Metformin Boosts Temozolomide Response in Glioblastoma: Insights from Patient-Derived Models and Multimodal Imaging

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Glioblastoma (GBM) is the most aggressive primary brain tumor and today is still incurable despite efforts like surgical intervention, coupled with radiation and chemotherapy utilizing temozolomide (TMZ). In a previous study, we demonstrated that Metformin (MET), a metabolic drug, increased the efficacy of TMZ in a classical phenotype of GBM cells. Here, we assess the efficacy of MET as add-on therapy to TMZ on patient-derived orthotopic xenografts models (PDOX) from mesenchymal and proneural GBM sphere-forming cells (GSCs) using a multimodal imaging approach.

NSG mice were intracranially injected with mesenchymal (MES1312) or proneural (PN0605) luciferase-expressing patient-derived GSCs and assigned to four treatment groups: vehicle, TMZ, MET, or both. Tumour growth was monitored weekly via Bioluminescence imaging (BLI). One week after treatment began, [^{18}F]FLT-PET was used to assess early response. Brains were collected post-sacrifice for immunohistochemistry (IHC).

Survival analysis revealed that the MES1312 GBM model was more aggressive than the PN0605 model, with a lower median survival (67 vs. 102.5 days). In the MES1312 GBM subtype, the combination of TMZ and MET extended the disease-free interval and reduced recurrence rates. In contrast, PN0605 tumors exhibited slower proliferation, as reflected in the comparable survival of vehicle- and MET-treated groups (102 and 98 days, respectively). However, PN0605 tumors did not respond to either TMZ alone or the combined treatment, as shown by stable BLI signal emission. MES1312 tumor-bearing mice showed high [18F]FLT uptake in the control group, which was significantly reduced following TMZ or TMZ+MET treatment. IHC also revealed distinct microglial morphology (IBA1 marker) between tumor region, where it appeared ameboid in nature, and the contralateral regions, where it appeared more ramified (MES1312 model). These findings underscore the heterogeneity between GBM subtypes and highlight the therapeutic potential of combined TMZ and MET treatment specifically in aggressive MES1312 tumors.

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