Long Noncoding RNA MALAT1 is Induced by DNA Damage in an NF-B- and P53-dependent Manner in Glioblastoma

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Introduction

Resistance to DNA damage-induced cytotoxicity plays a major role in the poor response of many glioblastoma (GBM) patients to chemotherapy. The oral alkylator, temozolomide (TMZ), is the most commonly used chemotherapeutic for the management of GBM yet, despite its routine use, overall response to TMZ remains modest(1). Among the factors that regulate the response to alkylation damage, NF-kB acts to both promote and block cytotoxicity(2, 3).

Methods

Using genome-wide expression analysis, we identified NF-kB-dependent factors significantly altered in response to the alkylator TMZ. Molecular laboratory techniques (ChIP, EMSA, Western Immunoblot, qPCR) were employed to validate and further investigate the expression array analysis. GBM xenografts were established in mice to evaluate the therapeutic benefit of targeting NF-kB-dependent factors identified in the expression analysis.

Results

We identified the long non-coding RNA (lncRNA) MALAT1 as one of the most significantly up-regulated NF-kB-dependent factors factors in response to TMZ treatment in GBM. MALAT1 is shown to be co-regulated by p50 (p105) and p53 via novel kB- and p53-binding sites in the proximal MALAT1 coding region. Mechanistically, TMZ inhibits p50 recruitment to its cognate element while concomitantly increasing p53 recruitment. Moreover, both the kB and p53 cis-elements are shown to be required for efficient transactivation in response to TMZ. Depletion of MALAT1 sensitizes GBM cells to cytotoxicity by TMZ and in vivo delivery of an anti-MALAT1 siRNA encapsulated in a nanoparticle prolongs survival of mice bearing intracranial GBM xenografts. Despite these observations, in-situ hybridization of GBM specimens and analysis of publically available datasets demonstrates that MALAT1 expression level is not prognostic of overall survival in GBM.

Conclusions

In sum, this work identifies MALAT1 as a non-coding transcript induced by TMZ in a manner dependent on both NF-kB and p53, that promotes resistance to TMZ therapy. These findings also indicate that MALAT1 is a potential target for chemosensitization of GBM.

Learning Objectives

By the conclusion of this session, participants should be able to:

1) Recognize that TMZ treatment in GBM results in a specific downstream gene expression profile which includes the induction of the lncRNA MALAT

2) Understand that TMZ induced MALAT1 expression is regulated in a p53 and NF-kb co-dependent manner

3) Identify the potential therapeutic benefit of targeting MALAT1 in GBM treatment

References

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