Differential Gene Expression in SHH Pathway Inhibition

During development, disruptions in sonic hedgehog (SHH) signaling can lead to medulloblastoma, the most common malignant pediatric brain tumor. Medulloblastoma tumor cells arise from cerebellar granule neural progenitors (CGNPs), which rely on SHH signaling to proliferate. Inhibiting the SHH pathway is a focus of research in treatment of medulloblastoma. It is known that SHH is closely linked with the cell cycle, but it was not known how SHH pathway inhibition affects gene expression in CGNPs. To simulate SHH-deprivation, we performed microarray analysis using RNA from wild-type progenitor cells cultured in the presence or absence of SHH to test the effects of SHH on gene expression. We found that in absence of SHH, there is significant suppression of genes in the cell cycle, confirming that CGNPs depend on SHH to proliferate. To investigate the effects of indirect SHH inhibition on gene expression, we used vismodegib, an FDA-approved inhibitor of the SHH ligand receptor SMOOTHEMED (SMO). Wild-type mice were injected with either vismodegib or a vehicle control and collected RNA from CGNPs. We performed RNA-sequencing analysis to compare expression levels of cell cycle/proliferation markers, neuronal/differentiation markers, and SHH markers. Our preliminary data suggest that vismodegib promotes differentiation and suppresses proliferation. We will use differential gene expression analysis to identify genes of interest and validate our findings through in situ hybridization. These biological markers could be used to further medulloblastoma treatment research and, more specifically, to identify cells that are unaffected by vismodegib and cause recurrence in medulloblastoma patients.