Gli1 inhibition as a strategy to enhance chemosensitivity in glioblastoma

Jilian Melamed[1], Kimberly Arnold[2], Jennifer Sims-Mourtada[2], Emily Day[1,2]

1. Department of Biomedical Engineering, University of Delaware
2. Center for Translational Cancer Research, Helen F. Graham Cancer Center

Background: Glioblastoma multiforme (GBM) is a lethal brain cancer subtype whose resistance to the frontline chemotherapy temozolomide (TMZ) is driven by the gene Gli1. This project aimed to validate small interfering RNA (siRNA)-mediated Gli1 inhibition as a strategy to enhance chemosensitivity in GBM, and to develop nanoparticles called spherical nucleic acids (SNAs) as siRNA delivery vehicles to neutralize Gli1 in GBM.

Methods: We used qRT-PCR to analyze expression of Gli1 and its targets BCRP, Bcl2, and Nanog in GBM cells exposed to control or Gli1 siRNA by Lipofectamine transfection. The impact of treatment on cell proliferation, efflux transporter activity, and viability was evaluated by EdU incorporation, Rhodamine efflux, and Alamar Blue viability assays, respectively. SNAs' ability to suppress Gli1 in GBM cells was assessed by qRT-PCR.

Results: Suppressing Gli1 with siRNA reduces TMZ-driven up-regulation of BCRP, Bcl2, and Nanog. Further, Gli1 inhibition reduces GBM cell proliferation by 58% and efflux transporter activity 2.5-fold, and increases GBM sensitivity to TMZ. Compared to Lipofectamine delivery, which requires 100 nM siRNA, 0.5 nM SNAs can reduce Gli1 in GBM cells by 50%.

Conclusions: Our studies validate that Gli1 suppression enhances chemosensitivity in GBM and that SNAs can be used to inhibit Gli1 in GBM cells. Future work will continue exploring Gli1 inhibitory SNAs for GBM treatment.

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