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Green tea epigallocatechin gallate enhances therapeutic efficacy of temozolomide in orthotopic mouse glioblastoma models.

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Abstract

The alkylating agent temozolomide, in combination with surgery and radiation, is the current standard of care for patients with glioblastoma. However, despite this extensive therapeutic effort, the inclusion of temozolomide extends survival only by a few short months. Among the factors contributing to chemoresistance is elevated expression of the endoplasmic reticulum (ER) chaperone GRP78 (glucose-regulated protein 78; BiP), a key pro-survival component of the ER stress response system. Because the green tea component EGCG (epigallocatechin 3-gallate) had been shown to inhibit GRP78 function, we investigated whether this polyphenolic agent would be able to increase the therapeutic efficacy of temozolomide in preclinical models of glioblastoma. Mice with intracranially implanted human U87 (p53 wild type) or U251 (p53 mutant) glioblastoma cells were treated with temozolomide and EGCG, alone and in combination. We found that EGCG alone did not provide survival benefit, but significantly improved the existing therapeutic effect of temozolomide, i.e., life extension was substantially greater under combination therapy as compared to temozolomide therapy alone. Immunohistochemical analysis of tumor tissue revealed increased expression levels of GRP78 in temozolomide-treated animals, which was diminished when temozolomide was combined with EGCG. Parallel in vitro experiments with siRNA targeting GRP78 or its major pro-apoptotic antagonist CHOP (CCAAT/enhancer binding protein homologous protein/GADD153) further established a critical role of the ER stress response system, where si-GRP78 sensitized cells to treatment with temozolomide, and si-CHOP provided protection from drug-induced toxicity. Thus, ER stress-regulatory components affect the chemotherapeutic response of glioblastoma cells to treatment with temozolomide, and inclusion of EGCG is able to increase the therapeutic efficacy of this DNA-damaging agent.

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