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HGG-46. PEDIATRIC RADIATION-INDUCED GLIOMA PATIENT SAMPLES AND NOVEL PATIENT-DERIVED MODELS REVEAL TRANSLATIONALLY RELEVANT TREATMENT SUSCEPTIBILITIES AND POTENTIAL GERMINE RISK FACTORS
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BACKGROUND: Pediatric radiation-induced glioma (RIG) is an incurable secondary high-grade glioma (HGG) affecting up to 4% of children who previously received cranial radiotherapy (RT) for other malignancies. RIG accounts for up to 10% of pediatric brain tumor deaths. It has no known genetic risk factors nor effective treatment and is uniformly fatal, partly due to extremely limited available models. Our recent molecular characterization of patient samples showed that while RIG and primary pediatric HGG share histological similarities, their genetic alterations and gene expression profiles differ. METHODS: We obtained germline DNA sequencing from 28 RIG patients and 112 matched controls who received RT but did not develop RIG. In addition, we developed cell culture and murine orthotopic patient-derived xenograft (PDX) models from four RIGs. We conducted single-cell RNA-seq (scRNA-seq), drug screening/validation, and CRISPR functional screening on our novel models. RESULTS: Germline mutations in TP53, PARP10, POLI, DCLRE1A, and MLH3 were more common in RIG patients than controls (p<0.002). Our matched cell culture and PDX models of RIG represent the genetic diversity of the disease. The PDX models form tumors in 30-120 days and closely recapitulate human RIG by histology and scRNA-seq. They show susceptibility across models to DNA-damaging treatments (etoposide, irinotecan, radiation), as well as MEK, PARP, and proteasome inhibition, with orthogonal supporting findings via CRISPR screening. Several two-treatment combinations also show efficacy and synergy across models, including radiation and trametinib in vivo (logrank p=0.029). Discussion: RIG is an understudied but major cause of pediatric CNS tumor mortality that differs genetically from primary pediatric HGG. Our findings suggest specific germline alterations in DNA repair pathways may put some patients at higher risk of developing RIG after cranial RT. We also introduce the first set of patient-derived RIG models in order to advance translational RIG research, with characterization of translationally relevant treatment susceptibilities.