Chloroquine enhances temozolomide cytotoxicity in malignant gliomas by blocking autophagy.

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Abstract

OBJECT: In a recent clinical trial, patients with newly diagnosed glioblastoma multiforme benefited from chloroquine (CQ) in combination with conventional therapy (resection, temozolomide [TMZ], and radiation therapy). In the present study, the authors report the mechanism by which CQ enhances the therapeutic efficacy of TMZ to aid future studies aimed at improving this therapeutic regimen.

METHODS: Using in vitro and in vivo experiments, the authors determined the mechanism by which CQ enhances TMZ cytotoxicity. They focused on the inhibition-of-autophagy mechanism of CQ by knockdown of the autophagy-associated proteins or treatment with autophagy inhibitors. This mechanism was tested using an in vivo model with subcutaneously implanted U87MG tumors from mice treated with CQ in combination with TMZ.

RESULTS: Knockdown of the autophagy-associated proteins (GRP78 and Beclin) or treatment with the autophagy inhibitor, 3-methyl adenine (3-MA), blocked autophagosome formation and reduced CQ cytotoxicity, suggesting that autophagosome accumulation precedes CQ-induced cell death. In contrast, blocking autophagosome formation with knockdown of GRP78 or treatment with 3-MA enhanced TMZ cytotoxicity, suggesting that the autophagy pathway protects from TMZ-induced cytotoxicity. CQ in combination with TMZ significantly increased the amounts of LC3B-II (a marker for autophagosome levels), CHOP/GADD-153, and cleaved PARP (a marker for apoptosis) over those with untreated or individual drug-treated glioma cells. These molecular mechanisms seemed to take place in vivo as well. Subcutaneously implanted U87MG tumors from mice treated with CQ in combination with TMZ displayed higher levels of CHOP/GADD-153 than did untreated or individual drug-treated tumors.

CONCLUSIONS: Taken together, these results demonstrate that CQ blocks autophagy and triggers endoplasmic reticulum stress, thereby increasing the chemosensitivity of glioma cells to TMZ.

KEYWORDS: 3-MA = 3-methyl adenine; BEC = brain endothelial cell; BECN1 = Beclin 1; Beclin 1; CFA = colony-formation assay; CHOP; CQ = chloroquine; ER = endoplasmic reticulum; GADD-153; GBM = glioblastoma multiforme; GRP78; PI3KC = class III phosphatidylinositol 3-kinase; PTEN = phosphatase and tensin homolog; TMZ = temozolomide; TMZR = TMZ resistant; TMZS = TMZ sensitive; TuBEC = tumor-derived brain endothelial cell; UPR = unfolded protein response; autophagy; chloroquine; endoplasmic reticulum stress; si = small interfering; temozolomide

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