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Abstract
Title: Metabolic Landscape Changes and Ferroptosis in Recurrent Glioma

Low-grade gliomas (LGGs) represent 10-20% of all primary central nervous system tumors. While mutations in isocitrate dehydrogenase-1 (IDH1) are a defining feature of LGGs, recurrence is frequent and often leads to aggressive high-grade glioma. Approximately 70% of LGG patients progress to high-grade glioma within a decade. Recent studies suggest that glioblastomas (GBMs) can be sensitized to ferroptosis, an iron-dependent form of cell death, yet this phenomenon remains unexplored in LGGs. Our ongoing research aims to investigate the role of ferroptosis in a novel cellular model of IDH1-mutated glioma. We are utilizing murine glioma cell lines expressing either IDH1WT or IDH1R132H (IDH1 mutant), which are serially transplanted into immune-competent mice to develop C266-6 (wildtype, IDH1WT) and C266-2 (mutant, IDH1R132H) cell lines. Current studies involve assessing ferroptosis-related activity and RNA expression profiles under various basal and treatment conditions. Preliminary findings indicate that IDH1 mutant cell lines exhibit resistance to ferroptosis induction compared to IDH1 WT glioma cells. Ferroptosis-related RNAs and proteins including Nrf2 and Keap1, have shown to be differentially expressed in IDH-1 mutant cells at baseline via RT-qPCR. RNA analysis has shown overexpression of Nrf2 and Keap1, which are involved in redox balance, tumorigenesis, and resistance to anti-cancer therapies. In contrast, there is a significant decrease in the expression of Slc7a11, a crucial gene in cysteine and ferroptosis regulation and a known target of Nrf2. In summary, our study is characterizing a new cell-based model for both WT and IDH1 mutant LGGs, emphasizing that ferroptosis is a critical cell death pathway differentiating these cells. This research could potentially provide novel therapies for IDH mutated cancers.