Resveratrol reverses temozolomide resistance by downregulation of MGMT in T98G glioblastoma cells by the NF-κB-dependent pathway.

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Abstract

Glioblastoma multiforme (GBM) is the most common intracranial tumor, with a dismal prognosis. Although temozolomide (TMZ)-based chemotherapy following neurosurgery has been proven to be effective, not all patients benefit clinically because of TMZ resistance. Given that protein expression of O(6)-methylguanine-DNA-methyltransferase (MGMT) is the most important determinant of TMZ resistance, great efforts have been made to suppress it by regulating MGMT-related transcription factors. The study presented here demonstrates that resveratrol, a natural polyphenol, is able to reverse TMZ resistance of glioblastoma T98G cells which have relatively high MGMT activity. The data showed that combination treatment with TMZ and resveratrol resulted in an enhanced antitumor potential of TMZ, decreased the 50% inhibiting concentration (IC50) of TMZ and increased the induction of apoptosis in TMZ-resistant T98G cells. Hoechst 33258 staining revealed increased apoptotic morphology, such as chromatin aggregation and nuclear and cytoplasmic condensation, in cells receiving combination treatment. Western blot analysis manifested a significant decreased intracellular content and nuclear translocation of NF-κB and increased cleavage of caspase-3 in cells exposed to combination treatment, compared to those in cells treated with TMZ alone. In addition, recombinant expression of NF-κB subunit p65 remarkably promoted nuclear translocation of NF-κB and abolished the TMZ-resistance reversal induced by combination treatment, suggesting an underlying NF-κB-dependent mechanism. Our study improved the knowledge on the mechanism of TMZ resistance and suggested a novel strategy for TMZ-based chemotherapy in glioblastoma patients.

PMID: 22426504 [PubMed - as supplied by publisher]