Increased Expression of System xc- in Glioblastoma Confers an Altered Metabolic State and Temozolomide Resistance.

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**Public Summary:**
Glioblastoma multiforme is the most aggressive malignant primary brain tumor in adults. Several studies have shown that glioma cells upregulate the expression of xCT (SLC7A11), the catalytic subunit of system xc-, a transporter involved in cystine import, that modulates glutathione production and glioma growth. However, the role of system xc- in regulating the sensitivity of glioma cells to chemotherapy is currently debated. Inhibiting system xc- with sulfasalazine decreased glioma growth and survival via redox modulation, and use of the chemotherapeutic agent temozolomide together with sulfasalazine had a synergistic effect on cell killing. To better understand the functional consequences of system xc- in glioma, stable SLC7A11-knockdown and -overexpressing U251 glioma cells were generated. Modulation of SLC7A11 did not alter cellular proliferation but overexpression did increase anchorage-independent cell growth. Knockdown of SLC7A11 increased basal reactive oxygen species (ROS) and decreased glutathione generation resulting in increased cell death under oxidative and genotoxic stress. Overexpression of SLC7A11 resulted in increased resistance to oxidative stress and decreased chemosensitivity to temozolomide. In addition, SLC7A11 overexpression was associated with altered cellular metabolism including increased mitochondrial biogenesis, oxidative phosphorylation, and ATP generation. These results suggest that expression of SLC7A11 in the context of glioma contributes to tumorigenesis, tumor progression, and resistance to standard chemotherapy.

**Scientific Abstract:**
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**IMPLICATIONS:** SLC7A11, in addition to redox modulation, appears to be associated with increased cellular metabolism and is a mediator of temozolomide resistance in human glioma, thus making system xC- a potential therapeutic target in glioblastoma multiforme. Mol Cancer Res; 14(12); 1229-42. (c)2016 AACR.

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