FoxM1 Inhibition Sensitizes Resistant Glioblastoma Cells to Temozolomide by Downregulating the Expression of DNA Repair Gene Rad51.

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Abstract

PURPOSE: Recurrent glioblastoma multiforme (GBM) is characterized by resistance to radiotherapy and chemotherapy and a poor clinical prognosis. In this study, we investigated the role of the oncogenic transcription factor FoxM1 in GBM cells' resistance to TMZ and its potential molecular mechanism.

EXPERIMENTAL DESIGN: FoxM1 expression levels were measured by immunohistochemical analysis in 38 pairs of primary and recurrent GBM tumor samples. Expression levels were also measured in primary recurrent GBM cell lines, and their responses to TMZ were characterized. In a mechanistic study, an siRNA array was used to identify downstream genes, and a chromatin immunoprecipitation assay was used to confirm transcriptional regulation.

RESULTS: Recurrent tumors that were TMZ resistant expressed higher levels of FoxM1 than did primary tumors. Recurrent GBM cell lines expressed higher levels of FoxM1 and the DNA damage repair gene Rad51 and were resistant to TMZ. TMZ treatment led to increased FoxM1 and Rad51 expression. FoxM1 knockdown inhibited Rad51 expression and sensitized recurrent GBM cells to TMZ cytotoxicity. FoxM1 directly regulated Rad51 expression through two FoxM1-specific binding sites in its promoter. Rad51 re-expression partially rescued TMZ resistance in FoxM1-knockdown recurrent GBM cells. A direct correlation between FoxM1 expression and Rad51 expression was evident in recurrent GBM tumor samples.

CONCLUSION: Targeting the FoxM1-Rad51 axis may be an effective method to reverse TMZ resistance in recurrent GBM.

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