TR-04. NANOPARTICLE siRNA DELIVERY VEHICLES INHIBIT DNA REPAIR AND SENSITIZE PEDIATRIC BRAIN TUMOR CELLS TO RADIATION THERAPY
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Radiotherapy (RT) is an integral component of the treatment for medulloblastoma (MB) and the only effective adjuvant therapy for ependymoma (EP), two of the most common pediatric brain tumors. However, survival is frequently accompanied by one or more radiation-induced adverse developmental and psychosocial sequelae. Therefore, strategies that enhance the tumoricidal action of RT while sparing adjacent normal brain are expected to reduce the amount of radiation required to generate a therapeutic effect in these tumors. The multifunctional DNA repair protein Ape1/Ref-1 has been implicated in conferring radiation resistance in pediatric brain tumors. However, inhibiting Ape1 activity in the clinic has been hindered by the lack of safe and effective drugs and siRNA delivery vehicles. Here, we used our nanoparticle delivery vehicles to deliver siRNA against Ape1 (siApe1) and improve cell kill after RT. Nanoparticles were loaded with siApe1, or siGFP as a control, and used to treat UW228 (MB) and Res196 (EP) cells. Ape1 expression and activity were measured using PCR, Western blot, and an abasic endonuclease activity assay. DNA repair and clonogenic survival were assessed after exposure to 137Cs-γ-rays. We found that nanoparticle-mediated siApe1 delivery reduced Ape1 expression and activity by greater than 80%, which was accompanied by a greater abundance of DNA damage. This diminished the shoulder of resistance in survival curves decreasing survival to ~50% at 1 Gy. Sensitization was specific to abasic site generating treatments as response to paclitaxel was not affected. Therefore, nanoparticle-mediated inhibition of Ape1 may help enhance the therapeutic effect of RT in pediatric brain tumor patients and reduce treatment-induced morbidity.