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MIR-603 Mediates Acquired Temozolomide and Radiation Resistance by Suppression of Methylguanine Methyltransferase (MGMT) Expression and Insulin Growth Factor (IGF) Signaling

Valya Ramakrishnan; Jie Li.; Jun Ma; Sanjay Dhawan M.D.; Beibei Xu PhD; Thien Nguyen.; Johnny Akers; Bob S. Carter MD, PhD; Clark C. Chen MD, PhD

Introduction

Acquired resistance to concurrent radiation and temozolomide (TMZ) treatment remains a major challenge in the clinical management of glioblastoma, the most common form of brain cancer in adults. We previously showed that high miR-603 expression in clinical glioblastoma specimens is a key determinant of good clinical response to concurrent radiation therapy. Here we explored the mechanisms by which miR-603 mediates resistance to radiation and temozolomide.

Methods

To identify miR-603 mediated resistance mechanisms, we profiled the mRNAs under miR-603 regulation as well the mRNAs that co-precipitated with biotinylated miR-603. Orthogonal intersection of these two data sets revealed target genes including MGMT and genes mediating IGF signaling (including IGF1R, IGF1, and IGFBP5).

Results

In MGMT producing glioblastoma lines, the predominant effect of miR-603 involves suppression of MGMT mRNA/protein expression and increasing TMZ sensitivity. These effects were observed in vitro and in vivo. Moreover, it is reversed by transfection with anti-miR-603. miR-603 affinity-precipitated with MGMT mRNA and suppressed luciferase activity in an MGMT-3'UTR-luciferase assay. Importantly, miR-603 levels inversely correlated with MGMT expression in clinical glioblastoma specimens. In non-MGMT producing glioblastoma lines, miR-603 induces radiation sensitivity by simultaneously suppressing IGF1R, IGF1, and IGFBP5 mRNA/protein expression. These targets were validated in vitro and in vivo as well as by miR-603 pull-down experiments and 3'UTR-luciferase assays. In vitro and in vivo, the radiation sensitizing effects of miR-603 can be reversed by the addition or expression of IGF1. Moreover, the radiation sensitizing effects of miR-603 are epistatic to the IGF1R inhibitor, cyclolignan picropodophyllin (PPP).

Conclusions

miR-603 is a master regulatory miRNA that controls key DNA repair processes that mediate glioblastoma resistance to TMZ and radiation by regulating MGMT and IGF signaling, respectively. These properties can be exploited for therapeutic and diagnostic purposes.

Learning Objectives

By the conclusion of this session, participants should be able to: 1)Describe the role of miR-603 in mediating acquired temozolomide and radiation resistance by the suppression of MGMT expression and IGF signaling.2) Discuss the prospects of utilizing the key regulatory properties of miR-603 for therapeutic and diagnostic purposes.3) Identify the epistatic behavior of the radiation sensitizing effects of miR-603 to the IGF1R inhibitor, cyclolignan picropodophyllin (PPP).

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