and phenformin-treated glioma cells exhibited less oxidative stress than those treated with BKM-120 alone. Additionally, we re-analyzed results of a multi-institutional clinical trial testing the effects of BKM-120 in patients with recurrent GBM. We found that patients given BKM-120 exhibited higher serum glucose levels and that their glucose levels inversely correlated with progression-free survival. These findings indicate that BKM-120-mediated insulin feedback may have contributed to poor progression-free survival in this trial. Our results demonstrate that lowering glucose utilization and insulin feedback increases efficacy of PI3K inhibition and decreases neuro-inflammation. By using the ketogenic diet to reduce systemic glucose levels, this strategy may enhance efficacy and reduce morbidity of PI3K inhibitors in this population.

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