MB-12. INDUCED CISPLATIN RESISTANCE IN MEDULLOBLASTOMAS
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INTRODUCTION: Medulloblastoma is the most common malignant brain tumor in children. Treatment typically involves surgery followed by chemotherapy, incorporating cisplatin. Tumor recurrence is common after treatment, especially in type 3 (C-MYC-expressing) medulloblastomas, and less commonly in sonic-hedgehog-associated tumors (type 2). Though clinically devastating, little is known about recurrent medulloblastomas compared to primary tumors and almost nothing is known about the mechanisms of chemotherapeutic resistance in medulloblastoma. OBJECTIVES: Develop a cellular model for medulloblastoma recurrence and drug resistance by establishing a cisplatin-resistant medulloblastoma cell line, and evaluate sensitivity of this model to other treatments. METHODS: Medulloblastoma cell lines DAOY and D341-MED, representative of type 2 and type 3 medulloblastoma were pulsed with cisplatin or cultured in escalating concentrations of cisplatin, respectively. Resistance to cisplatin was assessed by cell proliferation assay (XTT). RESULTS: XTT analysis at 48 hours revealed an 8-fold increase in IC-50 between the wild-type D341 and cisplatin-resistant D341 cell line (termed CR4). DAOY cells evaluated similarly at 72 hours showed an ~3 fold difference between wild type and cisplatin-pulsed DAOY (CR5P). Interestingly, CR4 cells displayed an increased sensitivity to doxorubicin relative to wild-type D341. DISCUSSION: Recurrent medulloblastoma show growth after repeated exposure to multiple chemotherapeutics. Our newly-created CR4 and CR5P cells represent this element of recurrent medulloblastoma, allowing analysis of biochemical and genetic differences between primary and recurrent medulloblastomas. We plan to further analyze hypersensitivity to other drugs with the aim of identifying candidates for combination chemotherapy. We also plan to evaluate the genetic, and phenotypic differences between wild type and resistant cells in response to cisplatin to better understand post-chemotherapy recurrence. CONCLUSION: We have created the first 2 medulloblastoma cell lines that show cisplatin resistance, serving as a novel model by which to study medulloblastoma recurrence.