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

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INTRODUCTION: Bioenergetics has recently been garnering attention as a promising avenue for the development of anti-cancer therapies. Many cancers, including brain tumors, have long been thought to undergo widespread metabolic reprograming, with most tumor cells relying exclusively on glucose fermentation for rapid energy production. Recently, metabolic heterogeneity has been described in animal models of glioblastoma (GBM), suggesting that these tumors do not exclusively rely on aerobic glycolysis. However, the precise nature of the cellular compartments harboring those various metabolic specificities has not been established yet.

OBJECTIVES: We previously reported cellular diversity in GBM based on cell cycle kinetics and described the presence of fast-cycling cells (FCCs) and slow-cycling cells (SCCs). SCCs exhibit enhanced tumorigenicity and treatment resistance, thus representing attractive therapeutic targets. Actively proliferative cells depend on aerobic glycolysis but SCCs appear to mostly rely on oxidative phosphorylation. Our objective is to characterize the GBM metabolic landscape and explore tumor metabolism as a targetable vulnerability specific to FCCs and treatment-resistant SCCs.

METHODS: GBM patient-derived FCCs and SCCs, which were isolated by flow cytometry based on their dye-retention properties, were compared with respect to their metabolic properties and adaptabilities.

RESULTS: Our study reveals the existence of a metabolic dichotomy between subsets of GBM cells. We found that SCCs are refractory to conventional treatment, drive tumor relapse, and do not rely on glucose fermentation, but rather exhibit functional mitochondrial oxidative activity that can be therapeutically targeted *in vitro* and *in vivo*. SCCs up-regulate lipid transport, storage, and metabolism, supporting their ability to survive and adapt to metabolic stresses such as glucose restriction.

CONCLUSION: Our studies characterize specific cellular subtypes/states with distinct metabolic characteristics, supporting the concept of metabolic heterogeneity and adaptability in GBM. Our findings also identify lipid pathway components whose pharmacological inhibition can deplete cell subpopulations associated with tumor recurrence.