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Glioblastomas: Hijacking Metabolism to Build a Flexible Shield for Therapy Resistance

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Abstract

Significance: Glioblastomas (GBMs) are among the most lethal tumors despite the almost exclusive localization to the brain. This is largely due to therapeutic resistance. Radiation and chemotherapy significantly increase the survival for GBM patients, however, GBMs always recur, and the median overall survival is just over a year. Proposed reasons for such intractable resistance to therapy are numerous and include tumor metabolism, in particular, the ability of tumor cells to reconfigure metabolic fluxes on demand (metabolic plasticity). Understanding how the hard-wired, oncogene-driven metabolic tendencies of GBMs intersect with flexible, context-induced metabolic rewiring promises to reveal novel approaches for combating therapy resistance. ***Recent Advances:*** Personalized genome-scale metabolic flux models have recently provided evidence that metabolic flexibility promotes radiation resistance in cancer and identified tumor redox metabolism as a major predictor for resistance to radiation therapy (RT). It was demonstrated that radioresistant tumors, including GBM, reroute metabolic fluxes to boost the levels of reducing factors of the cell, thus enhancing clearance of reactive oxygen species that are generated during RT and promoting survival. ***Critical Issues:*** The current body of knowledge from published studies strongly supports the notion that robust metabolic plasticity can act as a (flexible) shield against the cytotoxic effects of standard GBM therapies, thus driving therapy resistance. The limited understanding of the critical drivers of such metabolic plasticity hampers the rational design of effective combination therapies. ***Future Directions:*** Identifying and targeting regulators of metabolic plasticity, rather than specific metabolic pathways, in combination with standard-of-care treatments have the potential to improve therapeutic outcomes in GBM.

Keywords: glioblastoma; metabolism; plasticity; redox.