Targeting the radiation-induced metabolic reprogramming overcomes acquired radioresistance of GBM

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Abstract: Glioblastoma (GBM) is a malignant primary brain tumor with median survival less than 15 months and radiotherapy is a standard treatment option for patients with GBM. Although radiotherapy has high therapeutic efficacy, some proportion of the tumor cells that survive after radiotherapy show poorer response to further therapies and lead to worse prognosis. In this study, we found that fructose 1,6-bisphosphatase 1 (FBP1) and CAP-Gly domain containing linker protein 3 (CLIP3) were repressed upon treatment with ionizing radiation (IR). Downregulated FBP1 increased glucose uptake and elevated glycolysis level, and downregulated CLIP3 coordinately shifted GBM cell glucose metabolism to favor glycolysis via facilitating GLUT3 trafficking to cellular membranes in GBM cells. As an anti-tumor metabolic regulator, we found that emodin, a natural substance inhibitor of phosphoglycerate mutase 1, and glimepiride, an FDA-approved medication for type 2 diabetes. Importantly, in combination with IR, glimepiride significantly disrupted GSCs maintenance and suppresses glycolytic activity by restoring CLIP3 function. In addition, combining radiotherapy and glimepiride remarkably reduced GBM growth and improved survival in a GBM orthotopic xenograft mouse model. Collectively, our data suggest that the metabolic regulators emodin and glimepiride could be an attractive strategy for eradicating GBM.