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TITLE

Infiltrative and drug-resistant slow-cycling cells support metabolic heterogeneity and adaptability in glioblastoma

HYPOTHESIS:

We hypothesize that functionally different glioblastoma (GBM) cell subpopulations depend on distinct metabolic pathways for their growth and survival.

BACKGROUND/AIMS:

The objective of this study is to characterize the metabolic landscape in GBM and explore tumor cell metabolic specificities as targetable vulnerabilities. Metabolic reprogramming, known as the Warburg effect, has been described in rapidly growing tumors, which are thought to contain cells, which have impaired mitochondrial function and rely mostly on aerobic glycolysis to fulfill their energy requirements. This study aims at first, determining whether all GBM cells exhibit this metabolic shift, thus demonstrating the existence of metabolic heterogeneity and adaptability.

METHODS:

We used three patient-derived cell lines and performed a combination of bioinformatics and metabolomics analysis, molecular biology assays, in vitro and in vivo functional testing, flow cytometry, and cellular microscopy to elucidate the different metabolic phenotypes expressed in human GBM.

RESULTS & CONCLUSIONS

We show that GBM slow-cycling cells (SCCs) display enhanced invasion and chemoresistance, underscoring their role in tumor recurrence. We demonstrate that fast-cycling cells harness aerobic glycolysis while SCCs utilize oxidative phosphorylation to support their growth and survival. SCCs demonstrate increased lipid content that is specifically metabolized in nutrient-deprived conditions. This elevated lipid content correlates with a rich network of autophagosomes/lysosomes, network that has been shown to be involved in catabolic pathways providing energy to tumor cells in response to metabolic stress. Furthermore, SCCs demonstrate increased fatty acid transport, which is prevented by FABP3 and FABP7 transporter inhibition. Importantly, pharmacological inhibition of FABP7 also decreases the proliferation and survival of SCCs in lowered glucose level conditions.

Our studies highlight the presence of GBM cellular subpopulations with distinct metabolic activities as well as identify lipid pathway components that could be pharmacologically targeted to inhibit the growth of highly infiltrative and treatment-resistant SCCs.