A tumor-targeting p53 nanodelivery system limits chemoresistance to temozolomide prolonging survival in a mouse model of glioblastoma multiforme.

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Abstract

Development of temozolomide (TMZ) resistance contributes to the poor prognosis for glioblastoma multiforme (GBM) patients. It was previously demonstrated that delivery of exogenous wild-type tumor suppressor gene p53 via a tumor-targeted nanocomplex (SGT-53) which crosses the blood-brain barrier could sensitize highly TMZ-resistant GBM tumors to TMZ. Here we assessed whether SGT-53 could inhibit development of TMZ resistance. SGT-53 significantly chemosensitized TMZ-sensitive human GBM cell lines (U87 and U251), in vitro and in vivo. Furthermore, in an intracranial GBM tumor model, two cycles of concurrent treatment with systemically administered SGT-53 and TMZ inhibited tumor growth, increased apoptosis and most importantly, significantly prolonged median survival. In contrast TMZ alone had no significant effect on median survival compared to a single cycle of TMZ. These results suggest that combining SGT-53 with TMZ appears to limit development of TMZ resistance, prolonging its anti-tumor effect and could be a more effective therapy for GBM.

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