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Enhancing temozolomide efficacy in glioblastoma with metformin: insights from multimodal imaging in patient-derived models

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Glioblastoma (GBM) is the most aggressive primary brain tumor and despite efforts like surgical intervention, coupled with radiation and chemotherapy utilizing temozolomide (TMZ), today is still incurable with a very poor prognosis. In a previous study, we demonstrated that Metformin (MET), a metabolic drug that acts on the PI3K/AKT pathway, increased the efficacy of TMZ in a classical phenotype of GBM cells. Here, we evaluate 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, [18F]FLT-PET was used to assess early response, measuring tumour-to-contralateral (CL) uptake ratios. Brains were collected post-sacrifice for immunohistochemistry.

Survival analysis showed a greater aggressiveness of the mesenchymal model than the proneural model, with a lower median survival (67 days vs 102,5 days). In this TMZ-sensitive mesenchymal GBM subtype, the combined treatment increased disease-free window reducing also the recurrance rate. PN0605 tumors had a lower proliferation rate confirmed by the mean survival of vehicle and MET groups (102 and 98 respectively). Unfortunately, PN0605 tumors neither responded to TMZ nor to the combined therapy in terms of decrease in emission of BLI signals. MES1312 tumor-bearing mice showed a high [18F]FLT tracer uptake in control group which was significantly reduced after TMZ and TMZ+MET. Immunohistochemical analysis also revealed a difference in microglia morphology (marker IBA1) between tumor and contralateral regions, especially in the mesenchymal model.

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