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Glioblastoma stem cells resistant to temozolomide-induced autophagy.

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BACKGROUND: Recent studies have demonstrated the existence of a small fraction of cells with features of primitive neural progenitor cells and tumor-initiating function in brain tumors. These cells might represent primary therapeutic target for complete eradication of the tumors. This study aimed to determine the resistant phenotype of glioblastoma stem cells (GSCs) to temozolomide (TMZ) and to explore the possible molecular mechanisms underlying TMZ resistance. **METHODS:** Freshly resected glioblastoma specimen was collected and magnetic isolation of GSCs was carried out using the Miltenyi Biotec CD133 Cell Isolation kit. The cytotoxic effect of TMZ on CD133(+) and CD133(-) glioblastoma cells was determined by using the 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) assay. Autophagy-related proteins (Beclin-1, LC3 and Atg5) and cleaved caspase-3 (p17) were analyzed by Western blotting. Immunofluorescent staining was used to detect Atg5, glial fibrillary acidic protein (GFAP) and CD133 expression in glioblastoma cells. Statistical analysis was carried out using SPSS 10.0 software. For all tests, the level of statistical significance was set at $P < 0.05$. **RESULTS:** CD133(+) glioblastoma cells exhibited neurosphere-like growth in vitro and high expression of CD133 stem cell marker. The growth-inhibiting rate in CD133(-) glioblastoma cells treated with 5 or 50 micromol/L TMZ was significantly higher than that in CD133(+) glioblastoma cells ((14.36 +/- 3.75)% vs (2.54 +/- 1.36)% or (25.95 +/- 5.25)% vs (2.72 +/- 1.84)%, respectively, $P < 0.05$). Atg5, LC3-II and Beclin-1 levels were significantly lower in CD133(+) glioblastoma cells than those in autologous CD133(-) cells after TMZ treatment ($P < 0.05$). Caspase-3 was mildly activated only in CD133(-) glioblastoma cells after exposure to TMZ ($P < 0.05$). Immunofluorescent staining revealed elevated expression of Atg5 in GFAP(+) cells following TMZ treatment. **CONCLUSIONS:** The GSCs display strong capability of tumor's resistance to TMZ. This resistance is probably contributed by the CD133(+) cells with down-regulation of autophagy-related proteins. Future treatment should target this small population of cancer stem cells in tumors to improve survival of patients.

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