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A Functional Screen Identifies miRs that Induce Radioresistance in Glioblastomas

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Introduction

The efficacy of radiotherapy in many tumor types is limited by normal tissue toxicity and by intrinsic or acquired radioresistance.

Methods

An unbiased functional microRNA screen identified four miRNAs (miR1, miR125a, miR150, and miR425) that induced glioblastoma radioresistance. We employed gain and loss of function approaches to validate the critical importance of these miRNAs as determinants of glioblastoma radiation resistance.

Learning Objectives

To identify four microRNAs -- miR1, miR125a, miR150, and miR425 -- that induce glioblastoma radioresistance and understand their functions.

Results

Overexpression of miR1, miR125a, miR150, and/or miR425 in glioblastoma promotes radioresistance through upregulation of the cell-cycle checkpoint response. Conversely, antagonizing with antagomiRs sensitizes glioblastoma cells to irradiation, suggesting their potential as targets for inhibiting therapeutic resistance. Analysis of glioblastoma datasets from The Cancer Genome Atlas (TCGA) revealed that these miRNAs are expressed in glioblastoma patient specimens and correlate with TGFb signaling. Finally, it is demonstrated that expression of miR1 and miR125a can be induced by TGFb and antagonized by a TGFb receptor inhibitor. Together, these results identify and characterize a new role for miR425, miR1, miR125, and miR150 in promoting radioresistance in glioblastomas and provide insight into the therapeutic application of TGFb inhibitors in radiotherapy.

Conclusions

Systematic identification of miRs that cause radioresistance in gliomas is important for uncovering predictive markers for radiotherapy or targets for overcoming radioresistance.

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