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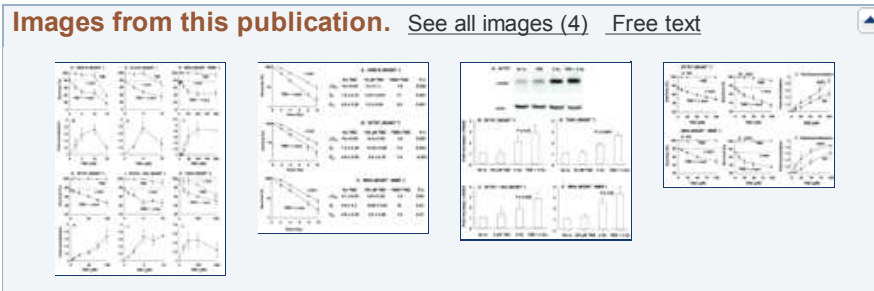
## Minimally cytotoxic doses of temozolomide produce radiosensitization in human glioblastoma cells regardless of MGMT expression.

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### Abstract

Concurrent treatment with the methylating agent temozolomide during radiotherapy has yielded the first significant improvement in the survival of adult glioblastomas (GBM) in the last three decades. However, improved survival is observed in a minority of patients, most frequently those whose tumors display CpG methylation of the O(6)-methylguanine (O(6)-meG)-DNA methyltransferase (MGMT) promoter, and adult GBMs remain invariably fatal. Some, although not all, preclinical studies have shown that temozolomide can increase radiosensitivity in GBM cells that lack MGMT, the sole activity in human cells that removes O(6)-meG from DNA. Here, we systematically examined the temozolomide dose dependence of radiation killing in established GBM cell lines that differ in ability to remove O(6)-meG or tolerate its lethality. Our results show that minimally cytotoxic doses of temozolomide can produce dose-dependent radiosensitization in MGMT-deficient cells, MGMT-proficient cells, and MGMT-deficient cells that lack mismatch repair, a process that renders cells tolerant of the lethality of O(6)-meG. In cells that either possess or lack MGMT activity, radiosensitization requires exposure to temozolomide before but not after radiation and is accompanied by formation of double-strand breaks within 45 minutes of radiation. Moreover, suppressing alkyladenine-DNA glycosylase, the only activity in human cells that excises 3-methyladenine from DNA, reduces the temozolomide dose dependence of radiosensitization, indicating that radiosensitization is mediated by 3-methyladenine as well as by O(6)-meG. These results provide novel information on which to base further mechanistic study of radiosensitization by temozolomide in human GBM cells and to develop strategies to improve the outcome of concurrent temozolomide radiotherapy.

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