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Metabolic targeting of glioblastoma cells

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Brain tumor account for less than 2% of all primary cancers; however still 1860 new cases of malignant gliomas are diagnosed each year in England and Wales. Standard care of treatment for patients with glioblastoma is surgery followed by adjuvant radiotherapy and chemotherapy. However, glioblastoma is a highly aggressive and infiltrating tumor and in spite of advances in radiotherapy, chemotherapy and surgical technique, there has not been significant improvement in patient survival. As cure for GBM remain elusive, it is important to identify new treatment modalities as well as modify existing therapies to possibly change malignant gliomas from a deadly disease into a chronic one. In this study, we initially investigated the effect of glucose deprivation on adult glioma cell viability. We have shown that glucose deprivation induced glioma cell death in vitro. We have also shown that free radical scavenger N-acetylcysteine and methyl pyruvate suppressed glucose deprivation induced cell death. We have shown that glucose deprivation induced cell death is not mediated by apoptosis, autophagy or necrosis. Glucose deprivation led to energetic and endoplasmic reticulum (ER) stress in glioma cells. We have also shown that hypoxia rescued glucose deprivation induced cell death whereas glutamine withdrawal had no effect on glucose deprivation induced cell death. We have shown that glucose deprivation and hypoxia promotes glioma cell migration. We then showed that metformin significantly enhanced glucose deprivation induced cell death which was not mediated by apoptosis, autophagy, necrosis or oxidative stress. We have also shown that AMPK mimic AICAR also promoted glucose deprivation induced cell death whereas 2-deoxyglucose (2DG) suppressed glucose deprivation induced cell death. We have also shown that metformin potentiated glucose deprivation induced energetic stress whereas it suppressed ER chaperone protein GRP78. We have shown that metformin and 2DG combination led to significant cell death in glioma cells which were caspase independent and not mediated by oxidative stress. Finally we have also showed that metformin potentiated 2DG mediated pAMPK up-regulation whereas it down-regulated 2DG mediated autophagy and ER chaperone protein GRP78 to induce cell death.

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