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Radiation therapy promotes unsaturated fatty acids to maintain survival of glioblastoma

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Abstract

Radiation therapy (RT) is essential for the management of glioblastoma (GBM). However, GBM frequently relapses within the irradiated margins, thus suggesting that RT might stimulate mechanisms of resistance that limits its efficacy. GBM is recognized for its metabolic plasticity, but whether RT-induced resistance relies on metabolic adaptation remains unclear. Here, we show in vitro and in vivo that irradiated GBM tumors switch their metabolic program to accumulate lipids, especially unsaturated fatty acids. This resulted in an increased formation of lipid droplets to prevent endoplasmic reticulum (ER) stress. The reduction of lipid accumulation with genetic suppression and pharmacological inhibition of the fatty acid synthase (FASN), one of the main lipogenic enzymes, leads to mitochondrial dysfunction and increased apoptosis of irradiated GBM cells. Combination of FASN inhibition with focal RT improved the median survival of GBM-bearing mice. Supporting the translational value of these findings, retrospective analysis of the GLASS consortium dataset of matched GBM patients revealed an enrichment in lipid metabolism signature in recurrent GBM compared to primary. Overall, these results demonstrate that RT drives GBM resistance by generating a lipogenic environment permissive to GBM survival. Targeting lipid metabolism might be required to develop more effective anti-GBM strategies.

Keywords: Apoptosis; ER stress; Fatty acid synthase; Glioblastoma; Lipid droplets; Lipid metabolism; Mass spectrometry imaging; Prostaglandin E2; Radiation therapy; Survival; Unsaturated fatty acids.