MB-27. PATHWAY ANALYSIS OF A HUMAN NEURAL STEM CELL MODEL OF AGGRESSIVE MEDULLOBLASTOMA REVEALS CKD INHIBITION AS A POTENTIAL THERAPEUTIC MODALITY

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Medulloblastoma, the most common malignant brain tumor in children, is divided into multiple subgroups with different associated mutations and clinical prognoses. To facilitate studying the biology and developing new therapeutic options, we created a model of aggressive medulloblastoma using human neural stem cells. Neural stem cells were obtained from the cerebellar anlage of first trimester fetal autopsy specimens and transfected using lentiviral vectors with different combinations of oncogenes associated with poor prognosis medulloblastoma: dominant-negative p53, hTERT, c-MYC, and constitutively active AKT. Cerebellar derived stem cells transformed with all four oncogenes formed fast growing, aggressive tumors that were histologically similar to primary anaplastic medulloblastoma tumors. We compared the expression profile of primary medulloblastoma tumors to our model, and confirmed that our model most closely matches the most aggressive and clinically devastating subgroup of medulloblastoma. The expression profile of our model was compared with a drug sensitivity database to identify therapeutic agents that could target our model. One class of drugs identified was cyclin-dependent kinase inhibitors. Because MYC also regulates the expression of CDKs 4/6, we hypothesized that flavopiridol (alvocidib), a cyclin dependent kinase inhibitor currently in clinical trials for a variety of tumor types would be effective against MYC-driven medulloblastoma. Our model and the medulloblastoma cell lines D425Med and D283Med were sensitive to treatment with flavopiridol. The IC50 of flavopiridol was less than 50nM for all cell lines tested. Flavopiridol decreased the growth and proliferation of both cell lines and our neurosphere model as measured by MTS assay and BrdU incorporation (p < 0.001). Flavopiridol also included apoptosis as determined by staining for cleaved caspase-3 and flow cytometry (p < 0.01). The data shown here demonstrate that our human neurosphere model of medulloblastoma can facilitate the identification of agents with therapeutic efficacy against aggressive medulloblastoma.