MB-33. THE CRITICAL ROLE OF OLIG2-EXPRESSING PROGENITORS IN THE INITIATION OF G-PROTEIN MEDIATED SONIC HEDGEHOG-DRIVEN MEDULLOBLASTOMA
Xuelian Lu and Richard Lu; Cincinnati Children’s Hospital Medical Center, Cincinnati, OH, USA

Medulloblastoma, the most common malignant childhood brain tumor, exhibits distinct molecular subtypes and cellular origins. Genetic alterations driving medulloblastoma initiation and progression remain poorly understood. Recently we identify GNAS, encoding the G-protein Gsα, as a potent tumor suppressor gene that defines a subset of aggressive Sonic Hedgehog (Shh)-driven human medulloblastomas. Ablation of the single Gnas gene in an anatomically-distinct progenitors is sufficient to induce Shh-associated medulloblastomas, which recapitulate their human counterparts. Gsα is highly enriched at the primary cilium of granule neuron precursors and suppresses Shh-signaling by regulating both the cAMP-dependent pathway and ciliary trafficking of Hedgehog pathway components. Elevation of a Gsα effector, cAMP, effectively inhibits tumor cell proliferation and progression in Gnas mutants. Furthermore, we identify a population of Olig2-expressing progenitor cells as the major source of tumor-propagating cells. Deletion of Olig2 leads to a delay of tumor progression. Eliminating the mitotic Olig2-expression inhibits tumor initiation. Thus, our present studies identify a previously unrecognized tumor suppressor function for Gsα that acts as a molecular link across Shh-group medulloblastomas of disparate cellular and anatomical origins, and reveal that Olig2-expressing progenitors are the critical cell origin of G-protein-mediated SHH subgroup medulloblastoma, illuminating potential therapeutic avenues for SHH medulloblastoma by targeting G-protein and Olig2-expressing glial progenitors.